
49th ANNUAL
EST. 1974
VAIL OB-GYN CONFERENCE
Week of Presidents' Day
February 18-23, 2024
Vail, Colorado
2024 Syllabus
Now available!
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Presented by
Obstetrics and Gynecology
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

Welcome to

the 49th ANNUAL

EST. 1974

VAIL OB-GYN CONFERENCE

Conference Co-Directors

Ronald S. Gibbs, MD
Vail Conference Co-Director
Professor Emeritus
Department of Obstetrics and Gynecology
University of Colorado, School of Medicine

Carolyn Lefkowits, MD, MPH, MS
Vail Conference Co-Director
Associate Professor and Colibri Endowed Professor
in Ovarian and Gynecologic Cancer Education
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Vail Conference Director
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Nanette F. Santoro, MD
Vail Conference Co-Director
Professor and E. Stewart Taylor Chair
Department of Obstetrics and Gynecology
University of Colorado, School of Medicine

Conference Learning Objectives

At the end of this activity, learners will be able to:

1. Identify increased obesity-related risks in pregnancy.
2. Develop treatment strategies for Von Willebrand disease in reproductive age women.
3. Counsel prospective patients on preimplantation genetic testing.
4. Implement appropriate DVT prophylaxis in obstetric candidates.
5. Identify risk factors for development of anal dysplasia in women.

Conference Accreditation

The University of Colorado School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The University of Colorado School of Medicine designates this live activity for a maximum of 20.5 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Table of Contents

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FEATURED GUEST SPEAKERS

Makeba Williams, MD, NCMP
Associate Professor
Vice Chair of Professional Development and Wellness
Division of Academic Specialists in Obstetrics and Gynecology
Department of Obstetrics and Gynecology
Washington University School of Medicine in St. Louis

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Department of Obstetrics and Gynecology
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Director, Fertility and Reproductive Medicine Center
Director, Reproductive Endocrinology and Infertility Fellowship
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Cedars-Sinai Medical Center

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Program Manager
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Director Robotic Surgery for UCHealth
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Jake Hirshberg, MD
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Patricia Huguelet, MD
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Fellowship Director
Medical Director, Spots and Dots Clinic, Hemophilia
and Thrombosis Center
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Assistant Residency Program Director
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Medical Director Obstetric Anesthesia Maternal Fetal Care Unit
Section of Anesthesia OB-GYN
Department of Anesthesiology
University of Colorado, School of Medicine

Sunday, February 18, 2024

4:00 PM **Welcome**

4:15 PM **What Is the "Pink Tax", Why Are Our Patients Paying It, and What Can We Do About It?**
Nanette F. Santoro, MD
University of Colorado, School of Medicine

4:45 PM **Q&A**

5:00 PM **Featured Guest Speaker**
"What Are My Options?": Nonhormone and Hormone Management of Vasomotor Symptoms
Makeba Williams, MD, NCMP
Washington University School of Medicine in St. Louis

5:30 PM **Q&A**

5:45 PM **Type 2 Diabetes Mellitus New Medications to Treat Co-Morbidities**
Michael T. McDermott MD
University of Colorado, School of Medicine

6:15 PM **Q&A**

6:30 PM – 7:30 PM **Reception**

**Please note that schedule and speakers are subject to change.*

Monday, February 19, 2024

6:45 AM **Breakfast on Menopause Therapies,** sponsored by Astellas**
Makeba Williams, MD, NCMP; Nanette F. Santoro, MD
Washington University School of Medicine in St. Louis; University of Colorado, School of Medicine

7:15 AM **Featured Guest Speaker**
The Utilization of Assisted Reproductive Technologies — It Is Not Just for Fertility Treatment
Margareta D. Pisarska, MD
Cedars-Sinai Medical Center

7:45 AM **Q&A**

7:55 AM **Featured Guest Speaker**
"Can We Talk?": Genitourinary Symptoms of Menopause in Cancer Survivors
Makeba Williams, MD, NCMP
Washington University School of Medicine in St. Louis

8:25 AM **Q&A**

8:35 AM **Anal Cancer Screening: What the OB-GYN Needs to Know**
Christine Conageski, MD, MSc
University of Colorado, School of Medicine

9:05 AM **Q&A**

9:15 AM – 3:30 PM **Mid-Day Break**

3:30 PM – 4:00 PM **Après-Ski**

4:00 PM **Featured Guest Speaker**
"Back so soon?": Postmenopausal and Perimenopausal Bleeding
Makeba Williams, MD, NCMP
Washington University School of Medicine in St. Louis

4:30 PM **Q&A**

4:45 PM **Break**

5:00 PM **Featured Guest Speaker**
Diagnosing Infertility — Helping Your Patients Through the Process
Margareta D. Pisarska, MD
Cedars-Sinai Medical Center

5:30 PM **Q&A**

5:40 PM **Featured Guest Speaker**
"I wasn't expecting you so soon": Premature Menopause Management
Makeba Williams, MD, NCMP
Washington University School of Medicine in St. Louis

6:10 PM **Q&A**

6:20 PM **Adjourn**

*Please note that schedule and speakers are subject to change. ** Not for CME credit.

Tuesday, February 20, 2024

6:45 AM **Breakfast with Professors**
Jaime Arruda, MD | Alex Mastroyannis, MD, MSCE | Cara Clure, MD, MSCS
Margareta D. Pisarska, MD | Conference Directors

7:15 AM **How to Develop a Culture of Safety and Quality in the OR**
Jaime Arruda, MD
University of Colorado, School of Medicine

7:45 AM Q&A

7:55 AM **Lower Genital Tract Dysplasia: Review and Updates**
S. Alex Mastroyannis, MD, MSCE
University of Colorado, School of Medicine

8:25 AM Q&A

8:35 AM **What's New and on the Horizon in Contraception?**
Cara Clure, MD, MSCS
University of Colorado, School of Medicine

9:05 AM Q&A

9:15 AM – 3:30 PM **Mid-Day Break**

3:30 PM – 4:00 PM **Après-Ski**

4:00 PM **Featured Guest Speaker**
Preconception Genetic Carrier Screening and PGT
Margareta D. Pisarska, MD
Cedars-Sinai Medical Center

4:30 PM Q&A

4:45 PM **Break**

5:00 PM **Palliative Care in Obstetrics & Gynecology**
Carolyn Lefkowits, MD, MPH, MS
University of Colorado, School of Medicine

5:30 PM Q&A

5:40 PM **Featured Guest Speaker**
How Infertility and Treatments Can Affect Human Placenta Function
Margareta D. Pisarska, MD
Cedars-Sinai Medical Center

6:10 PM Q&A

6:20 PM **Adjourn**

*Please note that schedule and speakers are subject to change.

Wednesday, February 21, 2024

6:45 AM **Breakfast with Professors**
Josephine C. Chou, MD, MS | Henry L. Galan, MD | Akshay Chauhan, MD | Conference Directors

7:15 AM **My Achy Breaky Heart: Heart Failure and Pregnancy**
Josephine C. Chou, MD, MS
University of Colorado, School of Medicine

7:45 AM Q&A

7:55 AM **Alloimmune Disorders in Pregnancy (RBC & Thrombocytopenia)**
Henry L. Galan, MD
University of Colorado, School of Medicine

8:25 AM Q&A

8:35 AM **Metabolic Bariatric Surgery in Women's Health**
Akshay Chauhan, MD
University of Colorado, School of Medicine

9:05 AM Q&A

9:15 AM – 3:30 PM **Mid-Day Break**

3:30 PM – 4:00 PM **Après-Ski**

4:00 PM **Featured Guest Speaker**
Are We Post-Pandemic? What's Next in COVID Management and Prevention
Torri Metz, MD, MS
University of Utah School of Medicine

4:30 PM Q&A

4:45 PM **Break**

5:00 PM **Management of Inherited Bleeding Disorders in Obstetrics and Gynecology**
Patricia Huguelet, MD
University of Colorado, School of Medicine

5:30 PM Q&A

5:40 PM **Justice/Equity in OB-GYN**

Gabrielle Whitmore, MD, MBS
University of Colorado, School of Medicine

Christy Angerhofer
University of Colorado Anschutz Medical Campus

6:10 PM Q&A

6:20 PM **Adjourn**

*Please note that schedule and speakers are subject to change.

Thursday, February 22, 2024

6:45 AM **Breakfast with Professors**
Patricia Huguelet, MD | Christy Angerhofer | Lauren Harrington, MD | Torri Metz, MD, MS
Conference Directors

7:15 AM **Featured Guest Speaker**
Cannabis Use During Pregnancy and While Breastfeeding: Sorting Through Hazy Evidence
Torri Metz, MD, MS
University of Utah School of Medicine

7:45 AM **Q&A**

7:55 AM **Female Sexual Medicine**
Lauren Harrington, MD
University of Colorado, School of Medicine

8:25 AM **Q&A**

8:35 AM **Primary HPV Screening: Is It Coming? Is That OK? Should We Do It? Do We Have a Choice? Does It Matter? What Next?**
L. Chesney Thompson, MD
University of Colorado, School of Medicine

9:05 AM **Q&A**

9:15 AM – 3:30 PM **Mid-Day Break**

3:30 PM – 4:00 PM **Après-Ski**

4:00 PM **Postpartum Laceration Complications and Management**
Lauren G. Rascoff, MD
University of Colorado, School of Medicine

4:30 PM **Q&A**

4:45 PM **Break**

5:00 PM **Hypoventilation, Hypoxia, and Hypercapnia Oh My! Pulmonary Disorders in Pregnancy**
Jake Hirshberg, MD
University of Colorado, School of Medicine

5:30 PM **Q&A**

5:40 PM **Featured Guest Speaker**
Hot Articles: Practice-Changing Publications in OB Research
Torri Metz, MD, MS
University of Utah School of Medicine

6:10 PM **Q&A**

6:20 PM **Adjourn**

*Please note that schedule and speakers are subject to change.

Friday, February 23, 2024

6:45 AM **Breakfast with Professors**
Lauren G. Rascoff, MD | Jake Hirshberg, MD | Shannon Son, MD, MSCI | Cristina Wood, MD
Conference Directors

7:15 AM **Lactation Suppression After Delivery or Termination**
Shannon Son, MD, MSCI
University of Colorado, School of Medicine

7:45 AM **Q&A**

7:55 AM **What's New in Anesthetic Management for OB-GYN Patients**
Cristina Wood, MD
University of Colorado, School of Medicine

8:25 AM **Q&A**

8:35 AM **Featured Guest Speaker**
Venous Thromboembolism Prevention in Obstetric Practice
Torri Metz, MD, MS
University of Utah School of Medicine

9:05 AM **Q&A**

9:15 AM **Adjourn**

**Please note that schedule and speakers are subject to change.*

THANK YOU TO OUR EXHIBITORS!

Astellas Pharma Inc.

Colorado Fetal Care Center

Conceptions Reproductive Associates of Colorado

Gynesonics

Sanofi

Shady Grove Fertility

ZERO GRAVITY

SUNDAY

What is the "Pink Tax", Why Are Our Patients Paying It, And What Can We Do About It?

Nanette Santoro, MD

Professor and E Stewart Taylor Chair of Obstetrics and Gynecology

University of Colorado School of Medicine

Learning Objectives

- Medicine is getting administratively harder to practice
- Women, in particular, are bigger users of the healthcare system and medications
- Even accounting for greater use, women pay more compared to men for their healthcare and medications
- It is worth paying attention to these issues, as OBGYNs we and our patients are disproportionately affected

The Favorite Part of My Day Is

Filling out medication pre authorizations
0%

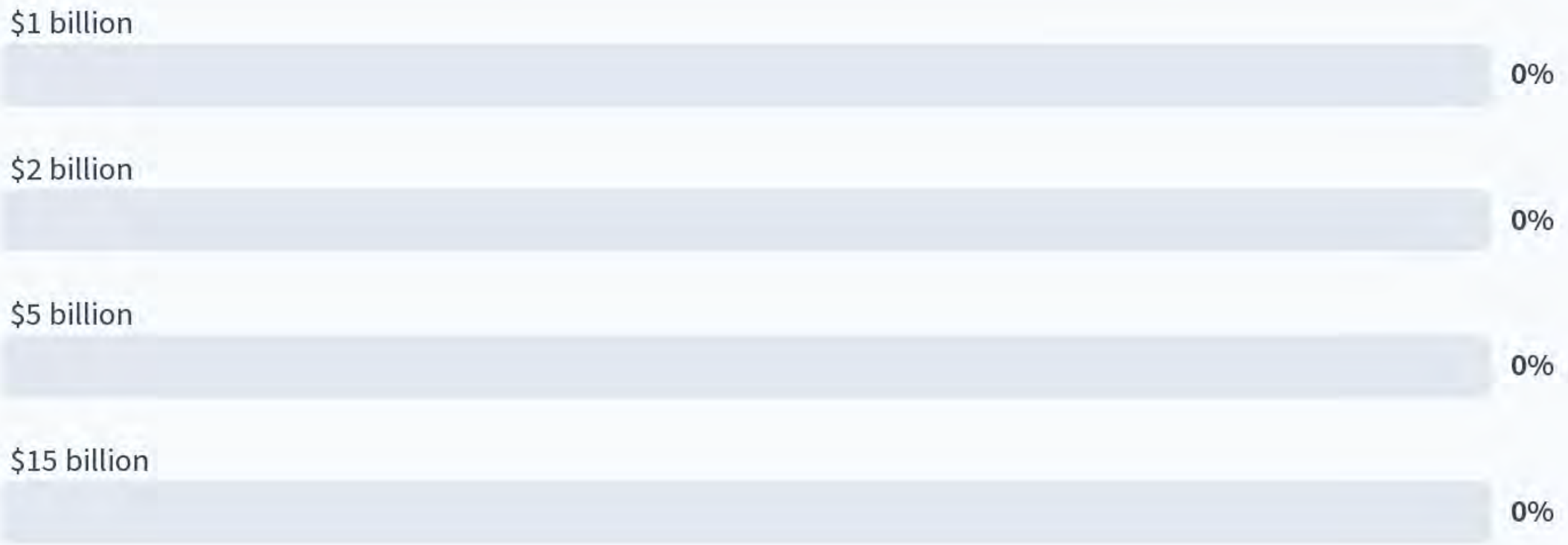
Re-filling out medication pre authorizations
0%

Sending my patient's medication to the pharmacy on record on her chart
0%

Re-sending my patient's medication to the specialty pharmacy that will fill her prescription for less money
0%

Making a peer to peer phone call to get a medication approved
0%

How Much More Do Women Spend Than Men in Health Care Costs Each Year?



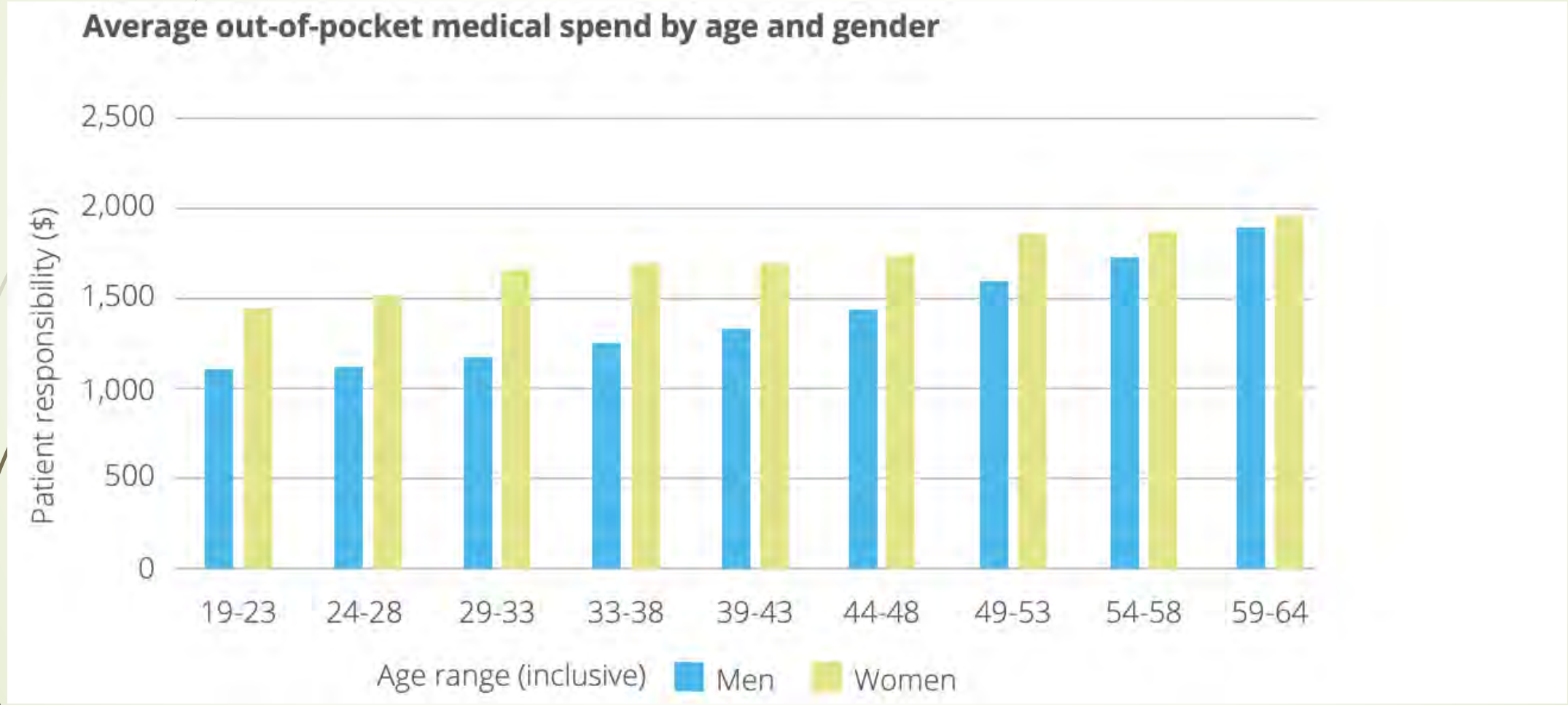
- $15.4B per year

Deloitte.

Hiding in plain sight:
The health care gender toll

Marielle Farina, FSA, MAAA

Women Have More Out-of-Pocket Costs Than Men in Every Age Group



This Effectively Widens the Wage Gap

Contributing Factors

- Average out of pocket cost for a single delivery is $2,900
- 40% of US babies are to unmarried women

Contributing Factors

- Ongoing policies that have not been re-evaluated for equity
- Women with employer-sponsored plans utilize more services from:
  - Radiology
  - Laboratory
  - Mental health
  - Emergency room
  - Office visits
  - PT/OT
  - Chiropractic

There is No Evil Genius Behind This

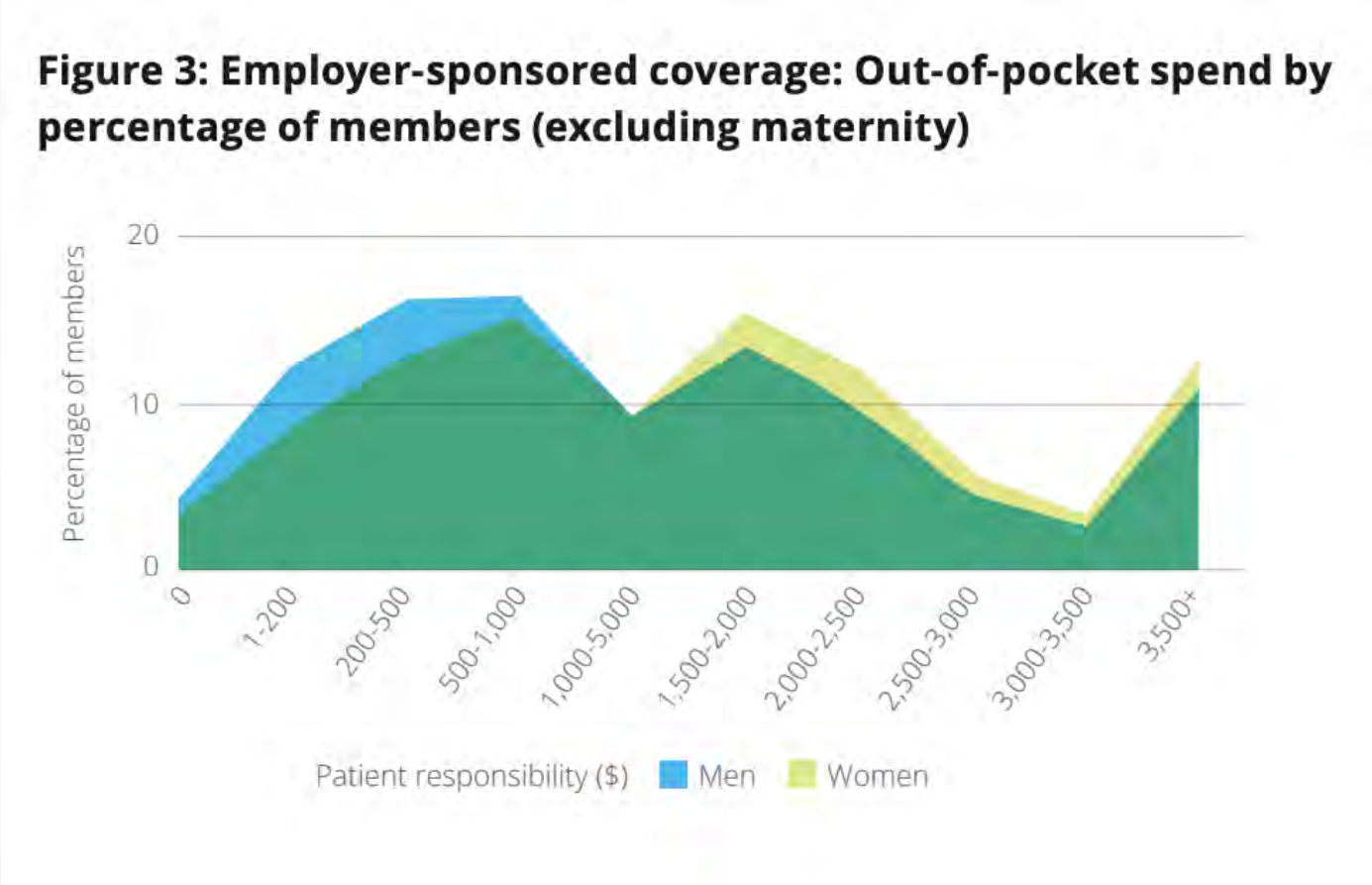
Contributing Factors

- High frequency of gynecological examinations
- Relatively high cost of breast cancer imaging compared to other types of cancer
- Menopause

Women Seek More Health Care and More Treatment Than Men

- Women experience 10% more in health expenditures (beyond childbirth)
- Women pay 18% more for medications and co-pays

Women Receive Less Actuarial Value Per Health Care Premium Dollar



How Does This Play Out in Real Life

- Higher co-pays
- Excluded services
  - Genetic carrier screening (pre conception)
- Excluded medications
  - Many hormone therapies
  - Contraceptives

What Would It Cost Employers to Close This Gap?

- $133 per enrolled employee annually

https://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-health-gender-gap.pdf

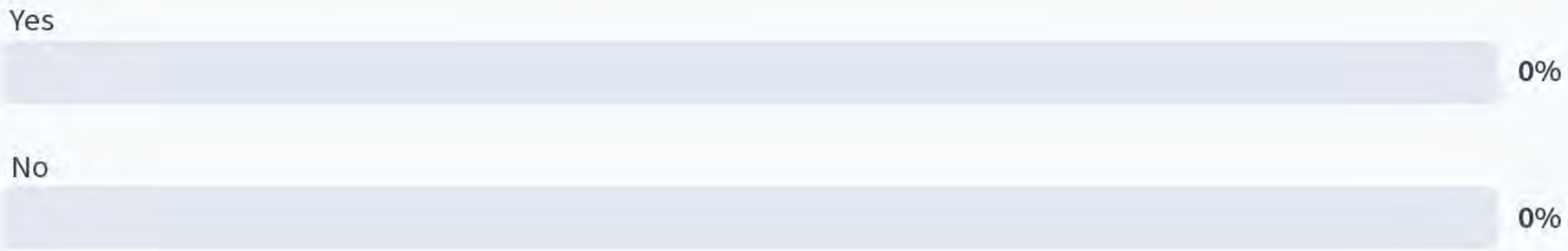
What Can We Do to Help?

- Point out to your pharmacies or frequently used insurance plans when FDA approved medications that are safe and effective for your patients are not covered
- Ask your local legislatures about their position on this issue or bring it to their attention
- ACOG state lobbying efforts should be directed towards this issue
- Appeal to hospital pharmacy committees to include key medications on formulary
- Encourage your patients to ask their insurance provider why indicated medications are not covered

What Can We Do to Help?

- Find the least expensive source of your most commonly prescribed meds
- Advocate for cost effective medications with your common insurance carriers
- Encourage your patients to petition pharmacy benefit managers to make medications available

Do You Prescribe Medications from Canadian Pharmacies to Incur Less Cost for Your Patients?



Relative Costs of Some Medications

Medication	US cost/3mos (goodrx)	Canadian cost
Estring	$498	$249
Leuprolide acetate depot 3.75mg	$1523	$502
Elagolix 150mg	$3012	$750
Mirabegron	$1305	$420
Semaglutide 1mg	$4158	$1410
Estradiol/norethindrone patch	$705	$210

Upsides and Downsides to Prescribing from Canada

- Source of the medication is not always known: usually Canada or UK but sometimes India
- Potential for less regulatory oversight (India)
- Substitutions not acceptable
- Many websites will indicate the source: if it is EU or Canada, regulatory processes are excellent and on a par with the FDA

Should We Be Re-Evaluating Our Routine Practices?

- USPSTF
- Biennial mammograms age 50-74
- Cervical cancer screening every 3-5 years
- NO recommendation for annual pelvic exam for women at any age other than cancer screening

- ACOG
- Offer mammograms starting at age 40-75 years, 1-2 year intervals
- Cervical cancer screening per USPSTF
- Pelvic exam ‘only when [a woman] has symptoms or has a medical history that requires it’

Can We as Individuals Husband Resources Better?

Do All of Our Patients Need Annual GYN Exams?

There is not much research on the usefulness of annual pelvic exams for women who aren't pregnant, experiencing symptoms, or at risk for gynecological conditions. The American College of Obstetricians and Gynecologists (ACOG) recommends women have pelvic exams only when they have symptoms or have a medical history that requires it.

Ultimately, you and your ob-gyn or other health care professional should make this decision together. Discuss your medical history and the risks and benefits of a pelvic exam.

BUT

Experts recommend that you visit your ob-gyn at least once a year for a well-woman visit. The purpose of this checkup is to help you stay healthy and prevent health problems at all stages of life.

Well-woman visits are an important part of your health care, even if you do not need a pelvic exam. They are a chance for you and your ob-gyn to talk about sex, birth control, planning for pregnancy, and more.

Breast Cancer Costs

- $29.8B per year
- 14% of all cancer treatment costs, highest treatment cost of any cancer
- Initial care phase costs $36,930
- End-of-life care phase costs $78,800
- Yet breast cancers detected early are much less expensive to treat

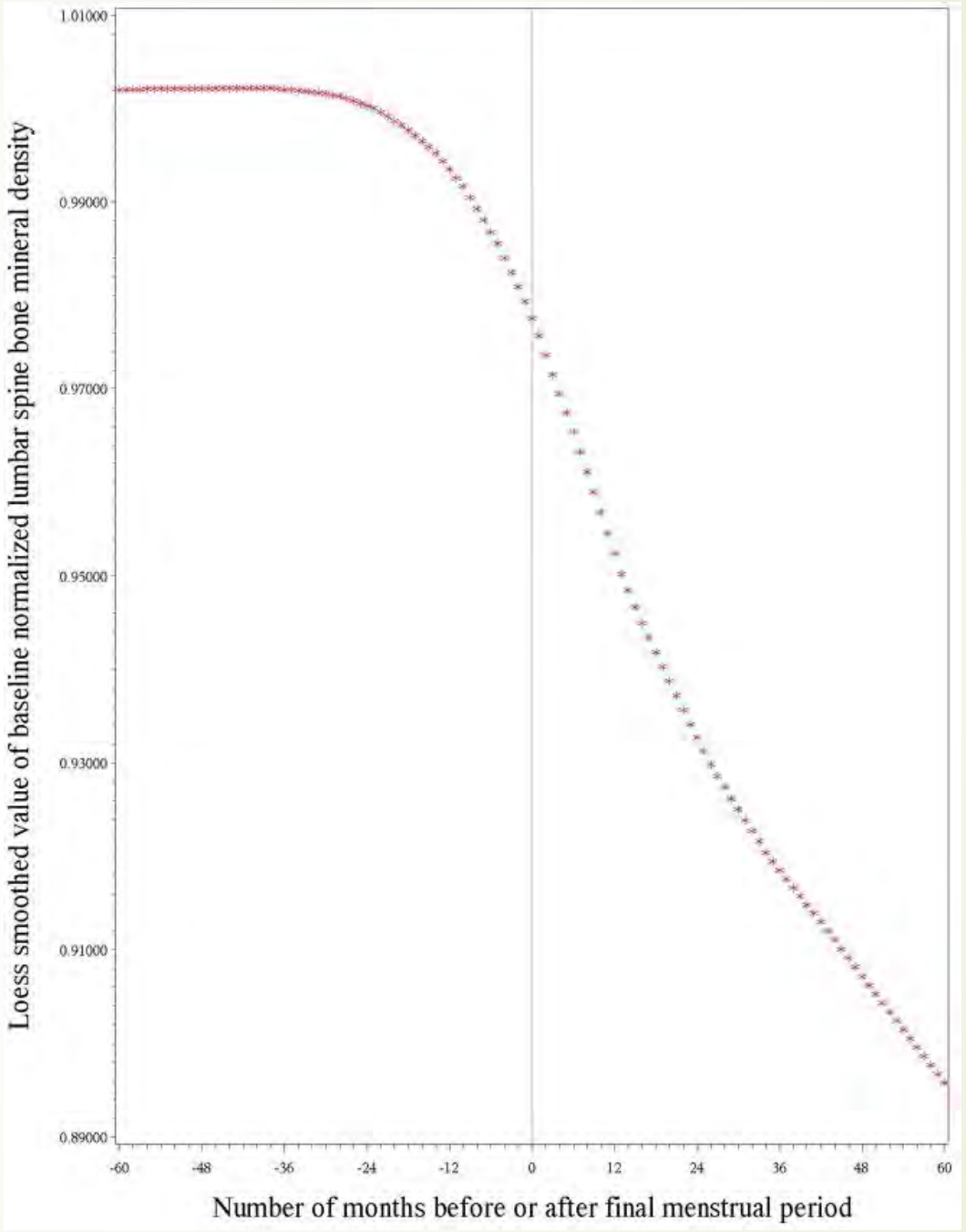
https://www.cdc.gov/chronicdisease/programs-impact/pop/breast-cancer.htm

Osteoporosis

- All cause costs: excess of 31K/fracture
- Hip fracture: excess cost of 54K
- Twice the pharmacy costs vs non-fracture group
- Twice the death rate

Williams, SA, et al, Annals of Pharmacotherapy 2021; 55:821

Lumbar Spine BMD Loss in Relation to FMP



Greendale J Bone Miner Res 2012; 27: 111

Recommendations

- USPSTF
- Screen at age 65
- Screen sooner if there is increased risk (based on formal risk assessment tool)

- ACOG
- Age 65 and older

Can We Make Life Easier for Ourselves?

Join the AMA: pre authorizations

Make friends with your pharmacy committee

"Prior authorization is overused, costly, inefficient, opaque and responsible for patient care delays"

Mass Amnesia of Health Insurance Pharmacy Benefits Every New Year

AMA Goals

- Cut the overall volume of PA
- Promote automation
- Establish 24-48hr response times
- **Adverse determination should be made only by a physician licensed in the state and of the same specialty that typically manages the patient's condition**
- Make each PA valid for at least one year
- Require public release of insurer's PA data

Summary

- We are women's health care providers
- Women are systematically overpaying for services and get less benefit per the health collars paid by their employers
- We are overburdened by the red tape that goes along with women's increased utilization of healthcare
- There are some actions we can take to call attention to these discrepancies and help fix the system

Sometimes You Have to Laugh

- https://jenniferlycette.com/blog/
- A physician's typical day, as envisioned by a non-clinician healthcare MBA: a satire

What are my options?

NONHORMONE AND HORMONE MANAGEMENT OF VASOMOTOR SYMPTOMS

Makeba Williams, MD, FACOG, MSCP
Associate Professor
Vice Chair of Professional Development and Wellness
Department of Obstetrics and Gynecology

Washington University School of Medicine in St. Louis

Disclosures

Relevant Disclosures:

The Menopause Society Board of Directors

Consultant: Astellas

No conflicts of interest

References:

I will discuss clinical studies of off label use of pharmaceuticals for vasomotor symptoms.

This presentation references people born with ovaries. I may use the terms women, she, and her. These terms may not capture the diversity of all those experiencing menopause. We need more research to explore how diverse people experience menopause.

59 years old

LMP: age 52

Symptoms: night sweats, soaks bedsheets, disrupted sleep

Gyn hx: sexually active, some dryness

PMH: HTN, well managed with lifestyle changes, previously used Amlodipine

Social: denies tobacco use, exercises daily, strength training 3x per week

Fam Hx: Mother dx with Breast cancer at age

Allergies: Black cohosh

Treatment: Exercise, dietary changes, cooling bed linens, bedside fan

“I want a natural treatment…”

PRIMAL QUEENS HANDPICKED 6 BEEF ORGANS FOR OPTIMAL FEMALE NUTRITION

- **Kidney** (more Iron than kale*)
- **Liver** (more Vitamin A than lettuce*)
- **Heart** (more CQ10 than cauliflower*)
- **Uterus** (more Vitamin B12 than spinach*)
- **Ovaries** (more Selenium than oats*)
- **Fallopians** (more Zinc than broccoli*)


Kroger
MIGHTY ICE POPS
BANANA
naturally and artificially flavored
8
ICE POPS

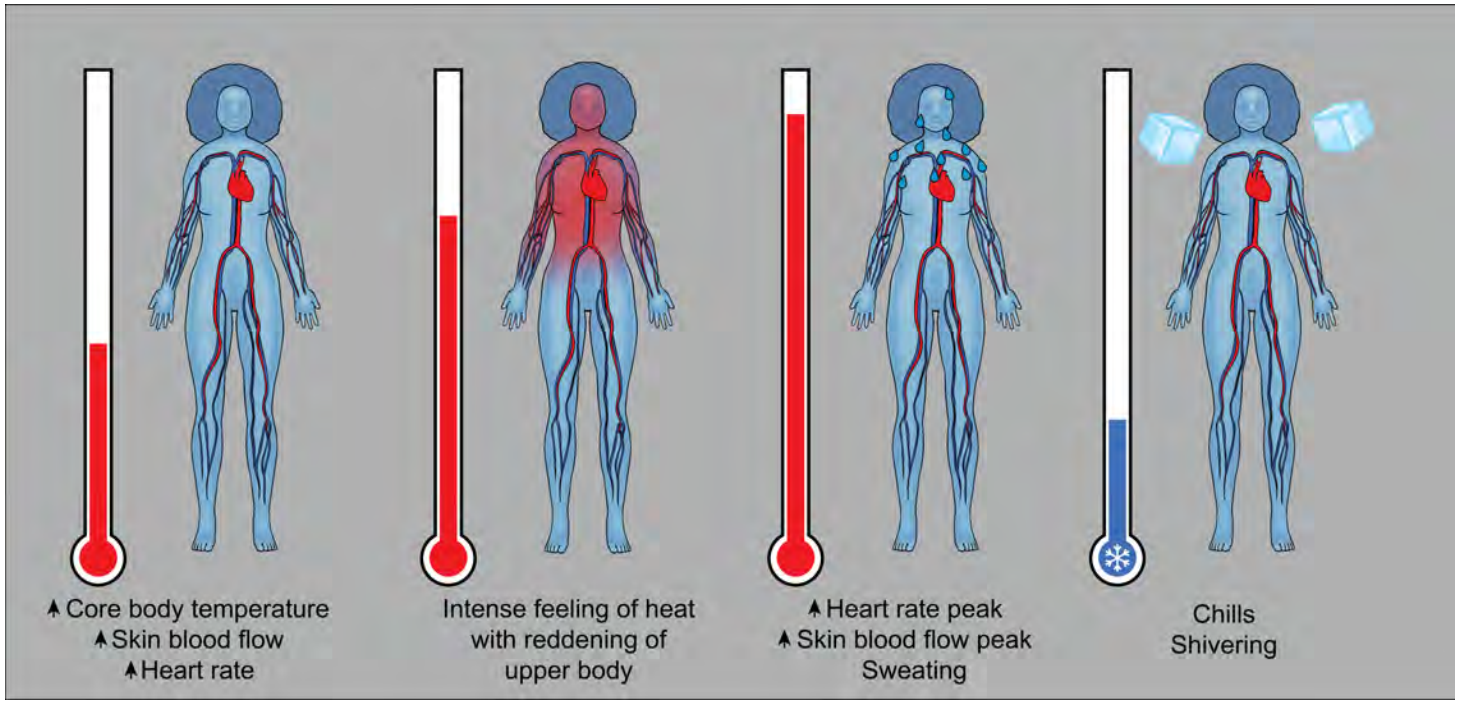
Hormone Therapy

2030: 1.3 billion Menopausal women

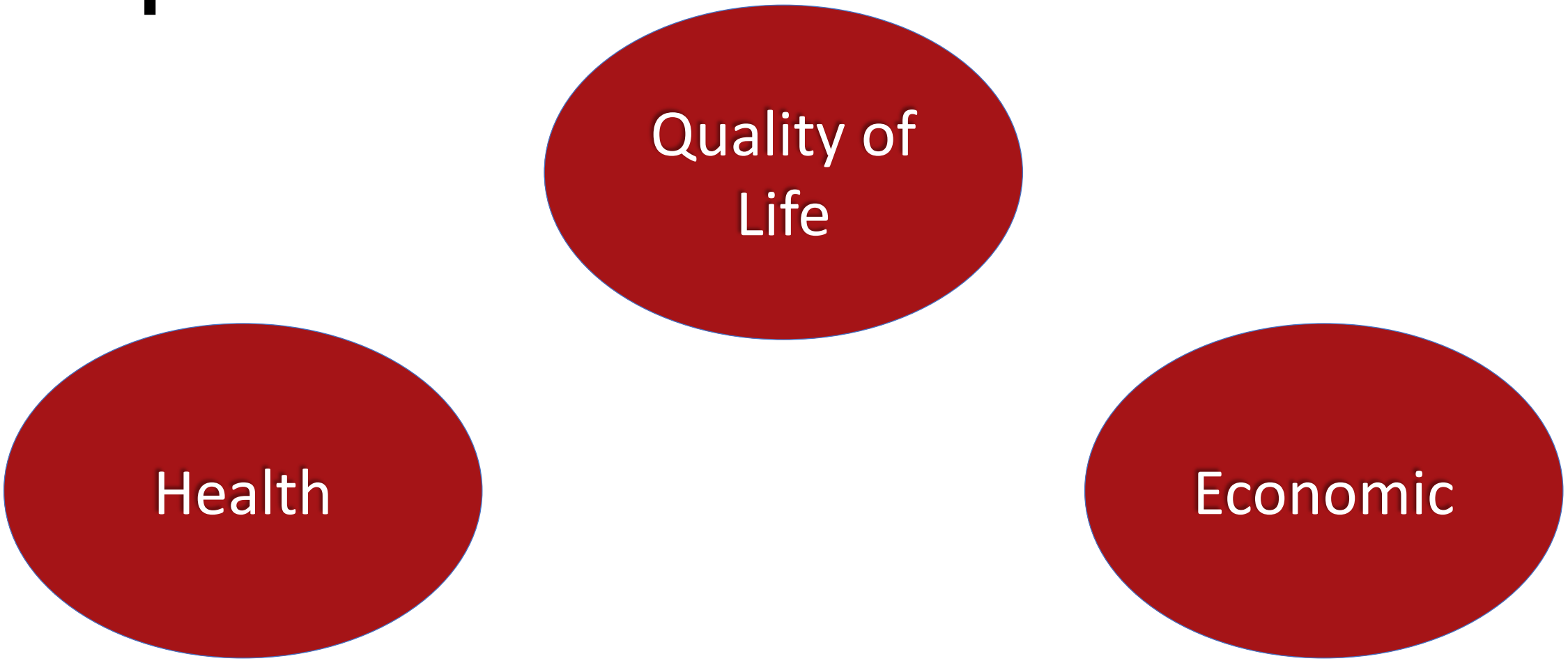
$600 Billion industry

Vasomotor Symptoms (VMS)

- Mild: **sensation of heat** without sweating
- Moderate: sensation of **heat with sweating**, able to continue activity
- <u>Severe: sensation of heat with sweating, causing **cessation of activity**</u>



Impact



Duration of Hot Flashes

Shorter	Longer	Median Years
Postmenopause with symptom onset	Pre/perimenenopause at symptom onset	3.4 v 11.8
Japanese/Chinese	African American race	4.8/5.4 vs 10.1
Non-Hispanic White	Hispanic	6.5 v 8.9
Education≥College	Education<College	7.7 v 9.9
Stress never/almost never	Stress at least sometimes	8.9 v 10.8
No depression	Depression	7.7 v 11.0
No anxiety	Anxiety (mild-severe)	5.0 v 7.4
	Financial strain	
	Poor social support	
	Obesity	
	Smoking	
	Single	

Gold EB, et al. *Am J Epidemiol*. 2000;152(5):463-473; Thurston RC, et al. *Obstet Gynecol Clin North Am*. 2011;38(3):489-501; Shobeirl F, et al. *J Menopausal Med*. 2016;22(1):78-85; Wilson LF, et al. *Maturitas*. 2016;91:1-7; Herber-Gast GC, et al. *Am J Clin Nutr*. 2013;97(5):1092-1099.

Treatment Options

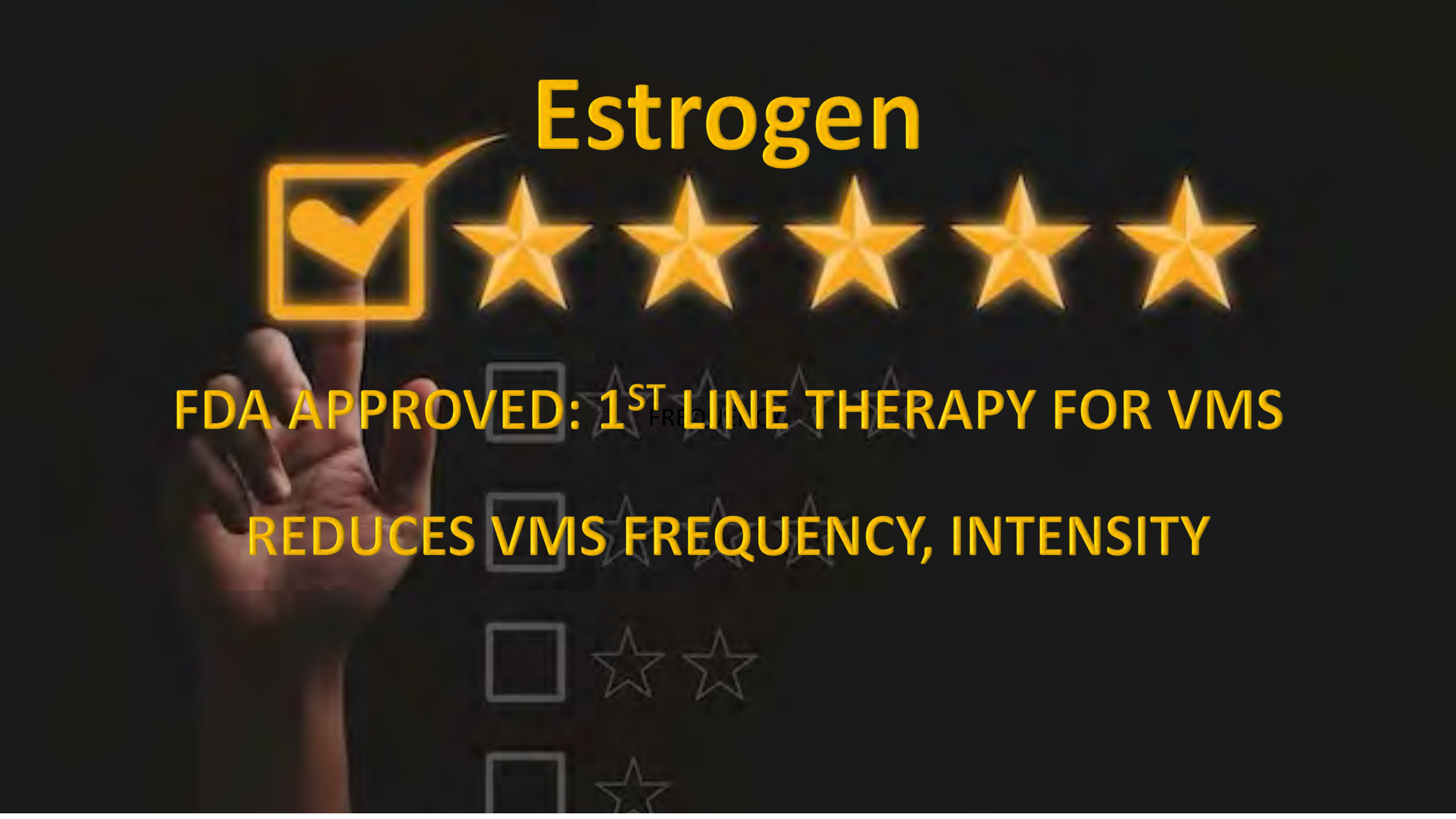
Hormone

- Estrogen
- Estrogen + Progesterone
- Estrogen + SERM

Non-hormone

- Pharmaceutical therapies
- Behavioral and lifestyle changes
- Dietary supplements

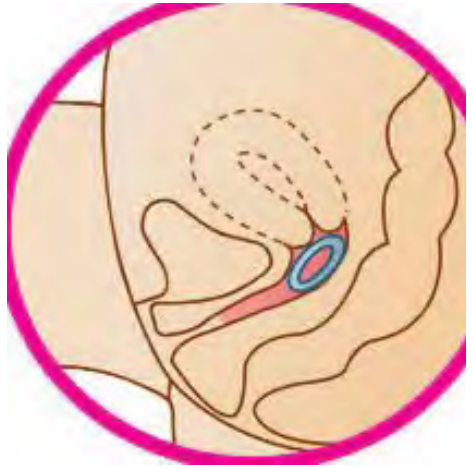
Estrogen



FDA APPROVED: 1ST LINE THERAPY FOR VMS

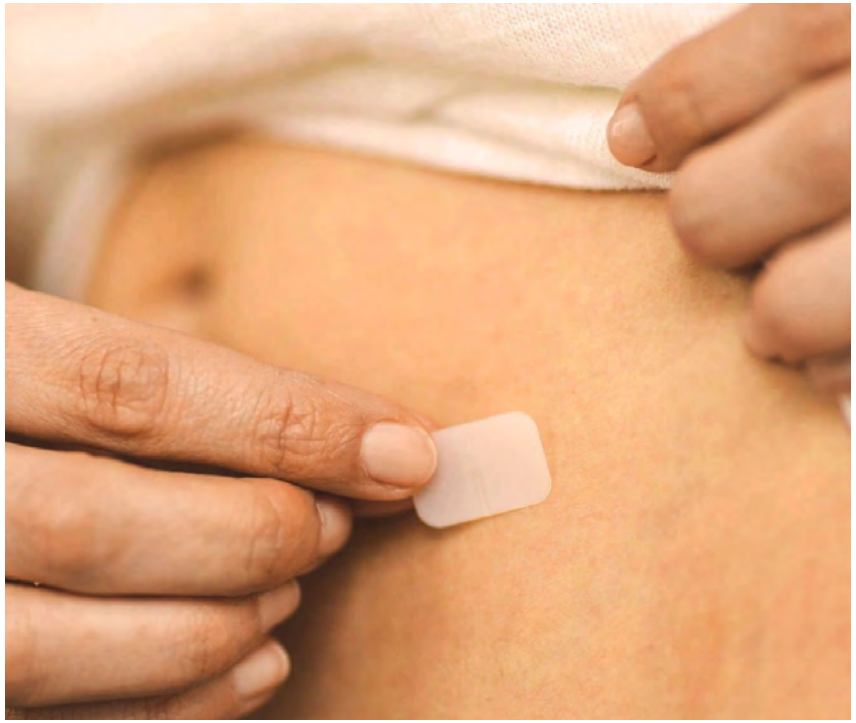
REDUCES VMS FREQUENCY, INTENSITY

Non-Oral Estrogen Therapy

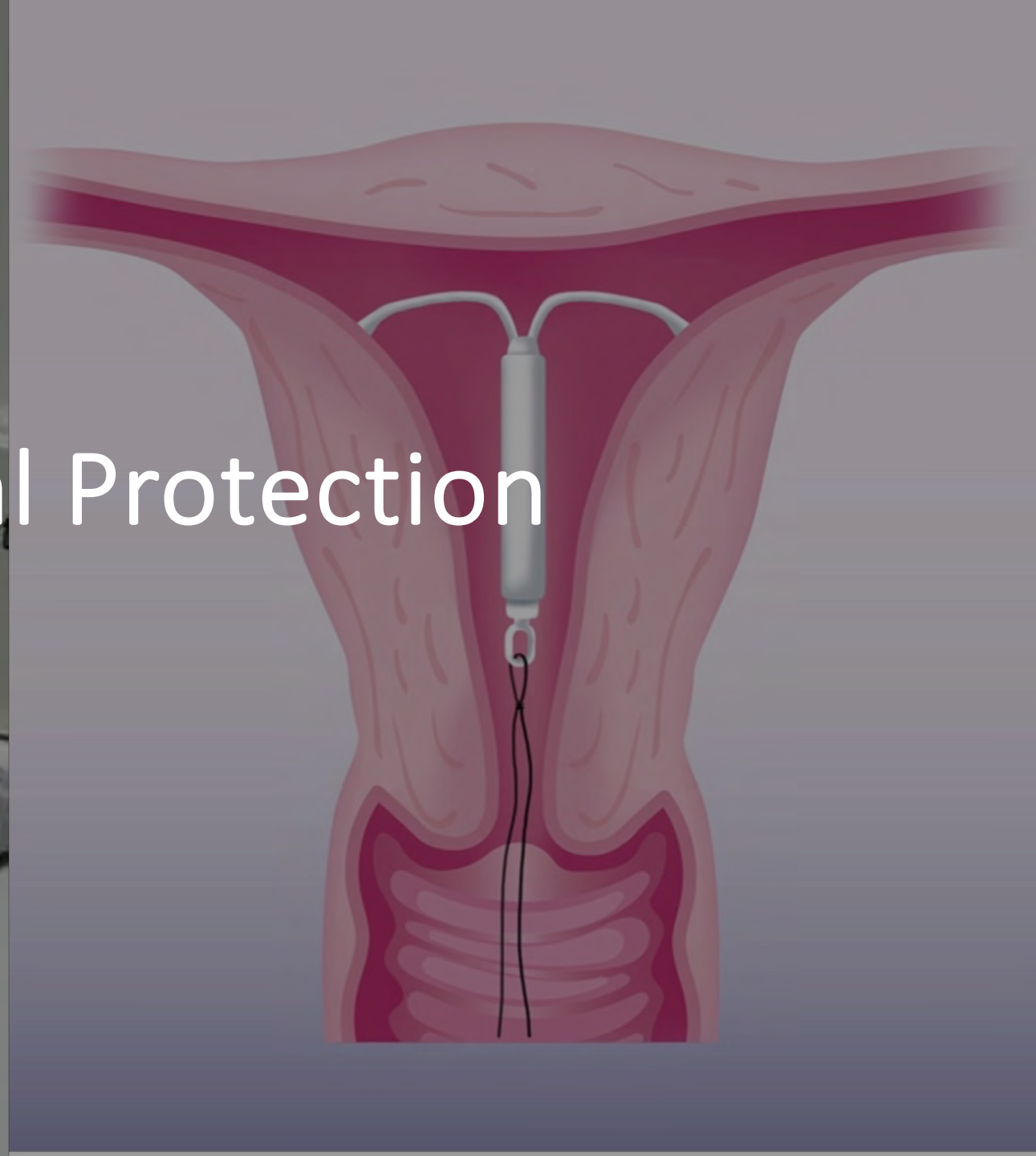


Transdermal/Topical/Vaginal

- Patch, gel, spray, and emulsion
- Avoids first-pass hepatic metabolism
- More stable serum levels
- Minimal effect on SHBG; minimized negative impact to sexual function
- Reduced risk of VTE/stroke compared to oral ET in observational studies



Endometrial Protection



Types of Progestogen Therapy

Micronized Progesterone

- Compound identical to endogenous progesterone
- Prometrium is the only FDA-approved bioidentical progestogen
- Contraindicated in women with peanut allergy
- Bedtime dosing advised because of sedating effects

Progestin

- Synthetic products with progesterone-like activity
  - Medroxyprogesterone acetate (MPA) is the most commonly used and studied in the United States for endometrial protection
  - Norethindrone aceta (NETA)

Schussler P, et al. *Psychoneuroendorinology*. 2008;33(8):1124-1131. Montplaisir J, et al. *Menopause*. 2001;8(1):10-16.

Methods of EPT Administration

Continuous-cyclic (sequential)

- Daily estrogen with progestogen added cyclically for 12-14 d each month
- 80% of women will experience bleeding with progestogen withdrawal

Continuous-combined

- Daily estrogen and progestogen
- Low rates of endometrial hyperplasia
- Higher rates of amenorrhea
- Decreased breakthrough bleeding after 2 yrs

Ettinger B, et al. *Obstet Gynecol*. 1994;83(5pt1):693-700; Ettinger B, et al. *Obstet Gynecol*. 2001;98(2):205-211; Odmark IS, et al. *Menopause.* 2005;12(6):699-707. Steiner AZ, et al. *Obstet Gynecol.* 2007;109(3):581-587. Prempro [package insert]. Philadelphia, PA: Wyeth; 2009. Furness S, et al. *Cochrane Database Syst Rev*. 2012;(8):CD000402. Casper RF, et al. *J Soc Gynecol Investig*. 1996;3(5):225-234.

Alternative Progestogen Options

- Levonorgestrel-containing IUD
- May provide endometrial cancer protection
- Off label
- Long-term efficacy data is needed

Warren MP, et al. *Am J Obstet Gynecol*. 1999;180(1 pt 1):42-48. Luo L, et al. *Cochrane Database Syst Rev*. 2018;12:CD009458.

ET Combined With an Estrogen Agonist/Antagonist

- Tissue-selective estrogen complex (TSEC)
- Daily estrogen combined with a daily selective estrogen-receptor modulator (SERM)
- Approved for treatment of VMS and prevention of osteoporosis
- Amenorrhea rates similar to placebo
- Safety profile comparable to placebo

Archer DF, et al. *Fertil Steril*. 2009;92(3):1039-1044. Pinkerton JV, et al. *Obstet Gynecol*. 2013;121(5):959-968. Pinkerton JV, et al. *J Clin Endocrinol Metab*. 2014;99(2):E189-E198. Pickar JH, et al. *Menopause*. 2018;25(9):1033-1045.

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Transdermal Hormone Therapy

Medications	Available doses*
Transdermal estrogen formulations for menopausal hormone therapy commonly prescribed in the United States	
Weekly estradiol patch	0.014 mg, 0.025 mg, 0.0375 mg, 0.05 mg, 0.06 mg, 0.075, 0.1 mg
	Standard: 0.0375–0.05 mg
	Low: 0.025 mg
	Ultra-low: 0.014 mg
Twice weekly estradiol patch	0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg
	Standard: 0.0375–0.05 mg
Combination transdermal estrogen-progestin formulations available*	
Estrogen	Progestin
Estradiol 0.05 mg	Norethindrone 0.14 mg, 0.25 mg
Estradiol 0.045 mg	Levonorgestrel 0.015 mg

*Daily release note

Oral Hormone Therapy

Medications	Available doses
Oral estrogen formulations for menopausal hormone therapy commonly prescribed in the United States	
Estradiol	0.5 mg, 1.0 mg, 2.0 mg
	Standard: 1.0 mg
	Low: 0.5 mg
Conjugated equine estrogen	0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg
	Standard: 0.625 mg
	Low: 0.3 mg, 0.45 mg
Combination oral estrogen-progestogen formulations available	
Estradiol (0.5 mg, 1.0 mg)	Drospirenone (0.25 mg, 0.5 mg)
Estradiol (0.5 mg, 1.0 mg)	Norethindrone acetate (0.1 mg, 0.5 mg)
Estradiol (1.0 mg)	Norgestimate (0.09 mg)
Estradiol (1.0 mg)*	Progesterone (100 mg)*
Ethinyl estradiol (2.5 µg, 5 µg)	Norethindrone acetate (0.5 mg, 1.0 mg)
Conjugated equine estrogen (0.3 mg, 0.45 mg, 0.625 mg)	Medroxyprogesterone acetate (1.5 mg, 2.5 mg, 5 mg)
Oral progestogen formulations for menopausal hormone therapy commonly prescribed in the United States	
Medroxyprogesterone acetate	2.5 mg, 5 mg, 10 mg
Progesterone*	100 mg, 200 mg

*Formulation contains peanut oil; hypnotic effect, so should be taken at bedtime.

Non-Hormone Prescription Therapies for VMS

- FDA-approved prescription treatments
  - Paroxetine 7.5 mg daily
  - Fezolinetant 45 mg daily
- Off-label prescription therapies
  - Selective serotonin reuptake inhibitors
  - Serotonin-norepinephrine reuptake inhibitors
  - Gabapentin
  - Oxybutynin

Carroll DG, et al. *Int J Womens Health*. 2015;7:615-624; Reddy SY, et al. *Obstet Gynecol*. 2006;108: 41-48; Rada G, et al. *Cochrane Database Syst Rev*. 2010;CD004923; Simon JA, et al. *Menopause*. 2016;23(11):1214-1221.

Non-Hormone Pharmaceuticals		
Fezolinetant	45 mg daily	Single dose, no titration needed
Selective Serotonin Reuptake Inhibitors		
Paroxetine salt	7.5 mg	Single dose, no titration needed
Paroxetine	10-25 mg/d	Start with 10 mg/d
Citalopram	10-20 mg/d	Start with 10 mg/d
Escitalopram	10-20 mg/d	Start with 10 mg/d (for sensitive or older women, start with 5 mg/d for titration, but this dose has not been evaluated for efficacy)
Serotonin Norepinephrine Reuptake Inhibitors		
Desvenlafaxine	100-150 mg/d	Start with 25-50 mg/d and titrate up by that amount each day
Venlafaxine	37.5-150 mg/d	Start with 37.5 mg/d
Gabapentin	900-2,400 mg/d	Start with 100-300 mg at night, then add 300 mg at night, then a separate dose of 300 mg in the morning (start 100 mg if concerned about sensitivity)
Oxybutynin	2.5-5 mg mg/d	Start with 2.5 mg daily and increase to 5 mg twice daily after one week

NON-HORMONES: RECOMMENDED

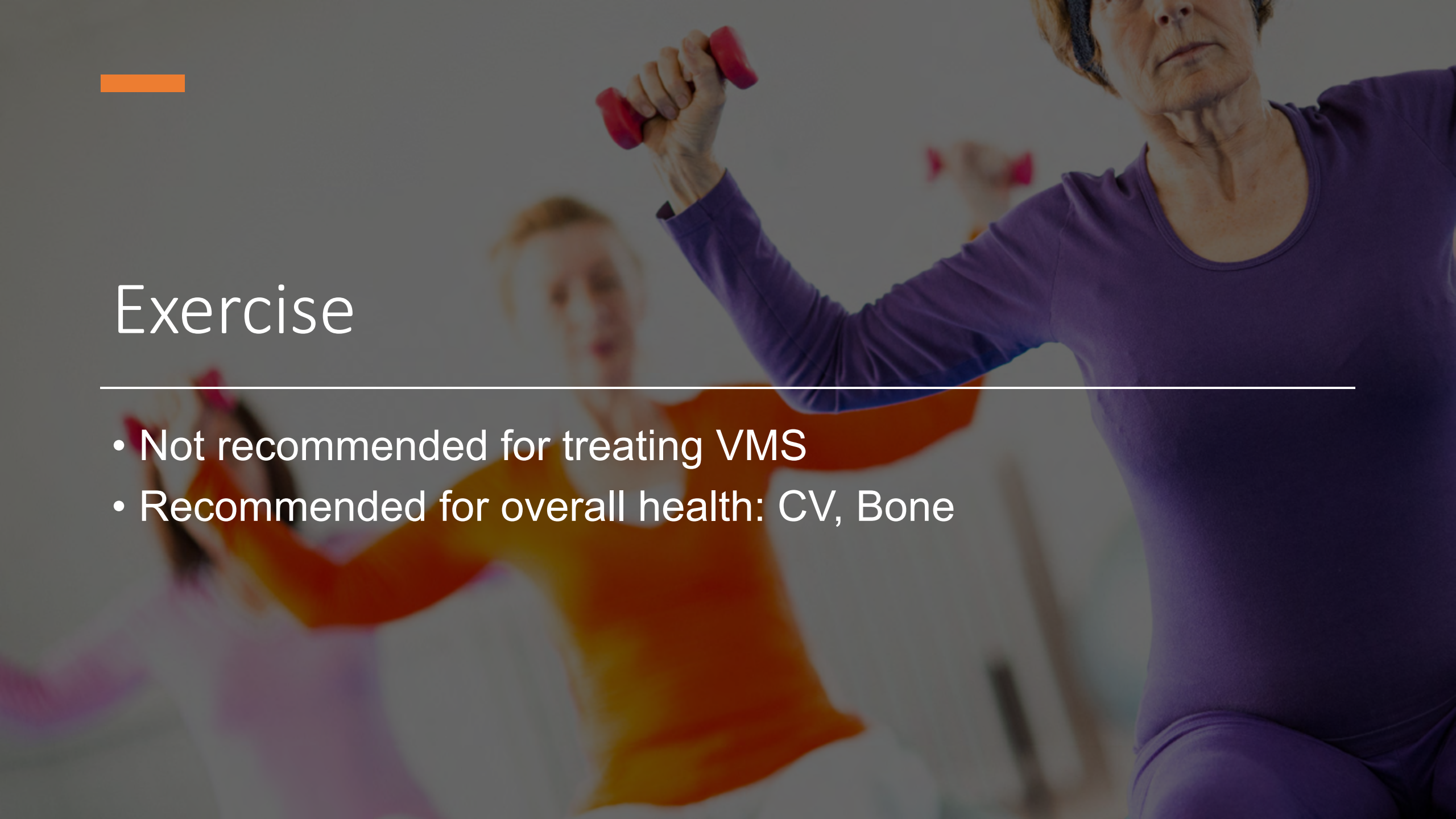
- Cognitive-behavioral therapy (Level I)
- Clinical hypnosis (Level I)
- Fezolinetant (Level I)
- Selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors (Level I)
- Gabapentin (Level I)
- Oxybutynin (Levels I-II)
- Weight loss (Levels II-III)
- Stellate ganglion block (Levels II-III)

Level I: Good and consistent scientific evidence.
Level II: Limited or inconsistent scientific evidence.
Level III: Consensus and expert opinion.

NON-HORMONES: NOT RECOMMENDED

- Paced respiration (Level I)
- Supplements/Herbal remedies (Levels I-II)
- Cooling techniques, avoiding triggers, exercise, yoga, mindfulness-based intervention, relaxation (Level II)
- Soy foods and soy extracts, soy metabolite equol (Level II)
- Cannabinoids (Level II)
- Chiropractic interventions and acupuncture (Levels I-III)
- Clonidine (Levels I-III)
- Dietary modification (Level III)
- Pregabalin (Level III)

Level I: Good and consistent scientific evidence.
Level II: Limited or inconsistent scientific evidence.
Level III: Consensus and expert opinion.



Exercise

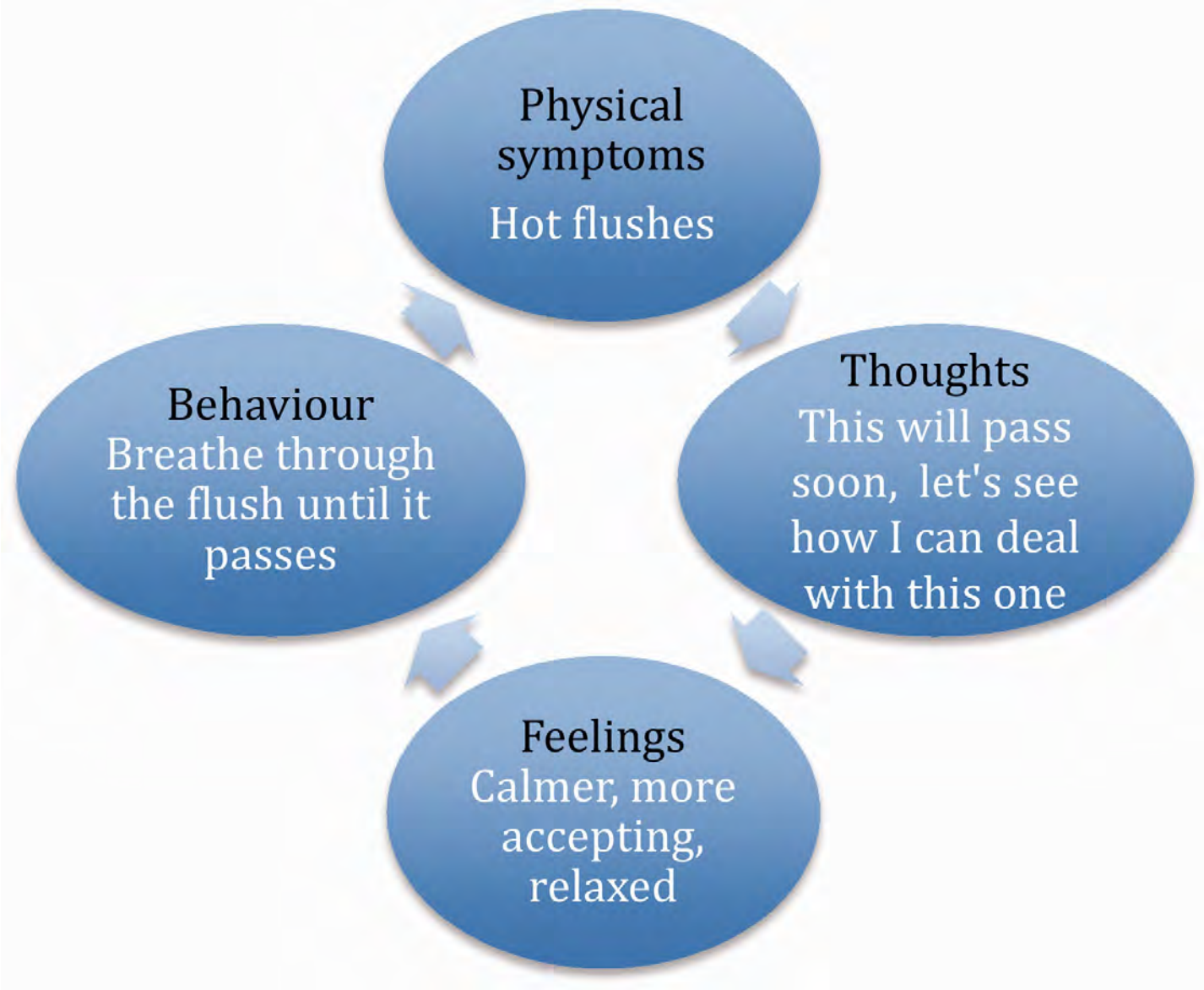
- Not recommended for treating VMS
- Recommended for overall health: CV, Bone

Weight loss

Reduces VMS

Cognitive Behavior Therapy (CBT)

Reduces VMS

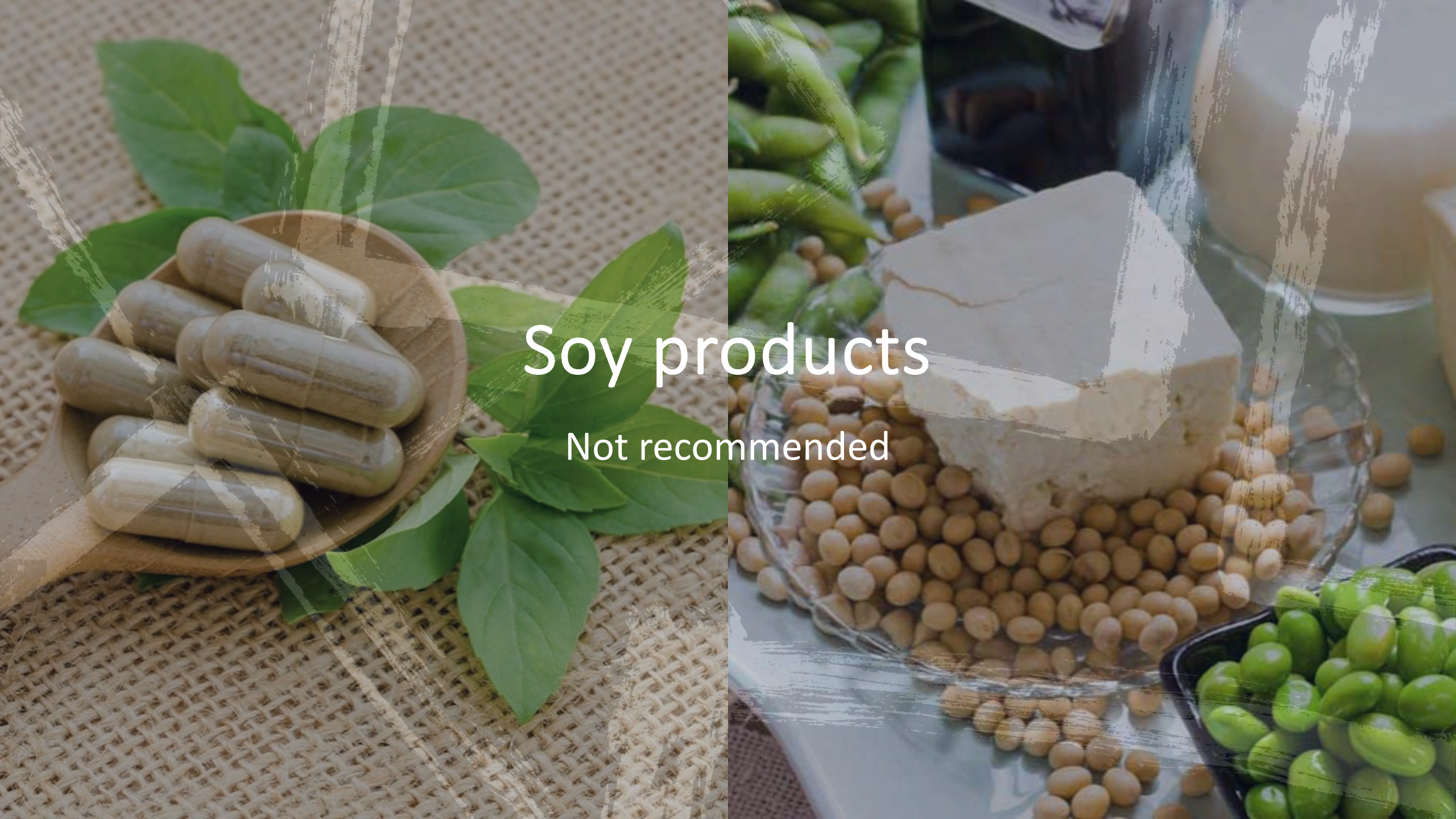


Dietary Supplements

Not recommended

Black Cohosh

Not recommended



Soy products

Not recommended

Cannabinoids

Not recommended

Stellate Ganglion Blockade

Recommended in select individuals

NON-HORMONES: NOT RECOMMENDED

- Paced respiration (Level I)
- Supplements/Herbal remedies (Levels I-II)
- Cooling techniques, avoiding triggers, exercise, yoga, mindfulness-based intervention, relaxation (Level II)
- Soy foods and soy extracts, soy metabolite equol (Level II)
- Cannabinoids (Level II)
- Chiropractic interventions and acupuncture (Levels I-III)
- Clonidine (Levels I-III)
- Dietary modification (Level III)
- Pregabalin (Level III)

Level I: Good and consistent scientific evidence.
Level II: Limited or inconsistent scientific evidence.
Level III: Consensus and expert opinion.

ELISE'S TREATMENT OPTIONS

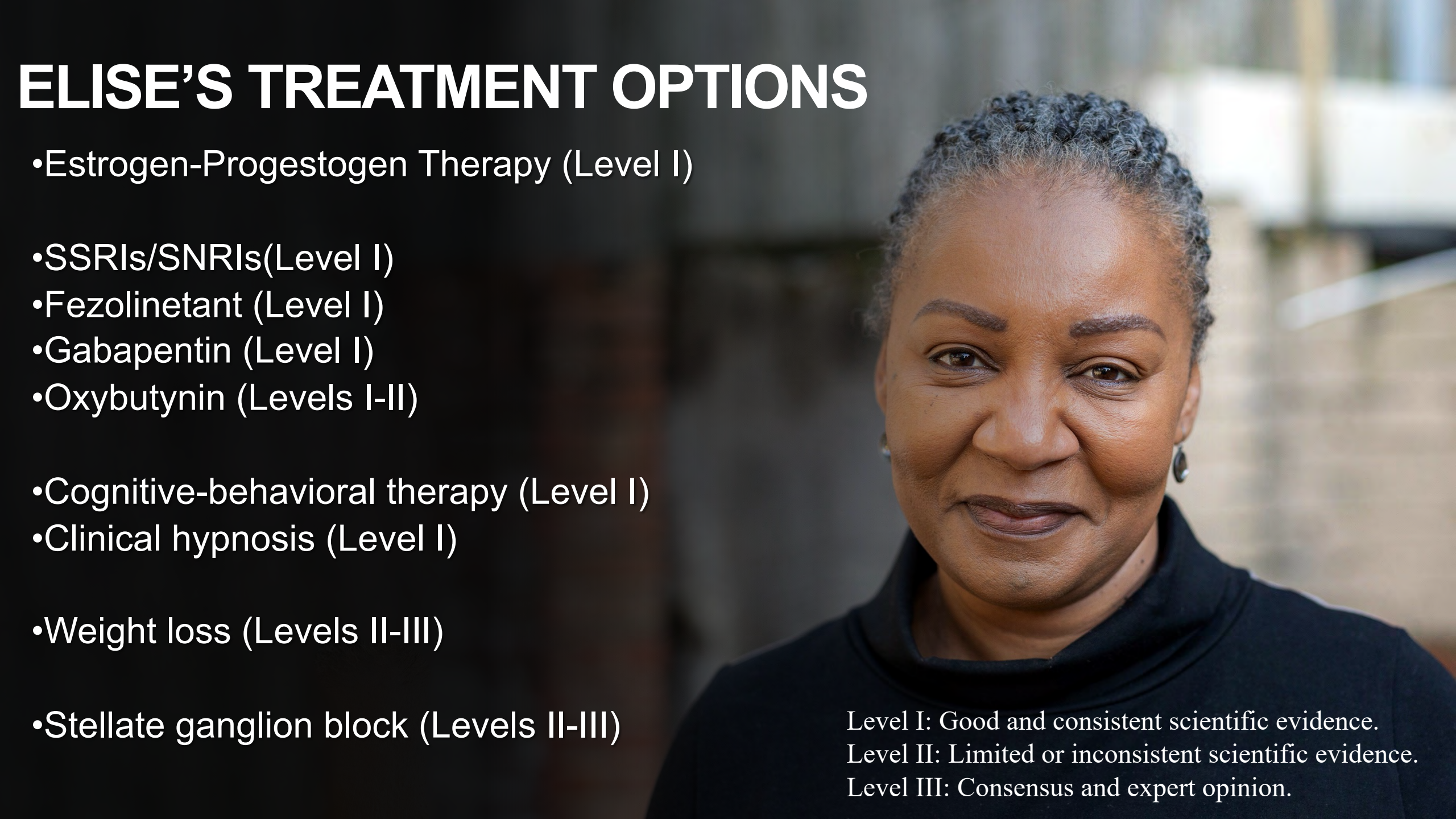
- Estrogen-Progestogen Therapy (Level I)

- SSRIs/SNRIs(Level I)
- Fezolinetant (Level I)
- Gabapentin (Level I)
- Oxybutynin (Levels I-II)

- Cognitive-behavioral therapy (Level I)
- Clinical hypnosis (Level I)

- Weight loss (Levels II-III)

- Stellate ganglion block (Levels II-III)



Level I: Good and consistent scientific evidence.
Level II: Limited or inconsistent scientific evidence.
Level III: Consensus and expert opinion.


Cultural Curiousity
Respectful Query
Connected Care
Culturally Responsive Care

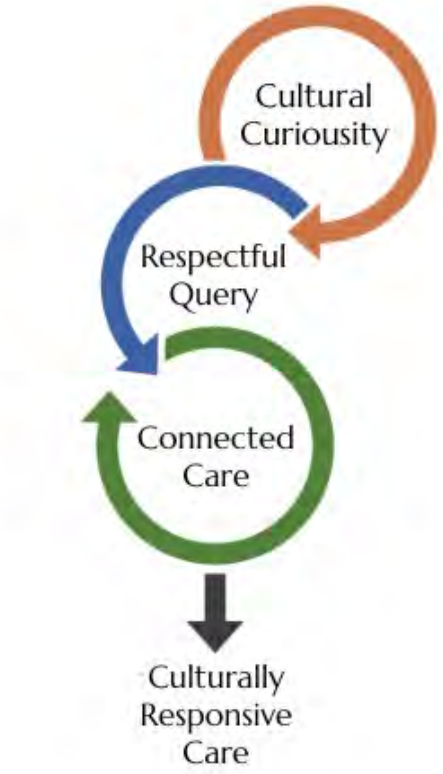
Cultural Curiosity

"I am sorry you've had such a challenging time with your symptoms. Everyone's experiences menopause symptoms differently. I would like to understand more about your unique experience and your preference for natural treatment options..."

Respectful Query

- How and what do you feel about going through menopause?
- What advice have you received about menopause?
- Are there any cultural practices related to menopause that are important for you to observe?
- Do you have a spiritual, religious or faith practice that influences your health care?
- How do you manage your menopausal symptoms? Foods, herbs, behaviors?

- *We all want to live our best lives. Are there things that get in the way of you taking care of yourself and living your best life?*



Connected Care

"Elise, I like to be sure that all of my patients receive information about all available and effective treatment options. You may not be interested in some of them, but I want to be sure that you have complete information before making a decision. Are you ok with me reviewing non-natural therapies?"

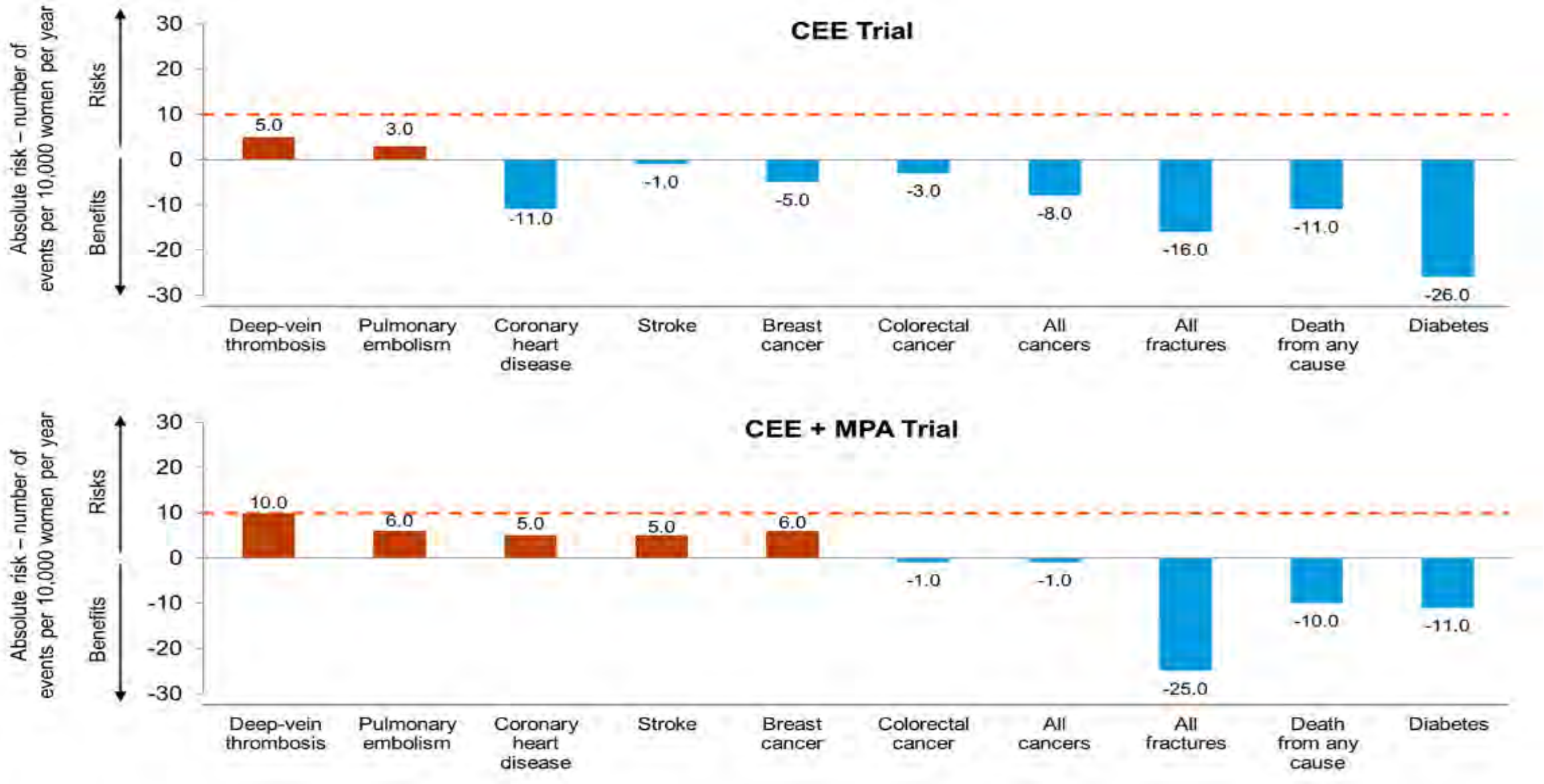


Fig. 1. Benefits and risks of the two hormone therapy formulations, conjugated equine estrogens (CEE) alone or in combination with medroxyprogesterone acetate (CEE + MPA), evaluated in the Women's Health Initiative for women aged 50 to 59 years. Risks and benefits are expressed as the difference in number of events (number in the hormone therapy group minus the number in the placebo group) per 10,000 women per year, with <10 per 10,000 per year representing a rare event (dashed red line). Adapted from Manson JE, et al. *JAMA* 2013;310:1353-1368.

Menopausal Hormone Therapy

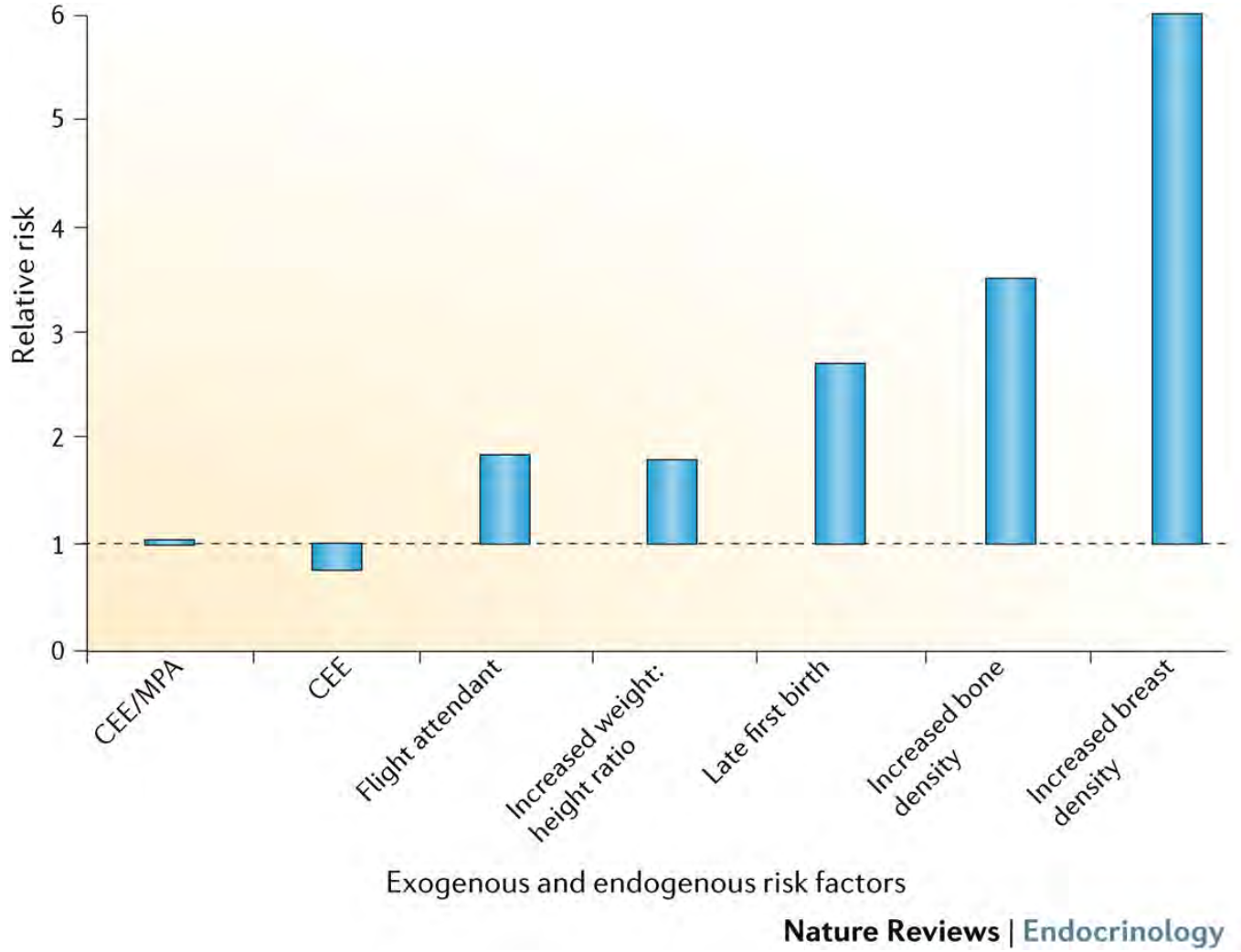
Low Risk HT
- Recent menopause
- Normal weight
- Normal blood pressure
- Physically active
- 10 year ASCVD risk <5%
- Low risk for breast cancer

Intermediate Risk HT
- Diabetes
- Smoking
- HTN
- Obesity
- Sedentary/ Limited mobility
- Autoimmune disease
- Hyperlipidemia
- Metabolic syndrome
- 10 years ASCVD risk ≥ 5 - 10%
- High risk for breast cancer

High Risk HT*
- Congenital heart disease
- ASCVD/CAD/PAD
- Venous thrombosis or pulmonary embolism
- Stroke/TIA or MI
- Breast cancer
- 10 year ASCVD risk ≥10%*

Leslie Cho. Circulation. Rethinking Menopausal Hormone Therapy: For Whom, What, When, and How Long?, Volume: 147, Issue: 7, Pages: 597-610, DOI: (10.1161/CIRCULATIONAHA.122.061559)

Breast Cancer Risk



Lobo, R. A. (2016) Hormone-replacement therapy: current thinking
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2016.164

Decision-making process

ELISE'S DECISION…

MenoNote

Nonhormone Treatments for Hot Flashes and Night Sweats

Hot flashes and night sweats, also called vasomotor symptoms (VMS), are feelings of warmth that can be associated with flushing and sweating. They are very common during menopause, occurring in up to 80% of women and lasting a mean of 7 to 10 years. Vasomotor symptoms may also contribute to sleep and mood issues that can negatively affect quality of life.

Women may choose to use hormone therapy (HT) to treat their VMS, but for those who cannot because of medical conditions (such as breast cancer or a history of heart attack, stroke, or blood clot) or for those who choose not to use HT, there are nonhormone options available to provide relief.

Nonhormone treatment options

Recommended

The treatments with research showing that they are effective for treating VMS include

- **Clinical hypnosis:** a mind-body therapy that involves a deeply relaxed state and individualized mental imagery and suggestion. This includes mental imagery for coolness as well as dissociation from VMS, along with a focus on future positive imagery.
- **Cognitive-behavioral therapy:** a form of biofeedback that includes education about the physiology of VMS as well as how thoughts and emotions may affect physical sensations, training in relaxation and paced breathing, identifying and challenging negative beliefs about VMS, monitoring and modifying triggers of VMS, and relaxation exercises.
- **Fezolinetant:** a neurokinin B antagonist that works in the brain to reduce VMS and is FDA approved for VMS management.
- **Gabapentin:** a drug used to treat seizures or nerve pain but has also been found to reduce VMS in multiple studies. Bedtime dosing may be a good choice for women with sleep issues because drowsiness is an adverse event. It can also help with pain and migraine.
- **Oxybutynin:** an antimuscarinic, anticholinergic therapy that is used for the treatment of overactive bladder and urinary urge incontinence and has been found to reduce VMS at low doses. Thus, it could be used to treat both urinary symptoms and VMS.
- **SSRIs/SNRIs:** multiple formulations have been studied and found to be beneficial for VMS management, including paroxetine, escitalopram, citalopram, venlafaxine, and desvenlafaxine, often at lower doses than those used for treatment of anxiety or depression. Only paroxetine mesylate 7.5 mg daily is FDA approved for VMS management specifically. These treatments may be ideal for women with coexisting mood or anxiety symptoms.
- **Stellate ganglion block:** a widely used treatment for pain, including for migraine and complex regional pain syndrome, that involves an injection of an anesthetic agent by a pain specialist targeting a bundle of sympathetic nerves in the front of your neck. It can be considered in select women but is associated with potential risks.
- **Weight loss:** weight loss has been shown to reduce VMS.

Not recommended

MenoNote

Deciding About Hormone Therapy Use

Many women experience hot flashes, vaginal dryness, and other physical changes with menopause. For some women, the symptoms are mild and do not require any treatment. For others, symptoms are moderate or severe and interfere with daily activities. Hot flashes improve with time, but some women have bothersome hot flashes for many years. Menopause symptoms often improve with lifestyle changes and nonprescription remedies, but prescription therapies also are available, if needed. Government-approved treatments for bothersome hot flashes include hormone therapy (HT) containing estrogen, as well as a nonhormone medication (paroxetine).

Hormone therapy involves taking estrogen in doses high enough to raise the level of estrogen in your blood in order to treat hot flashes and other symptoms. Because estrogen stimulates the lining of the uterus, women with a uterus need to take an additional hormone, progestogen, to protect the uterus. Women without a uterus just take estrogen. If you are bothered only by vaginal dryness, you can use very low doses of estrogen placed directly into the vagina. These low doses generally do not raise blood estrogen levels above postmenopause levels and do not treat hot flashes. You do not need to take a progestogen when using only low doses of estrogen in the vagina. (The *MenoNote* "Vaginal Dryness" covers this topic in detail.)

Every woman is different, and you will decide about whether to use HT based on the severity of your symptoms, your personal and family health history, and your own beliefs about menopause treatments. Your healthcare professional will be able to help you with your decision.

Potential benefits

Hormone therapy is one of the most effective treatments available for bothersome hot flashes and night sweats. If hot flashes and night sweats are disrupting your daily activities and sleep, HT may improve sleep and fatigue, mood, ability to concentrate, and overall quality of life. Treatment of bothersome hot flashes and night sweats is the principal reason women use HT. Hormone therapy also treats vaginal dryness and painful sex associated with menopause. Hormone therapy keeps your bones strong by preserving bone density and decreasing your risk of osteoporosis and fractures. If preserving bone density is your only concern, and you do not have bothersome hot flashes, other treatments may be recommended instead of HT.

Potential risks

As with all medications, HT is associated with some potential risks. For healthy women with bothersome hot flashes aged younger than 60 years or within 10 years of menopause, the benefits of HT generally outweigh the risks. Hormone therapy might slightly increase your risk of stroke or blood clots in the legs or lungs (especially if taken in pill form). If started in women aged older than 65 years, HT might increase the risk of dementia. If you have a uterus and take estrogen with progestogen, there is no increased risk of cancer of the uterus. Hormone therapy (combined estrogen and progestogen) might slightly increase your risk of breast cancer if used for more than 4 to 5 years. Using estrogen alone (for women without a uterus) does not increase breast cancer risk at 7 years but may increase risk if used for a longer time.

Some studies suggest that HT might be good for your heart if you start before age 60 or within 10 years of menopause. However, if you start HT further from menopause or after age 60, HT might slightly increase your risk of heart disease. Although there are risks associated with taking HT, they are not common, and most go away after you stop treatment.

Type 2 Diabetes Mellitus

New Medications to Treat Co-Morbidities

2024

Michael T. McDermott MD
Director, Endocrinology and Diabetes Practice
University of Colorado Hospital

Disclosure

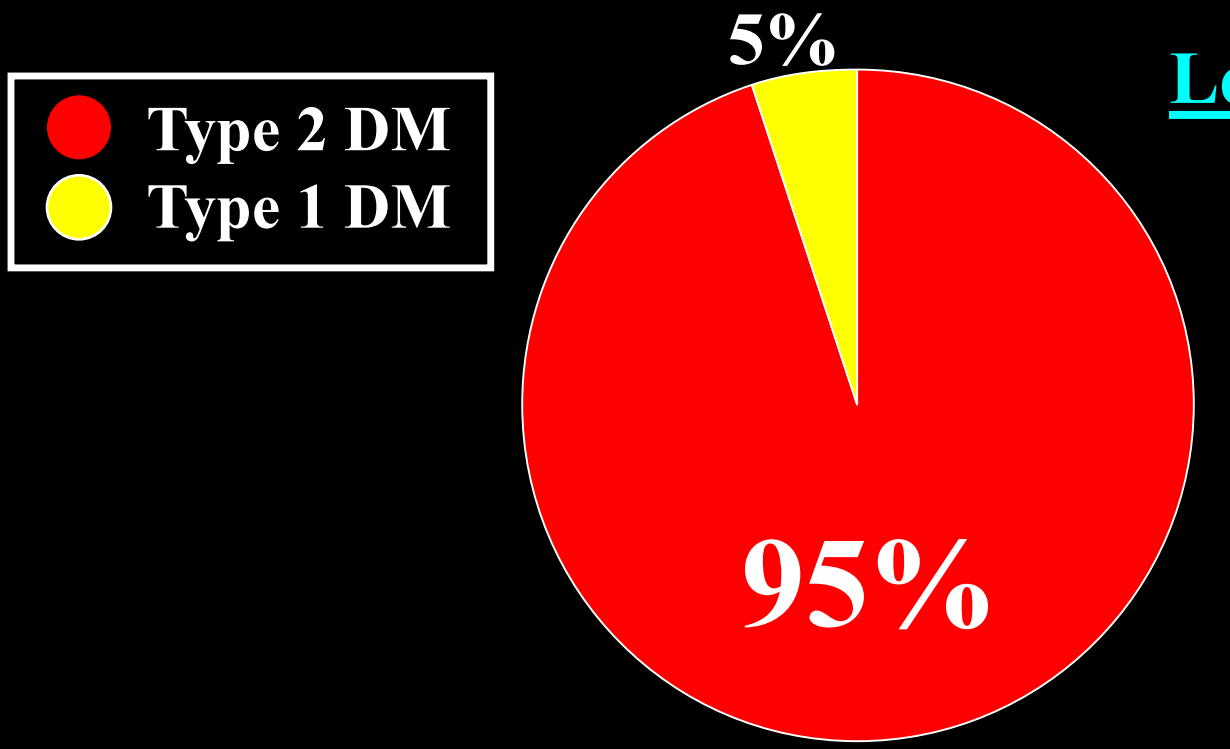
Michael McDermott has no conflict of interest or relationships to disclose in relation to this educational activity.

Learning Objectives

- Review mechanism of action of Glucagon-like Peptide Receptor Agonists (GLP-1 RA) and Sodium Glucose Transporter Inhibitors (SGLT2-I).
- Discuss effects of GLP-1 RA and SGLT2-I on Co-morbidities associated with Type 2 Diabetes Mellitus.
- Develop strategies for optimal use of GLP-1 RA and SGLT2-I in people with Type 2 Diabetes Mellitus.

Diabetes Mellitus

36 Million Americans in 2023



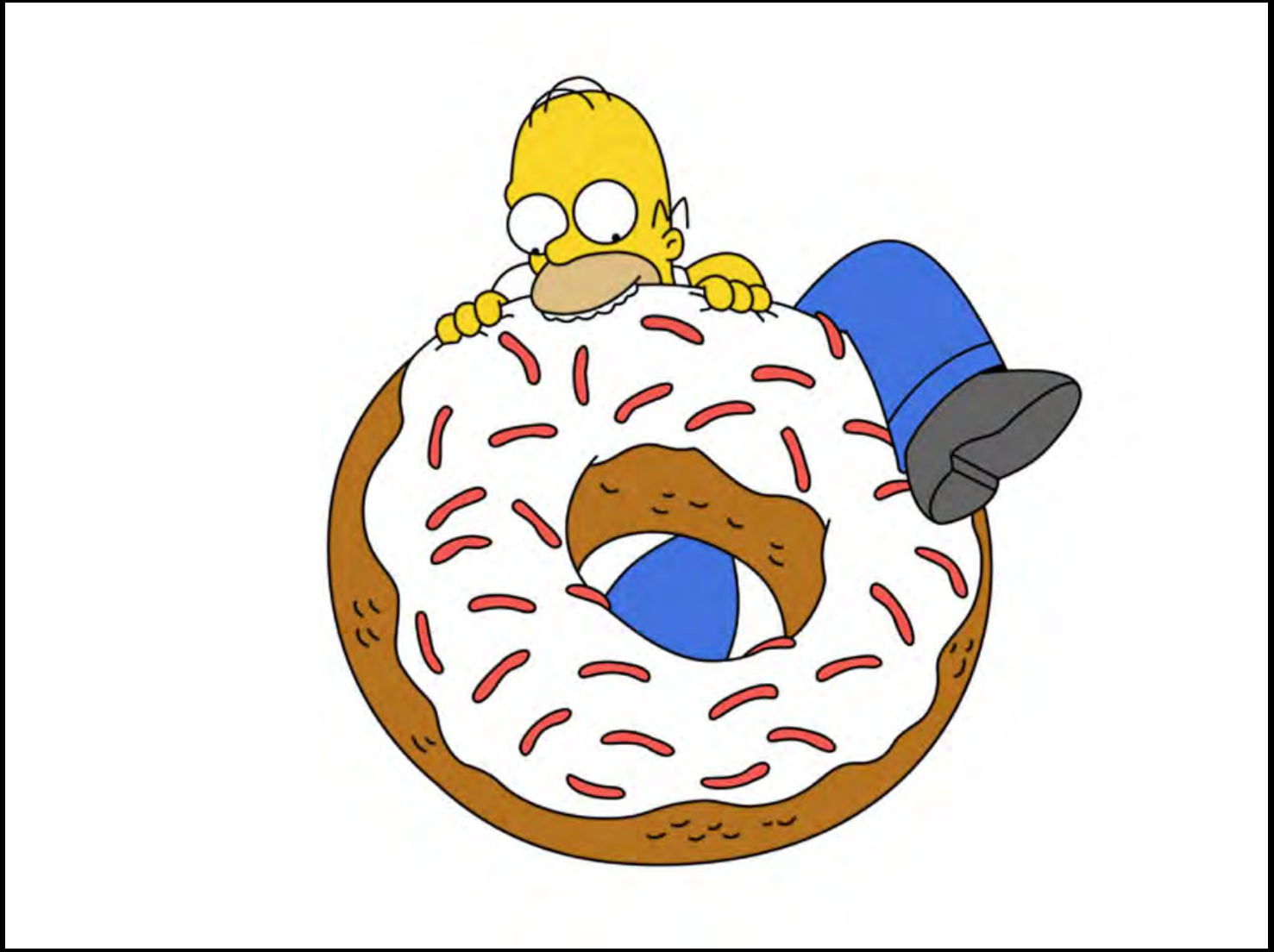
Leading US Cause

Kidney Failure
Amputations
Blindness

Major CV Risk Factor

5,000 New Cases Every Day
2,000,000 New Cases Every Year

Excess Caloric Intake



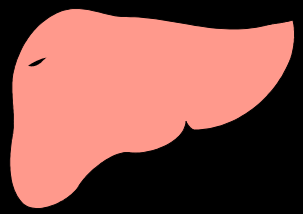
Reduced Exercise

No Exercise

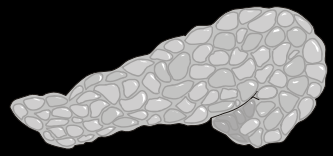
Type 2 Diabetes Mellitus

Pathophysiology

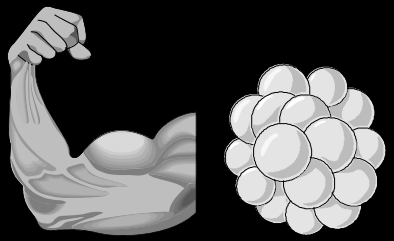
↑ Glucose Production



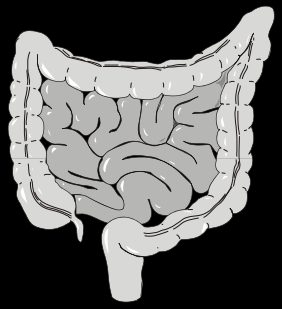
↓Insulin Secretion



Hyperglycemia



↑ Insulin Resistance

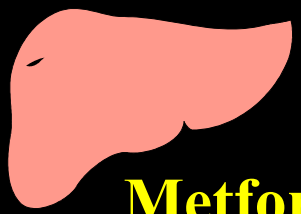


↓ Incretin Effect

Type 2 Diabetes Mellitus

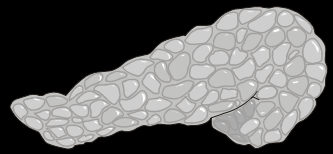
Pathophysiology Based Therapy

↓ Glucose Production



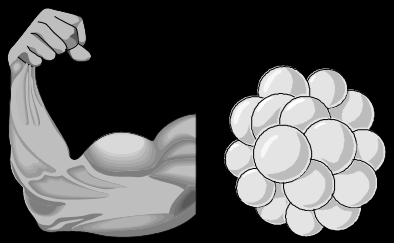
Metformin

↑Insulin Secretion



Sulfonylurea
Meglitinide

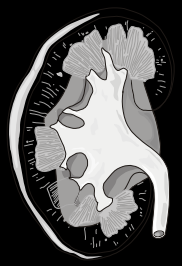
Euglycemia



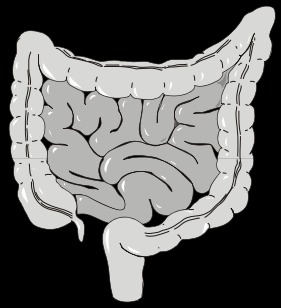
↓ Insulin Resistance

Thiazolidinedione

SGLT-2 Inhibitor

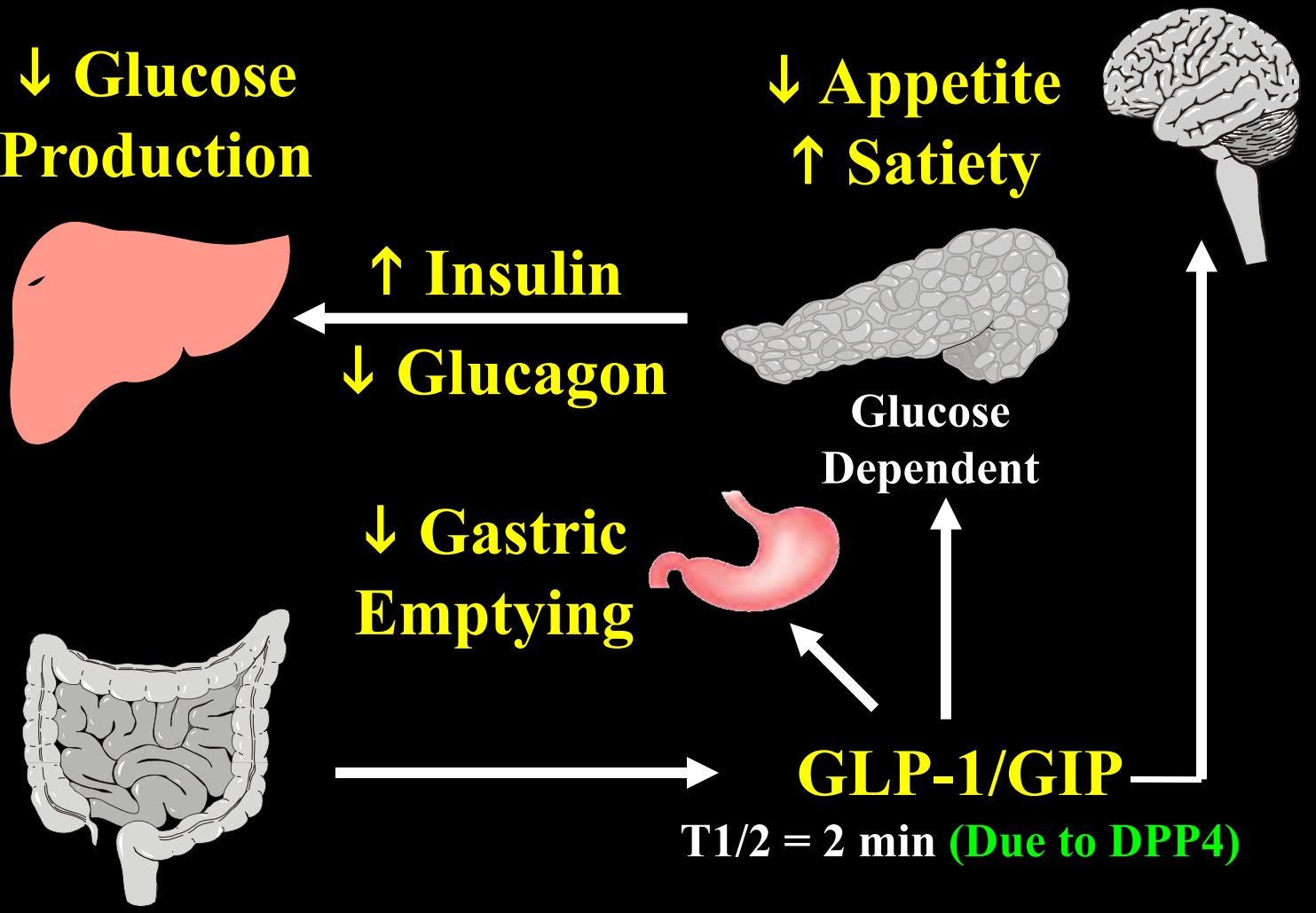


↑ Glycosuria



↑ Incretin Effect
GLP-1 RA
GLP-1/GIP RA
DPP4 Inhibitor

Incretin Physiology



GLP-1 = Glucagon Like Peptide-1

DPP4 = Dipeptidyl Peptidase 4

GIP = Glucose Dependent Insulinotropic Peptide

Incretin Based Therapy

GLP-1/GIP Receptor Agonists

- Resistant to DPP4
- Prolonged duration of action

GLP-1 = Glucagon Like Peptide-1 DPP4 = Dipeptidyl Peptidase 4
GIP = Glucose Dependent Insulinotropic Peptide

Incretin Based Therapy

GLP-1 Receptor Agonists

Exenatide (Byetta) SQ BID

Liraglutide (Victoza) SQ Daily

Lixisenatide (Adlyxin) SQ Daily

Exenatide QW (Bydureon) SQ Weekly

Dulaglutide (Trulicity) SQ Weekly

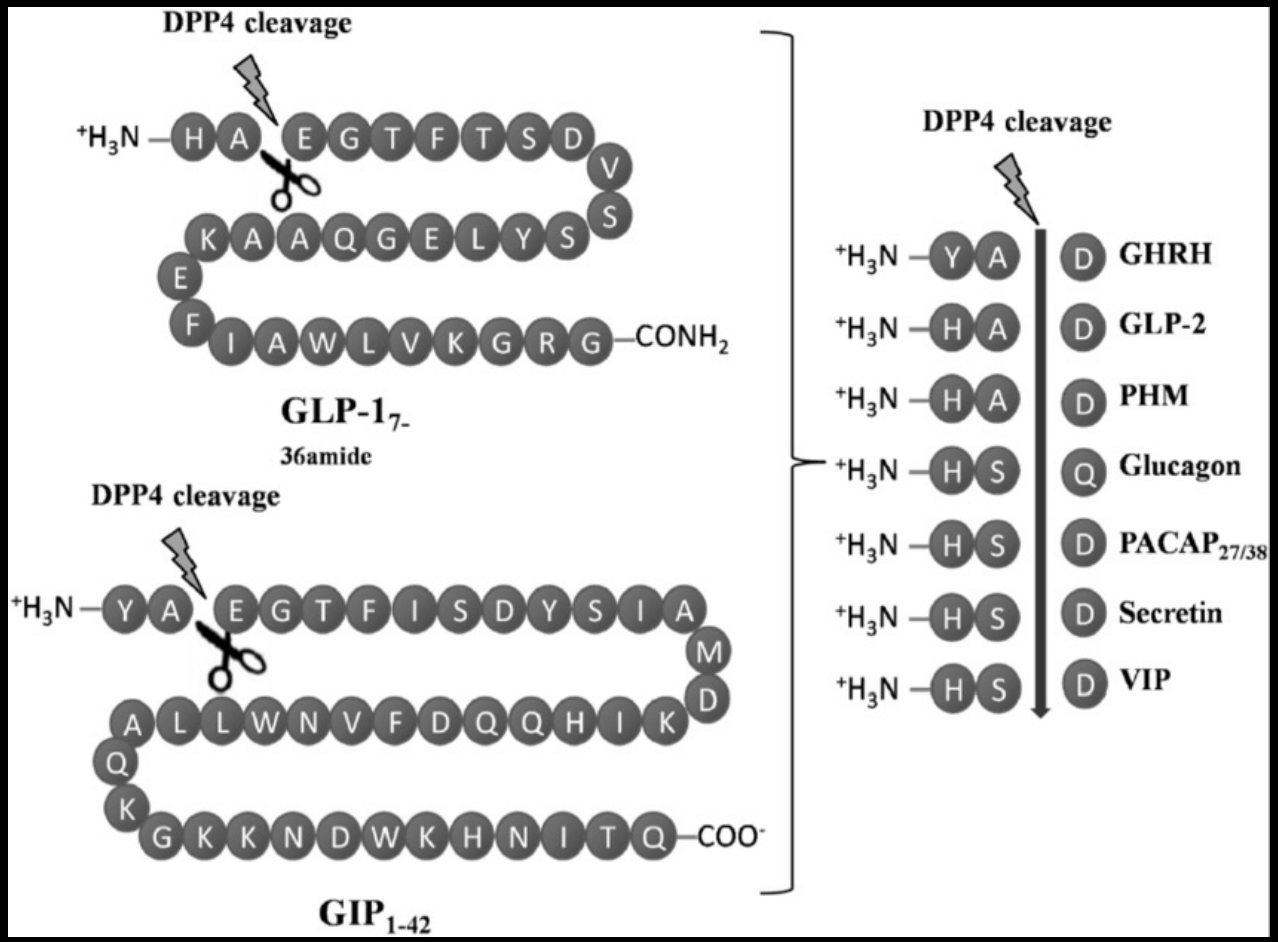
Semaglutide (Ozempic) SQ Weekly

Semaglutide (Rybelsus) PO Daily

GLP-1 / GIP Receptor Agonist

Tirzepatide (Mounjaro) SQ Weekly

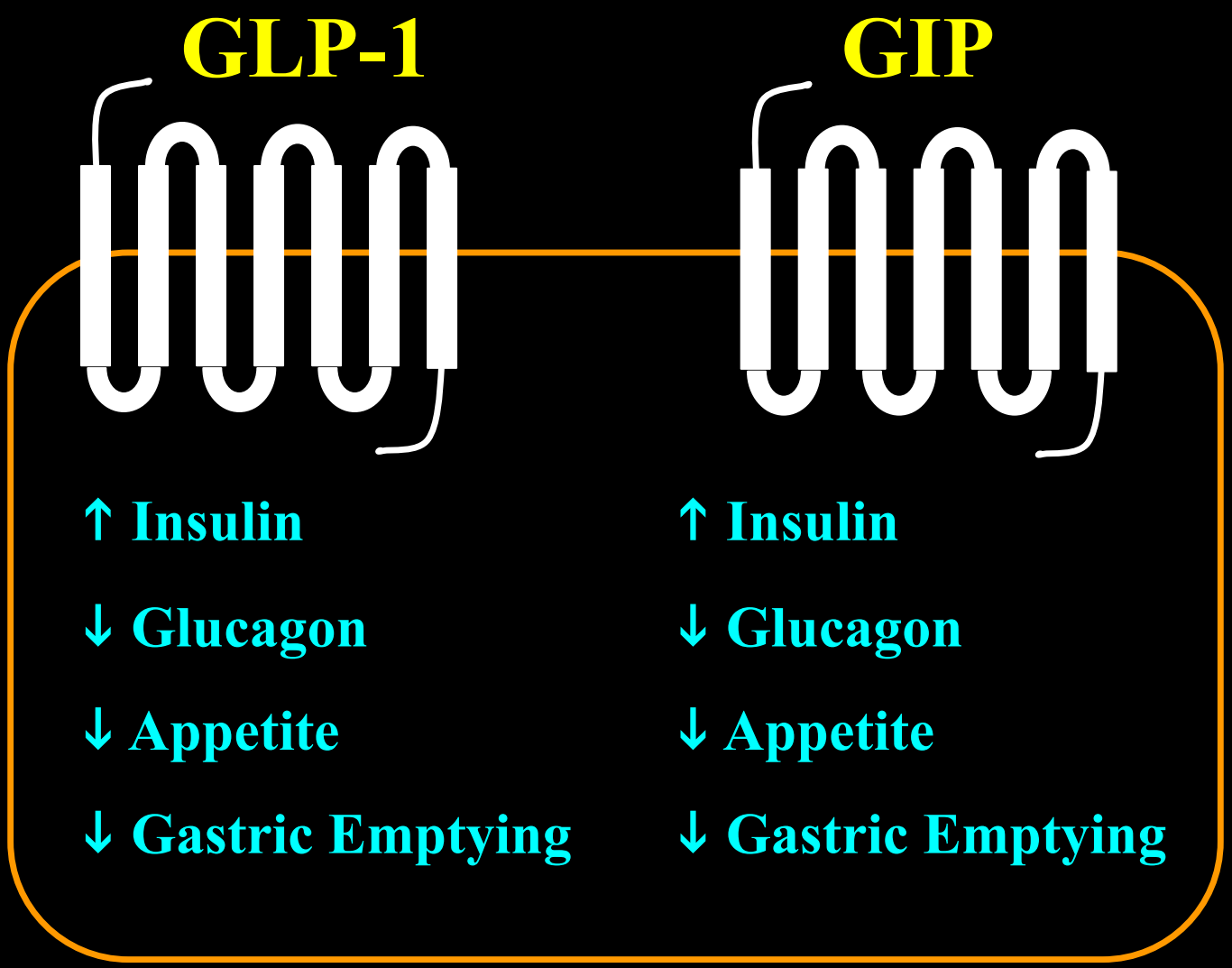
GLP-1 and GIP



GLP-1: Glucagon Like Peptide 1

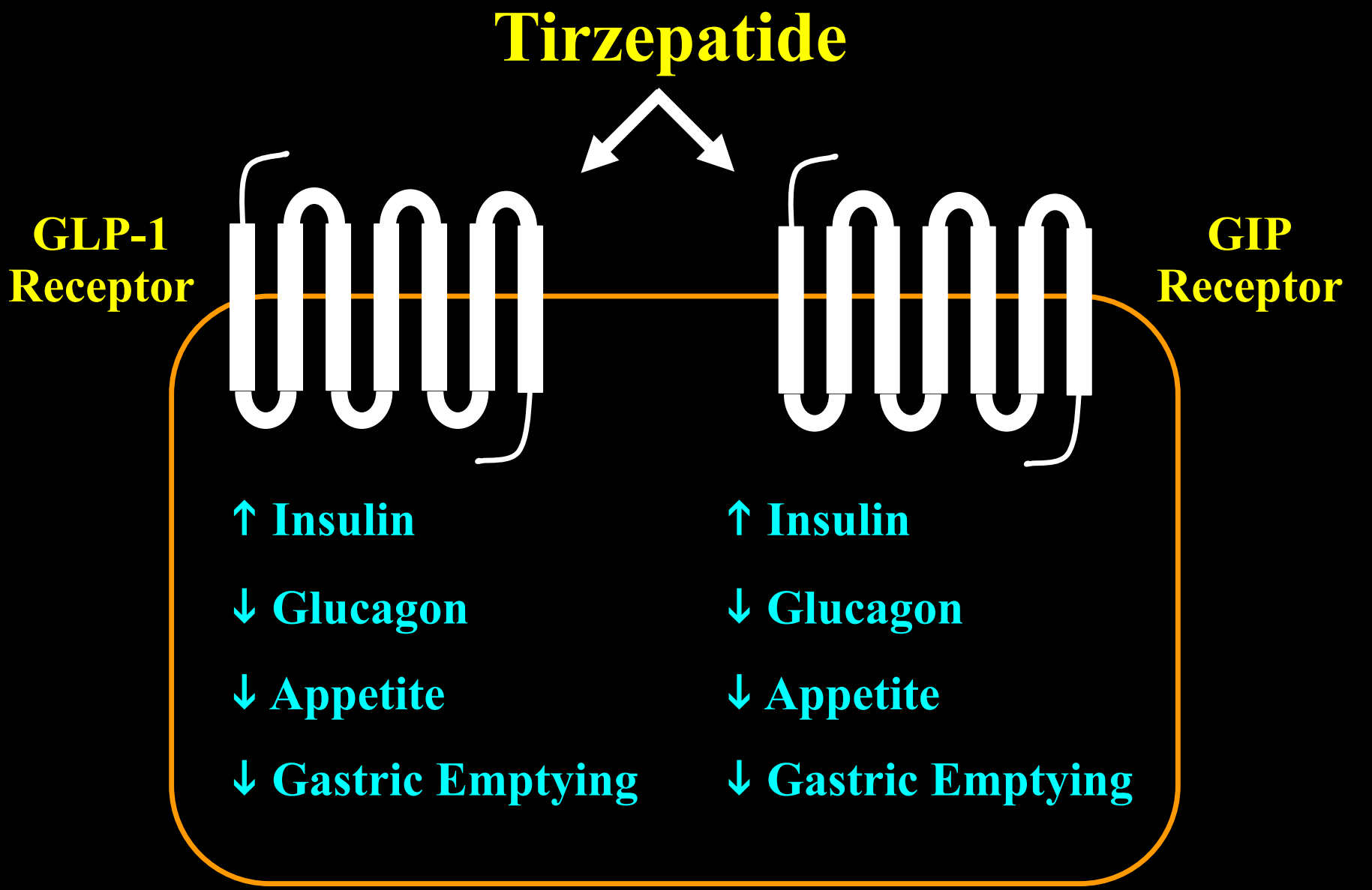
GIP: Glucose Dependent Insulinotropic Peptide

GLP-1 and GIP Receptors



GLP-1 Receptor Agonist

GLP-1 and GIP Receptor Agonist



Liraglutide: LEADER

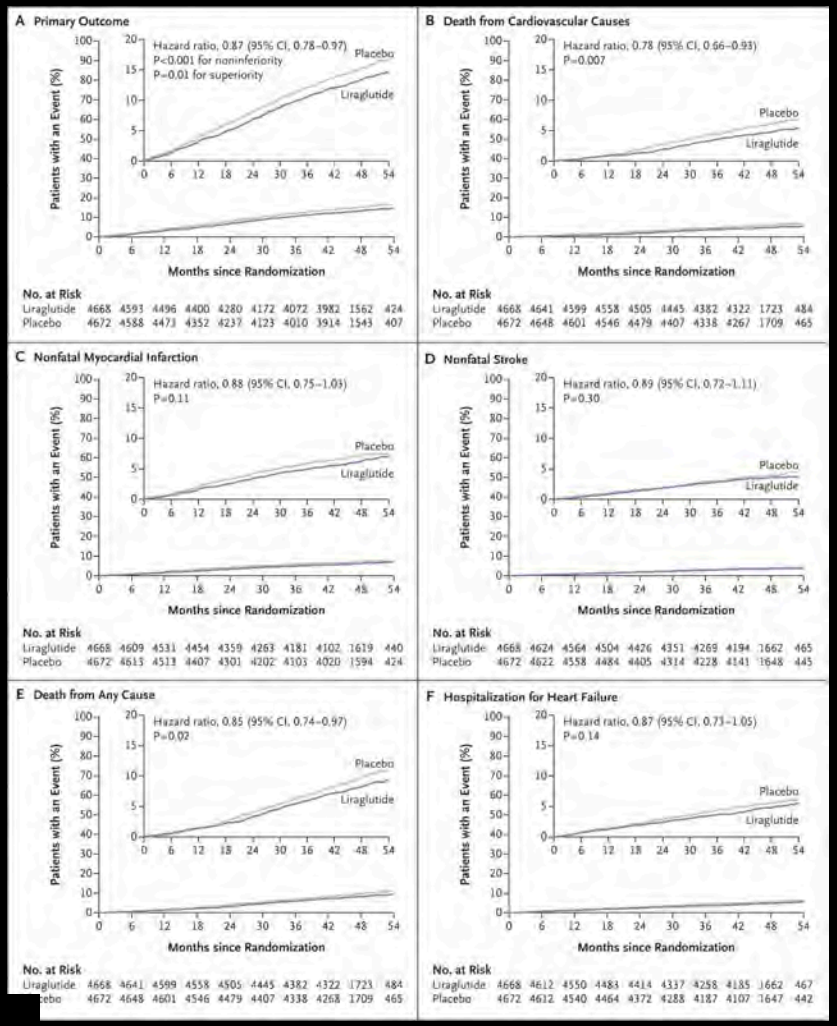
Cardiovascular Death, Nonfatal MI, Nonfatal Stroke

RCT (9340 DM2 Patients): Liraglutide or Placebo x 4.5 years

Primary Outcome
HR: 0.87
CI: 0.78-0.97
P = 0.01

Nonfatal MI
HR: 0.88
CI: 0.75-1.03
P = 0.11

All Cause Mortality
HR: 0.85
CI: 0.74-0.97
P = 0.02



CV Mortality
HR: 0.78
CI: 0.66-0.93
P = 0.007

Nonfatal Stroke
HR: 0.89
CI: 0.72-1.11
P = 0.30

Heart Failure Hospitalization
HR: 0.87
CI: 0.73-1.05
P = 0.14

The NEW ENGLAND JOURNAL of MEDICINE

Marso SP. N Engl J Med 2016;375:311-322

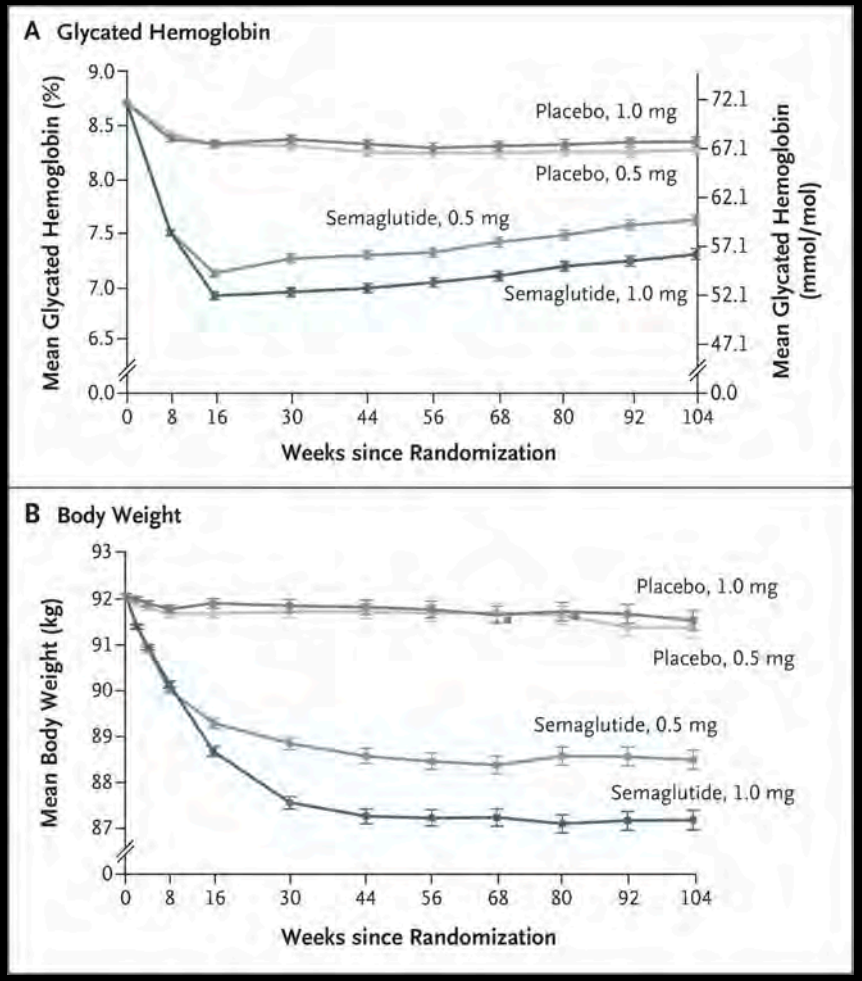
Semaglutide: Sustain-6

Cardiovascular Death, Nonfatal MI, Nonfatal Stroke

RCT (3297 DM2 Patients – High CV Risk): Semaglutide or Placebo x 2.1 years

A1C

Body Weight



The NEW ENGLAND JOURNAL of MEDICINE

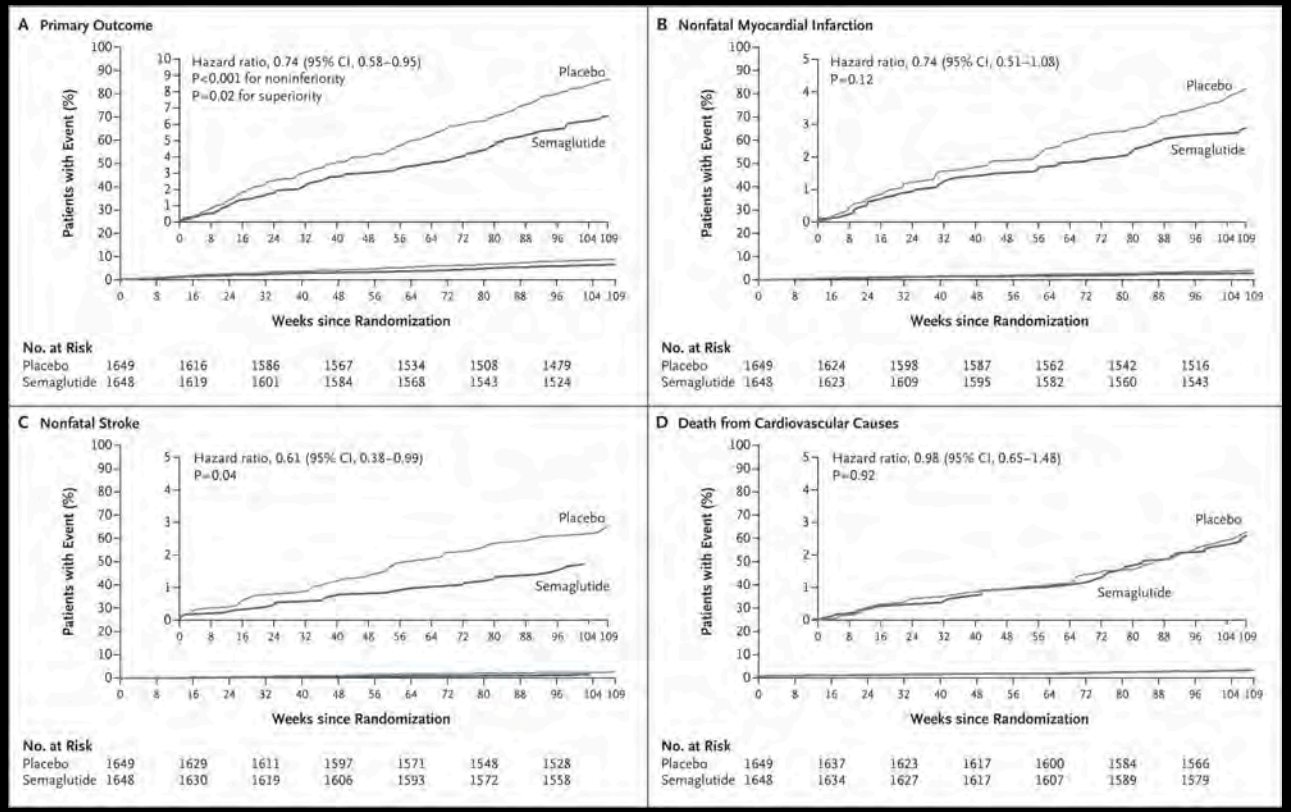
Marso SP. N Engl J Med 2016;375:1834-1844

Semaglutide: Sustain-6

Cardiovascular Death, Nonfatal MI, Nonfatal Stroke

RCT (3297 DM2 Patients – High CV Risk): Semaglutide or Placebo x 2.1 years

Primary Outcome HR 0.74 P = 0.02



Nonfatal MI HR 0.74 P = 0.12

Nonfatal Stroke HR 0.61 P = 0.04

CV Death HR 0.98 P = 0.92

The NEW ENGLAND JOURNAL of MEDICINE

Marso SP. N Engl J Med 2016;375:1834-1844

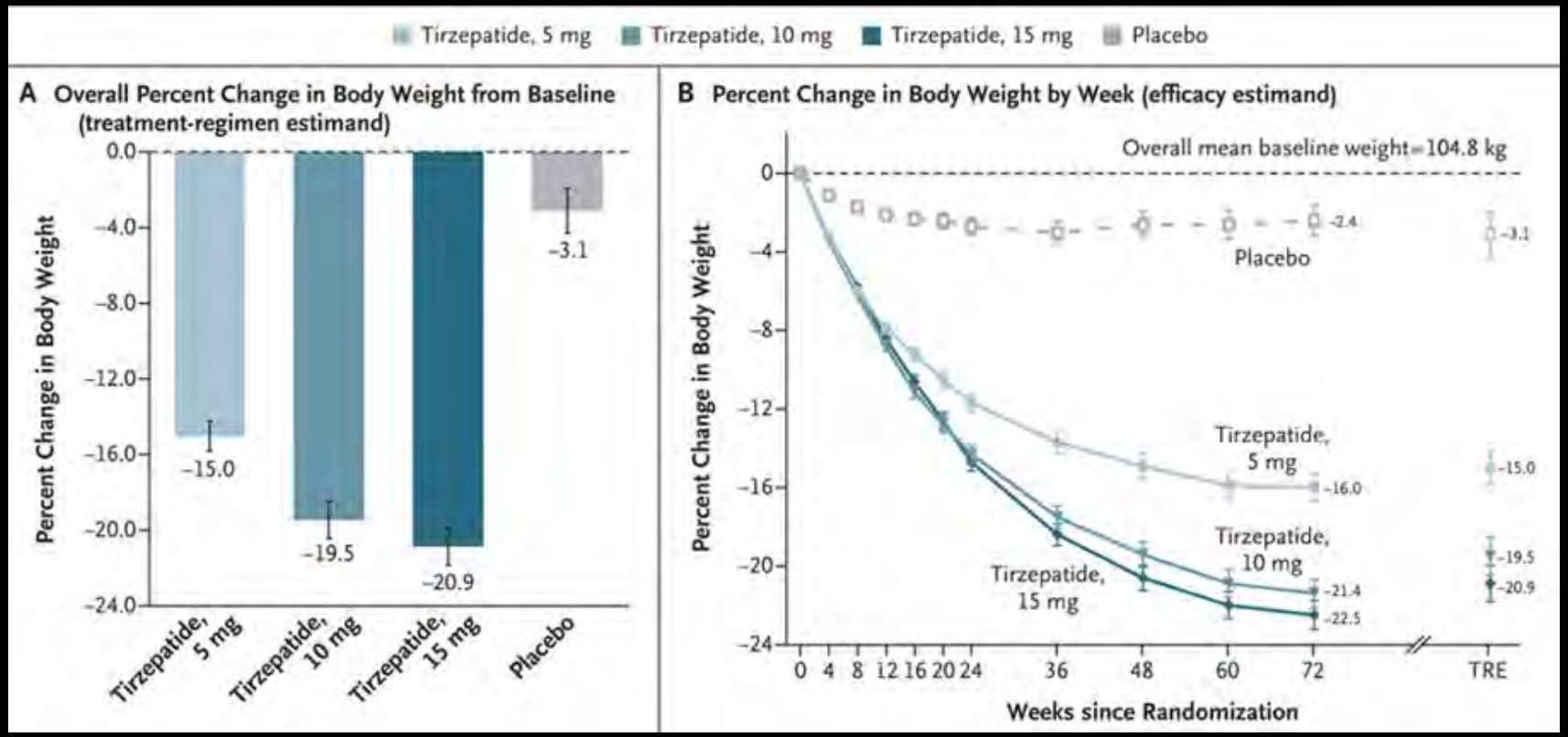
GLP-1/GIP Receptor Agonist

2539 Obese Adults (BMI > 30 or > 27 + Co-morbidity

Tirzepatide vs Placebo x 72 weeks

Body Weight
% ↓ c/w Baseline

Body Weight
% ↓ by Week



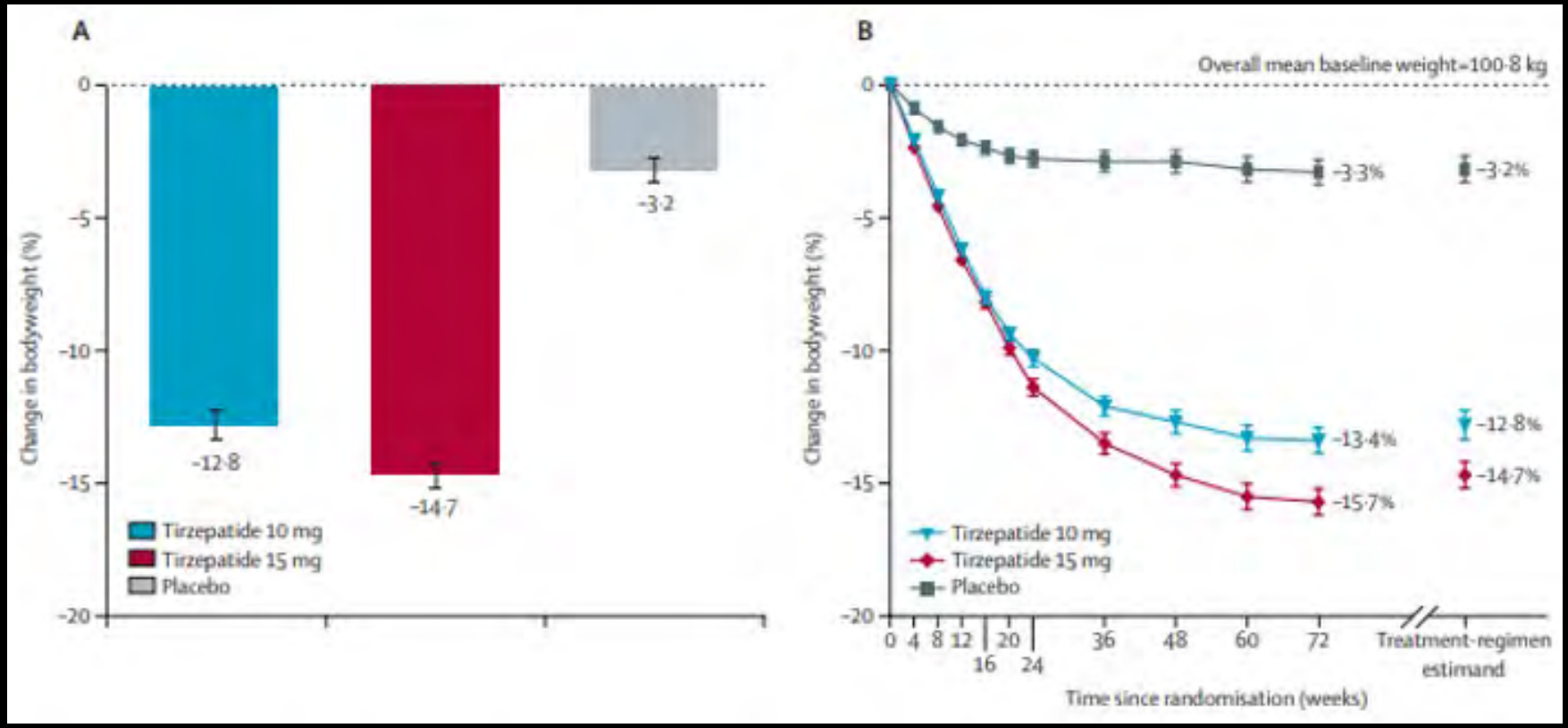
Surmount-1. Jastreboff AM. N Engl J Med 2022;387:205-16.

GLP-1/GIP Receptor Agonist

938 DM2 Adults (BMI > 27): Tirzepatide vs Placebo x 72 weeks

Body Weight
% ↓ c/w Baseline

Body Weight
% ↓ by Week

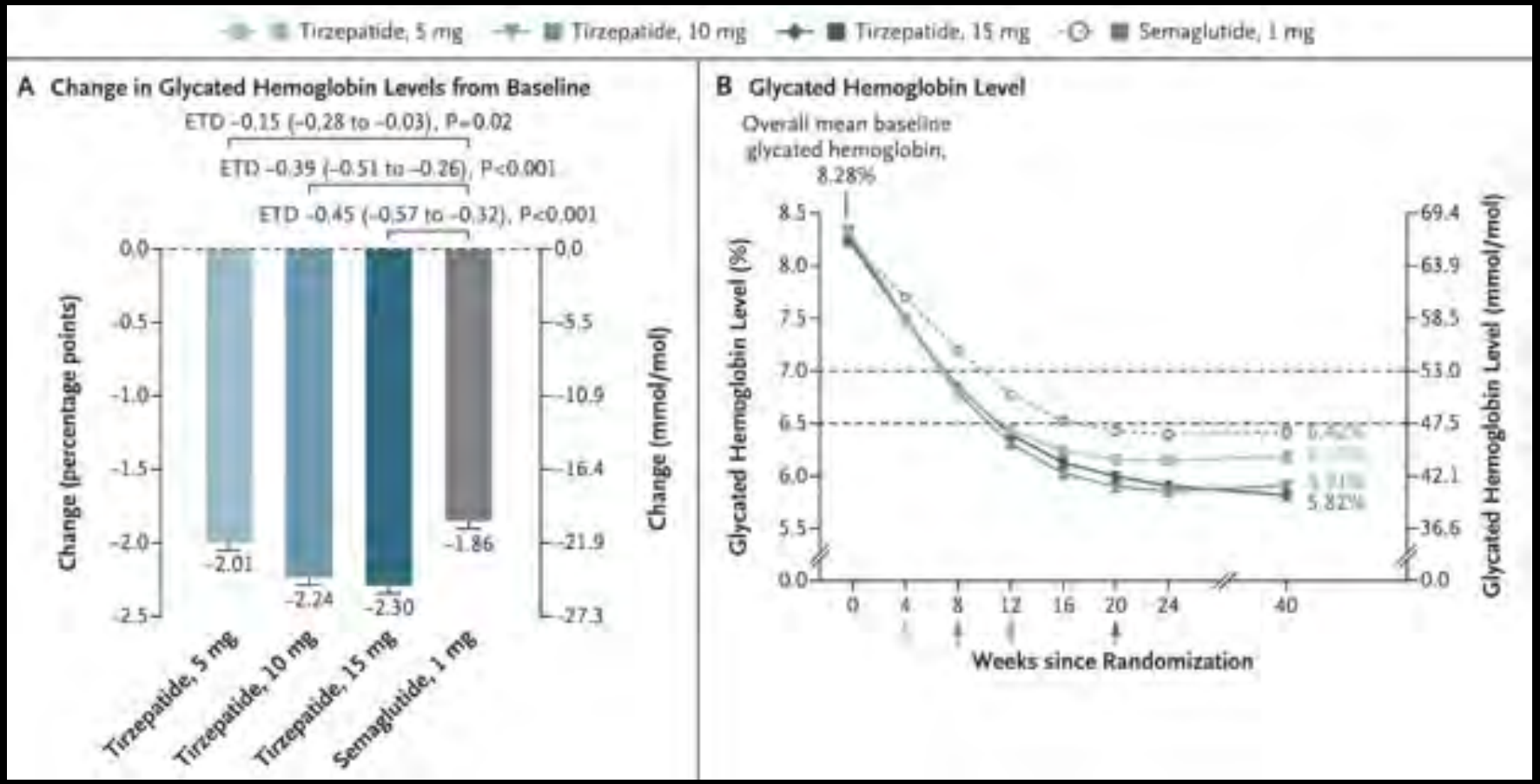


Surmount-2. Garvey WT. Lancet 2023; 402: 613-26.

GLP-1/GIP Receptor Agonist

1879 DM2 Adults: Tirzepatide vs Semaglutide x 40 weeks

A1C % ↓ c/w Baseline **A1C % ↓ by Week**



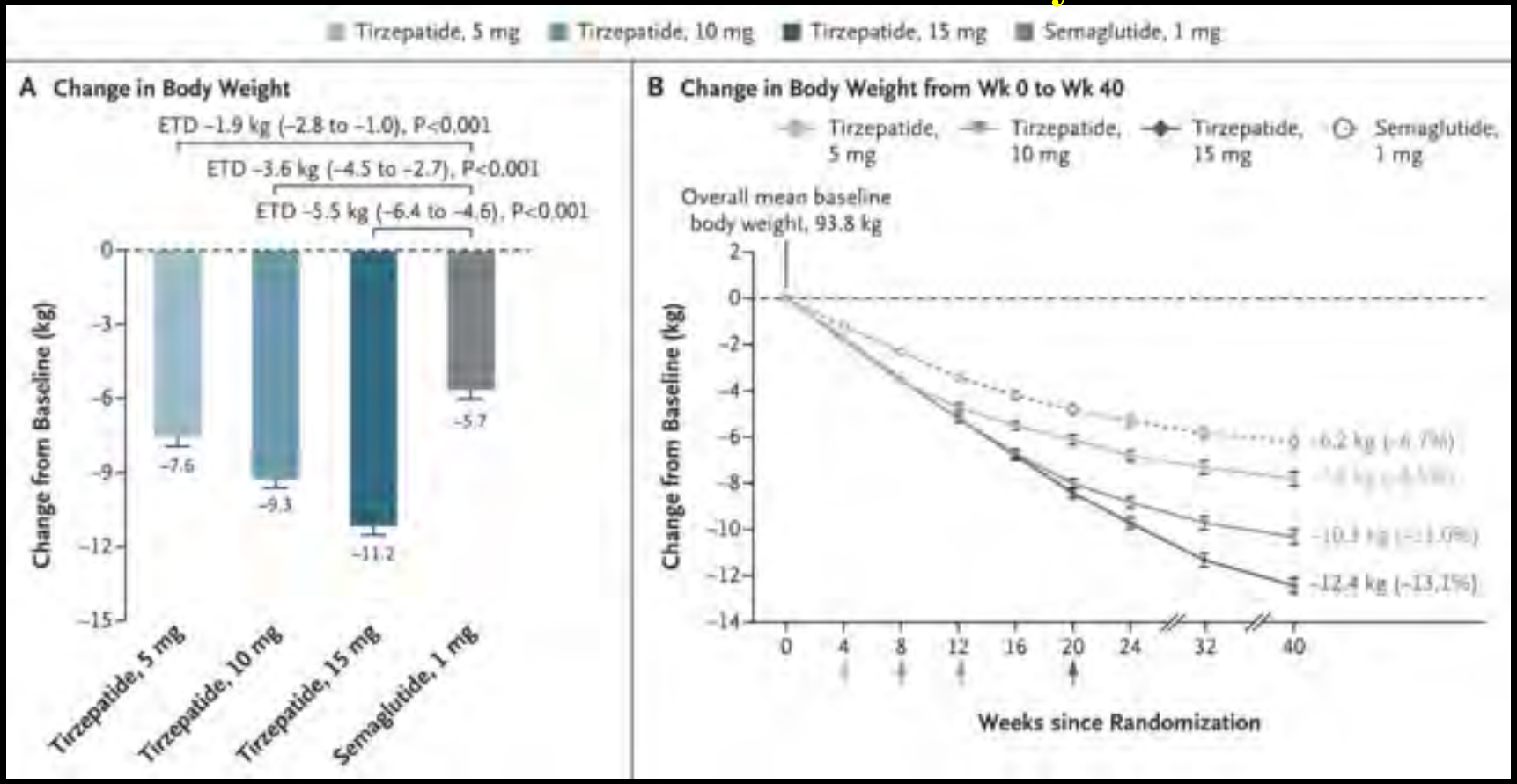
Surpass-2. Frias JP. N Engl J Med 2021; 385:503-15.

GLP-1/GIP Receptor Agonist

1879 DM2 Adults: Tirzepatide vs Semaglutide x 40 weeks

Body Weight
% ↓ c/w Baseline

Body Weight
% ↓ by Week



Surpass-2. Frias JP. N Engl J Med 2021; 385:503-15.

GLP-1 Receptor Agonist
Benefits

- Glucose Lowering (1.0-1.5% ↓ A1C)
- Cardiovascular Benefit
- Stroke Benefit
- Renal Benefit
- NAFL Benefit
- Weight Loss (10-15 lb)

GLP-1/GIP Receptor Agonist

Benefits

- Glucose Lowering (2.0-2.8% ↓ A1C)
- Weight Loss (20-50 lb)
- Under Investigation
  - Cardiovascular Benefit
  - Stroke Benefit
  - Renal Benefit
  - NAFL Benefit

GLP-1/GIP Receptor Agonist

Risks

- Medullary Thyroid Cancer
- Retinopathy Worsening
- Acute Pancreatitis
- Gall Bladder / Biliary Disease
- Gastroparesis

GLP-1/GIP Receptor Agonist

Medullary Thyroid Cancer

- Medullary Thyroid Cancer Risk (Black Box*)
- Differentiated Thyroid Cancer - Uncertain

* Contraindicated in people with personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)

GLP-1/GIP Receptor Agonist

Acute Pancreatitis

- **Post-marketing case reports: potential link**
- **Retrospective and observational studies: inconsistent**
- **Systematic reviews and meta-analyses: no association**
- **FDA: causal relationship could not be established**
- **Use with caution in people with prior history of pancreatitis, particularly when cause is unknown or persists**

Egan AG. New Engl J Med 2014;370:794-797
Monami M. Diabetes Obes Metab 2017;19:1233-1241
Storgaard H. Diabetes Obes Metab 2017;19:906-908

GLP-1/GIP Receptor Agonist

Retinopathy Worsening

Meta-Analyses

- **Bethel: GLP-1 RA use not associated with worsening retinopathy (OR 1.10; 95% CI 0.93-1.30)**
  - **Positive association with magnitude of A1C reduction**
- **Yoshida: GLP-1 RA use associated with worsening retinopathy (OR 1.23; 95% CI 1.05-1.44)**

Bethel MA. Diabetes Care 2021; 44:290-96.
Yoshida Y. J Diab Complications 2022; 36(8):108255

GLP-1/GIP Receptor Agonist

Anesthesia

Prior to Procedure:

Daily GLP-1 RA: consider holding GLP-1 RA the day of the procedure.
Weekly GLP-1 RA: consider holding GLP-1 RA a week prior to procedure.

If GLP-1 RA are held for longer than the dosing schedule, consider consulting an endocrinologist for bridging the antidiabetic therapy to avoid hyperglycemia.

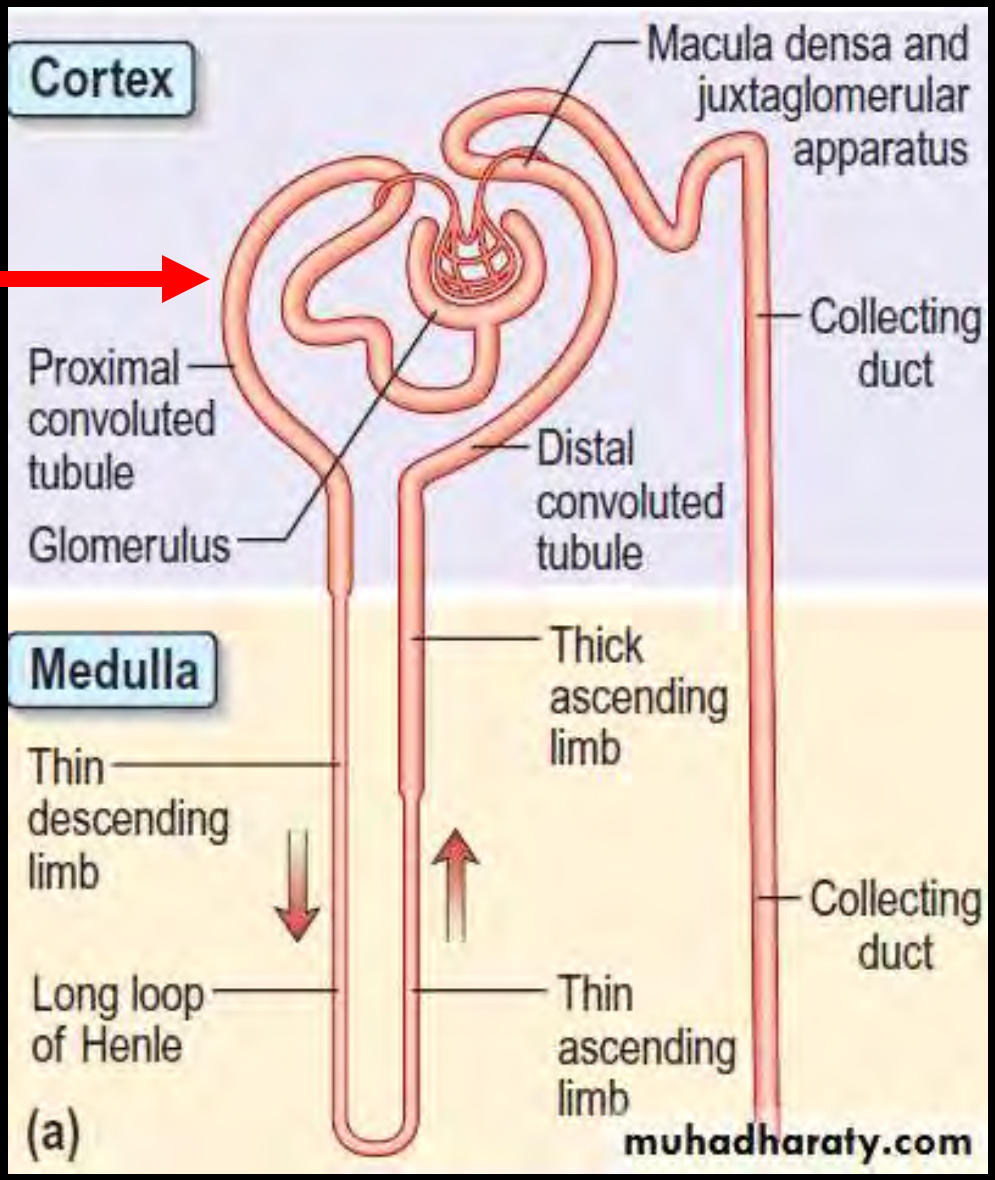
Day of Procedure:

GI symptoms present (severe nausea/vomiting/retching/bloating/pain): consider delaying elective procedure and discuss concerns of potential risk of regurgitation and pulmonary aspiration of gastric contents with the proceduralist and patient.
GI symptoms absent, but GLP-1 RA was not held as advised: proceed with 'full stomach' precautions or consider evaluating gastric volume by ultrasound. If the stomach is empty, proceed. If the stomach is full or if gastric US inconclusive, consider delaying the procedure or treat the patient as 'full stomach'.

Joshi GP. American Society of Anesthesiologists Consensus Based Guidance on Preoperative Management of Patients on Glucagon-Like Peptide-1 Receptor Agonists

Sodium Glucose Transporter 2 Inhibitors

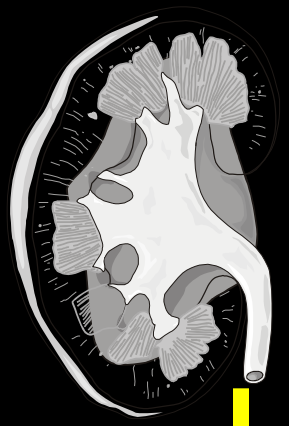
SGLT2



Sodium Glucose Transporter 2 Inhibitors

Kidneys Filter + Reabsorb Glucose: 180 g/day
SGLT2 (proximal tubules): 90%

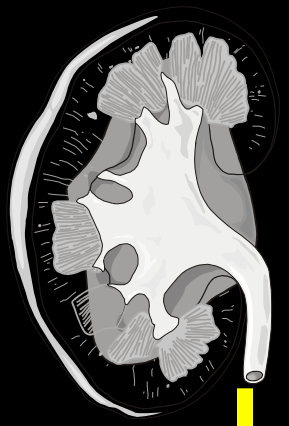
Normal



Glycosuria

BG > 180 mg/dl

SGLT2 Inhibitor



Glycosuria

BG > 80 mg/dl

Glucose Loss
80-100 g/day
320-400 kcal/day

Blood Glucose ↓
Weight Loss

No Renal Damage

GU Infections / UTI

Sodium Glucose Transporter 2 Inhibitors

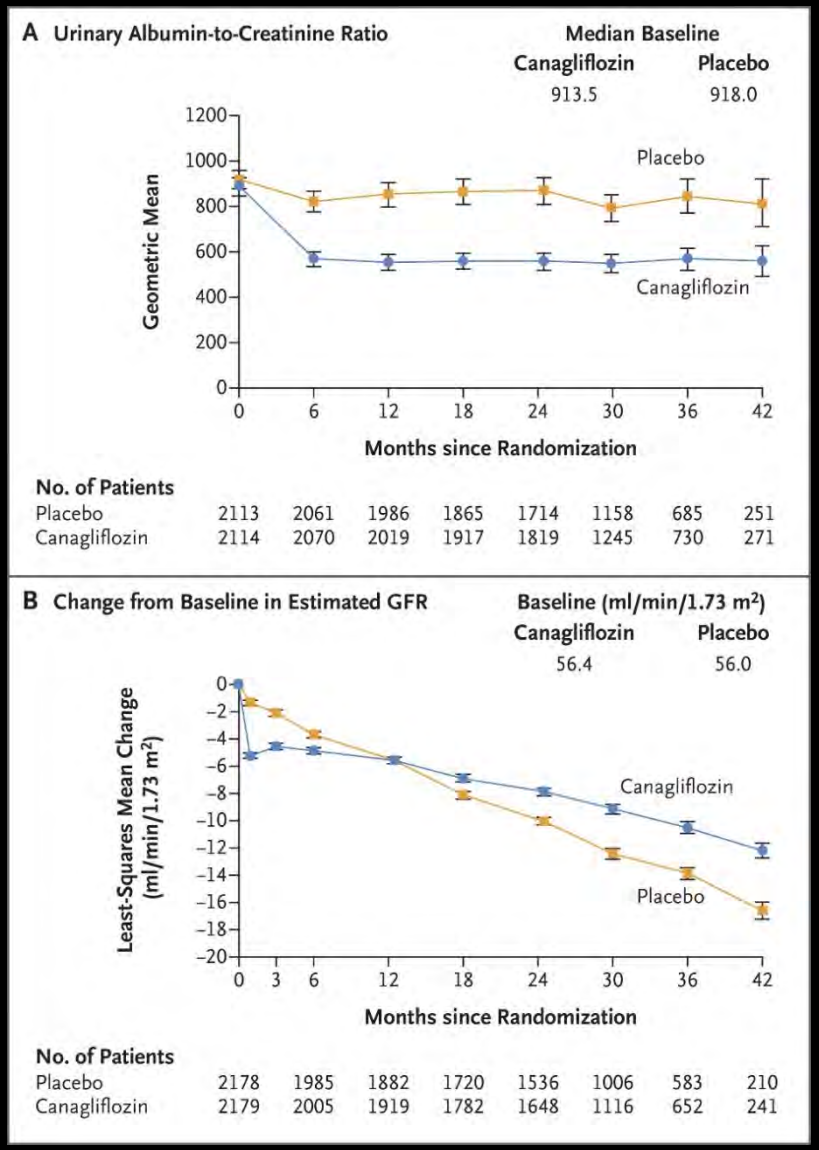
Generic	Trade Name	Doses
Canagliflozin	Invokana	100, 300 mg
Dapagliflozin	Farxiga	5, 10 mg
Empagliflozin	Jardiance	10, 25 mg
Ertugliflozin	Steglatro	5, 15 mg
Bexagliflozin	Brenzavvy	20 mg

Canagliflozin - Credence Trial

Renal Outcomes

Albumin/Creatinine Ratio

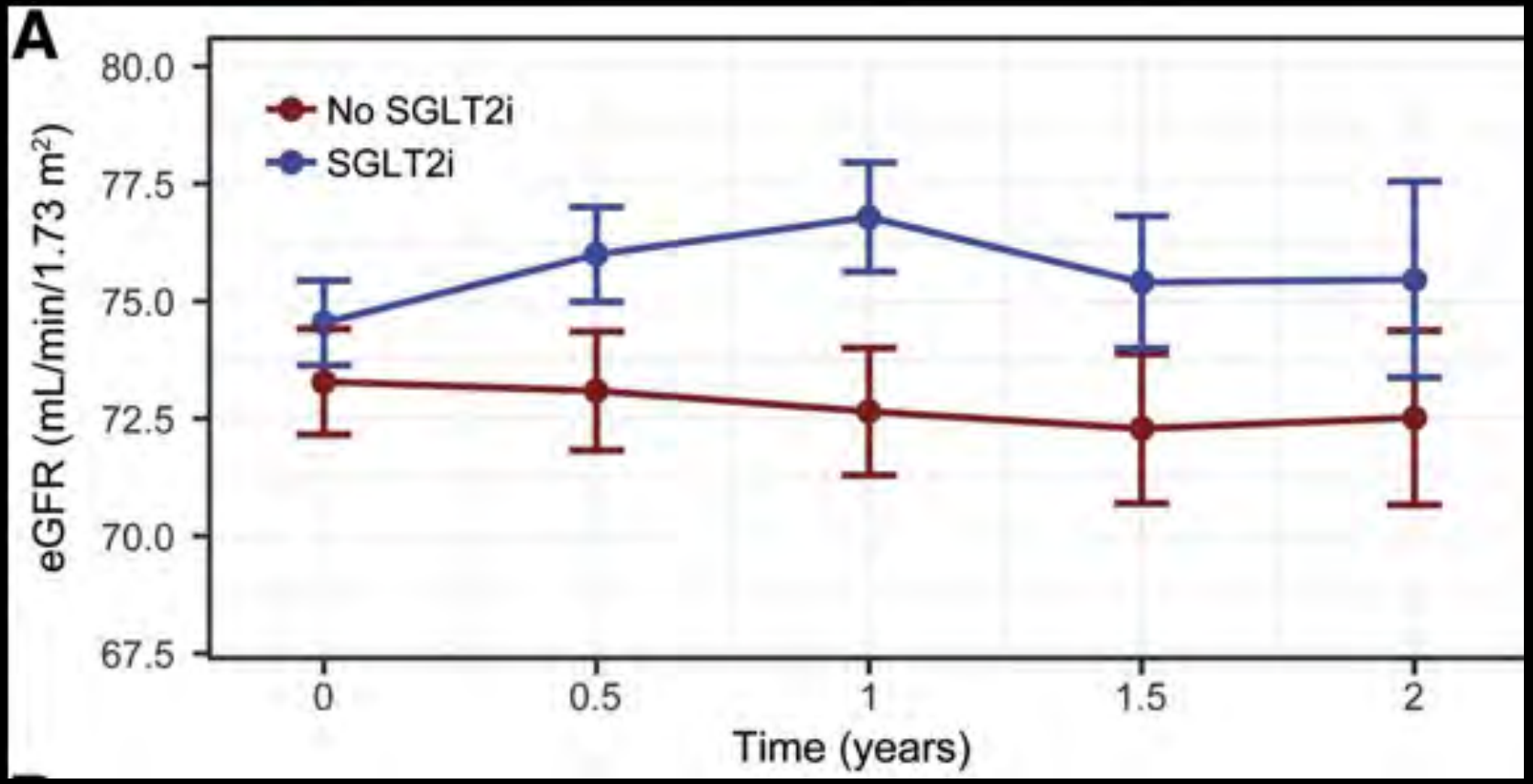
GFR: Change From Baseline



Perkovic V, N Engl J Med 2019; 380:2295-306

SGLT2 Inhibitors

Renal



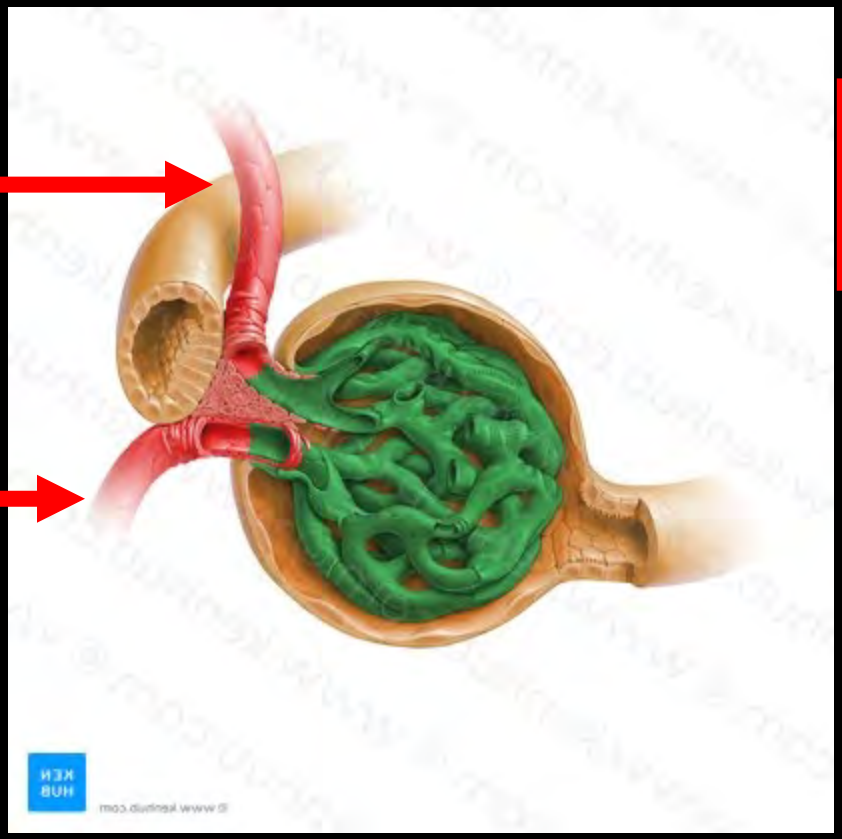
Clegg LE, Diabetes Care 2019; 42:318-26

Intraglomerular Pressure

Effects of SGLT2-I and ACE/ARB

Afferent Arteriole

Efferent Arteriole



SGLT2-I Constrict AA

ACE/ARB Dilate EA

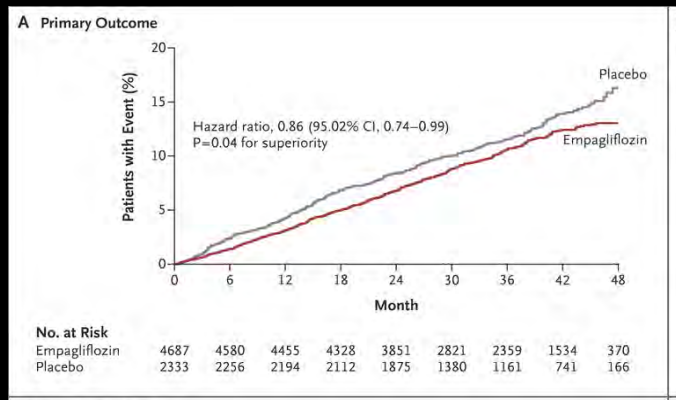
SGLT2-I and ACE/ARB Reduce Hyperfiltration Synergistically

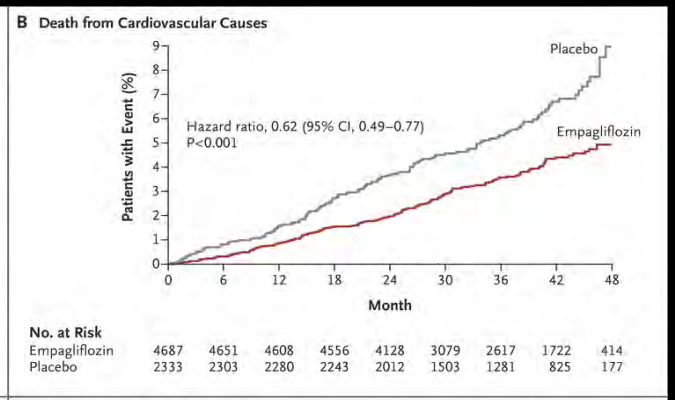
Empagliflozin: EMPA-REG

Cardiovascular Death, Nonfatal MI, Nonfatal Stroke

RCT (7020 DM2 Pts): Empagliflozin 10 mg, 25 mg or Placebo x 3.1 yr

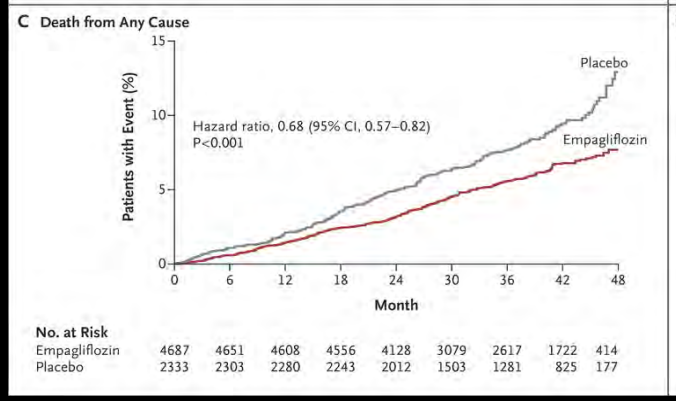
Primary Outcome HR 0.86 P = 0.04

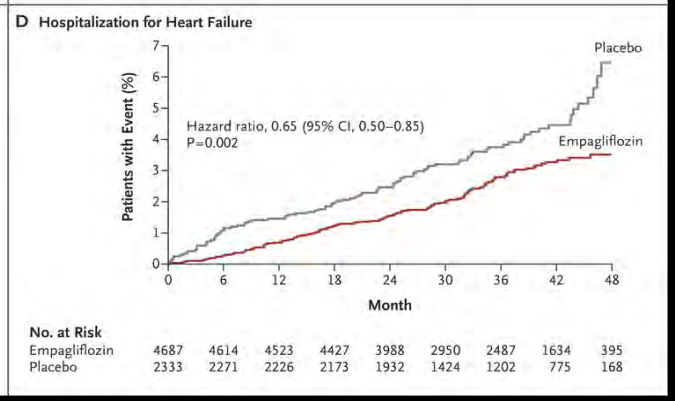




CV Death HR 0.62 P < 0.001

All Cause Death HR 0.68 P < 0.001





HF Hospitaliz HR 0.65 P = 0.002

The NEW ENGLAND JOURNAL of MEDICINE

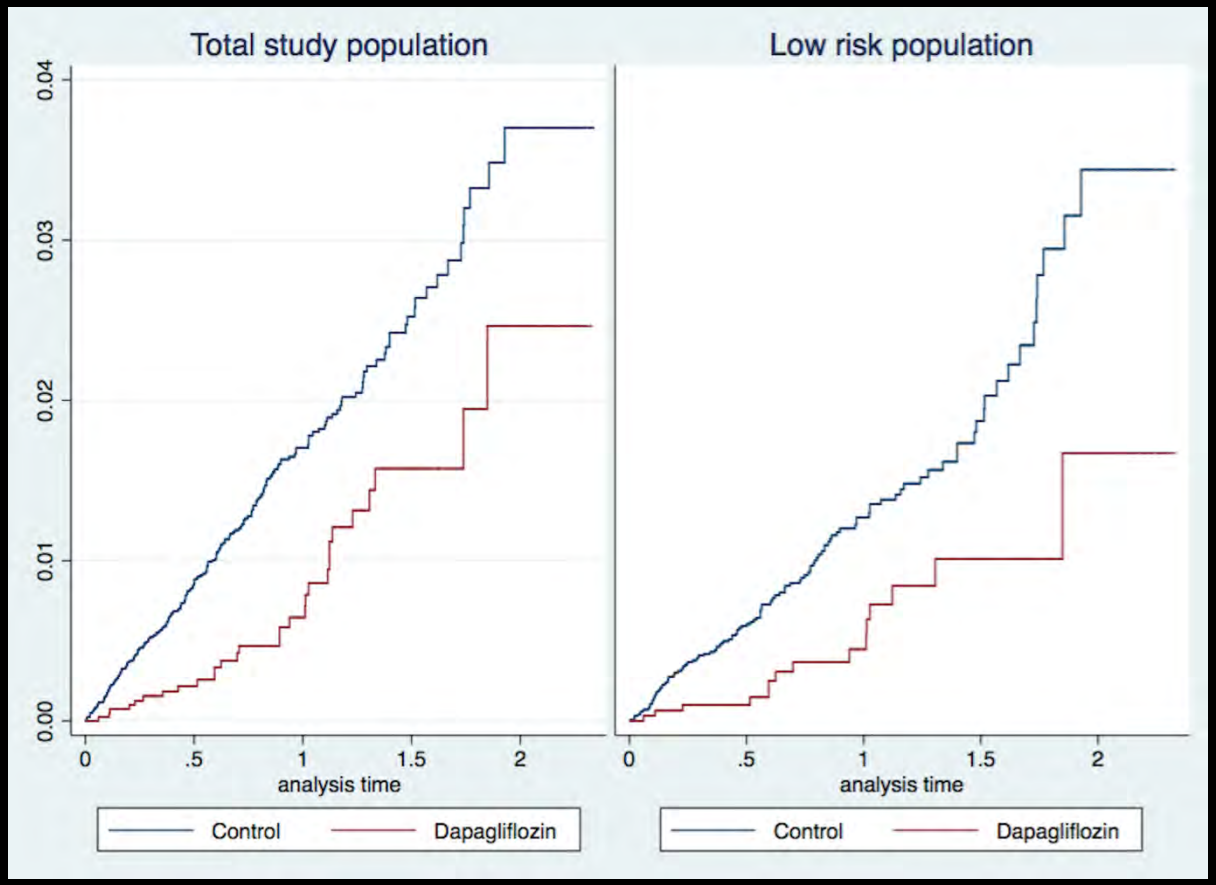
Zinman B, N Engl J Med 2015; 373:2117-28

Dapagliflozin

All Cause Mortality

Retrospective Cohort (22,124 DM2 Patients): Dapagliflozin in 4,444 Patients

P = .0001



P = .002

aIRR: 0.50, CI: 0.33-0.75 **aIRR: 0.44, CI: 0.25-0.78**

aIRR=adjusted incidence rate ratio

Toulis KA, J Clin Endocrinol Metab 2017; 102:1719-25

Sodium Glucose Transporter 2 Inhibitors

Benefits

- Glucose Lowering (0.5-1.0% ↓ A1C)
- Cardiovascular Benefit
- Heart Failure Benefit
- Renal Benefit
- NAFL Benefit
- Weight Loss (5-10 lb)

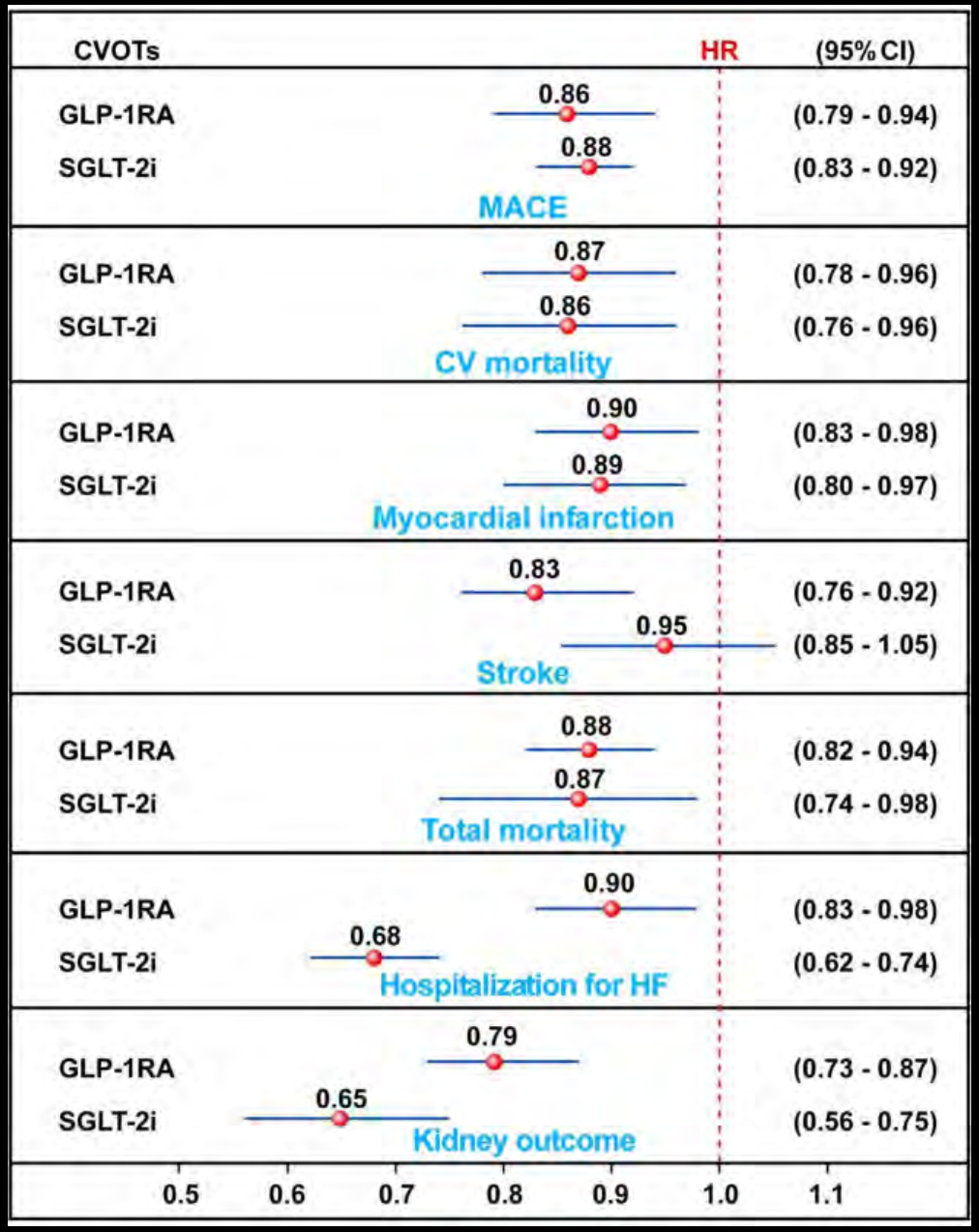
Sodium Glucose Transporter 2 Inhibitors

Risks

- Genitourinary Mycotic Infections
- Urinary Tract Infections
- Euglycemic DKA*
- Dehydration
- Fournier's Gangrene – Perineum
- Lower Limp Amputations (Canagliflozin)

*** Euglycemic DKA (BG < 200):** Occasionally Develops
Common Precipitants: Fasting, NPO, Low Carb Diets

GLP-1 RA vs SGLT2 Inhibitors



Giugliano D. Cardiovasc Diabetol 2021: 20: 205

GLP-1 RA vs SGLT2 Inhibitors

	SGLT2-I	GLP-1 RA	GLP-1/GIP RA
A1C Reduction	0.5-1.0%	1.0-1.5%	2.5-2.8%
Weight Loss	5-10 lb	10-15 lb	20-50 lb
Hypoglycemia	Low Risk	Low Risk	Low Risk
CKD Protection	Benefit	Benefit	Probable
CVD Protection	Benefit	Benefit	Probable
HF Protection	Benefit	Benefit	
Stroke Protection		Benefit	
NAFL/NASH	Benefit	Benefit	

Personalized Diabetes Care

Choose Agent with Adequate Potency to Achieve Goal

↓ A1C > 2%	↓ A1C > 1-2%	↓ A1C > 0.5-1%
Insulins GLP-1 RA GLP-1/GIP RA Usually With Metformin	Metformin Pioglitazone Sulfonylureas GLP-1 RA GLP-1/GIP RA Insulins	SGLT-2 Inhibitors DPP4 Inhibitors

Adapted from: Diabetes Care 2023 (Jan 1); Volume 46

Personalized Diabetes Care

Choose Agent with Proven Benefits for Co-Morbidities

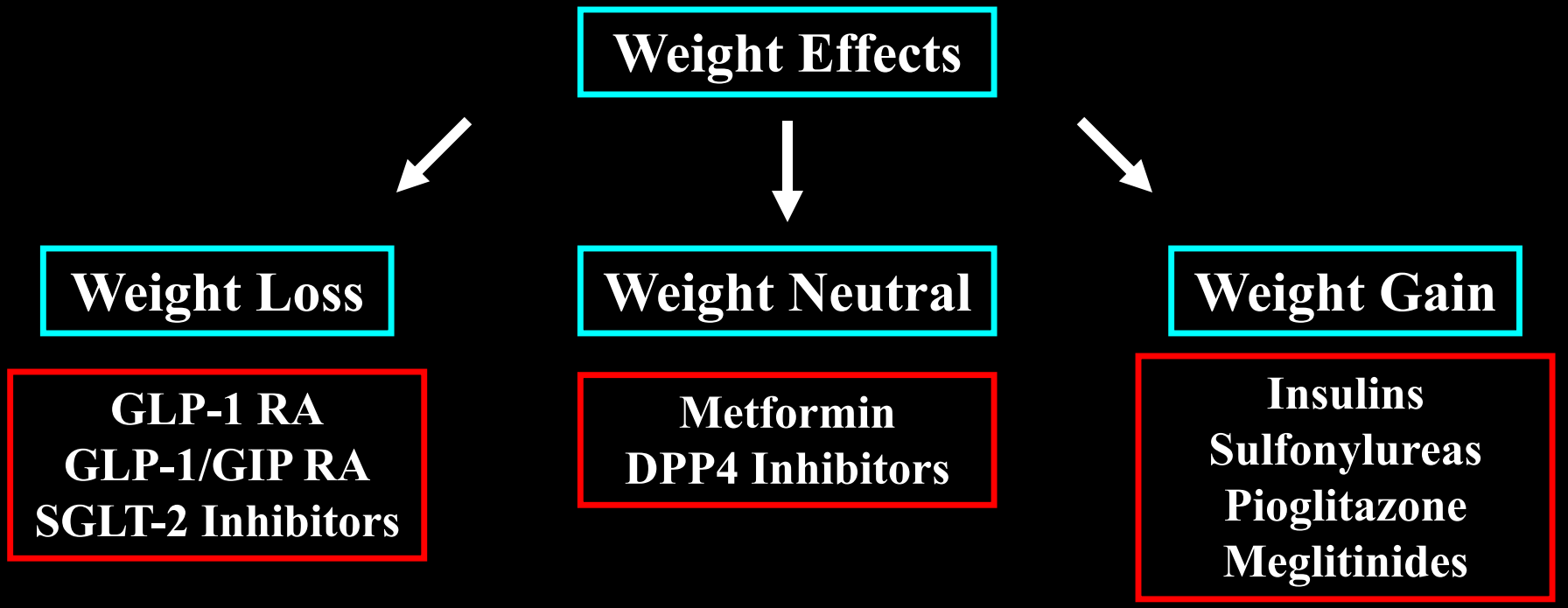
CKD	CVD	HF
GLP-1 RA SGLT-2 Inhibitors	GLP-1 RA SGLT-2 Inhibitors	SGLT-2 Inhibitors GLP-1 RA?

NAFL/NASH
Pioglitazone GLP-1 RA

Adapted from: Diabetes Care 2023 (Jan 1); Volume 46

Personalized Diabetes Care

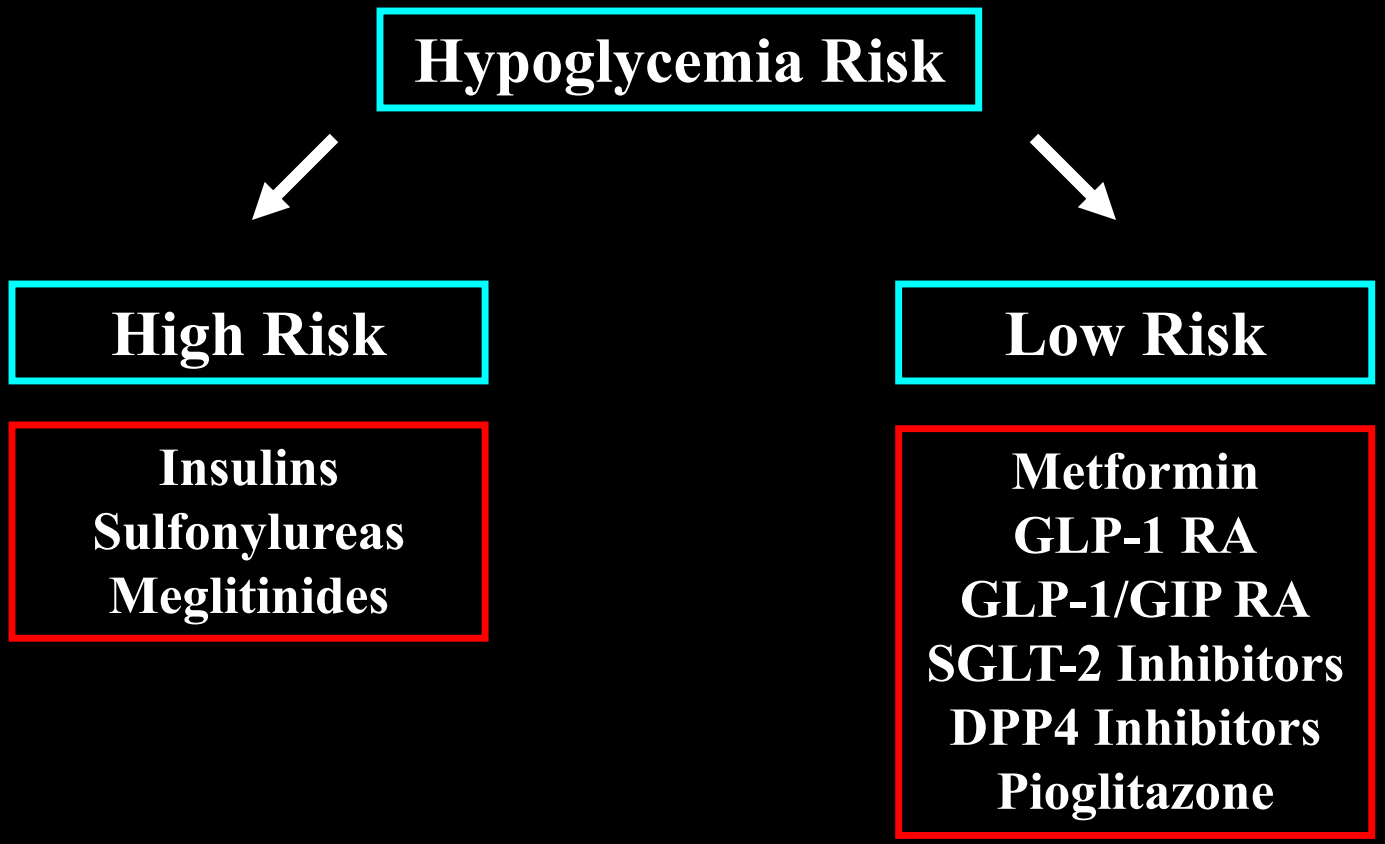
Promote Weight Loss or Minimize Weight Gain



Adapted from: Diabetes Care 2023 (Jan 1); Volume 46

Personalized Diabetes Care

Minimize Hypoglycemia



Adapted from: Diabetes Care 2023 (Jan 1); Volume 46

Personalized Diabetes Care

Minimize Cost

High Cost	Low Cost
GLP-1 RA GLP-1/GIP RA SGLT-2 Inhibitors DPP4 Inhibitors Insulin Analogs	Metformin Sulfonylureas Pioglitazone Human Insulins (NPH, Regular)

Adapted from: Diabetes Care 2023 (Jan 1); Volume 46
Davies MJ. Diabetes Care 2018; 41:2669-2701

Thank You

MONDAY

The Utilization of Assisted Reproductive Technologies – It is not just for Fertility Treatment

Margareta D. Pisarska, MD

Director, Division of Reproductive Endocrinology and Infertility

Director, Center for Reproductive Medicine

Professor, Cedars-Sinai Medical Center

Disclosures

- Ferring
- Natera

Objectives

- Utilization of ART in the US
- Changes in trends for ART
- Outcomes for fertility preservation
- Patient attitudes toward banking
- A unique population – the physician

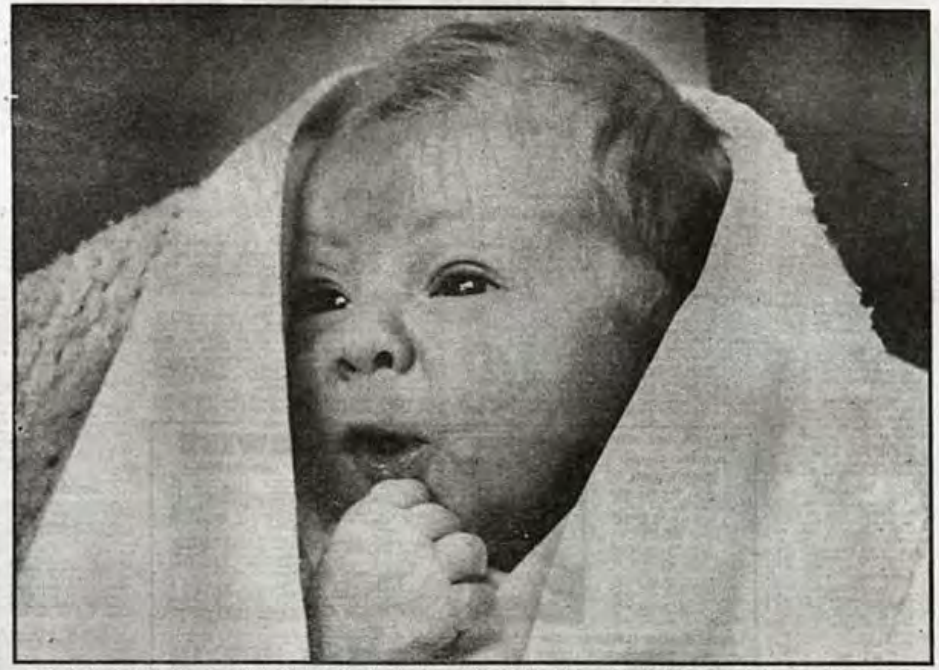
Daily Mail

THURSDAY, JULY 27, 1978 8p

WORLD EXCLUSIVE

And here she is...

THE LOVELY LOUISE



LOUISE BROWN, bright-eyed at 18 hours old: The test tube baby in hospital yesterday

Daily Mail World Exclusive Picture by Bill Cross © World Copyright Associated Newspapers Group Ltd., 1978. *Full story and more pictures inside*

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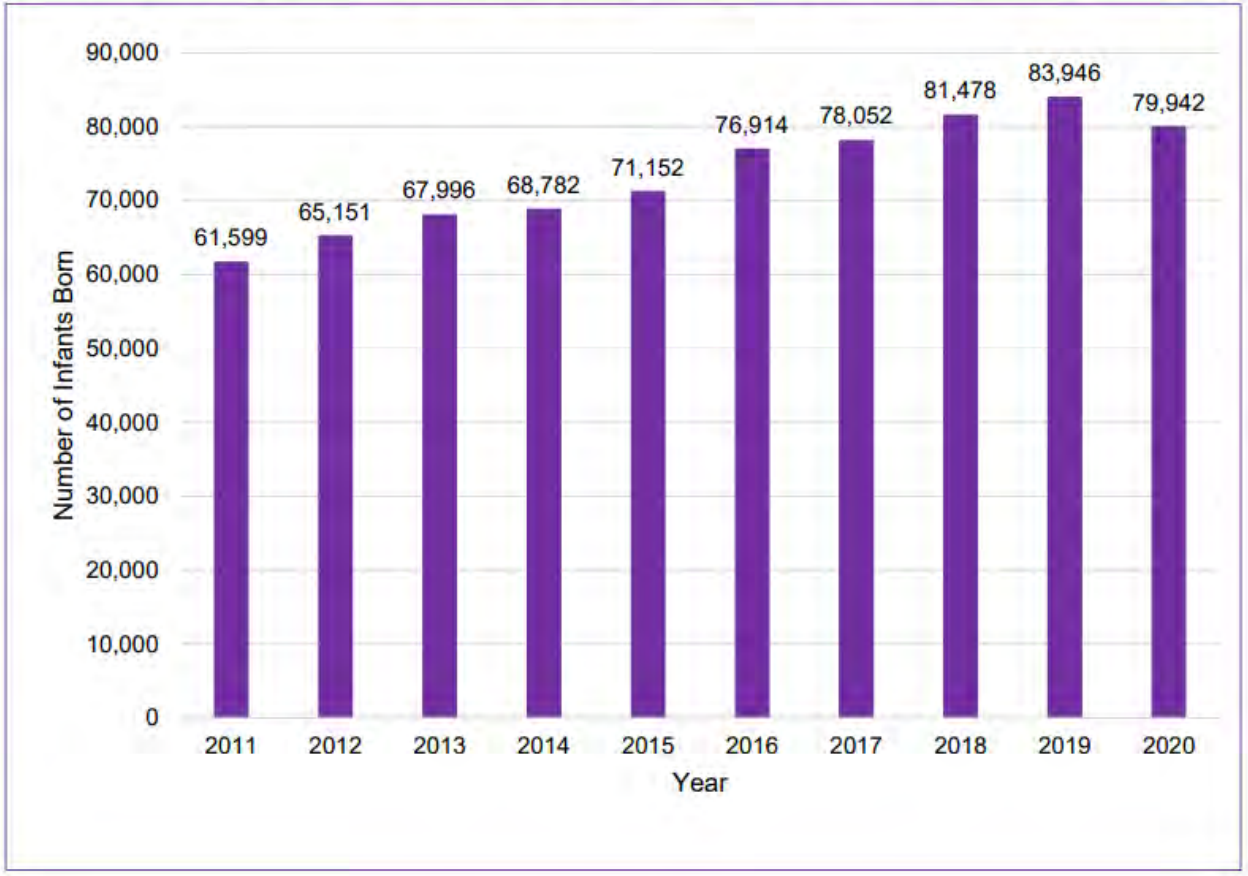
Infertility

Number of Infants Born Who Were Conceived Through ART, United States, 2011–2020



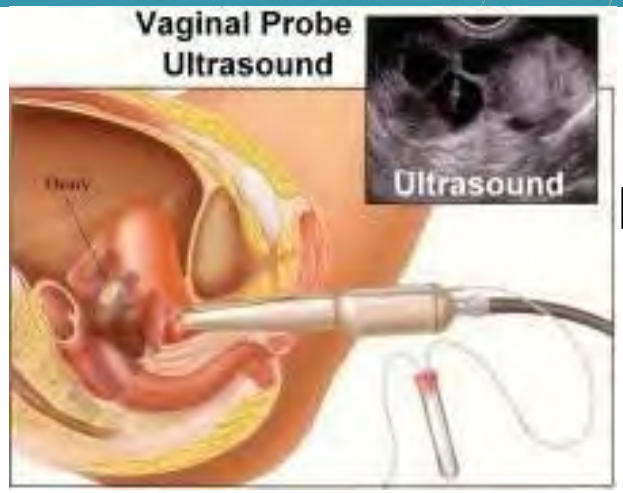
1.9% live births in US

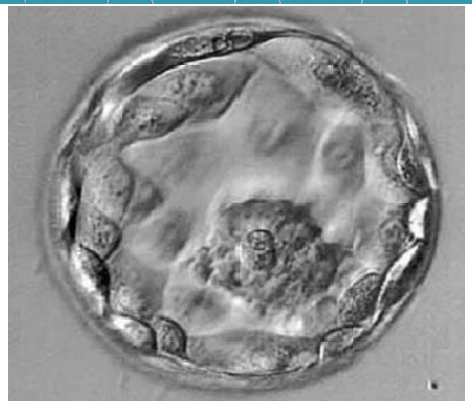
8 million babies born worldwide

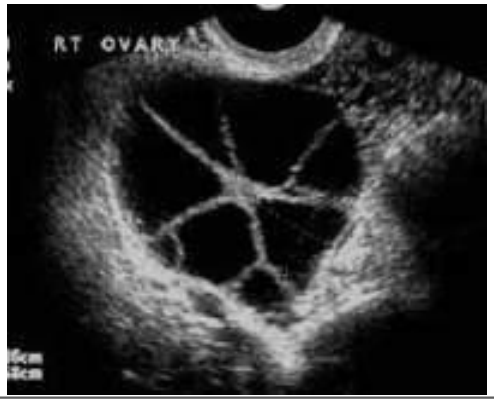
Cedars Sinai

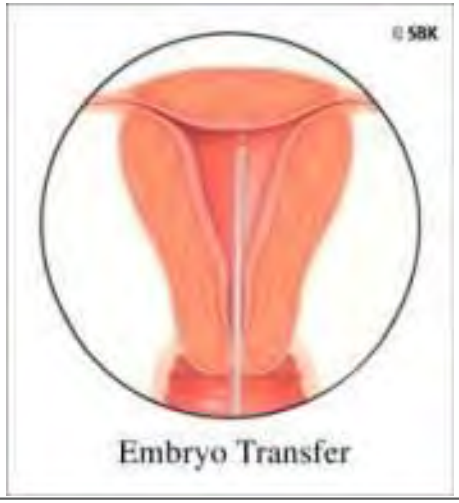
Pisarska, et al. *J Clin Endocrinol Metab,* 2018
National Health Statistics Reports 2018
CDC, National Center for Health Statistics 2017
Centers for Disease Control and Prevention. 2020 Assisted Reproductive Technology Fertility Clinic and National Summary Report. US Dept of Health and Human Services; 2022.

Assisted Reproductive Technologies in vitro fertilization

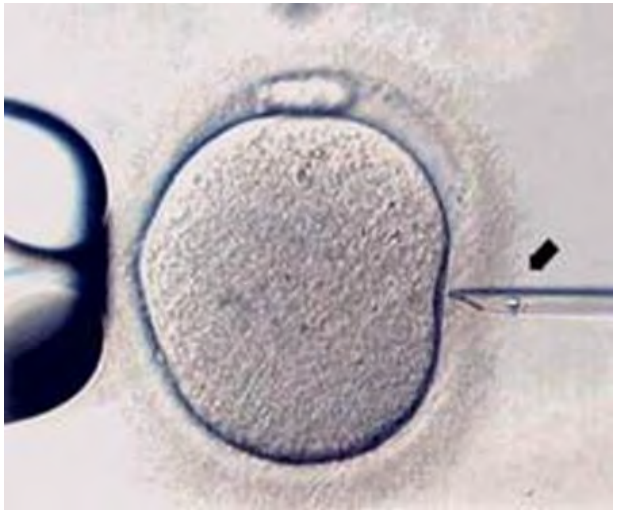


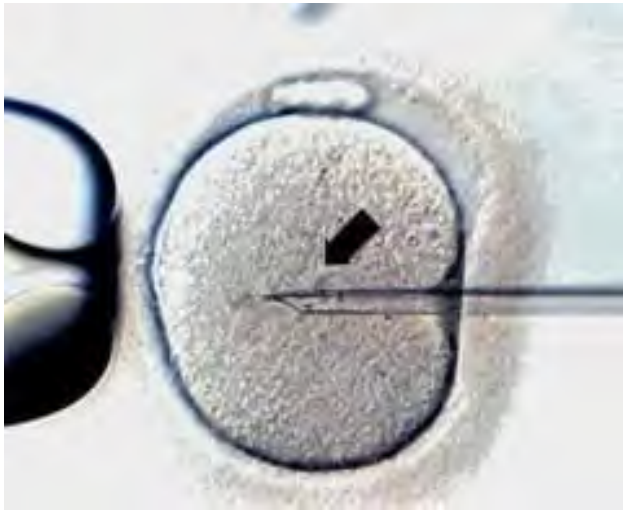


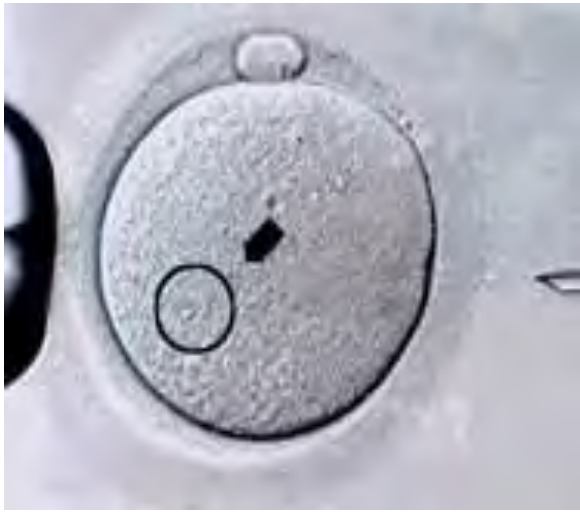




Intracytoplasmic Sperm Injection

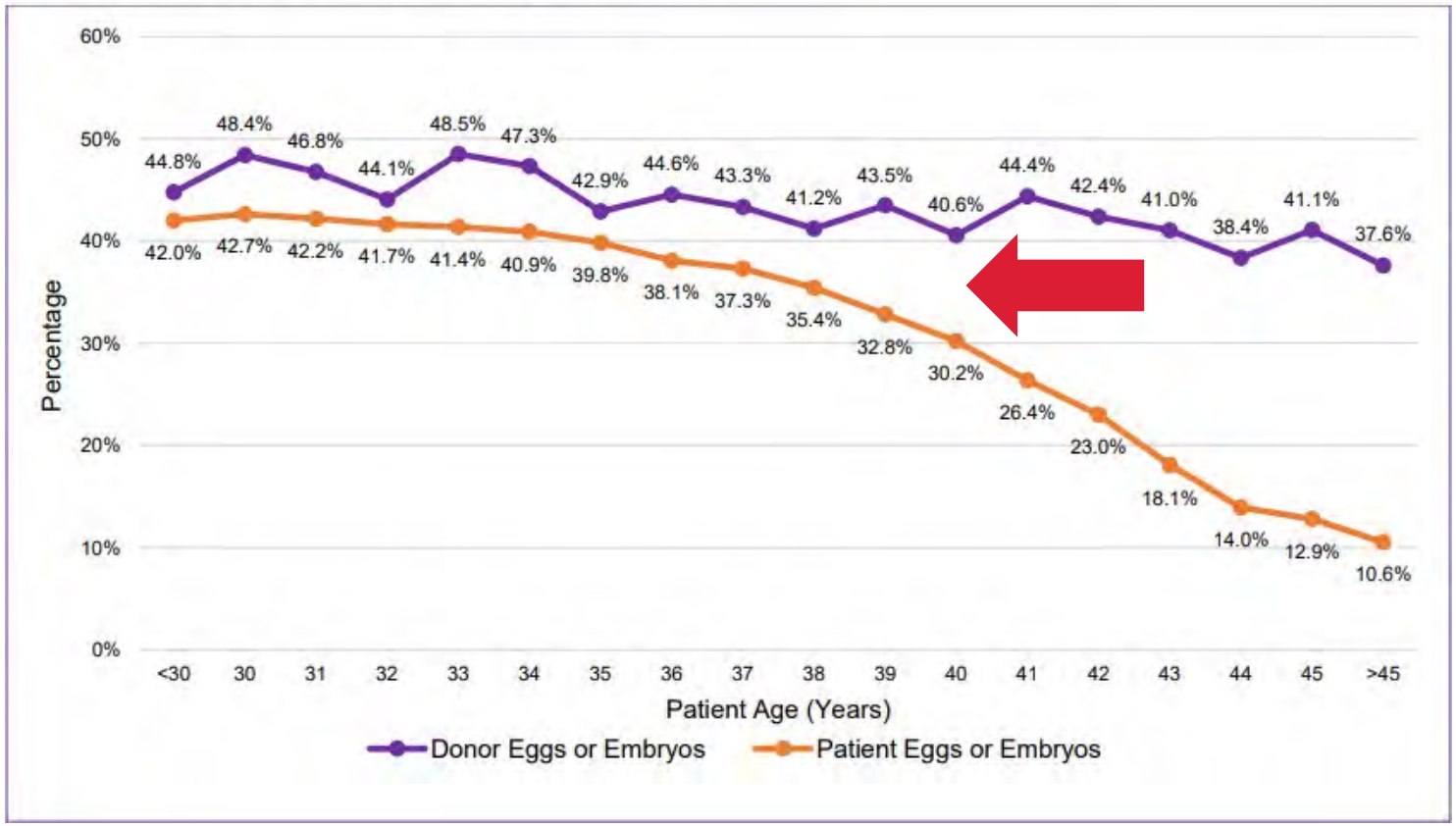






Success rates

Percentage of Embryo Transfers That Resulted in Live-Birth Delivery, by Patient Age and Egg or Embryo Source, United States, 2020



New Beginnings

ASRM PAGES

Mature oocyte cryopreservation: a guideline

The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

Society for Reproductive Medicine and Society for Assisted Reproductive Technology, Birmingham, Alabama

As of October 2012, the ASRM states "evidence indicates that oocyte vitrification and warming should no longer be considered experimental."

Medical Indications for Oocyte Cryopreservation

- **Postmenarchal women facing gonadotoxic therapies**
- Cancer patients (chemotherapy, pelvic radiation)
- Patients undergoing oophorectomies

- **Genetic conditions predisposing to primary ovarian insufficiency**
- Fragile X premutation
- Mosaic monosomy X

Elective/Social Egg Freezing – Social Media (2014)

"Perk Up: Facebook and Apple Now Pay for Women to Freeze Eggs"

"Cold Comfort: Tech Jobs and Egg Freezing"

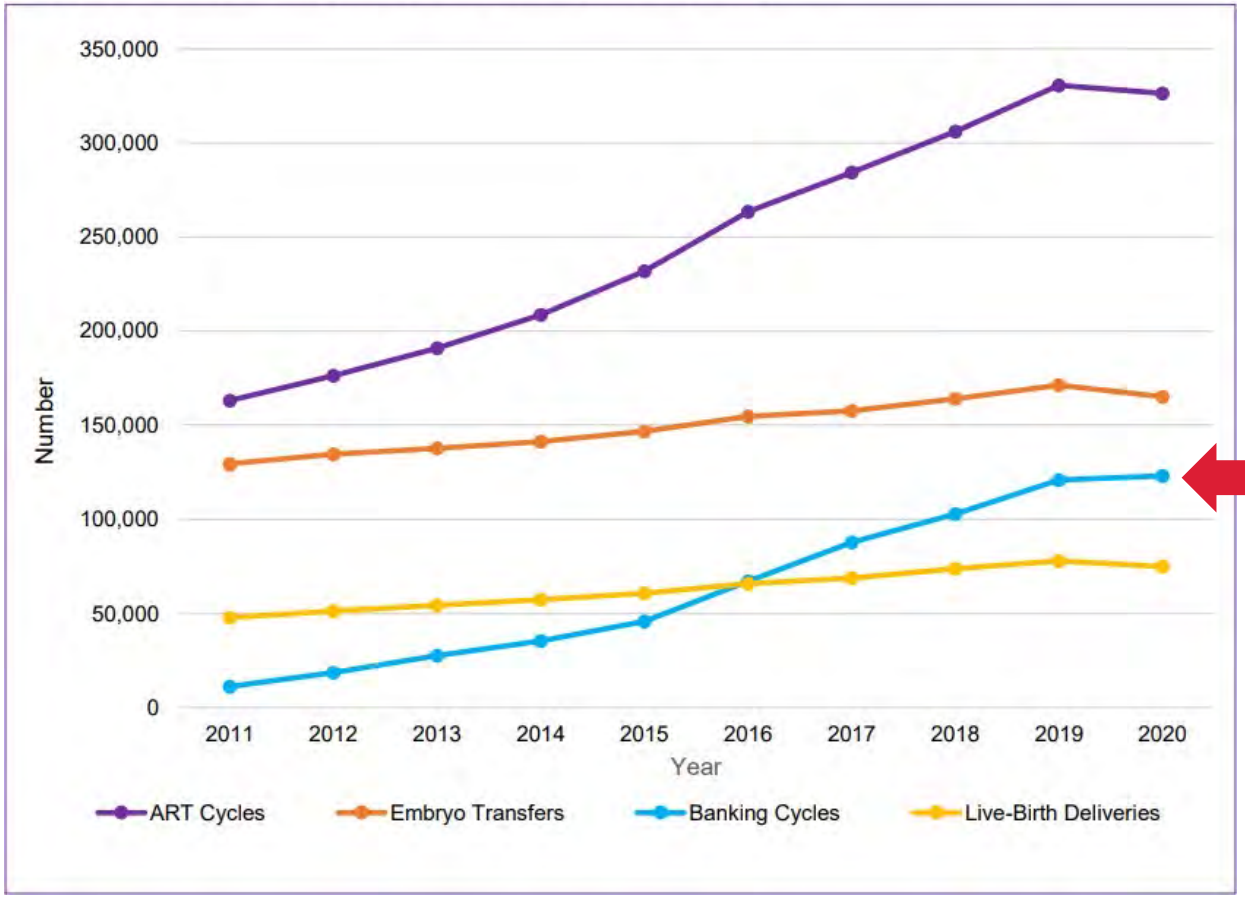
"Career women are having 'egg-freezing' parties"

"5 Celebrities Who Froze Their Eggs"

Perk Up: Facebook and Apple Now Pay for Women to Freeze Eggs (nbcnews.com)

Utilization of ART - Banking

Number of ART Cycles, Embryo Transfer Cycles, and Banking Cycles That Were Performed and Resulted in Live-Birth Deliveries, United States, 2011–2020



880% increase in oocyte cryopreservation cycles 2010-2016

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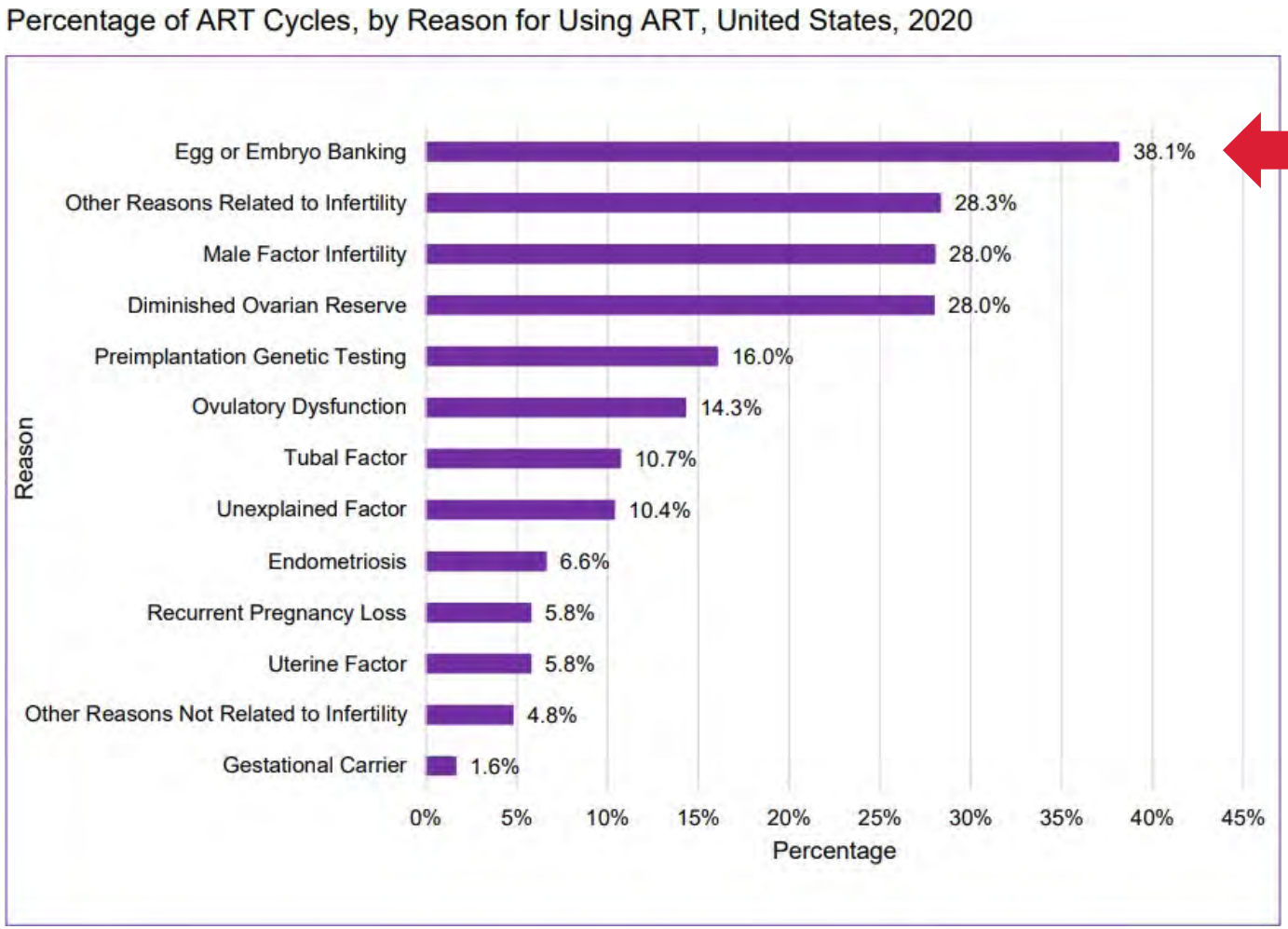
Johnston et al, Hum Reprod 2021, 36(3):624-635
The 2020 Assisted Reproductive Technology Fertility Clinic and National Summary Report, CDC

Percentage of ART Cycles, by Reason for Using ART



ART - Now

"All the years and years and years of speculation... It was really hard. I was going through IVF, drinking Chinese teas, you name it. I was throwing everything at it. ***I would've given anything if someone had said to me, 'Freeze your eggs. Do yourself a favor.'*** You just don't think it. So here I am today. The ship has sailed."

December 2022

NEW PATIENT FERTILITY CONSULTATION TRENDS PRE- AND POST-COVID-19 PANDEMIC

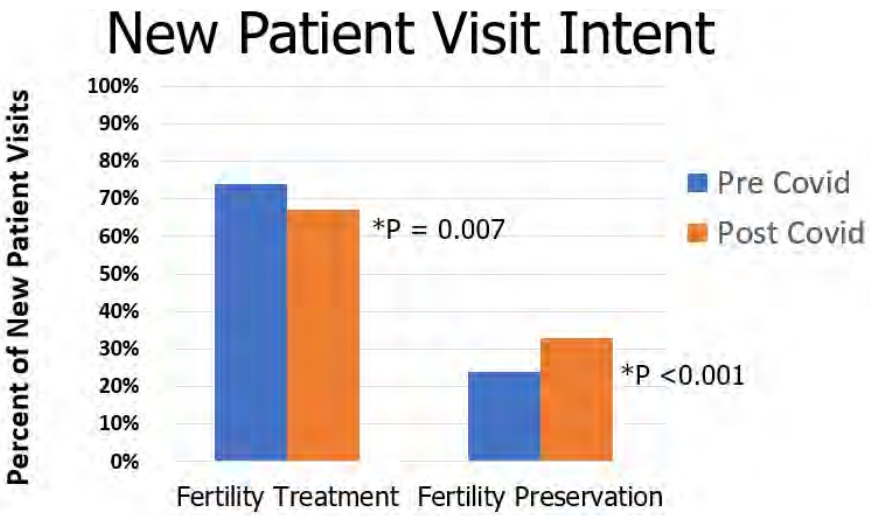


Figure 1. New patient visit intent pre vs post-Covid. There was a significant decrease in FT visits post-Covid (74% vs 67%, P=0.007), and a corresponding significant increase in FP visits post-Covid (24% vs 33%, P<0.001).

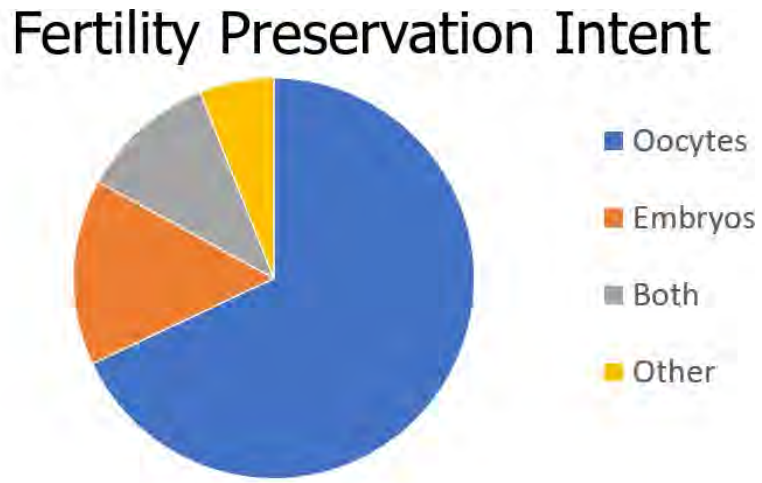


Figure 2. In the overall FP cohort, 68% intended to freeze oocytes, 15% embryos, 11% both, and 6% were undecided.

Wilson BE, et al. New Patient fertility consultation trends pre and post COVID-19 pandemic. ASRM 2023 Scientific and Expo.

NEW PATIENT FERTILITY CONSULTATION TRENDS PRE- AND POST-COVID-19 PANDEMIC

Demographics of Fertility Preservation Cohort	Pre-Covid	Post-Covid	P value
AMH (ng/mL ± SD)	2.2±2.3	2.7±2.5	0.03*
Insurance coverage (% of all new patients)	0.62%	30.40%	<0.001*
Proceeded to treatment (% of all new patients)	37%	45%	0.086

Table 1. Demographics of fertility preservation cohort. *P<0.05 is statistically significant.

In age-adjusted analyses, the odds of proceeding with fertility preservation treatment was not associated with fertility preservation insurance coverage (OR 1.09, 95% CI 0.82-1.46).

Success Rates

Doyle et al, Fertility & Sterility 2016

- 2009-2015
- 1171 oocyte cryopreservation cycles for 875 women
- 117 (10%) returned to use their oocytes

	Vitrified Oocytes	Control Group	P-value
Age at OC	34.9	35.5	NS
# oocytes used	8.0	10.1	0.0002
Fertilization rate	70%	72%	NS
Implantation rate	43%	35%	0.046
Clinical pregnancy rate	57%	44%	0.011
Live birth rate	39%	35%	NS

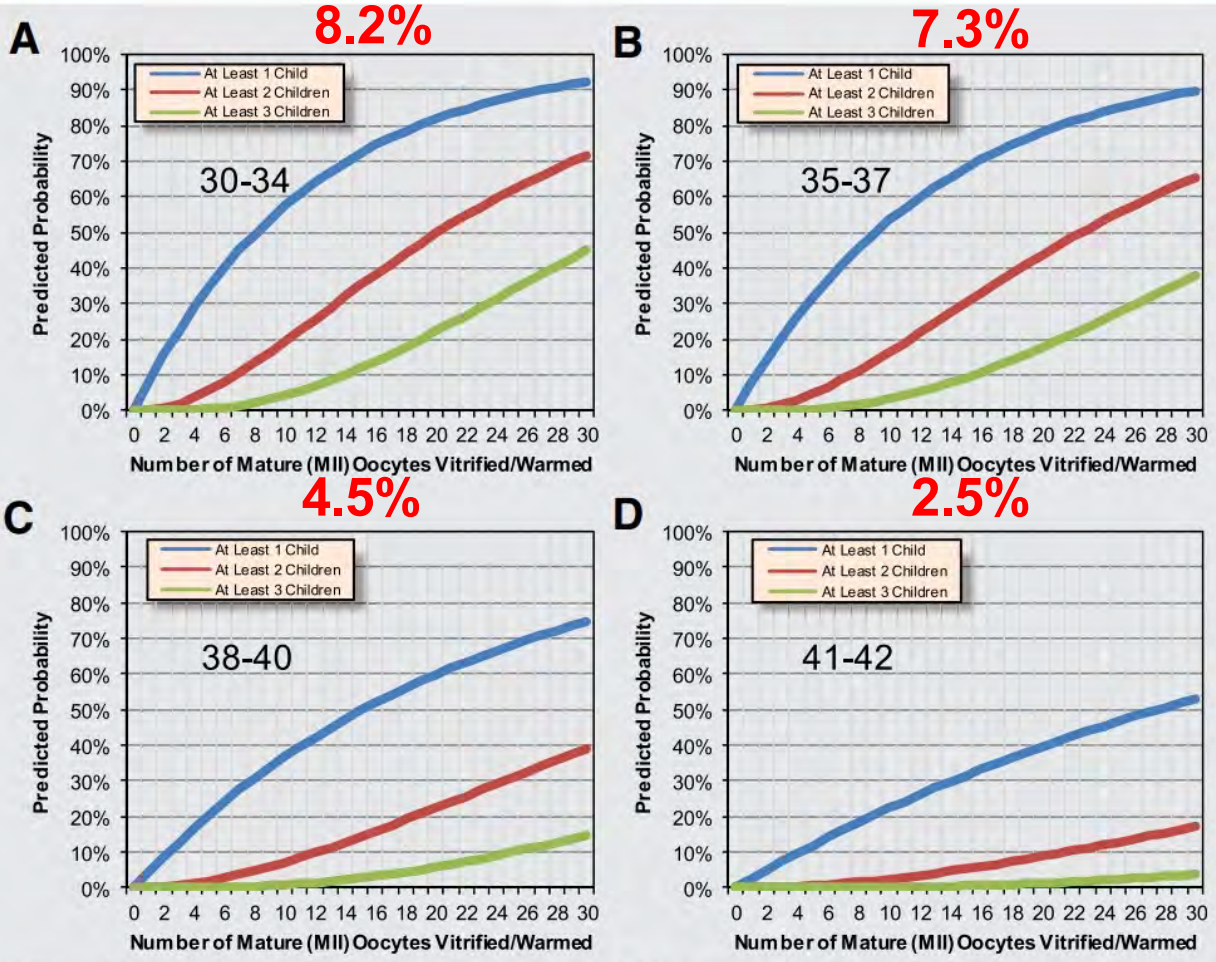
Efficiency Per Oocyte

- **Vitrified-warmed oocytes to live born child efficiency = 6.4%**
- Ranges between 5.2% to 7.4% depending on age at the time of planned OC
- 55 live born-children
  - 5 children for women 41-42yo at the time of planned OC

Doyle et al Fert Steril 2016; 105:459-66

Predicted Probabilites

FIGURE 1



Predicted probabilities of having at least one, two, and three live-born children according to the number of mature oocytes cryopreserved for elective fertility preservation, according to age at oocyte retrieval and the associated oocyte to live-born child efficiency estimates: (**A**) 30–34 years, 8.2% efficiency; (**B**) 35–37 years, 7.3% efficiency; (**C**) 38–40 years, 4.5% efficiency; (**D**) 41–42 years, 2.5% efficiency.

Doyle. Autologous vitrified oocyte IVF outcomes. Fertil Steril 2016.

Cedars Sinai

Doyle et al Fert Steril 2016; 105:459-66

Leung et al Repro Biomed Online 2021

- 2006-2020
- 921 women underwent planned oocyte cryopreservation cycles
- 68 (7.4%) returned to use their oocytes

	<38yo	≥38yo	P-value
Age at OC	36.6	39.6	0.02
Time interval between OC and thaw, years	4.1	3.2	NS
# oocytes used	14.5	14.2	NS
Clinical pregnancy rate	54.5%	39.3%	NS
Live birth rate	48.5%	28.6%	NS
Cumulative live birth rate per pt	38.9%	25.0%	NS

Cedars Sinai

Leung et al RBMO 2021; 43(4): 671-679

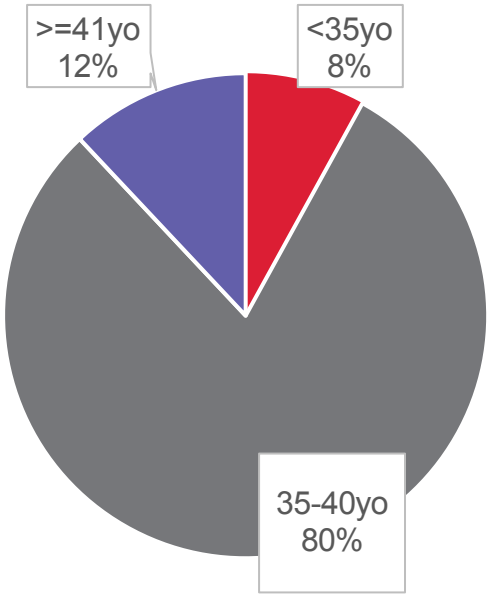
- Only 7.4% of patients (68/921) return to use their oocytes
- 32% (22/68) achieved a live birth
- 22% (15/68) did not have an embryo for transfer
- No patient ≥40yo at the time of planned oocyte cryopreservation was successful

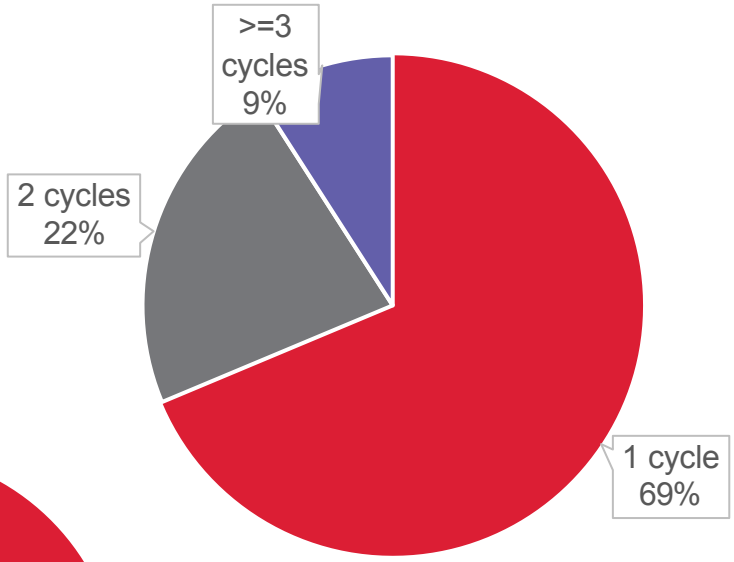
Leung et al RBMO 2021; 43(4): 671-679

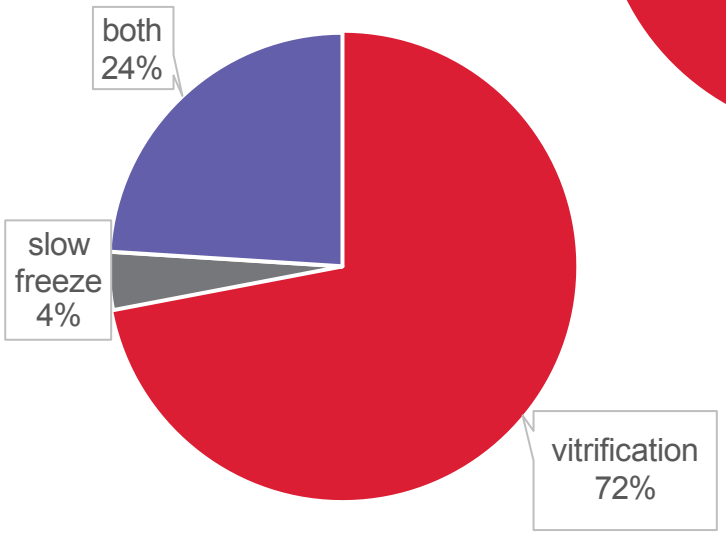
Cascante et al Fertility & Sterility 2022

- **2004-2020**
- **543 patients underwent 800 oocyte cryopreservation cycles, 605 thaws, 436 transfers**
- **332 pts (61%) had ≥1 embryo transfer**
- **166 pts (31%) had no transfer**
  - No oocytes survived
  - No fertilization
  - Embryo arrest
  - No euploid embryos

Demographics







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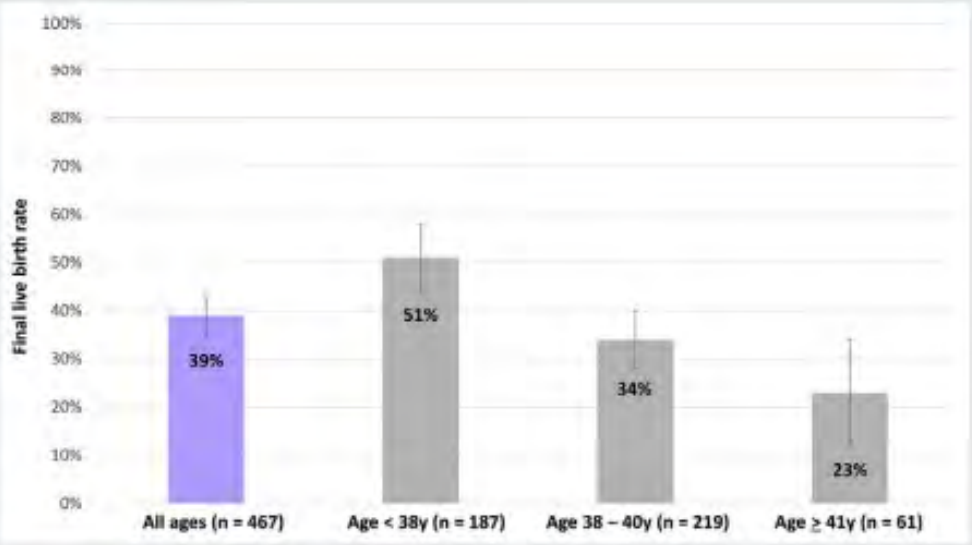
Cascante et al Fert Steril 2022; 118:158-66

Median age	38.3 (36.8-39.7) Oldest 44y
Median time from freeze to thaw, years	4.2 (2.9-5.6)
Median # oocytes	12 (8-18)
Oocyte survival	79%
Final live birth rate	39%

Cascante et al Fert Steril 2022; 118:158-66

FIGURE 2



Final live birth rate per patient by age at the first cryopreservation; 95% confidence intervals are shown. Live births include 1 pregnancy with an unknown outcome (ongoing at last contact). The median number of oocyte cryopreservation cycles for each group was 1. n = number of patients.

Cascante. Fifteen years of oocyte thaw outcomes. Fertil Steril 2022.

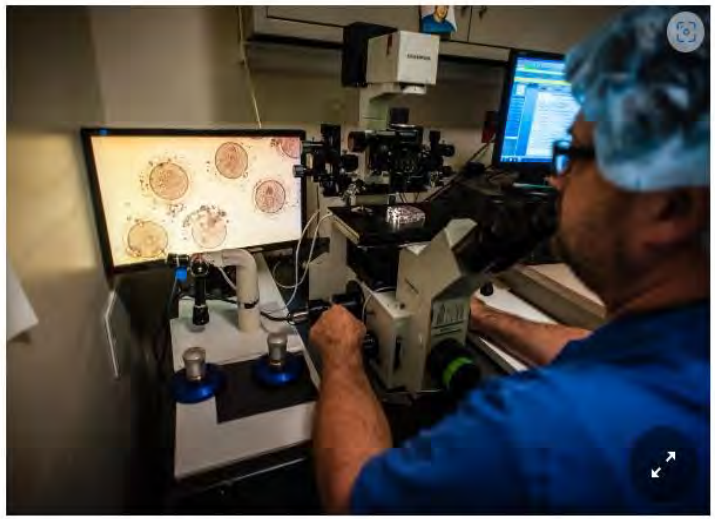
- **Pts <38yo who thawed >20 eggs had a 70% FLBR**
- **211 children from thawed oocytes**
- **162 with 1 live birth, 24 with ≥2 live births**

The New York Times

'Sobering' Study Shows Challenges of Egg Freezing

Data from a fertility center showed many women did not get pregnant because of the age at which they froze their eggs and because they did not preserve enough of them.

Give this article 161



Eggs under a microscope at a fertility clinic in Maryland. "I always tell patients, 'There's not a baby in the freezer. There's a chance to get pregnant,' " said one fertility expert. Andre Chung for The Washington Post, via Getty Images

1/3 of patients who return to use frozen eggs are successful

Cedars Sinai

'Sobering' Study Shows Challenges of Egg Freezing - The New York Times (nytimes.com)

How do we counsel women on elective fertility preservation?

- **"Live birth rates are improved when oocyte cryopreservation is performed in younger compared to older women" (ASRM 2021 Guideline)**

- Optimal age is ≤35 yo
- Newest data suggest 32 – 35 yo (Bakkensen et al, Fertility Sterility, 2022)

- **Fertility preservation is not a guarantee**

32 is the New 35

TABLE 2

Probability of live birth and cost-effectiveness by delayed reproduction treatment strategy

Treatment strategy	Probability of ≥ 1 LB	Probability of 2 LB	Average individual cost	Maximum individual cost	Cost per percentage point increase in success, 1 LB	Cost per percentage point increase in success, 2 LB
Desires 1 child						
No OC + IVF/PGT	50%	0%	$62,308	$84,536	*Ref*	
OC	73%	0%	$30,333	$37,992	−$1,376	
Desires 2 children						
No OC + IVF/PGT without embryo banking	76%	19%	$79,057	$145,018	*Ref*	*Ref*
No OC + IVF/PGT with embryo banking	78%	48%	$79,728	$97,802	$278	$23
OC 1 cycle + IVF/PGT	93%	61%	$76,100	$122,528	−$176	−$71
OC 2 cycles	94%	77%	$52,479	$63,092	−$1,441	−$458

See Figure 1 and methods for a detailed description of each treatment strategy. Negative cost per percentage point increase in live birth reflects a net cost savings. OC, oocyte cryopreservation; IVF/PGT, in vitro fertilization with preimplantation genetic testing for aneuploidy; LB, live birth; *Ref*, referent strategy.

Bakkensen. Cost-effectiveness of planned OC. Fertil Steril 2022.

Patient experiences following elective oocyte cryopreservation

- **Stoop et al, Hum Reproduction, 2015**
- 95% would choose to do planned OC again
- 96% would recommend planned OC to others
- 76% wish that froze eggs at a younger age

- **Greenwood et al, Fertility Sterility, 2018**
- 88% increased control over reproductive planning
- 89% happy they froze eggs even if they never use them

- **Seyhan et al, Reproductive Sciences, 2021**
- 72% felt more secure in reproductive potential
- 98.8% would recommend to a friend

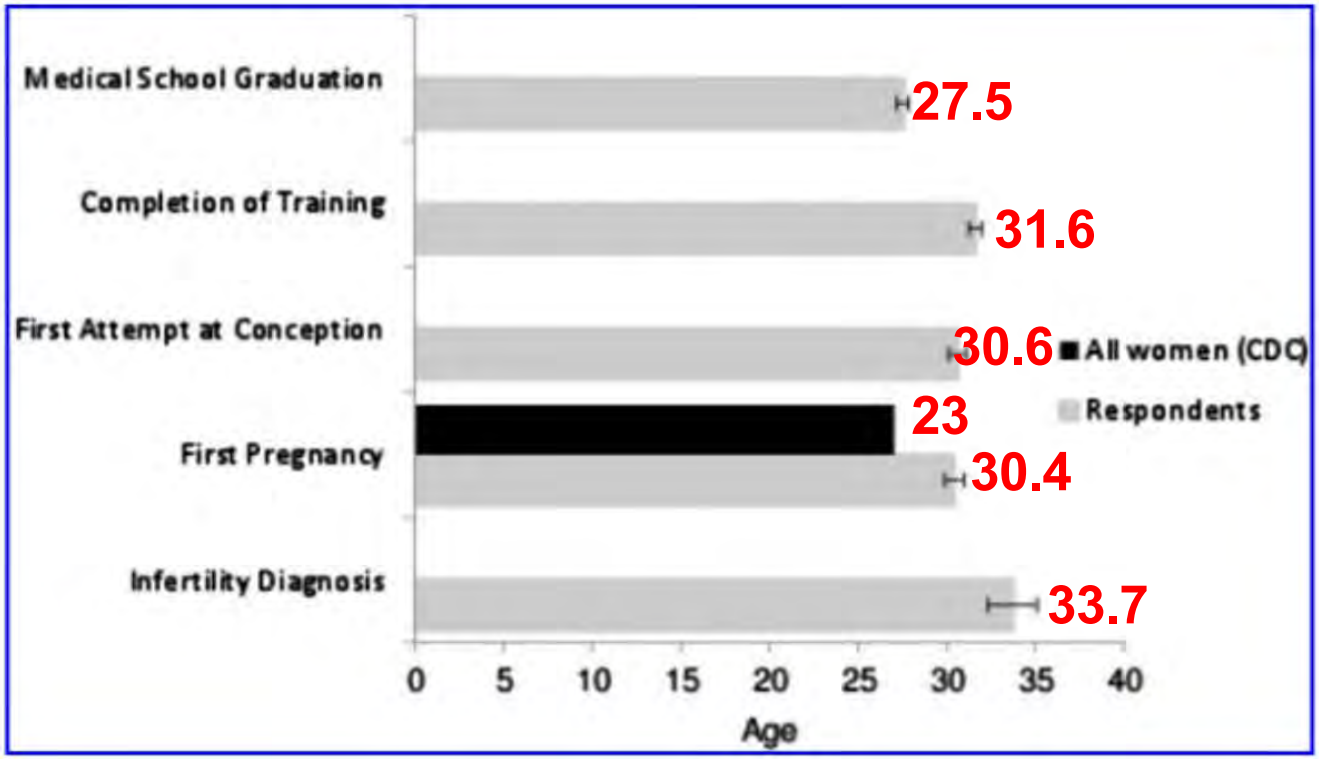
Fertility considerations in female physicians

Stentz et al, Journal of Women's Health 2016

- 2012-2013 random survey of 600 female physicians from AMA
- 55% response rate (n=327)
  - 54% of respondents from OBGYN/Pediatrics/Family Medicine
  - 32% of respondents from Medicine/Subspecialties
  - 9% of respondents from hospital based specialists
  - 4% of respondents from Surgery/Subspecialties

- **1 in 4 were diagnosed with infertility – the mean age at diagnosis was 33.7 years**

Fertility considerations in female physicians



Cedars Sinai

Stentz et al, Journal of Women's Health 2016

Fertility considerations in female physicians

Perspective FREE PREVIEW

The NEW ENGLAND JOURNAL of MEDICINE

One in Four — The Importance of Comprehensive Fertility Benefits for the Medical Workforce

Erica C. Kaye, M.D., M.P.H.

The New York Times

A Medical Career, at a Cost: Infertility

Physicians are raising awareness of the reproductive toll that work stress, long hours, sleep deprivation and years of training can exact.

Fertility considerations in female physicians

JAMA Netw Open. 2022 Oct; 5(10): e2237558.
Published online 2022 Oct 31. doi: 10.1001/jamanetworkopen.2022.37558:
10.1001/jamanetworkopen.2022.37558
PMCID: PMC9623435
PMID: 36315148

Family Planning, Fertility, and Career Decisions Among Female Oncologists

31% reported infertility, n=1004

30.4% reported infertility, n=398

Featured Article

Fertility & childbearing outcomes of female plastic surgeons: How far have we come in 25 years?

Kshipra Hemal [a], Juliana Remark [a], Wendy Chen [b], Debra A. Bourne [c,*]

54% reported infertility, n=351

Cedars Sinai

Fertility considerations in female physicians

Smith et al, JAMA Network, 2022

Table 1. Themes and Subthemes Regarding Fertility Knowledge Among Women in Medicine That Arose From Qualitative Interviews With 16 Physicians

Theme	Subthemes	Exemplary quotations[a]
Fertility knowledge	Inadequate formal education	"The majority of what I learned about from a fertility standpoint was basic sort of how the reproductive system works. ... I do think that aging and fertility is something that we were told about, but infertility in women under 35 is something we didn't hear about." (1010)
		"I think it [age and infertility] was briefly touched upon in medical school during my OB/GYN rotation, but not much more than at age 35 your risk for Down syndrome goes up markedly. ... I wouldn't say that it was really emphasized at all. I don't think that I had any sort of opportunity to go to an REI [reproductive endocrinology] clinic or had any exposure to that in medical school." (1001)
		"I would add it to your residency orientation, because I think you're capturing people in their 20s for the most part. I think that's an ideal age, and I think that if people have it in the back of their mind, they are going to be more cognizant ..." (1006)
		"Medical school is when people are still considering different fields and telling us different fields may affect their fertility choices and options ... so, before you're in the time where you're really thinking about starting a family, to have the information ahead of time would be good." (1008)
	Improving medical education for medical trainees	"I would add it to your residency orientation, because I think you're capturing people in their 20s for the most part. I think that's an ideal age, and I think that if people have it in the back of their mind, they are going to be more cognizant ..." (1006)
		"Medical school is when people are still considering different fields and telling us different fields may affect their fertility choices and options ... so, before you're in the time where you're really thinking about starting a family, to have the information ahead of time would be good." (1008)

"I would add it to your residency orientation, because I think you're capturing people in their 20s for the most part. I think that's an ideal age, and I think that if people have it in the back of their mind, they are going to be more cognizant ..." (1006)

"Medical school is when people are still considering different fields and telling us different fields may affect their fertility choices and options ... so, before you're in the time where you're really thinking about starting a family, to have the information ahead of time would be good." (1008)

Fertility considerations in female physicians

Smith *et al. BMC Medical Education* (2023) 23:147
https://doi.org/10.1186/s12909-023-04075-w

BMC Medical Education

RESEARCH Open Access

Anxiety, attitudes, and education about fertility among medical students in the United States

D. Grace Smith[1*], Abigail Ross[2], Elena HogenEsch[3], Rachel Okine[4], Marissa L. Bonus[3], Eve C. Feinberg[5] and Lia A. Bernardi[5]

65% reported plans to delay childbearing (planned age of 31 +/- 2 years), n=351

Research Report

Childbearing Decisions in Residency: A Multicenter Survey of Female Residents

Shobha W. Stack, PhD, MD, Reshma Jagsi, MD, DPhil, J. Sybil Biermann, MD, Gina P. Lundberg, MD, Karen L. Law, MD, Caroline K. Milne, MD, Sigrid G. Williams, MD, MPH, Tracy C. Burton, MD, Cindy L. Larison, MA, and Jennifer A. Best, MD

61% reported they were delaying childbearing, n=1537

Cedars Sinai

Fertility considerations in female physicians

Research Report

Childbearing Decisions in Residency: A Multicenter Survey of Female Residents

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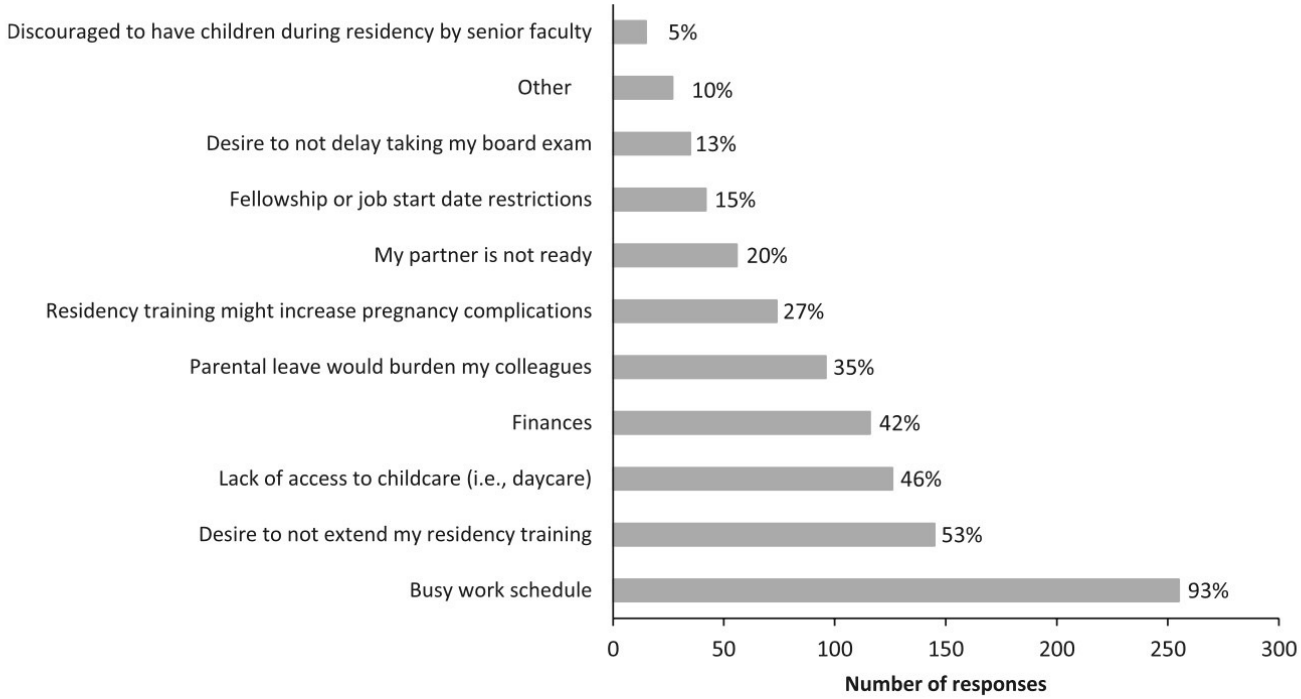

Figure 1 Self-reported reasons for delaying childbearing among 274 female residents participating in a multicenter survey of female residents, 2017. Responses are not mutually exclusive; respondents indicated up to 3 selections. The survey is available as Supplemental Digital Appendix 1 at http://links.lww.com/ACADMED/A984.

Conclusions

- **ART is not only for infertility**

- **The number of oocyte/embryo cryopreservation cycles is increasing exponentially on a national level**

- **We are young in every way, with the exception of our ovaries (i.e. we are limited by our ovarian reserve)**
  - Live birth rates are improved when oocyte cryopreservation is performed in younger compared to older women
  - Ideal time for oocyte cryopreservation is ≤32yo
  - Number of oocytes 20 (may need more than 1 cycle)
  - Not a guarantee (1/3 are successful)

Conclusions

- **>90% of women are happy they underwent planned oocyte cryopreservation**
  - Most women wish they did so at a younger age

- **Female physicians are a unique population –**
  - Delaying childbearing during medical training
  - 1 in 4 female physicians is diagnosed with infertility

- **Counseling regarding future family building should be addressed at all well women visits and in the medical school curriculum**

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- *CFRM Staff*

Our patients for participating in our studies to improve outcomes!

Cedars Sinai

Disclosures

Relevant Disclosures:

The Menopause Society Board of Directors

Consultant: Astellas

No conflicts of interest

References:

I will discuss clinical studies of off label use of pharmaceuticals for vasomotor symptoms.

This presentation references people born with ovaries. I may use the terms women, she, and her. These terms may not capture the diversity of all those experiencing menopause. We need more research to explore how diverse people experience menopause.

Can we talk?

Genitourinary Symptoms of Menopause in Cancer Survivors

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Vice Chair of Professional Development and Wellness
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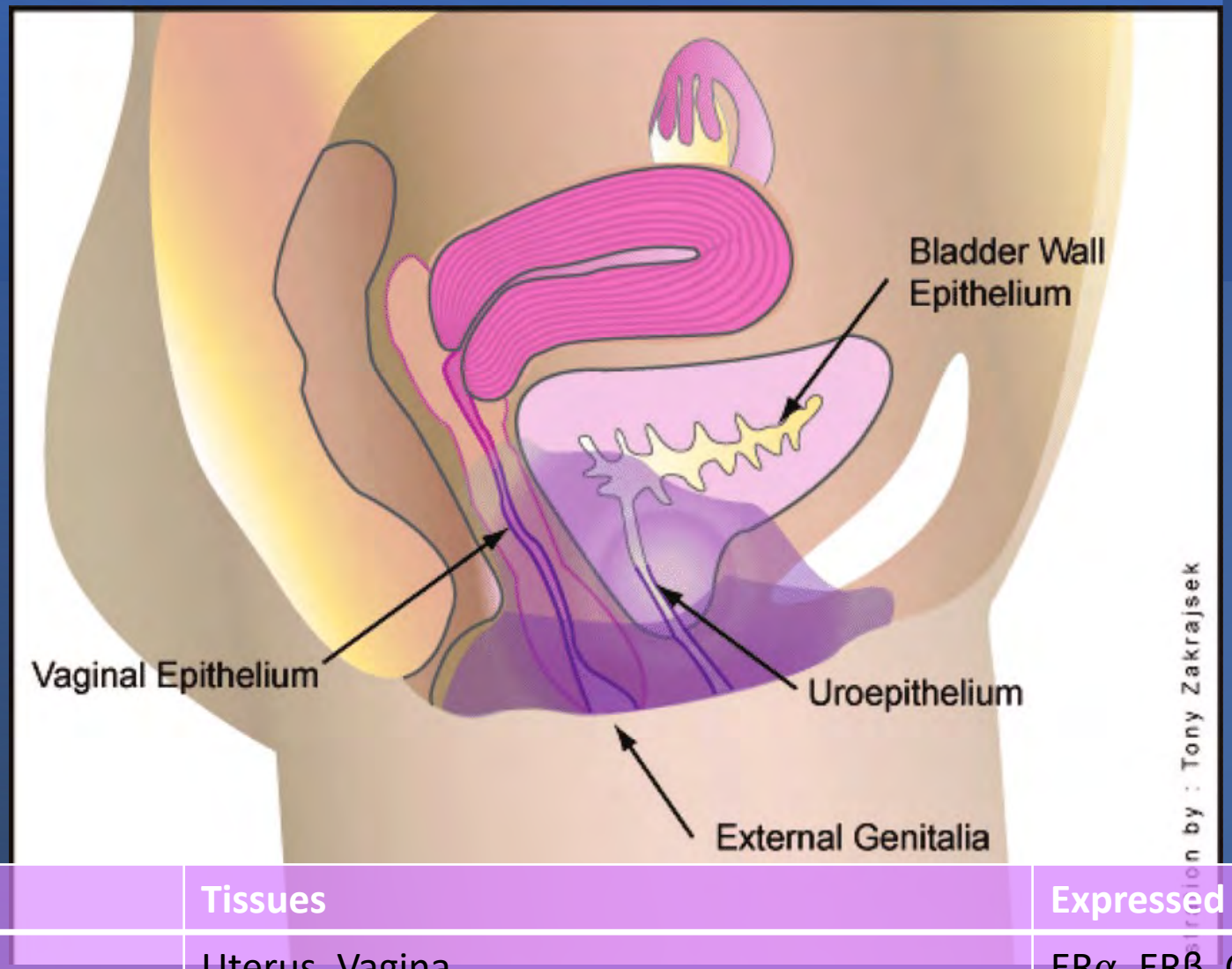
Washington University School of Medicine in St. Louis

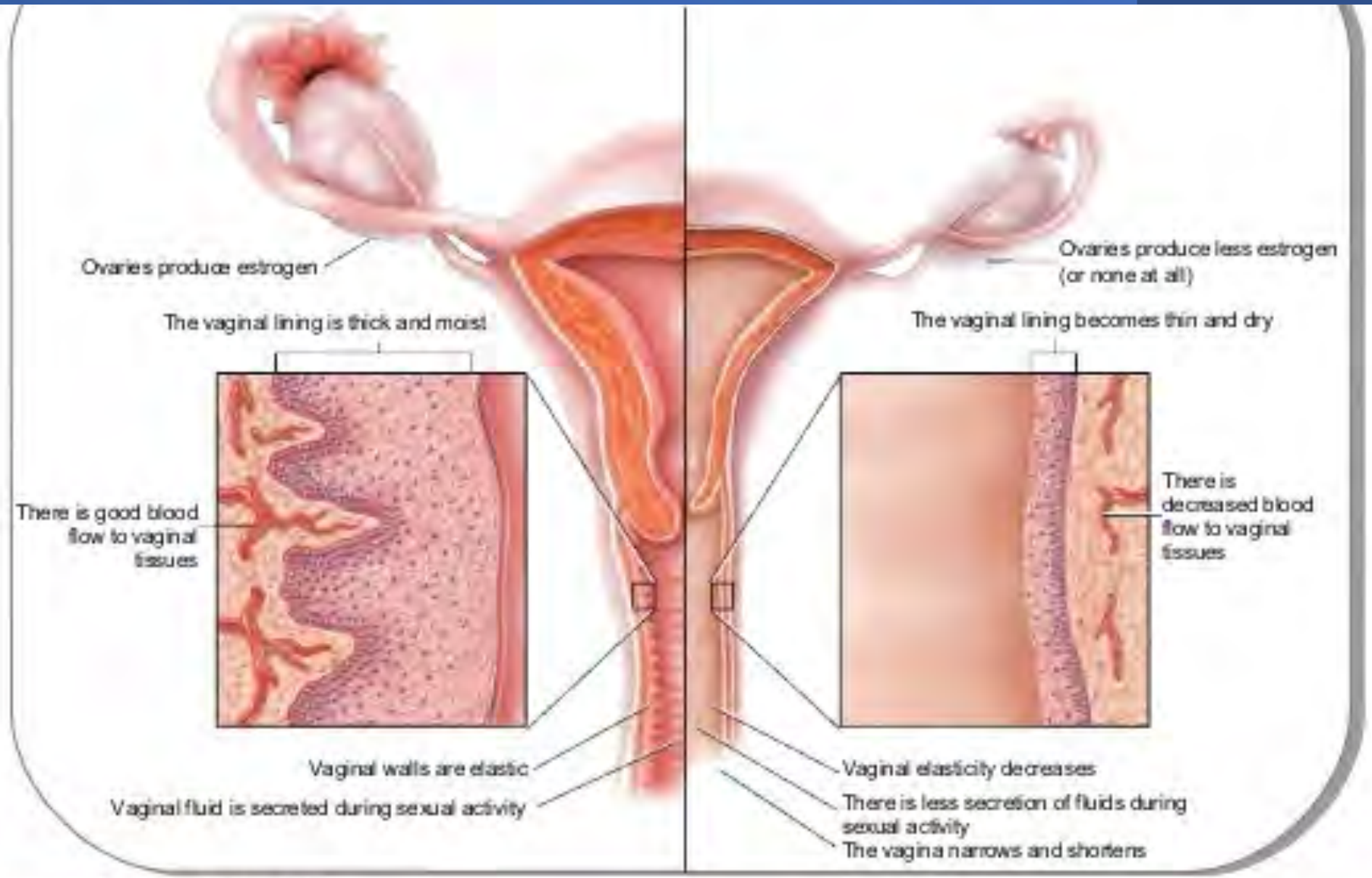
Objectives

- Discuss symptom presentation of the genitourinary syndrome of menopause in cancer survivors

- Review consensus recommendations for treating the genitourinary syndrome of menopause in cancer survivors



System	Tissues	Expressed Estrogen Receptors (ER)
Reproductive	Uterus, Vagina	ERα, ERβ, GPER
Urinary	Bladder, Urethra	ERβ
Gastrointestinal	Bowel, External Anal Sphincter	ERα, ERβ
Musculoskeletal	Pelvic Floor Muscles, Uterosacral Ligaments	ERα, ERβ



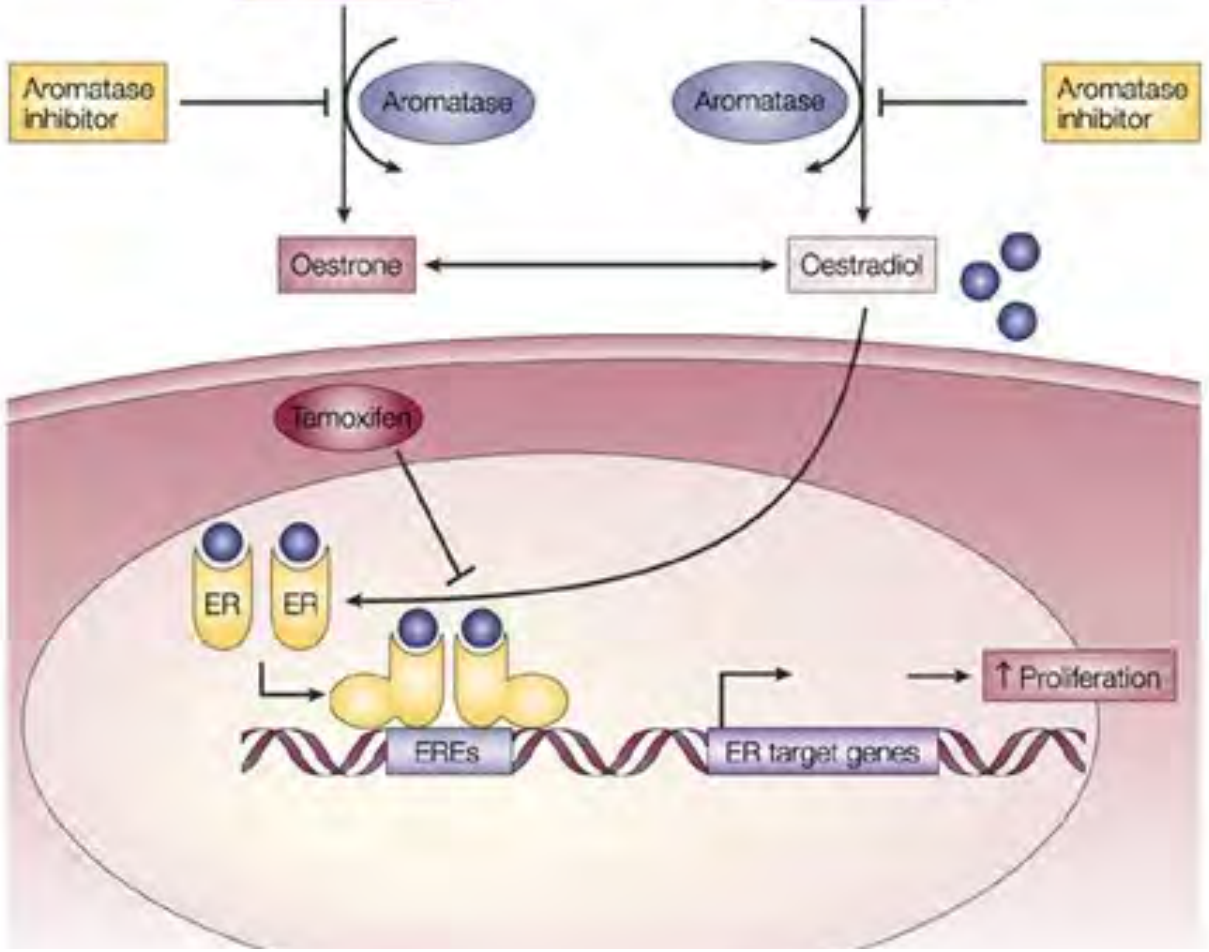
Johnston SL. *Geriatrics & Aging*. 2002;5(7):9-15.

Surgery: Oophorectomy, Vulvectomy, Hysterectomy

Chemotherapy: ovarian toxicity and dysfunction, neuropathy

Pelvic Radiation: direct tissue damage, radiation vaginitis, vaginal fibrosis, mucositis, shortening, stenosis

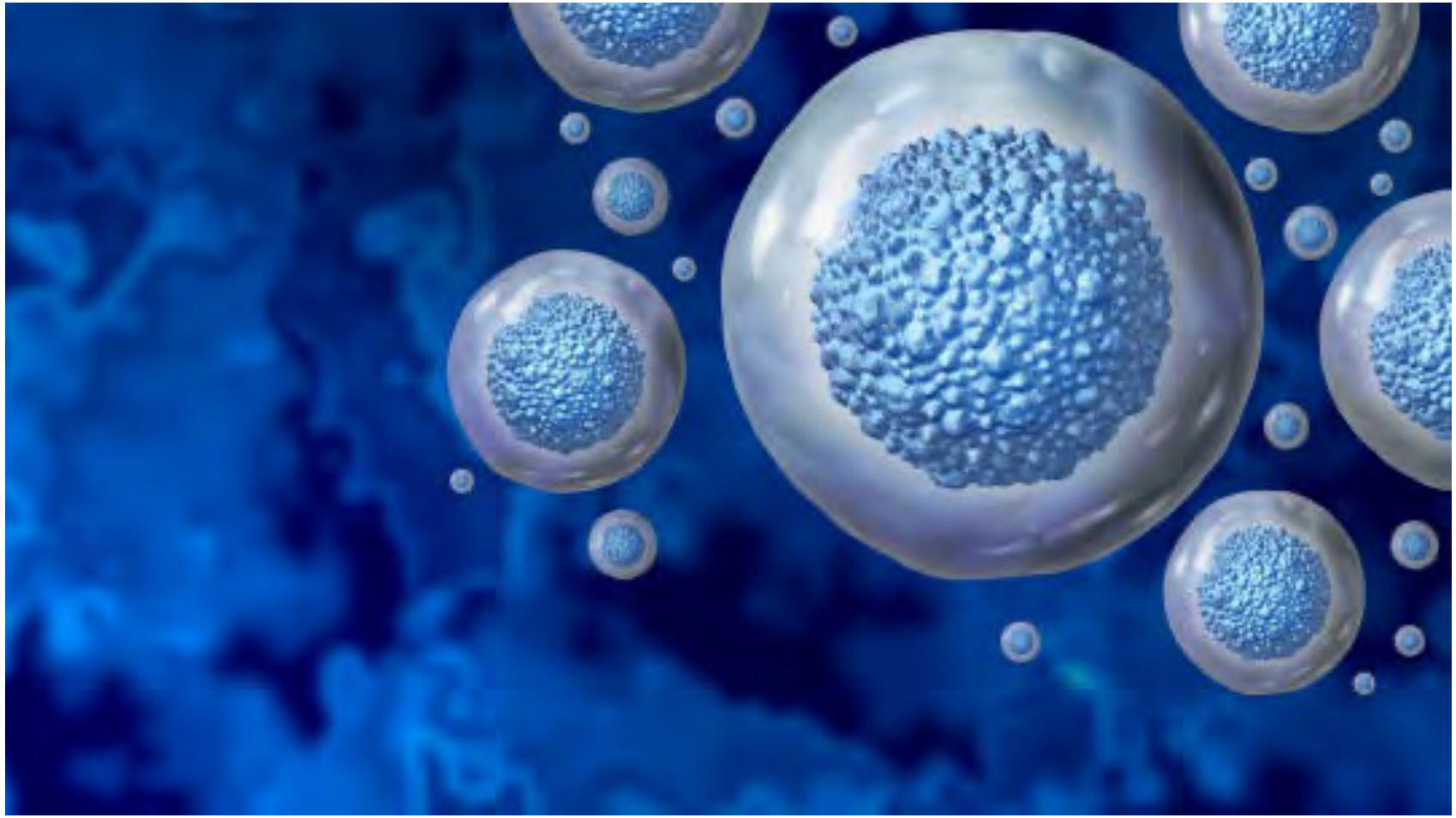
Tamoxifen: estrogenic effect, increased vaginal secretions



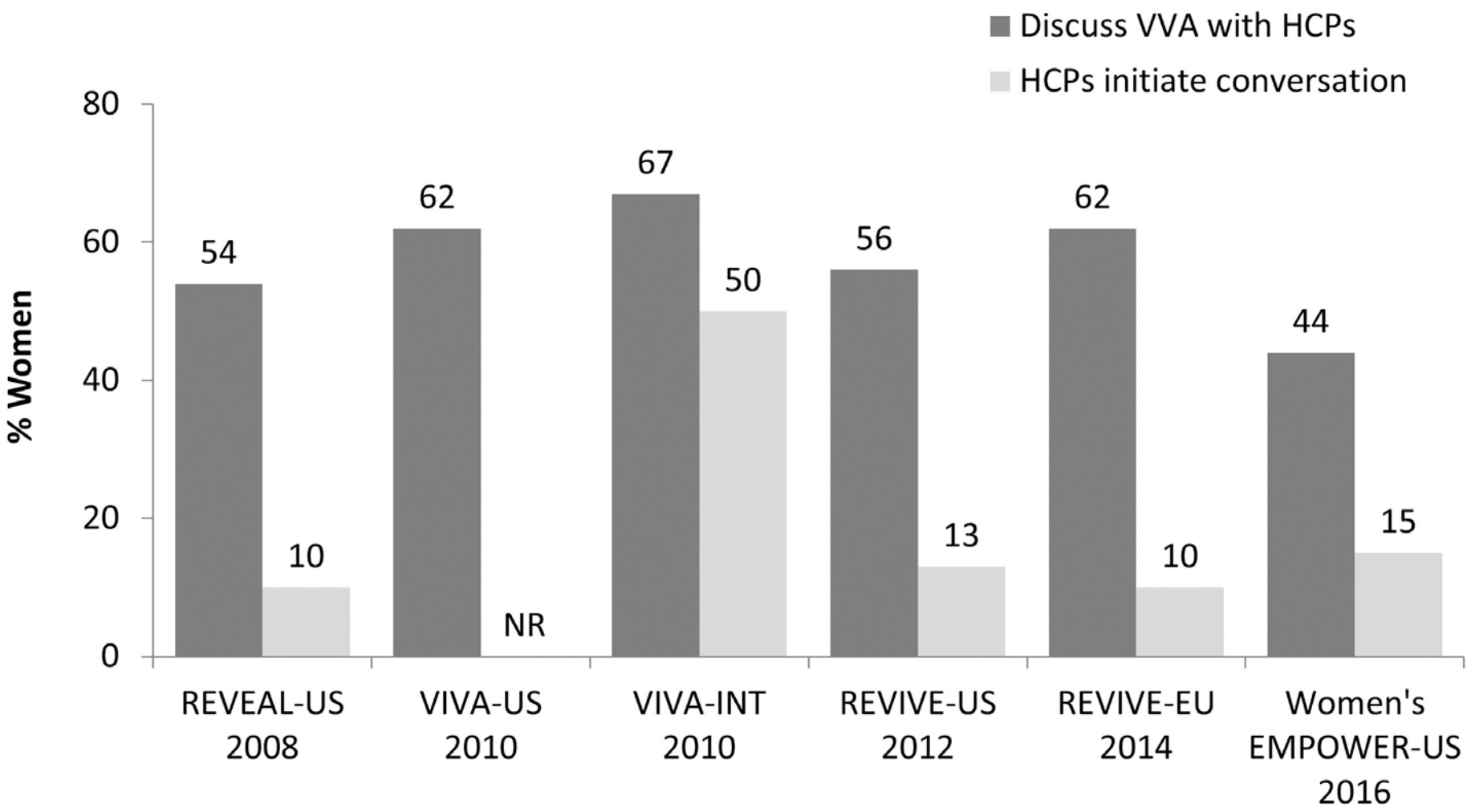
Aromatase Inhibitors :

marked vaginal dryness, vulvar thinning, sexual discomfort

Immunotherapy: inflammation, GSM pain exacerbation



Stem Cell Transplant: GVHD: vulvovaginal dryness, pain, dyspareunia

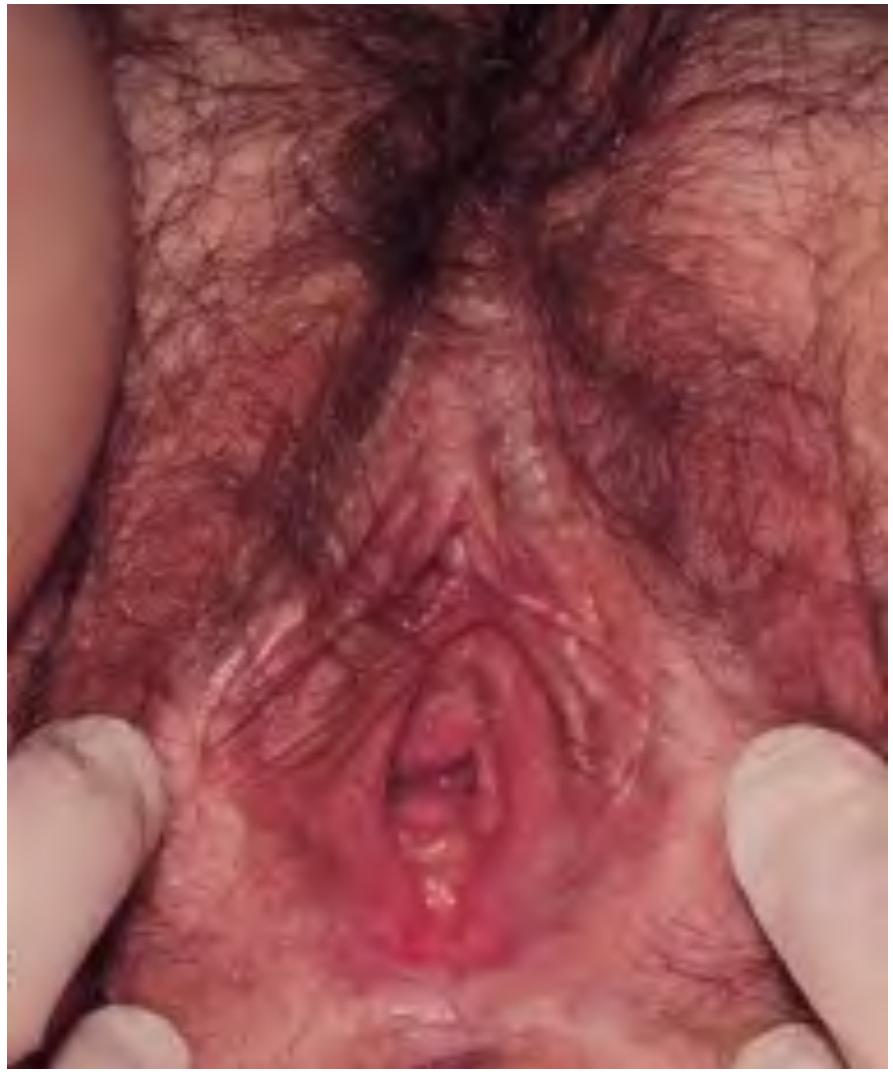


The Journal of Sexual Medicine 2017 14, 425-433DOI: (10.1016/j.jsxm.2017.01.011)


DO ASK
DO TELL

Symptoms

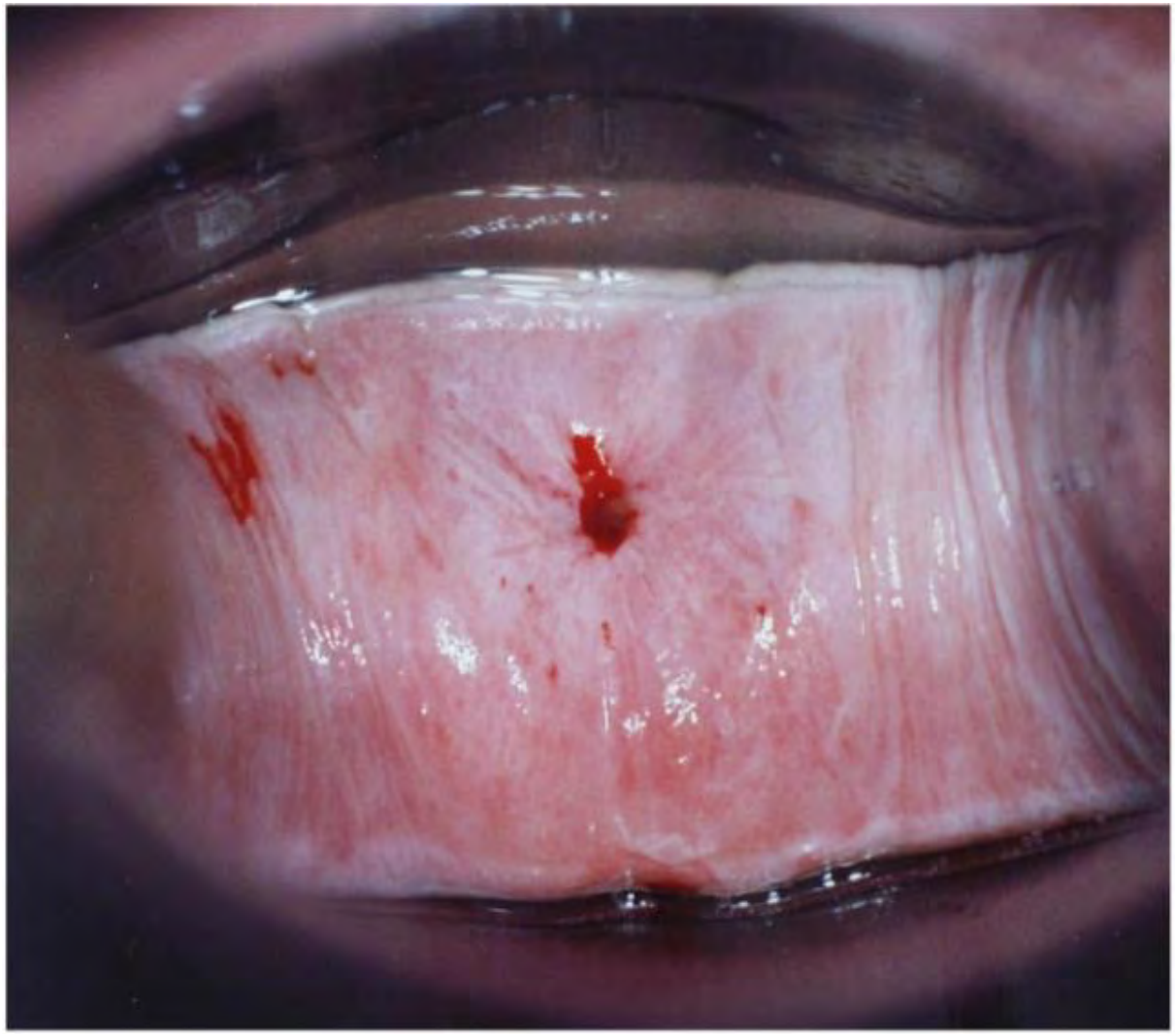
- Genital dryness
- Decreased lubrication with sexual activity
- Discomfort or pain with sexual activity
- Post-coital bleeding
- Decreased arousal, orgasm, desire
- Irritation/Burning/Itching of vulva or vagina
- Dysuria
- Urinary frequency/urgency

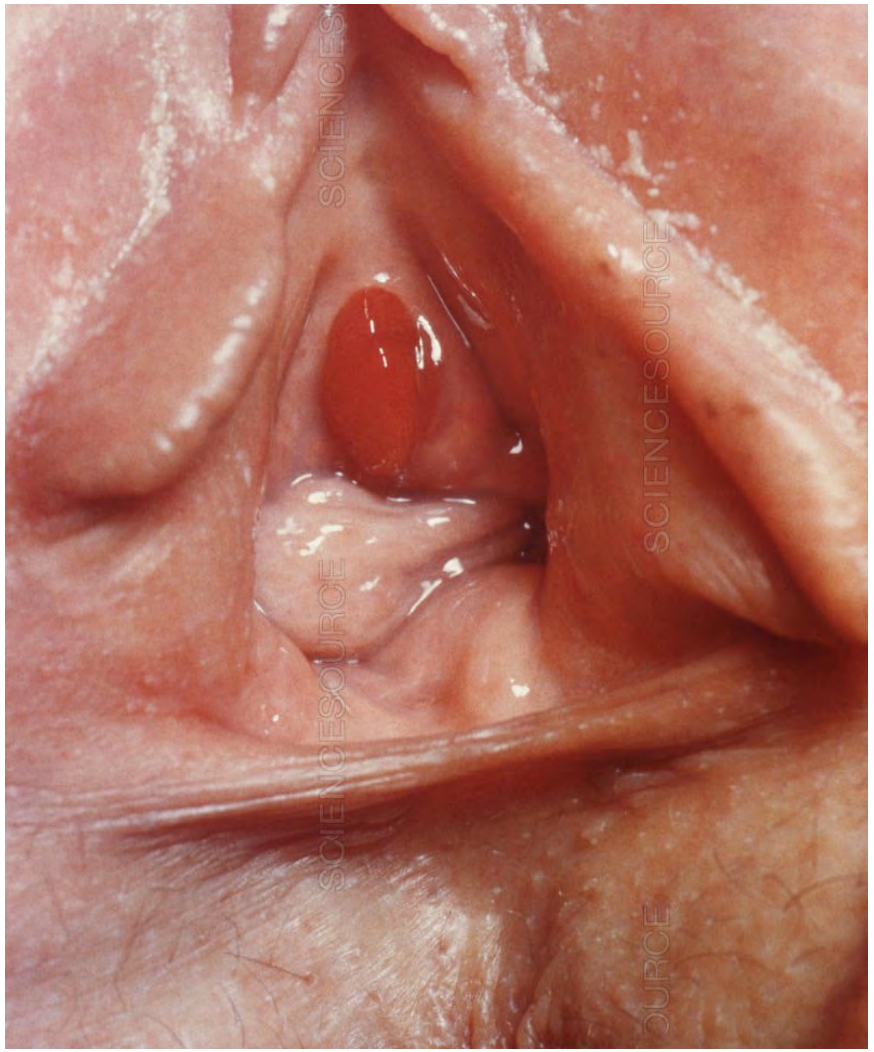


Signs

- Decreased moisture
- Decreased elasticity
- Labia minora resorption
- Pallor/Erythema
- Loss of vaginal rugae
- Tissue fragility/fissures/petechiae
- Urethral eversion or prolapse
- Loss of hymenal remnants
- Prominence of urethral meatus
- Introital retraction
- Recurrent urinary tract infections

Genitourinary Syndrome of Menopause





GSM in Cancer Survivors

GSM: History and Evaluation

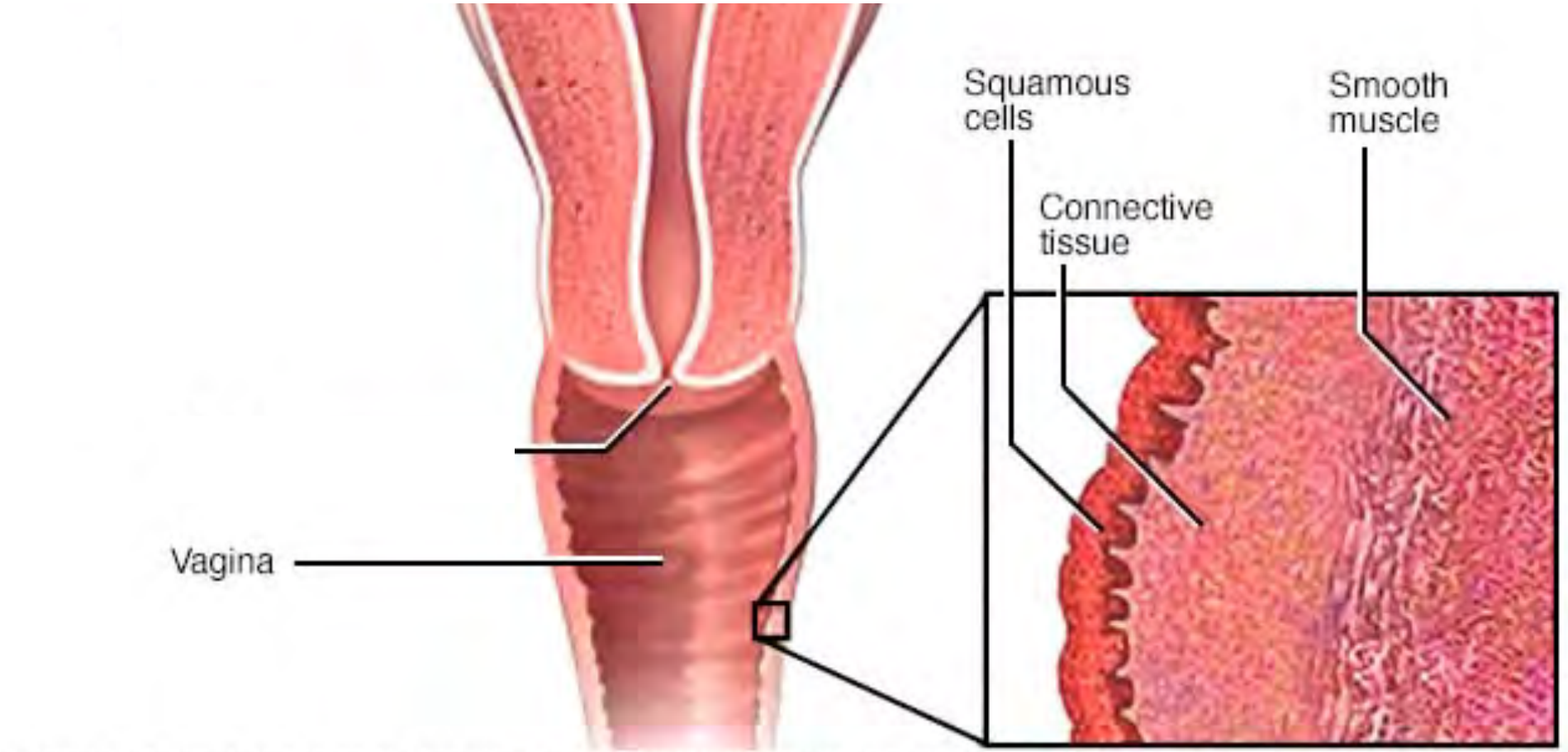
- Complete medical history
  - Symptom characterization, prior treatments
  - Review of vaginal irritants
- Sexual history
- Physical examination
  - Vaginal pH and wet prep as indicated
  - Vulvar/Vaginal cultures as appropriate
  - Biopsy white, pigmented, or thickened lesions

➢ Any vulvar lesion that does not respond to treatment should be biopsied

- 41% of oncologists are refer patients with GSM to gynecologists
- Only 35% of oncologist manage symptoms independently
- Shared Decision making

GSM: Treatment

The 3Rs



Layers of Vaginal Tissue

Treatments for GSM: Lubricants

- Reduce friction
- Short term comfort
- One size does not fit all-encourage patients to try different formulations: water based vs. silicone
- Consider osmolality and pH
  - Ideal osmolality: of < 380 mOsm/kg,
  - Ideal pH>3.0
- Avoid additives irritating additives: parabens, glycerin, flavors, spermicides

Treatments for GSM: Moisturizers

- Retain moisture
- One size does not fit all-encourage patients to try different formulations
- More frequent use compared to naturally menopausal women:
  - Consider daily use
  - Titrate to patient preference/tolerance

Treatments for GSM: Lubricants and Moisturizers

Lubricants		Moisturizers
Water based Astroglide Liquid Astroglide Gel Liquid Astroglide Good Clean Love Just Like Me K-Y Jelly Pre-Seed Slippery Stuff Liquid Silk YES WB SYLK Sliquid	*Silicone based* Astroglide X ID Millennium K-Y Intrigue Pink Pjur Eros Uberlube Sliquid *Oil based* Elégance Women's Lubricants Olive oil YES OB	Replens Me Again Feminease K-Y SILK-Eluvena Revaree Silken Secret Hyalo-gyn

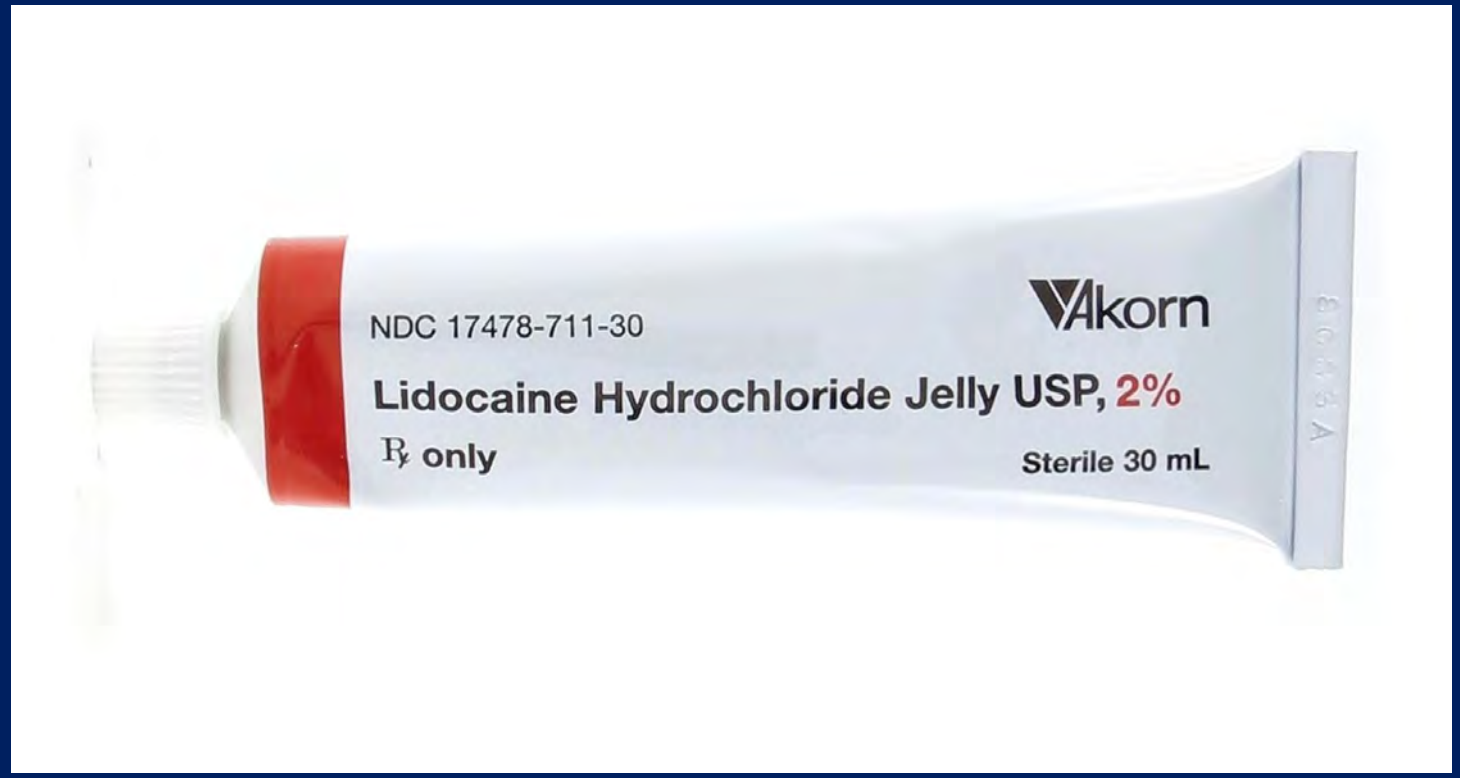
The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel. *Menopause.* 2020;27(9):976-992.

Treatments for GSM: Kitchen cabinet?

- Natural oils: olive, coconut may be associated with vaginal infections
- Probiotics: could be helpful to microbiome, need comprehensive trials

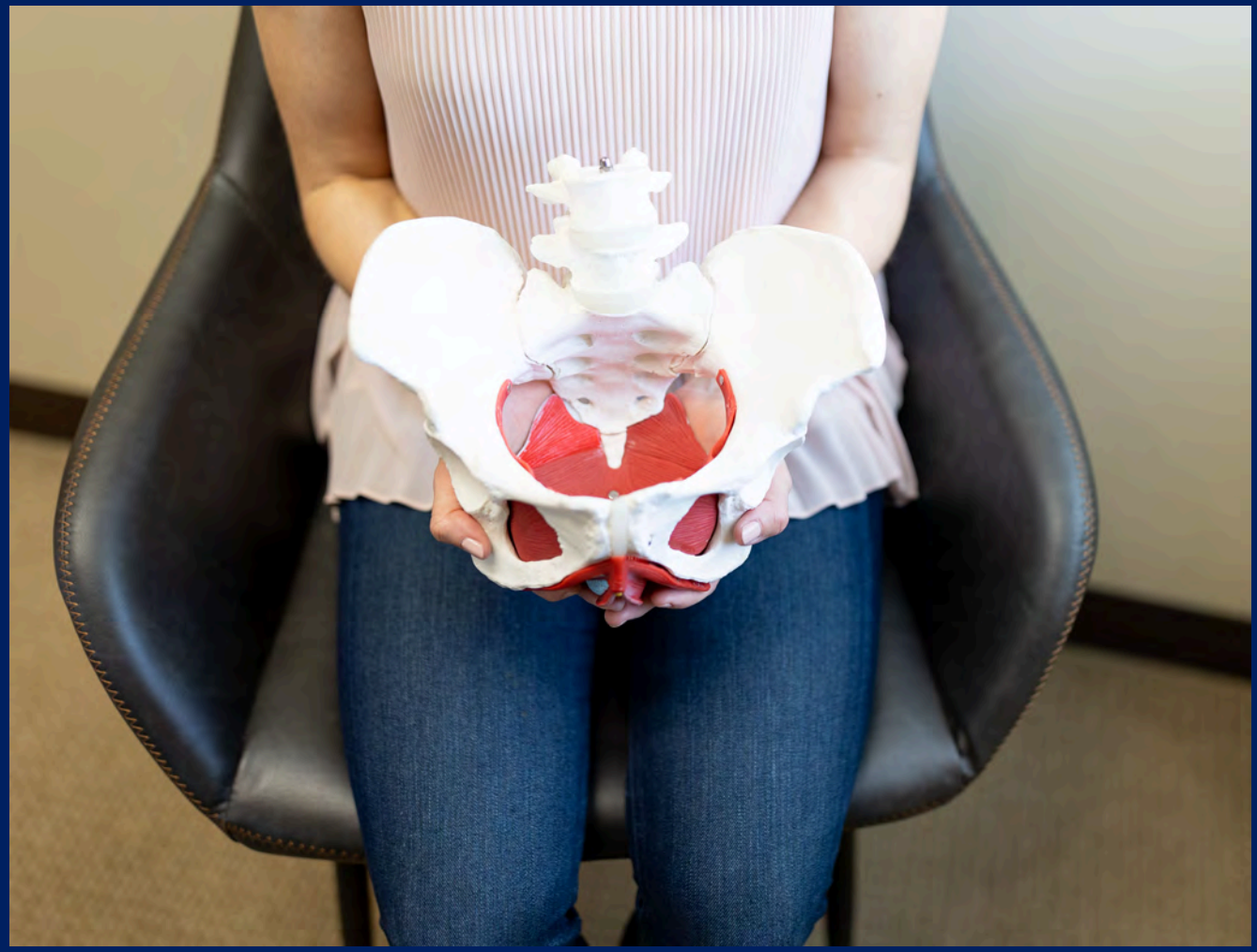
Treatments for GSM: Lidocaine

- Apply with cotton swab ~3 minutes before penetration



Treatments for GSM: Vaginal Dilators

Treatments for GSM: PFPT



Treatments for GSM: Psychosocial Support

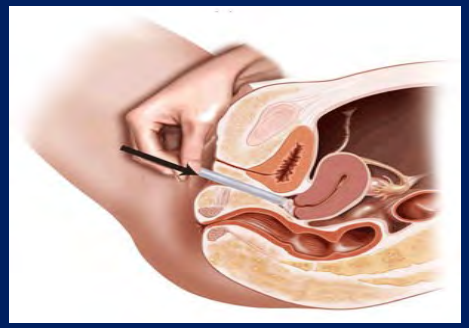
- Counseling
- Psychotherapy: CBT
- Support groups
- Group and individual education

Treatment Options

GSM Treatment Options: Vaginal Estrogen

10 mcg Estradiol hemihydrate vaginal tablet

17β Estradiol Vaginal ring



Estradiol or Conjugated Equine Estrogen Cream

4 or 10 mcg Estradiol vaginal insert

Hormone Treatments: Low-dose Vaginal Estrogen

- Restores vaginal blood flow
- Decreases vaginal pH
- Improves thickness and elasticity of vulvovaginal tissues
- Many different formulations: vaginal ring, tablets, inserts, creams
- Improvements within a few weeks, full efficacy in 2-3 mo
- Serum levels typically in postmenopause range
- Large observational studies show no increased risk of endometrial cancer, breast cancer, or CVD
- Progestogen generally is not indicated
- Controversial data/guidance in hormone sensitive cancer survivors: Shared Decision-Making

Rahn DD, et al. *Obstet Gynecol*. 2014;124(6):1147-1156; Handa VL, et al. *Obstet Gynecol*. 1994;84(2):
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Local Estrogen Therapy

Women at high risk for breast cancer

- failed nonhormonal treatment

Women with ER positive breast cancers on tamoxifen

- persistent, severe symptoms with failed nonhormonal treatments and factors suggesting a low risk of recurrence

Women with ER positive breast cancers on AI

- persistent, severe symptoms with failed nonhormonal treatments and factors suggesting a low risk of recurrence
- consult with the oncologist to consider switching to tamoxifen

Women with triple negative breast cancers

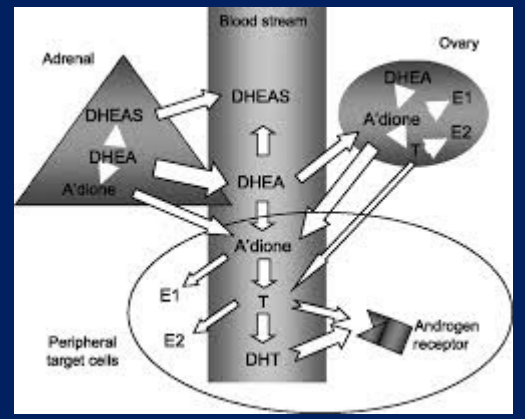
- Theoretically reasonable data are lacking

Women with metastatic disease

- QoL, comfort, and intimacy may be a priority for many women with metastatic disease

Hormone Treatments: Dehydroepiandrosterone (DHEA)

- 0.5%/6.5 mg DHEA vaginal suppository: Prasterone
- Indication: FDA approved for moderate to severe dyspareunia secondary to VVA
- Directions: inserted once daily at bedtime
- Phase 3 RCT showed significantly improved
  - Vaginal maturation index (VMI)
  - Vaginal pH
  - Signs of atrophy
  - Vaginal dryness
  - Dyspareunia
- Serum steroid levels remained within the normal postmenopause range
- Only adverse event (AE): vaginal discharge because of melting of the vehicle
- Safety: endometrial safety confirmed at 1 y



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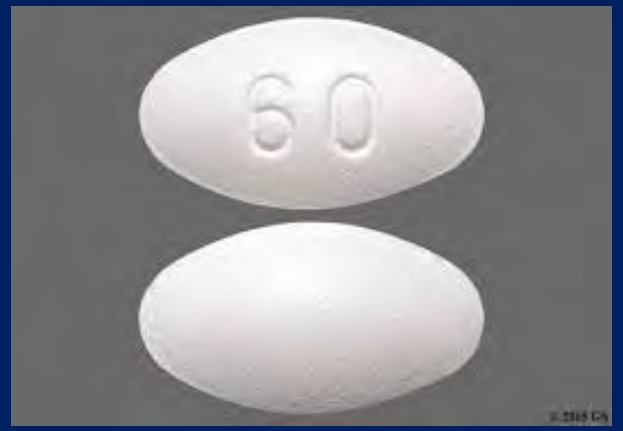
Hormone Treatments: Ospemifene

- **Oral** SERM: estrogen agonist/antagonist
- Indication: FDA approved for moderate to severe dyspareunia associated with VVA
- Dose: 60 mg/day
- Improves
  - VMI
  - Vaginal pH
  - Symptoms of VVA
  - May take 6 months to achieve full efficacy
- Safety
  - No endometrial hyperplasia or cancer (at 52 w)
  - Can increase VMS
  - May increase the risk of venous thromboembolism (VTE)
- Antiestrogenic effects on breast but not approved for women with breast cancer
- NOT RECOMMENDED IN BREAST CANCER PATIES



Portman DJ, et al. *Menopause*. 2013;20(6):623-630; Bachmann GA, et al. *Menopause*. 2010;17(3):480-486; Simon J, et al. *Maturitas*. 2014;77(3):274-281; Soe LH, et al. *Int J Womens Health*. 2013;5:605-611; The NAMS 2020 Genitourinary Syndrome of Menopause Position Statement Editorial Panel. *Menopause*. 2020;27(9):976-992.

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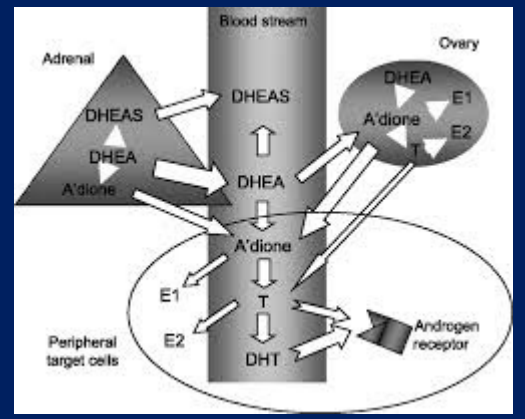
Hormone Treatments: Dehydroepiandrosterone (DHEA)

- 6.5 mg DHEA vaginal suppository: Prasterone
- Indication: FDA approved for moderate to severe dyspareunia secondary to VVA
- Directions: inserted once daily at bedtime
- Phase 3 RCT showed significantly improved
  - Vaginal maturation index (VMI)
  - Vaginal pH
  - Signs of atrophy
  - Vaginal dryness
  - Dyspareunia
- Serum steroid levels remained within the normal postmenopause range
- Only adverse event (AE): vaginal discharge because of melting of the vehicle
- Safety: endometrial safety confirmed at 1 y
- CAN BE CONSIDERED IN BREAST CANCER PATIENTS



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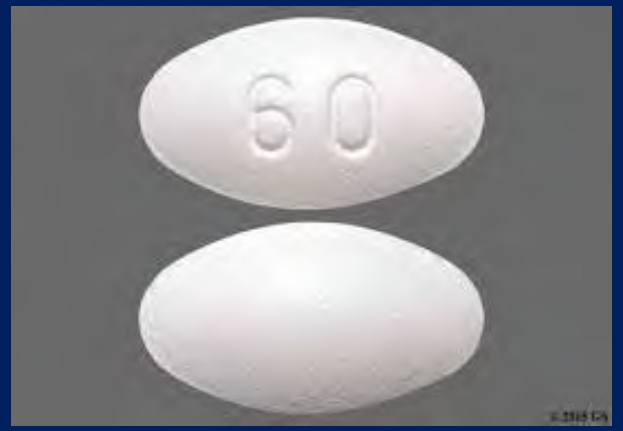
  - — May take 6 months to achieve full efficacy
- Safety
  - — No endometrial hyperplasia or cancer (at 52 w)
  - — Can increase VMS
  - — May increase the risk of venous thromboembolism (VTE)
- Antiestrogenic effects on breast but not approved for women with breast cancer
- Favorable effects on bone



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Treatments for GSM: Laser

Laser therapy may be considered in women who prefer a nonhormonal approach; women must be counseled regarding lack of long-term safety and efficacy data

Take Aways

- Load the Boat: Multidisciplinary Team Approach
- Reduce friction: Lubricants
- Retain moisture: Moisturizers
- Restore vaginal and urogenital tissues: Estrogen therapy
- Reduce pain: Lidocaine
- Maintain patency and caliber: Dilators
- Low threshold for PFPT
- Individualization and Shared Decision Making for all patients, especially those with hormone sensitive cancers using Ais:
    - Consult oncologic team
    - Evaluate patient preference, goals and concerns
    - Shared decision making with patient
    - Mitigate risk

Local Estrogen Therapy

Women at high risk for breast cancer

- failed nonhormonal treatment

Women with ER positive breast cancers on tamoxifen

- persistent, severe symptoms with failed nonhormonal treatments and factors suggesting a low risk of recurrence

- Observational data do not suggest increased risk of breast cancer with systemic or local estrogen therapies beyond baseline risk

Women with ER positive breast cancers on AI

- persistent, severe symptoms with failed nonhormonal treatments and factors suggesting a low risk of recurrence
- consult with the oncologist to consider switching to tamoxifen

Women with triple negative breast cancers

- Theoretically reasonable data are lacking

Women with metastatic disease

QoL, comfort, and intimacy may be a priority for many women with metastatic disease

Questions?

Anal Cancer Screening: What the OBGYN Needs to Know

Christine Conageski, MD MS

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University of Colorado SOM

Disclosures

- I am the site PI of a Teal Health Study. I receive no direct funding, but funds support our research staff.
- I previously was the site PI for a Pfizer vaccine study. This study has ended.

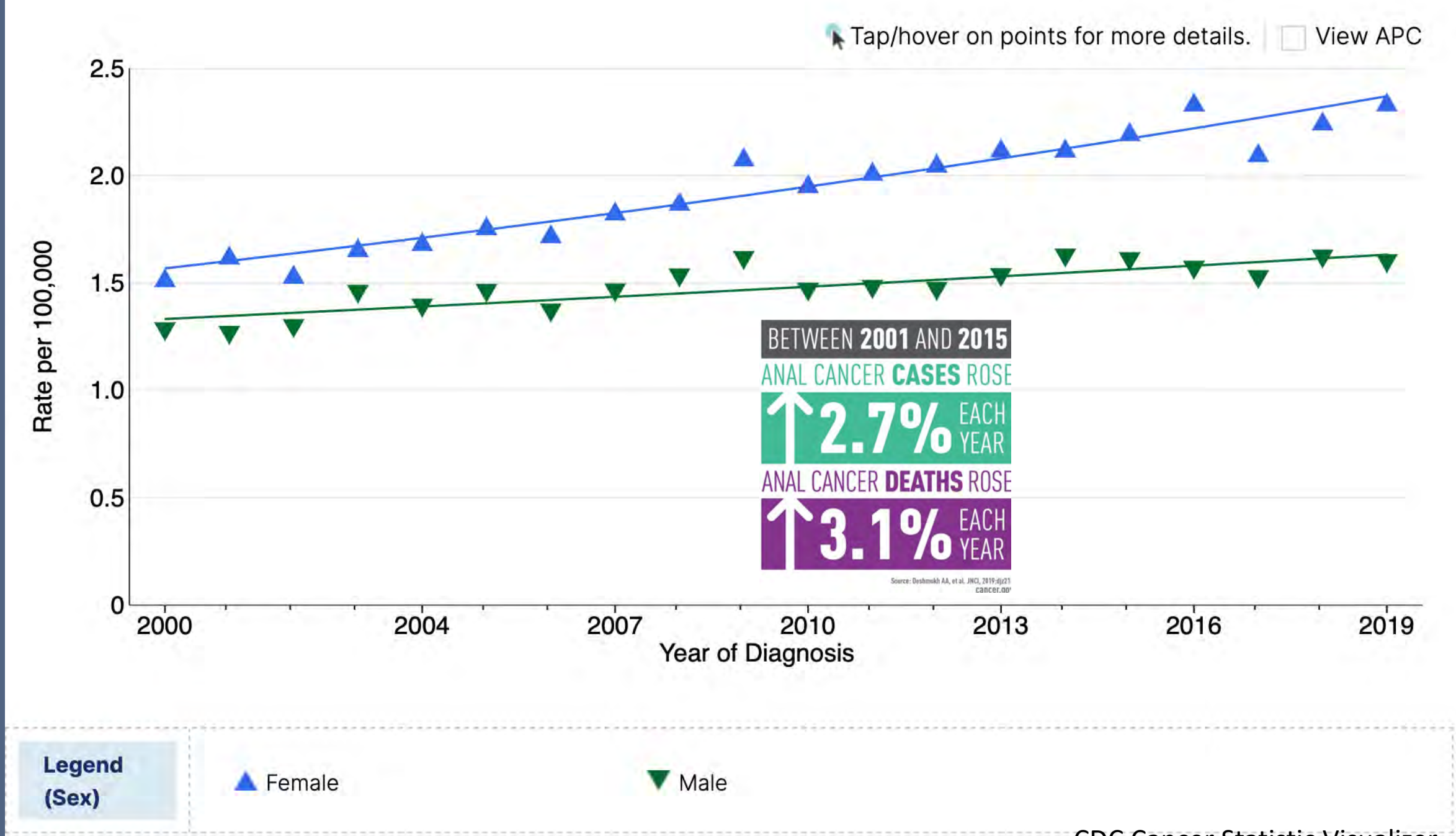
- I am currently the Secretary of the ASCCP and serve on several committees for the International Anal Neoplasia Society (IANS)

Objectives

- Define anal cancer and describe the epidemiology
- Associate HPV and anal cancer
- Describe the role of an OBGYN in anal cancer screening
- Identify anal cancer screening strategies

Anal Cancer Epidemiology

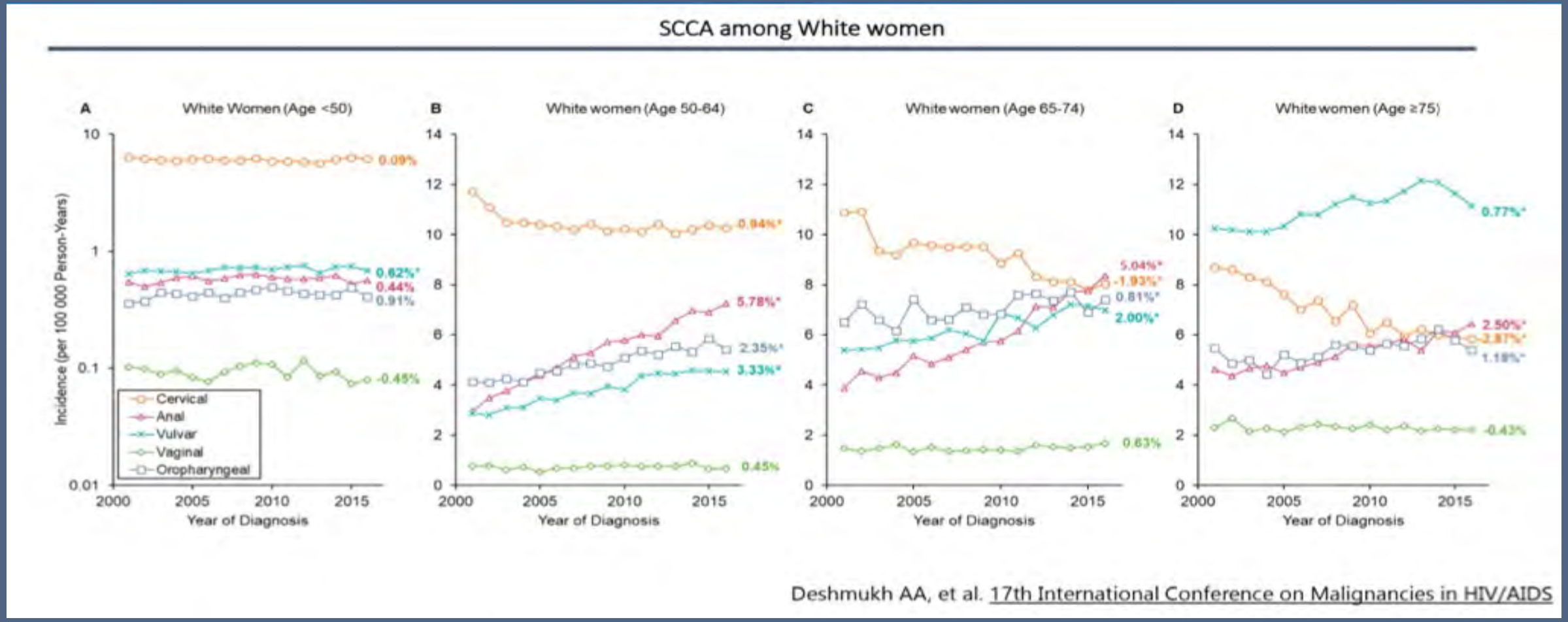
- 9440 new cases annually (3150 in men and **6290 in women**)
- 1670 deaths annual (**930 in women** and 740 in men)
- Most common in white *women* and black men
- Anal cancer rates are rising



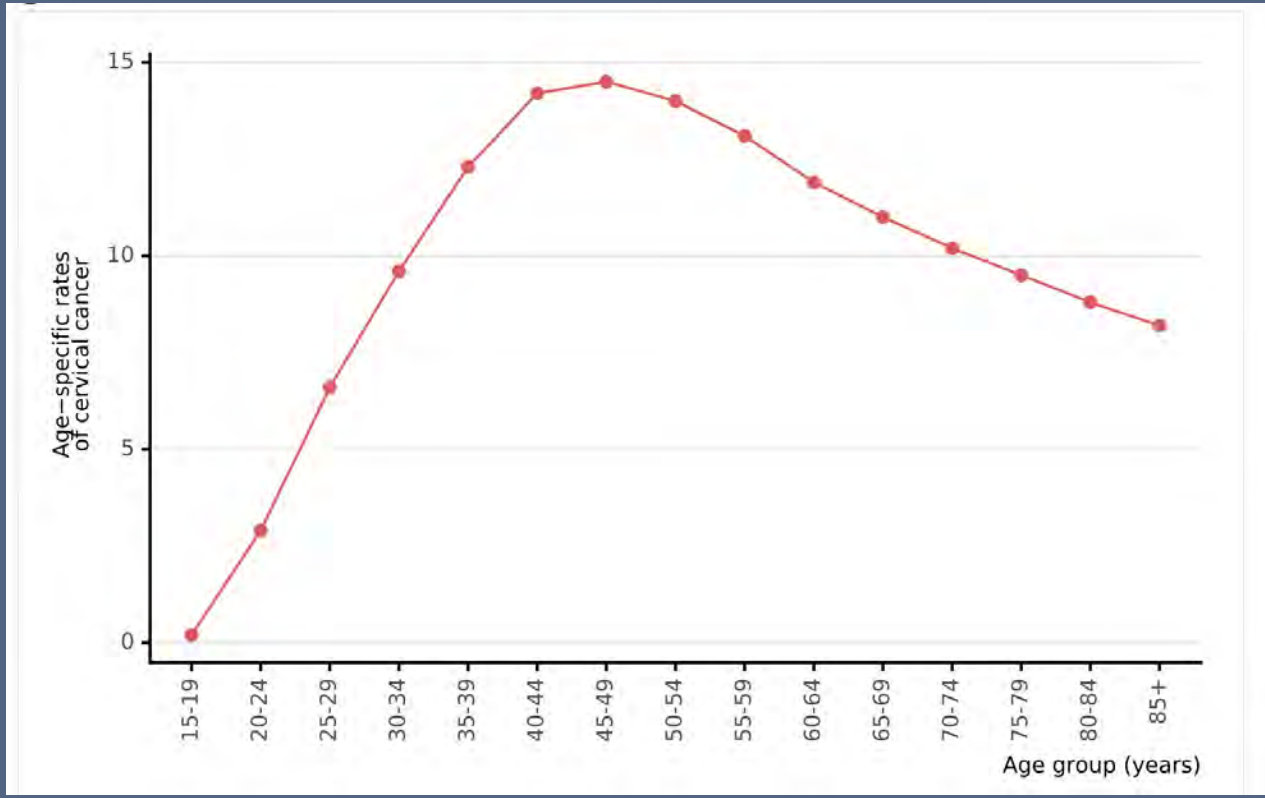
CDC Cancer Statistic Visualizer

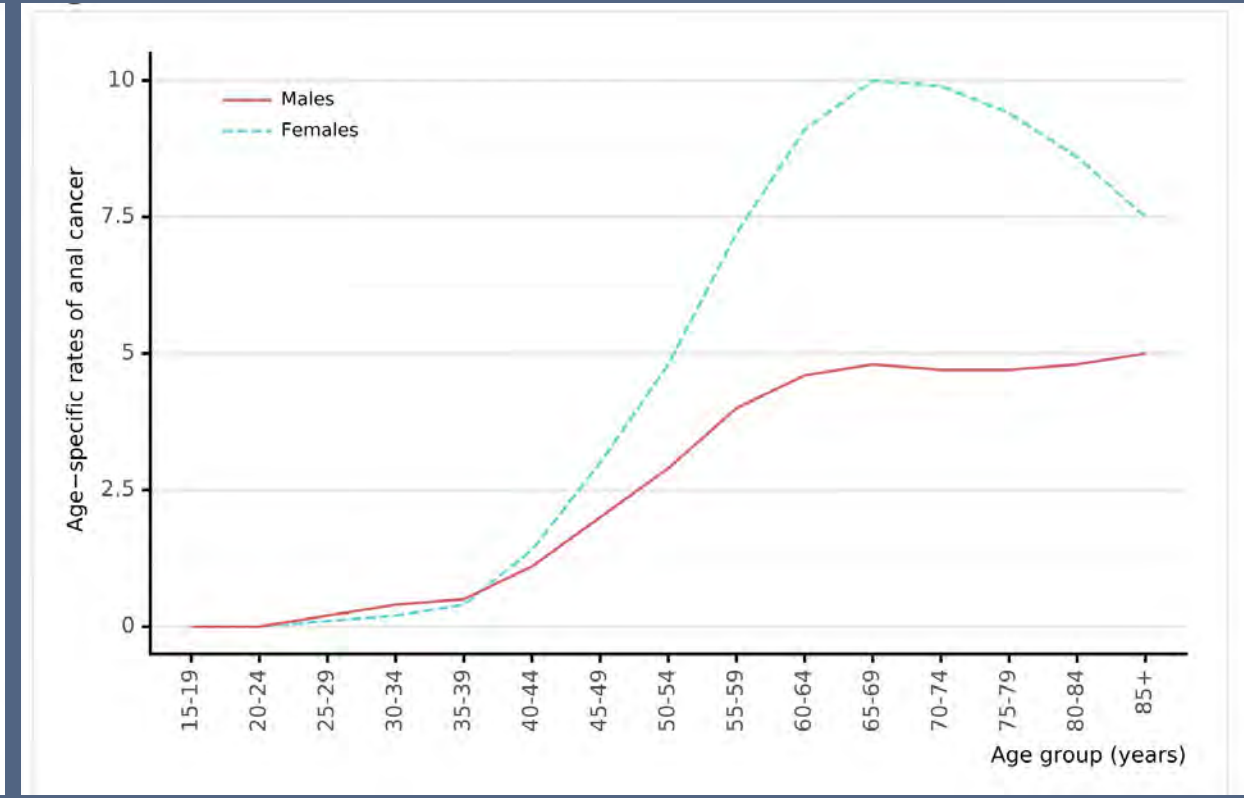
Anal Cancer

- Most commonly in women between 55-64 years of age



Age specific incidence rates for cervical and anal cancers in the US





Bruni L et L. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in United States of America. Summary Report 22 October 2021.

Anal Cancer

- Predominately squamous cell cancers (perianus and anus)
- Symptoms
  - Rectal bleeding (45%)
  - Feeling of a mass (30%)
  - Asymptomatic (20%)
- Treatments
  - Radiation
  - Chemotherapy
  - May need colostomy due to tumor, cancer, or complications of treatment
    - Colostomy-free 5-year survival rate 65-86%

Anal Cancer

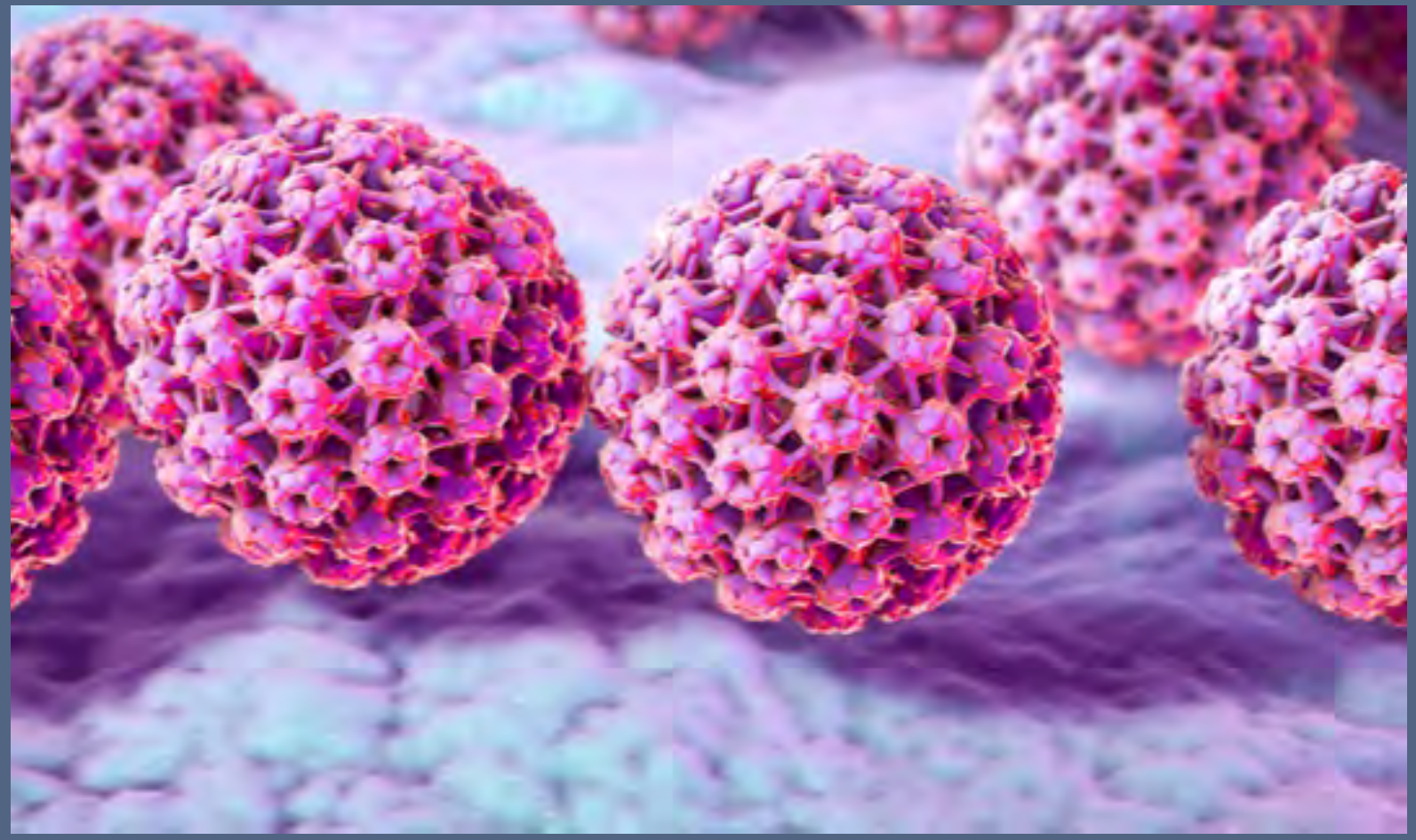
- 50% of anal cancers are diagnosed at stage II or worse
- 5-year survival (all cases) = 71.1%
- 37% positive LNs at diagnosis

Stage	5- year Survival Rate (%)
T2N0	82
T3N0	74
T4N0	57
T2N+	70
T3N+	57
T4N+	42

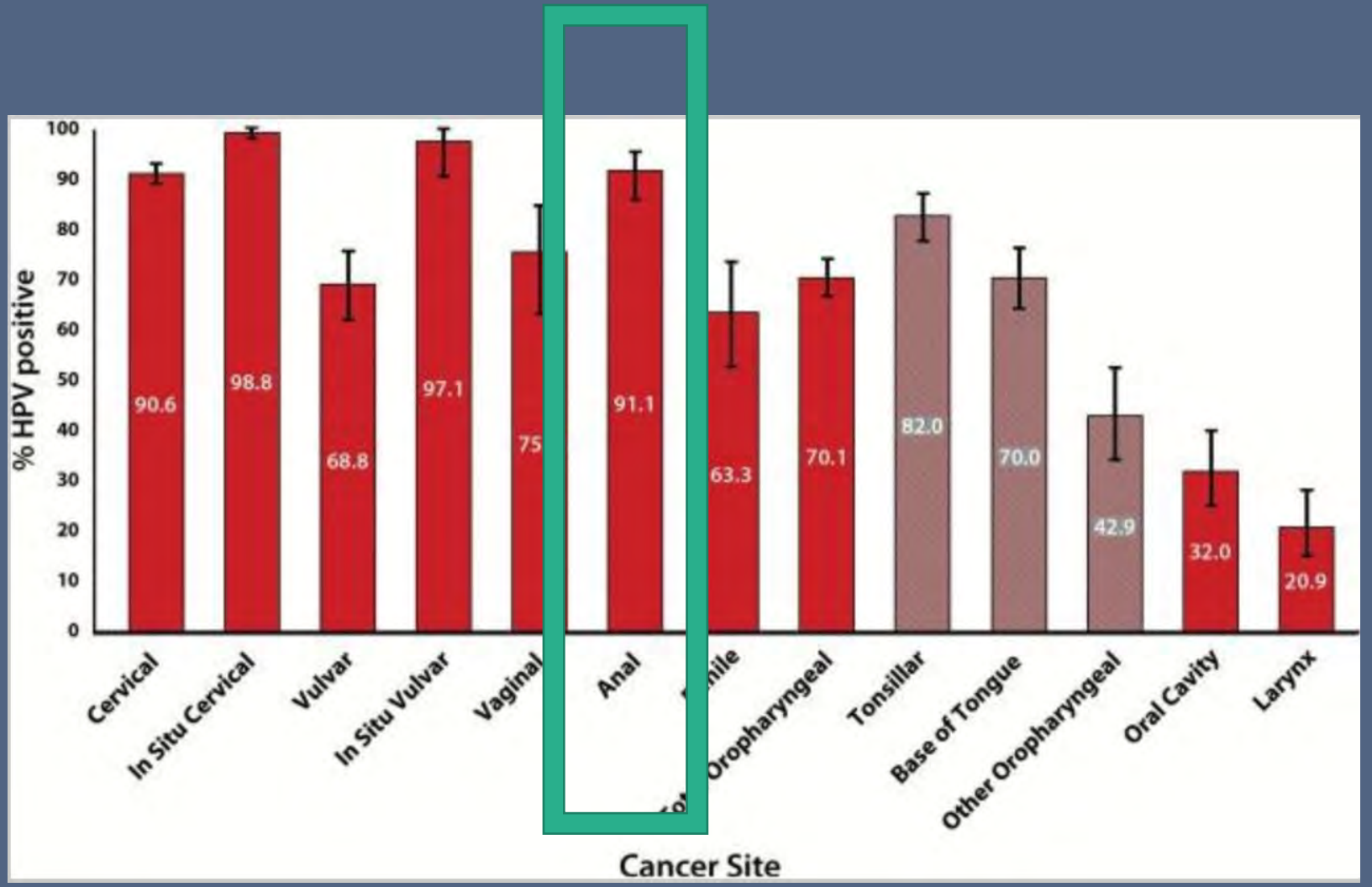
Risk Factors for Anal Cancer

- Any factor associated with new HPV acquisition
  - Multiple sexual partners
  - Anal condylomas
  - Anal receptive intercourse
  - PWC: history of cervical, vulvar, vaginal dysplasias and cancer
- Age
- Tobacco
- Defects in cell-mediated immunity
  - HIV
  - Immunsuppression

Epidemiology of Anal HPV & Anal Neoplasias

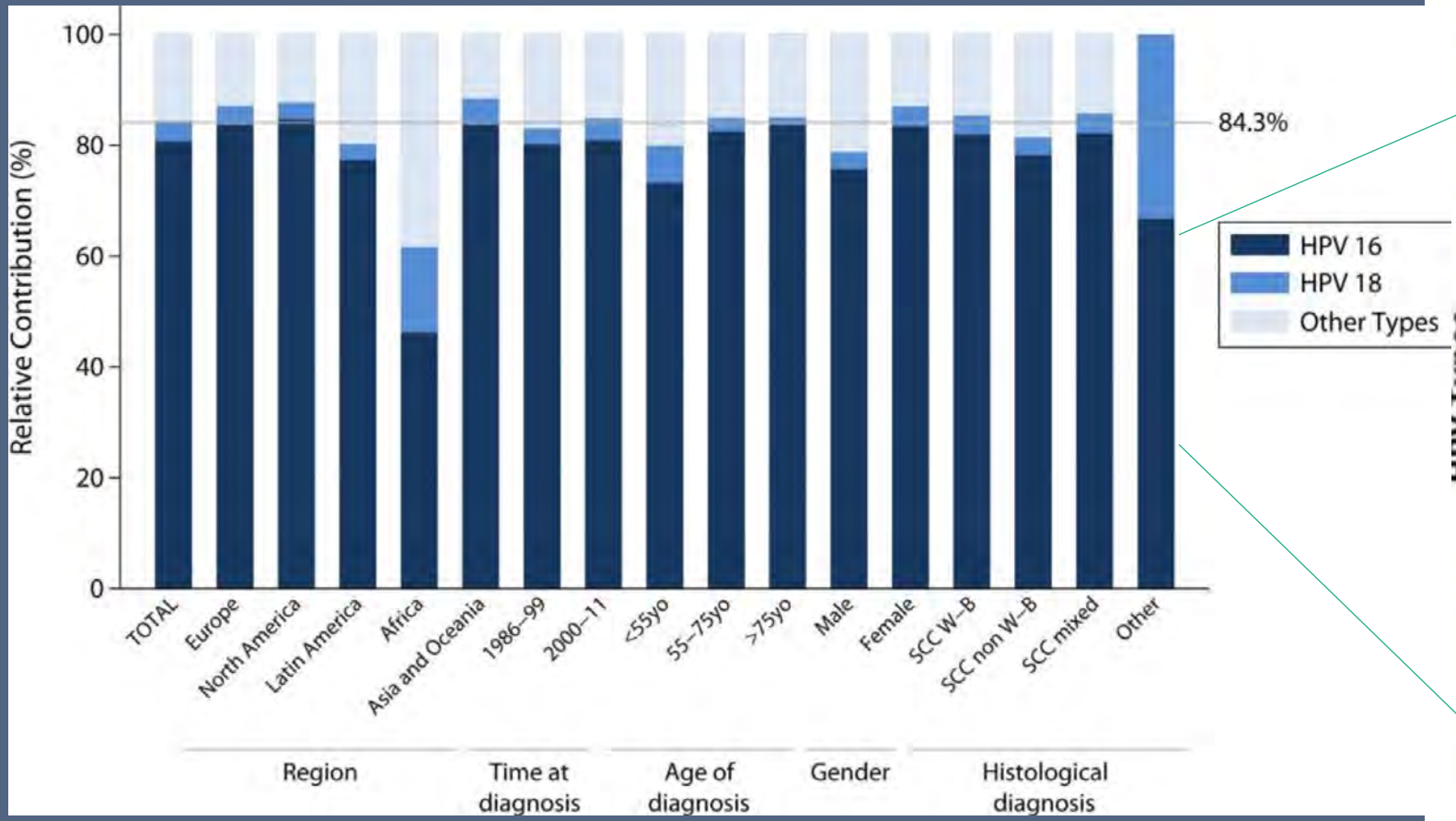


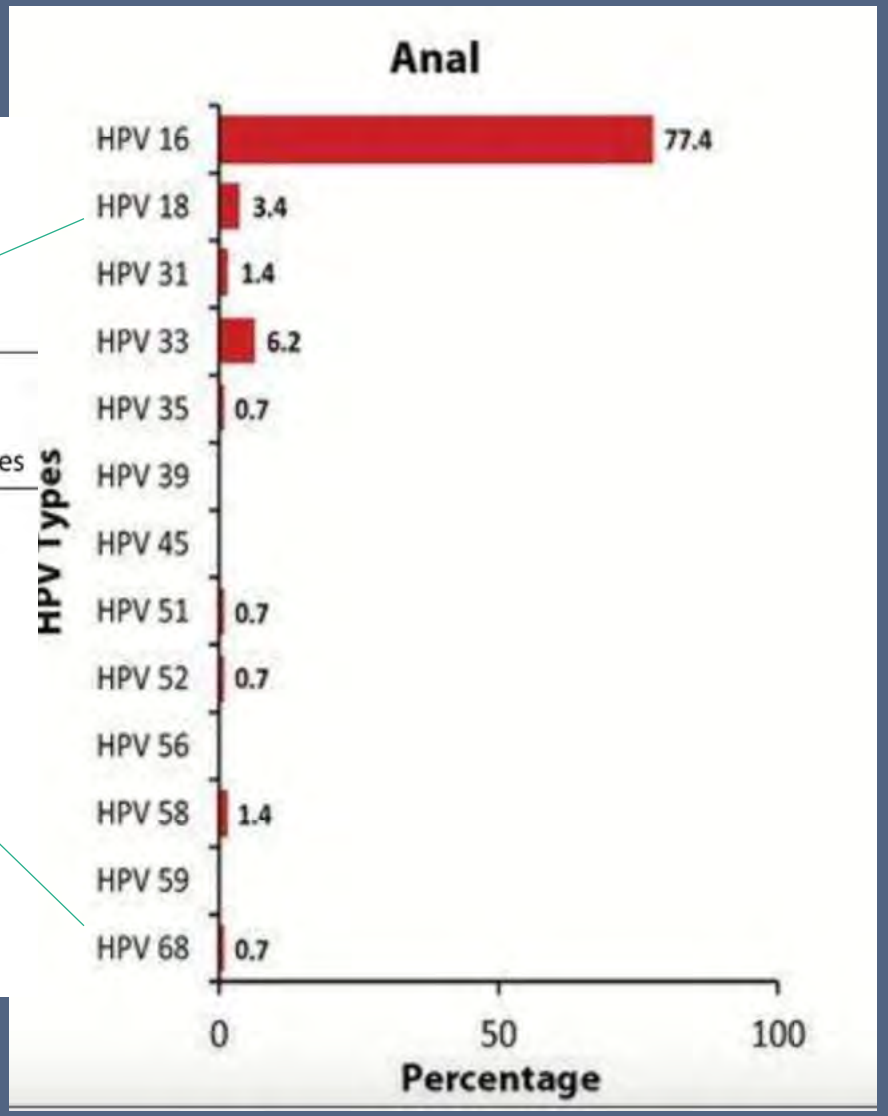
HPV association with Anal Cancer



https://www.cdc.gov/cancer/hpv/statistics/cases.htm

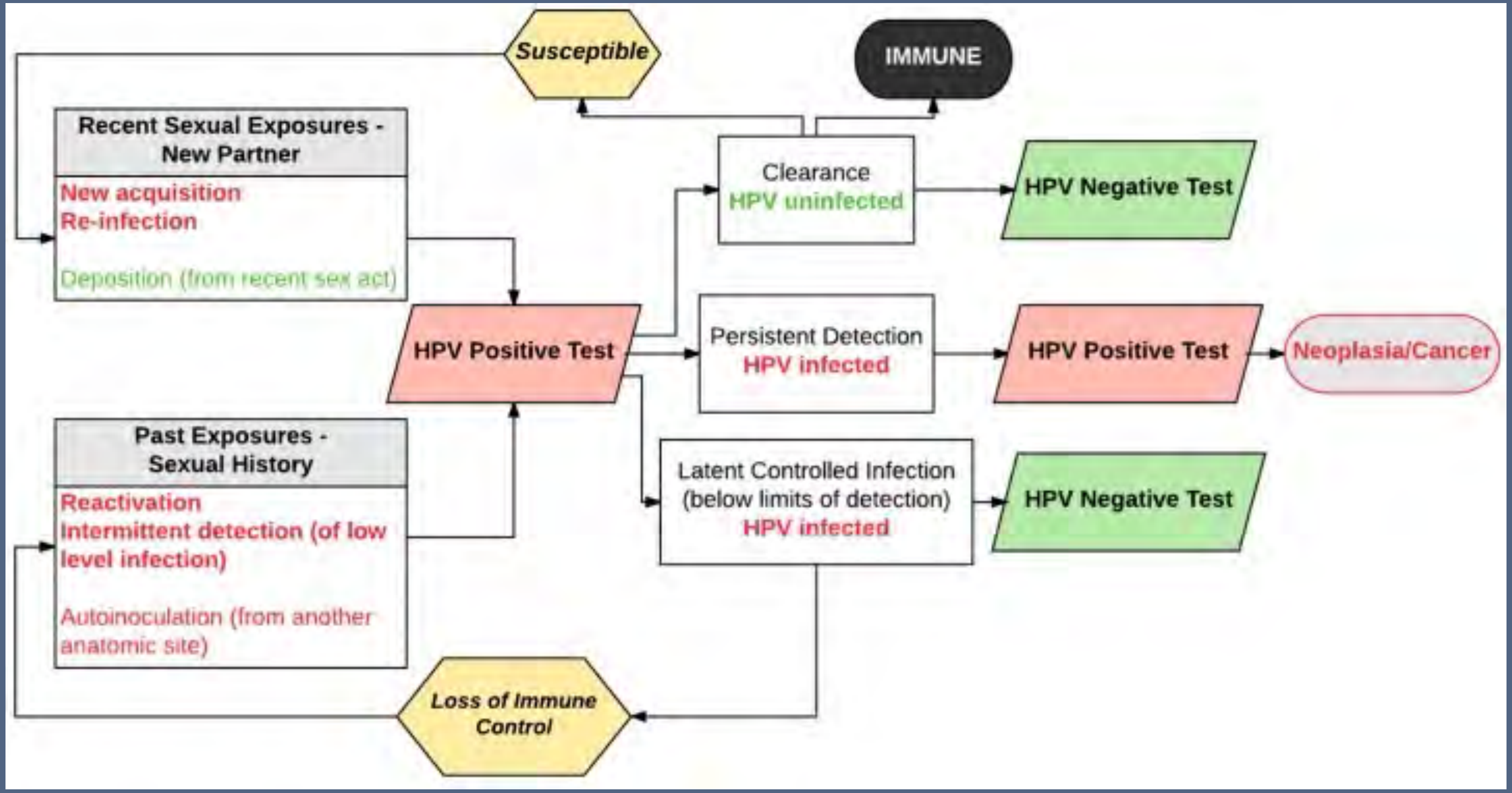
HPV association with Anal Cancer





Lessons from the cervix – anal assumptions

- High Grade Squamous Intraepithelial Lesions (HSIL) is the anal cancer precursor lesion
- Natural history of HPV, HSIL, and anal cancer is similar to cervical HPV, HSIL, and cervical cancer
- Hypothesized that:
  - *Screening at risk populations-> Identification of anal HSIL -> treatment of anal HSIL -> prevent progression of anal cancer*



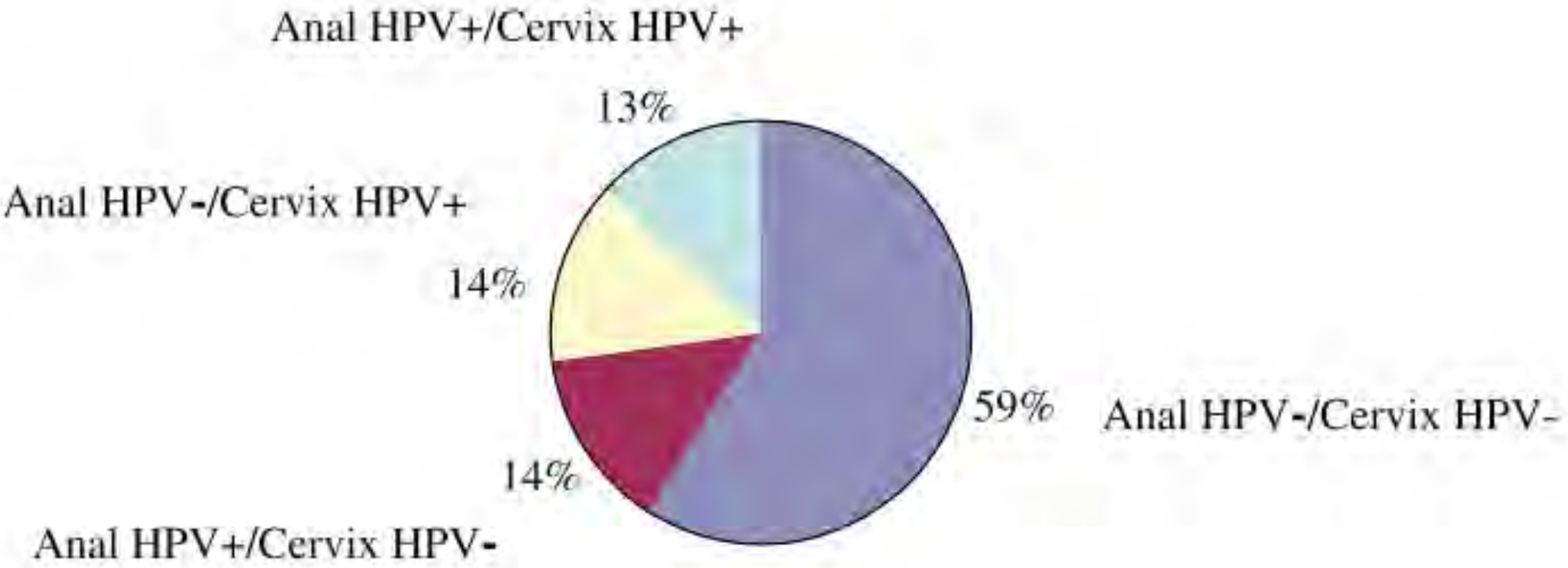
Gravitt. Viruses 2017

HPV in Women in the General Population – Hawaiian Cohort Study

- 1378 ethnically diverse healthy women > 18 years of age
  - Mean age 38 years
- Underwent cervical and anal sampling for HPV
  - Baseline
    - 29% had cervical HPV
    - 27% had anal HPV
  - 3-fold increased risk of anal infection if cervix positive
- 80% shared at least one HPV type between sites

Hernandez. Cancer Epi Biomarkers Prev 2005

HPV in Women in the General Population – Hawaiian Cohort Study



Hernandez. Cancer Epi Biomarkers Prev 2005

HPV in Women in the General Population – Costa Rica Vaccine Trial

- Control of the HPV vaccine trial
  - 2107 women ages 22-29 years
  - Single anal swab provided at year 4
- Anal and cervical HPV prevalence was high
  - Cervical prevalence 31.6% and anal prevalence 36.5%
  - Anal HR HPV prevalence 22.0%
  - Increased risk in women with history of anal intercourse

Castro. JID 2011

Table 2. Univariate and Multivariate Analyses of Determinants for Any Anal Human Papillomavirus (HPV) Infection Among 2107 Young Adult Women From Costa Rica

Characteristic	No. of Women	Univariate		Multivariate
		HPV Positivity, No. (%) of Women	OR (95% CI)	OR[a] (95% CI)
Lifetime no. of sex partners				
1	552	96 (17.4)	1.0	1.0
2	440	127 (28.9)	**1.9 (1.4–2.6)**	**1.6 (1.2–2.3)**
3	335	109 (32.5)	**2.3 (1.7–3.1)**	**1.8 (1.2–2.5)**
≥4	780	334 (42.8)	**3.6 (2.7–4.6)**	**2.3 (1.7–3.1)**
P for trend			**<.0001**	**<.0001**
Lifetime no. of anal intercourse partners				
No history of anal intercourse[b]	1655	470 (28.4)	1.0	1.0
1[c]	367	147 (40.1)	**1.7 (1.3–2.1)**	**1.6 (1.3–2.1)**
≥2	85	49 (57.6)	**3.4 (2.2–5.3)**	**2.8 (1.7–4.5)**
P for trend			**<.0001**	**<.0001**
Anal fissures				
No	2064	648 (31.4)	1.0	1.0
Yes	43	18 (41.9)	1.6 (.9–2.9)	1.6 (.8–3.2)
Cervical HPV status at 4-year study visit				
Negative	1339	250 (18.7)	1.0	1.0
Positive	768	416 (54.2)	**5.1 (4.2–6.3)**	**4.8 (3.9–5.9)**

Anal HPV infection in the CVT

- Independent risk factors for anal HPV detection among women who report anal intercourse
  - Cervical HPV (aOR 5.4 95%CI 3.4-8.2)
  - Number of sexual partners (aOR 2.2; 95% CI 1.1-4.6) for > 4 partners
  - Number of anal intercourse partners (aOR 1.9; 95% CI 1.1-3.3) for > 2
- Independent risk factors for anal HPV detection among women who reported NO anal intercourse
  - Cervical HPV (aOR 4.7; 95% CI 3.7-5.9)
  - Number of sexual partners (aOR 2.4; 95%CI 1.7-3.4)
  - Report of anal fissures (aOR 2.3; 95% CI 1.1-4.8)

Castro. JID 2011

Why is anal cancer more common among women?

- Anal HPV infection is more common among women than men

- Among men, main acquisition is receptive anal intercourse
  - Relatively small proportion of the population

- Among women there are two methods:
  - Receptive anal intercourse
  - Spread of HPV from the vulva and cervicovaginal tract

How do Women get anal HPV infections?

- Cross sectional study of women with a previous HPV-mediated gynecologic neoplasia in Tasmania, Australia
- Women presenting for follow-up GYN care had anal swab samples taken for anal cytology and HPV genotyping
- Women with abnormal anal cytology were referred for HRA

Simpson. Cancer Epi 2016

How do Women get anal HPV infections?

- Of the 123 women tested for HR HPV DNA, 48 (39.0%) had anal HR HPV detected
- Front to back wiping was associated with significantly increased prevalence of cytological and histological abnormality and HR HPV carriage/co-carriage (prevalence 1.99-3.6)
- Dabbing post-toilet was significantly associated with decreased prevalence (PR range 0.5-0.62)

Simpson. Cancer Epi 2016

Why Should Gynecologists Care about Anal Cancer Screening?

Your patients will ask!

Actress Marcia Cross

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On Battling Anal Cancer and Breaking the Stigma of HPV

Farrah Fawcett Foundation

Published Jan 20, 2022

Actress Marcia Cross Beat Anal Cancer & She's Made a Point to Give Her Daughters the HPV Vaccine: Here's What You Should Know about the Vaccine and HPV-Linked Cancers

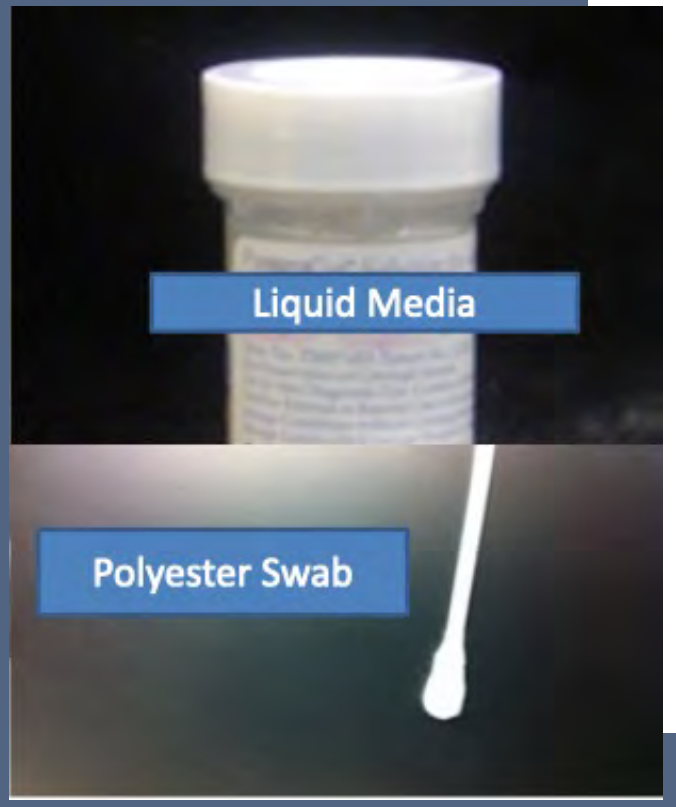
Leading Ladies Affected by Anal Cancer Brings New Awareness to Rare Disease

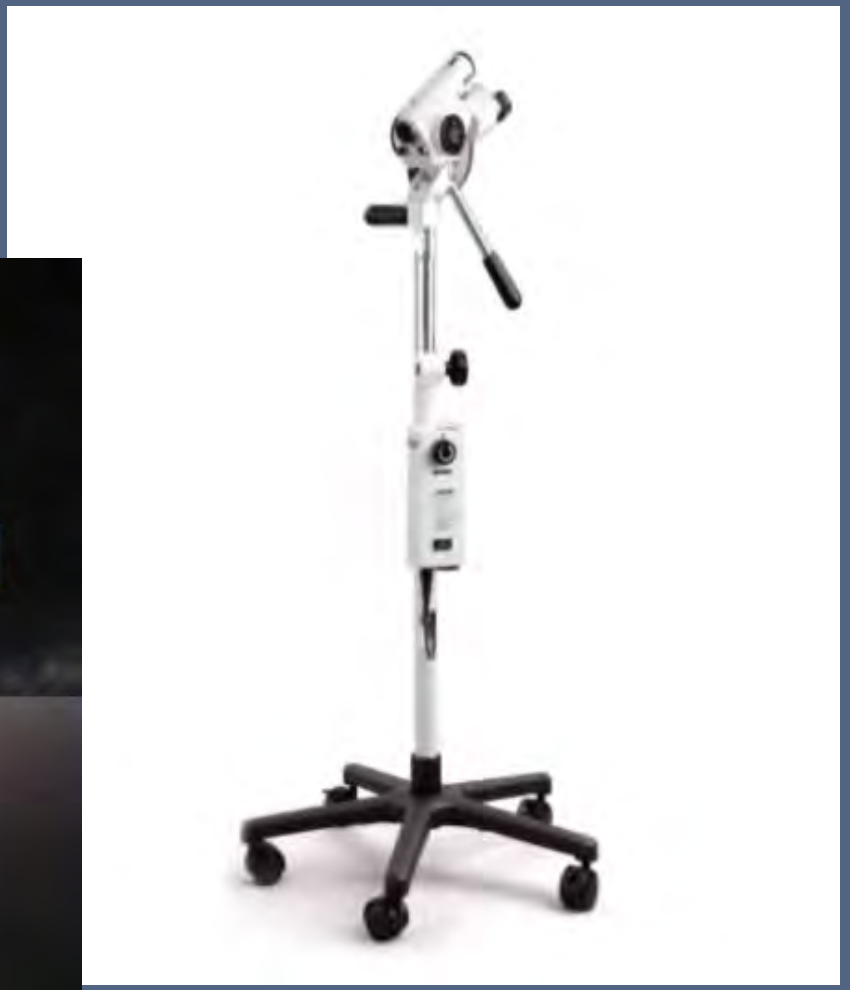
TODAY

What are the symptoms of anal cancer? Farrah Fawcett put disease in spotlight

Why Should Gynecologists Care about Anal Cancer Screening?

- You already have most of the tools!!





Why Should Gynecologists Care about Anal Cancer Screening?

- Experts in HPV-related dysplasias and colposcopy
  - High prevalence of anal HPV in women with cervical and vulvar HPV
  - Anal cancer most commonly diagnosed in women
  - Risk of *multi-zonal disease*

Multi-Zonal Disease

- Definition – presence of high-grade squamous intraepithelial lesions (HSIL)/carcinoma concurrently at two or more of the following sites/zones: perianus, anal canal, vulva, vagina, or cervix

- Retrospective study from London (Homerton Anogenital Neoplasia Service)
  - January 2012-March 2017
  - All patients who underwent multizonal anogenital neoplasia (MZN) assessment
  - History of any lower genital tract neoplasia (LSIL, HSIL or cancer)

Albuquerque. BMC Cancer 2021

Multi-Zonal Disease

- MZN Assessment
  - Vulvar, vaginal and cervical colposcopy
  - Examination of the perianus
  - High resolution anoscopy
  - Biopsy any area suspicious for HSIL
- 253 patients underwent MZN
  - Median age 47 years
  - Median duration of followup 12 months
  - 20% history of anogenital cancer

Table 1 Characteristics of the women with multizonal anogenital neoplasia assessment included in this study (*n*=253)

Parameter	Descriptive statistics[a]
Age at first visit (years) median (IQR)	47 (36-56)
Duration of the follow-up (months) median (IQR)	12 (21)
Previous cervical HSIL/cancer, n (%)	94/251 (37)
Previous vulval HSIL/cancer, n (%)	91 (36)
Previous vaginal HSIL/cancer, n (%)	16 (6)
Previous anal HSIL/cancer, n (%)	62 (25)
Ptevious perianal HSIL/cancer, n (%)	34 (13)
Previous history of anogenital tract HSIL/cancer any site, n (%)	191(75)
One site HSIL/cancer, n (%)	112 (59)
Two sites HSIL/cancer, n (%)	61 (32)
Three sites HSIL/cancer, n (%)	14 (7)
Four sites HSIL/cancer, n (%)	3 (1.5)
Five sites HSIL/cancer, n (%)	1 (0.5)
Previous anogenital cancer/per patient, n (%)	51 (20)
Cervical	9
Vulval	16
Anal	21
Perianal	8
One anogenital cancer site, n (%)	48 (94)
Two anogenital cancers sites, n (%)	3 (6)

Albuquerque. BMC Cancer 2021

First Visit

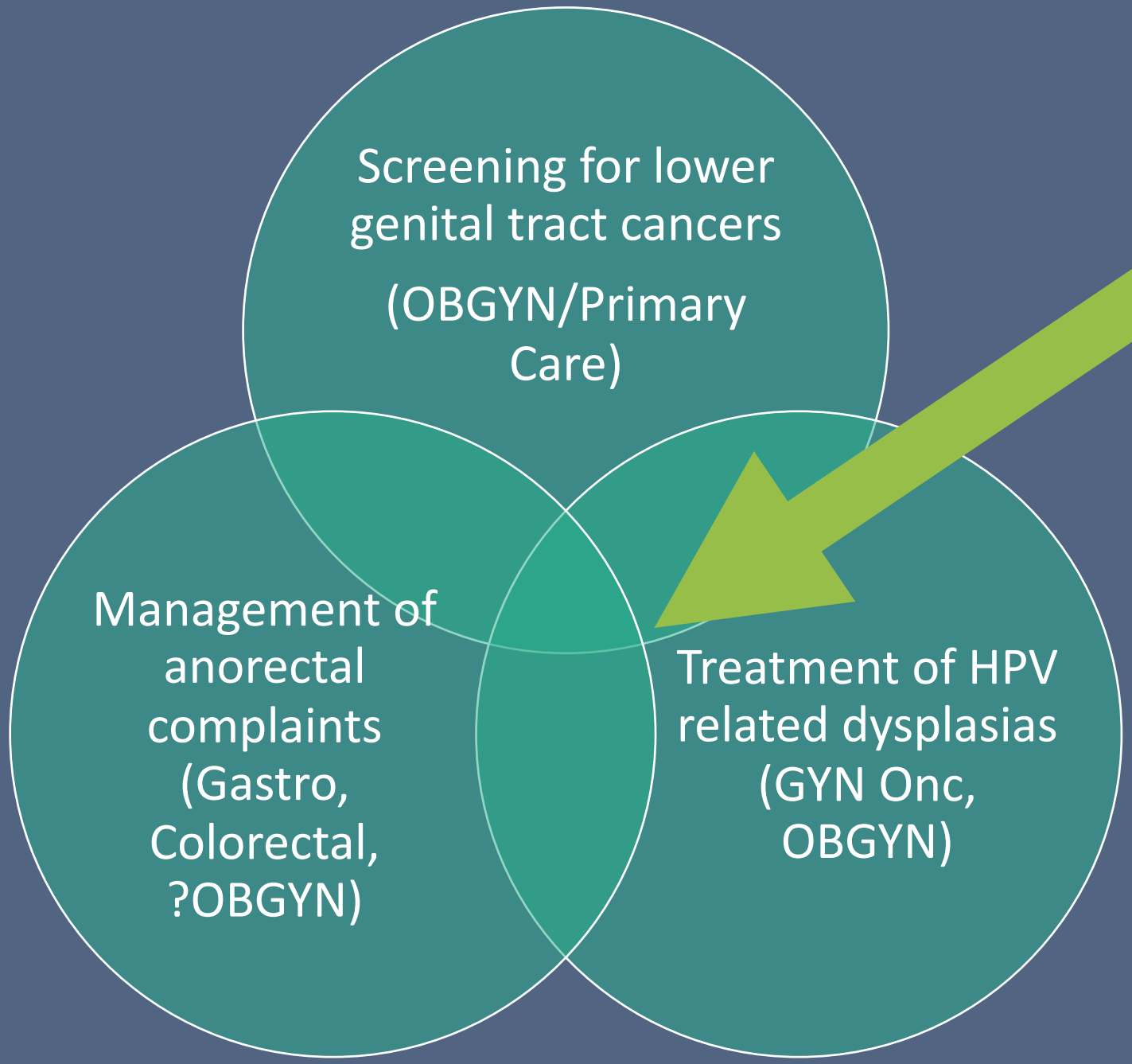
MZN At first visit (*n*=50)	
Disease location	
Site	**Number of cases HSIL/cancer**
Cervical	3
Vulval	37
Vagina	14
Anal	34
Perianal	10
Number of sites HSIL/cancer	**N (%)**
Two sites	27 (54)
Three sites	18 (36)
Four sites	5 (10)
Five sites	0 (0)

- 20% with MZN at first visit
  - Most common sites anal canal or perianus
- Most unsuspected or new zone
- Cancer diagnosed in 9 patients

Follow-up Visits

MZN at follow-up (*n*=20)	
Disease location	
Site	**Number of cases HSIL/cancer**
Cervical	2
Vulval	12
Vagina	8
Anal	13
Perianal	13
Number of sites HSIL/cancer	**N (%)**
Two sites	13 (65)
Three sites	6 (30)
Four sites	1 (5)
Five sites	0 (0)

- 11% with MZN during followup
  - New diagnosis
  - Most common sites anal canal or perianus
- 4 new cancers diagnosed during followup



OBGYNs

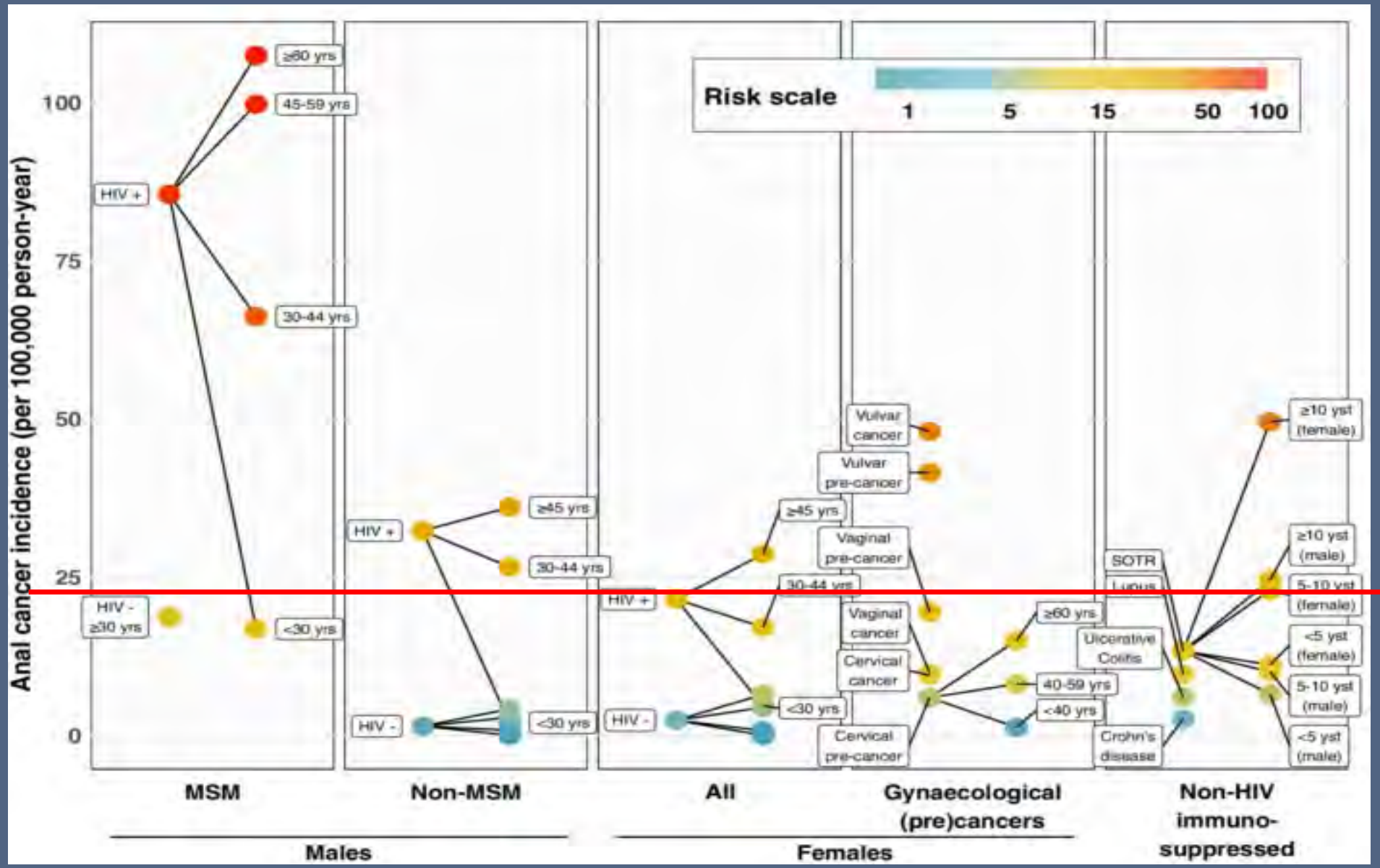
- Screen recommendations
- Treat and manage HPV related dysplasia
- Provide treatments and recommendations for anorectal complaints (hemorrhoids, colorectal screening)

If not gynecologists, then who??

Anal Cancer Screening – Who to screen?

- HIV positive women (SIR 18-47)
- Women with HPV-associated cancers (SIR 13.6)
- History of vulvar cancer (SIR 45.5)
- History of cervical cancer (SIR 6.3)
- History of CIN 3/HSIL (SIR 5.9-6.7)
- Condyloma (SIR 7.8-9)

Anal Cancer Screening – Who to Screen?



Clifford. Int J Cancer 2021

International Anal Neoplasia Society's Consensus Guidelines for ACS

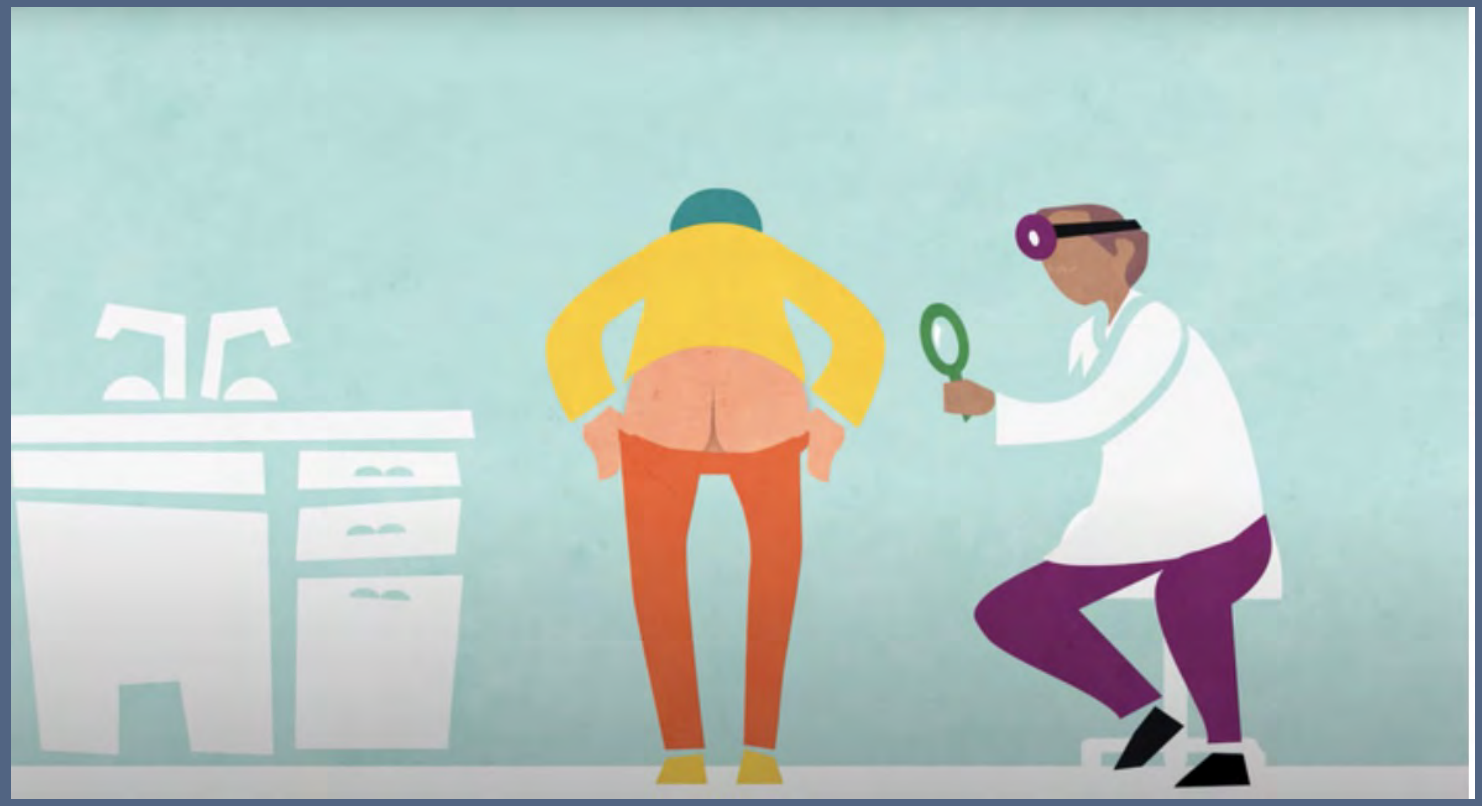
TABLE 1 Populations for screening.

Population—Risk category	When	Anal cancer incidence[2,5] per 100,000 person-years
Risk Category A (incidence ≥ 10-fold compared to the general population)		
MSM and TW with HIV	Age 35	>70/100,000 age 30–44 >100/100,000 age 45+
Women with HIV	Age 45	>25/100,00 age 45+
MSW with HIV	Age 45	>40/100,000 age 45+
MSM and TW not with HIV	Age 45	>18/100,000 age 45–59 >34/100,000 age 60+
History of vulvar HSIL or cancer	Within 1 year of diagnosis	>40/100,000
Solid organ transplant recipient	10 years post-transplant	>25/100,000
Risk Category B (incidence up to 10-fold higher compared to the general population)		
Cervical/vaginal cancer	Shared decision age 45[a]	9/100,000
Cervical/vaginal HSIL	Shared decision age 45[a]	8/100,000
Perianal warts (male or female)	Shared decision age 45[a]	Unknown
Persistent cervical HPV 16 (>1 year)	Shared decision age 45[a]	Unknown
Other immunosuppression (e.g., Rheumatoid arthritis, Lupus, Crohn's, Ulcerative colitis, on systemic steroid therapy)	Shared decision age 45[a]	6/100,000
Incidence among the general population: 1.7 per 100,000[8]		

Stier. Int J Cancer 2024

Screening Strategies for Anal Neoplasia

- Digital Anal Rectal Exam
- Cytology
- High-Risk HPV (HR HPV)
- High Resolution Anoscopy (HRA)



Summary Recommendations for Anal Cancer Screening in Individuals with Cervices

Population at Risk	SIR Per 100,000	PE Symptoms pain/bleeding	DARE	Anal Cytology	HRA
Women with HIV (age over 45 years)	27		X	X	X
Current or hx of vulvar HSIL or vulvar cancer	45-47		X	X	X
Current or history of cervical or vaginal HSIL	10	X	X		
Organ Transplant Recipients (> 10 years ago)	51		X	X	X
Healthy individuals with cervices with none of the above risk factors	< 25	X	X		

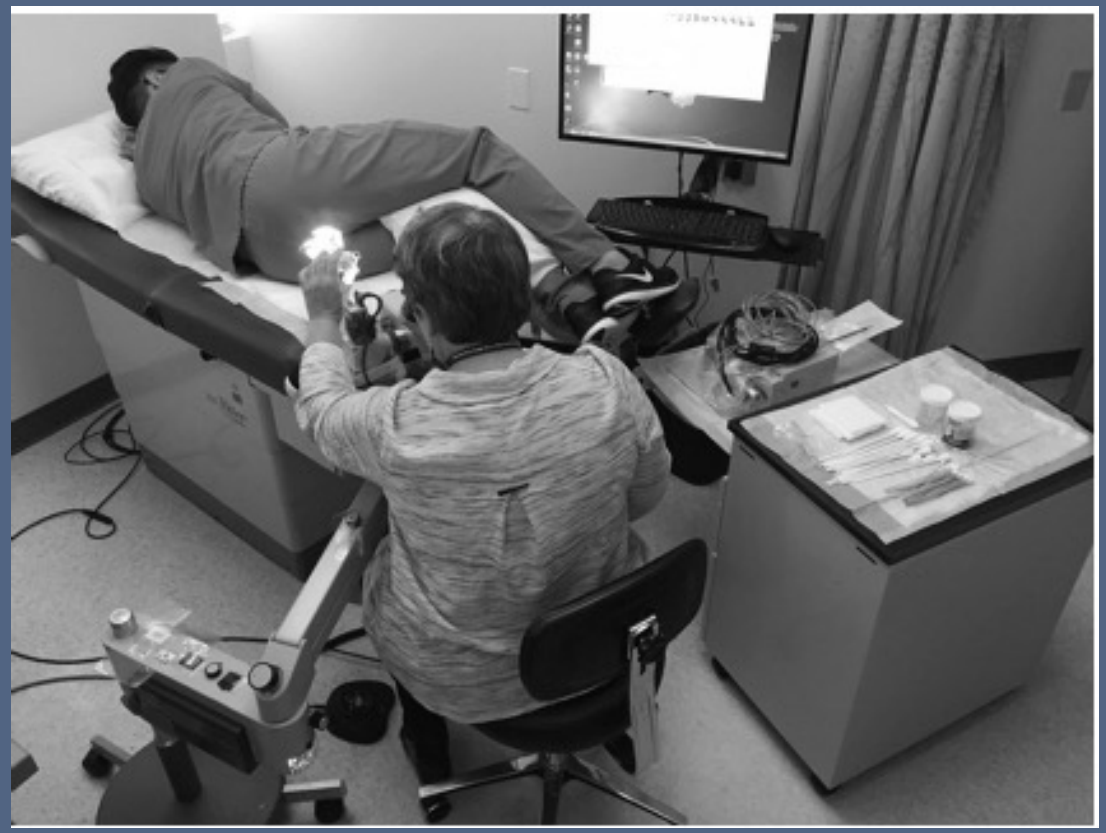
DARE as a Screening Tool for Anal Cancer

- DARE = Digital Anal Rectal Exam
  - Definition: Palpation of the complete anal canal and visual inspection and palpation of the anal margin (5 cm distal to the anal verge)
  - Goal = Identify palpable lesions in the anal canal
  - Sensitive to palpation of lesions as small as 3 mm
  - Found to be acceptable and low cost

- Necessary to perform in women with symptoms (bleeding or pain)

Hillman. J Low Genit Dis. 2019

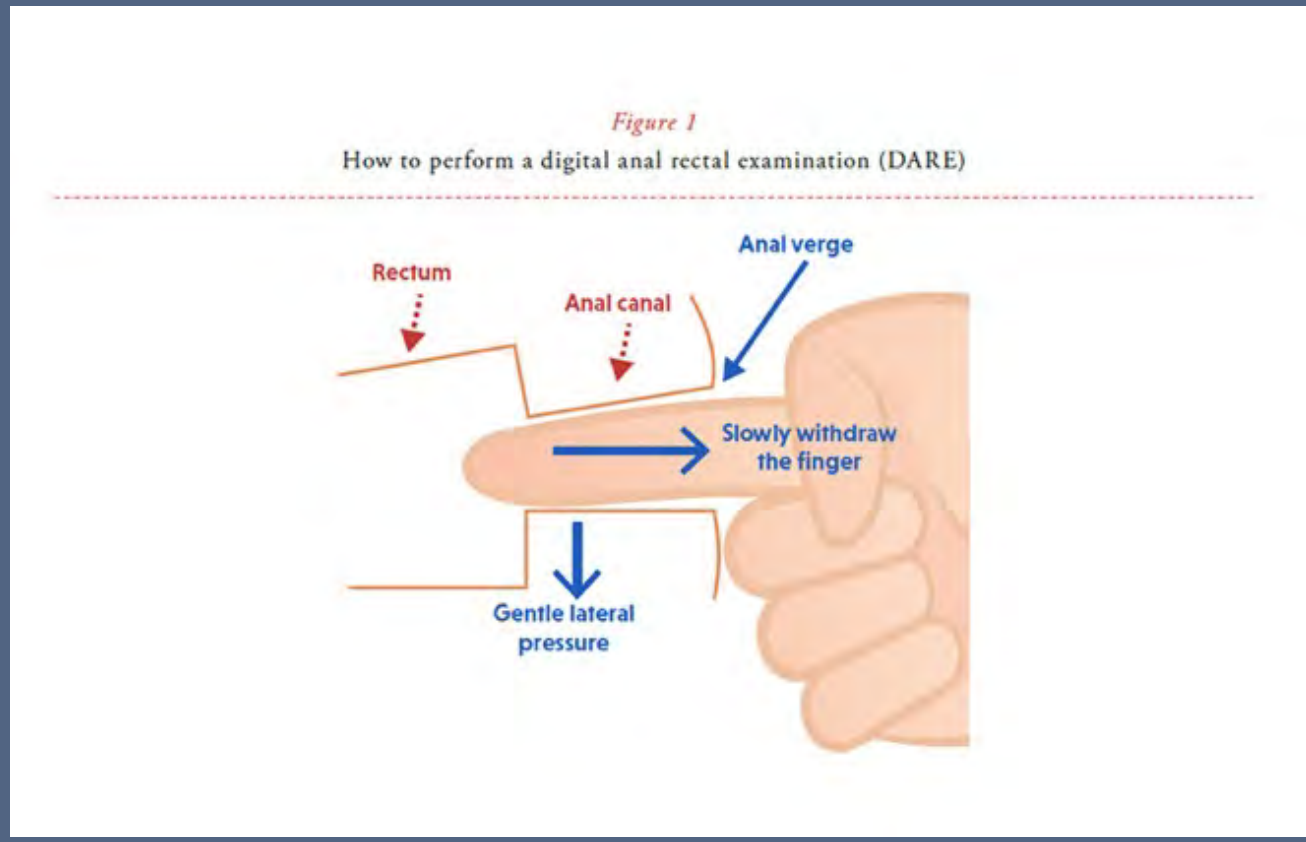
DARE Positioning



Jay. Sem Colon Rectal Surg, 2017

The DARE

- Expose the anus by separating the buttocks
- Use lubricated, gloved index finger to apply gentle pressure on the anal verge and enter the anal canal
- Pull your finger back to the sphincter feeling the circumference of the anal canal; palpate the perianal region
- Sweep the finger 360 in the rectum applying gentle pressure to the lateral walls



Hillman. J Low Genit Dis. 2019

Anal Cytology as a Screening Strategy for Anal Neoplasia

Studies	Sensitivity	Specificity	PPV	NPV
Moscicki 2016	55-93%	32-81%	26-57%	82-88%
Ramos-Cartagena 2020	85.4%	38.8%	45.6%	81.6%
Chiao 2020	83%	50%	37%	
Sambursky 2018	89%	51%	24%	96%
Heard 2015	82%	76%	22%	98%
Albuquerque 2018	71%	73%	55%	84%

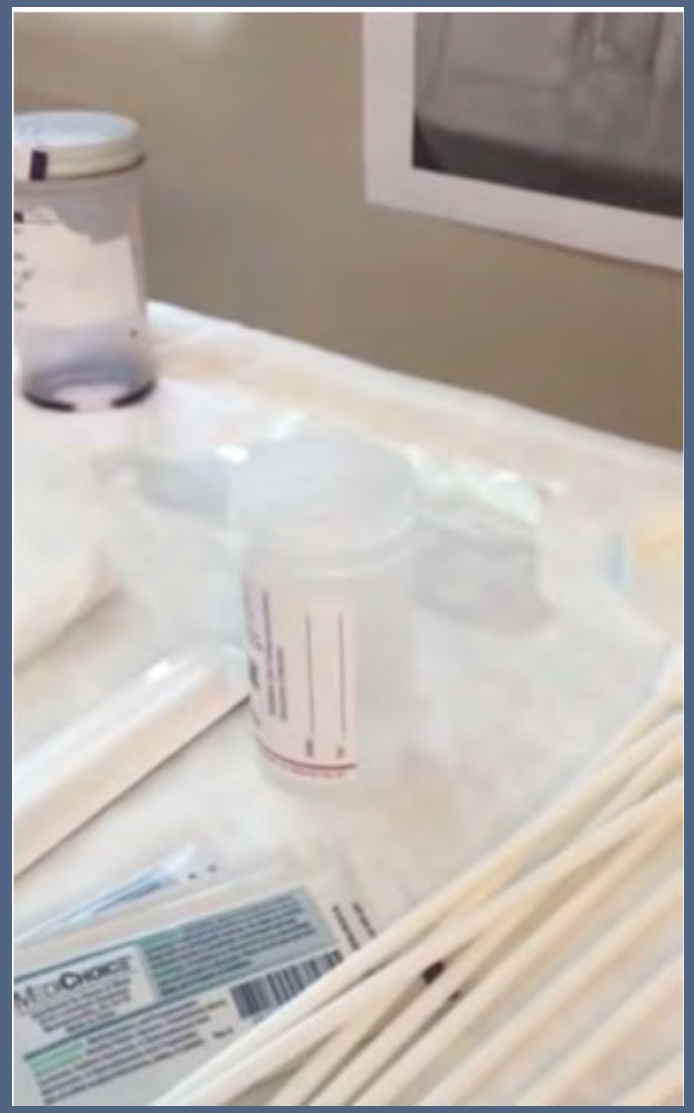
Sensitivity, Specificity, PPV and NPV for Anal Cytology to predict anal HSIL

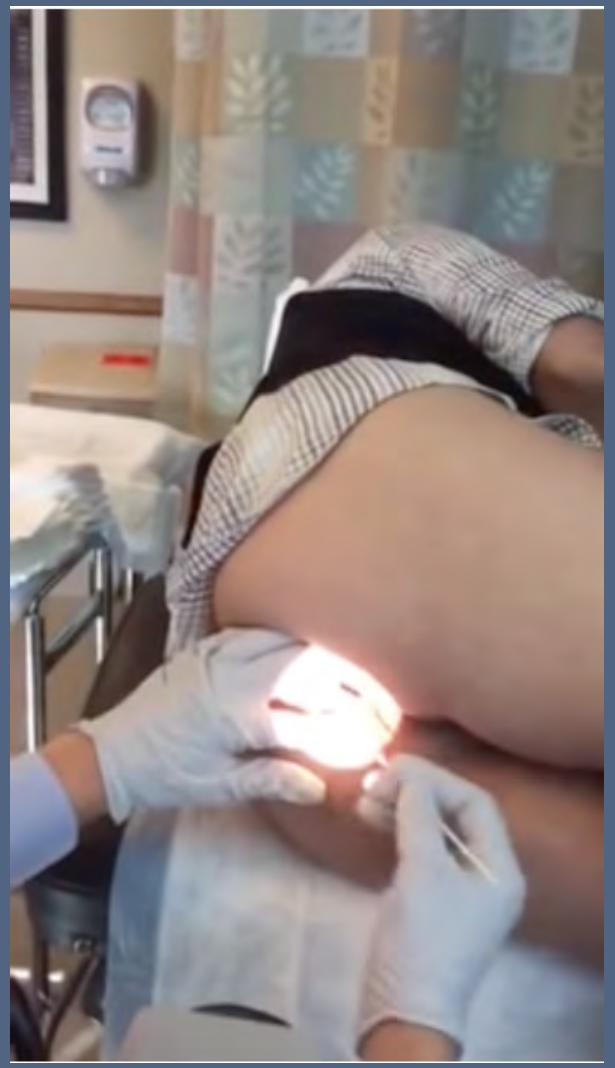
High-Risk HPV as a Screening Strategy for Anal Neoplasia

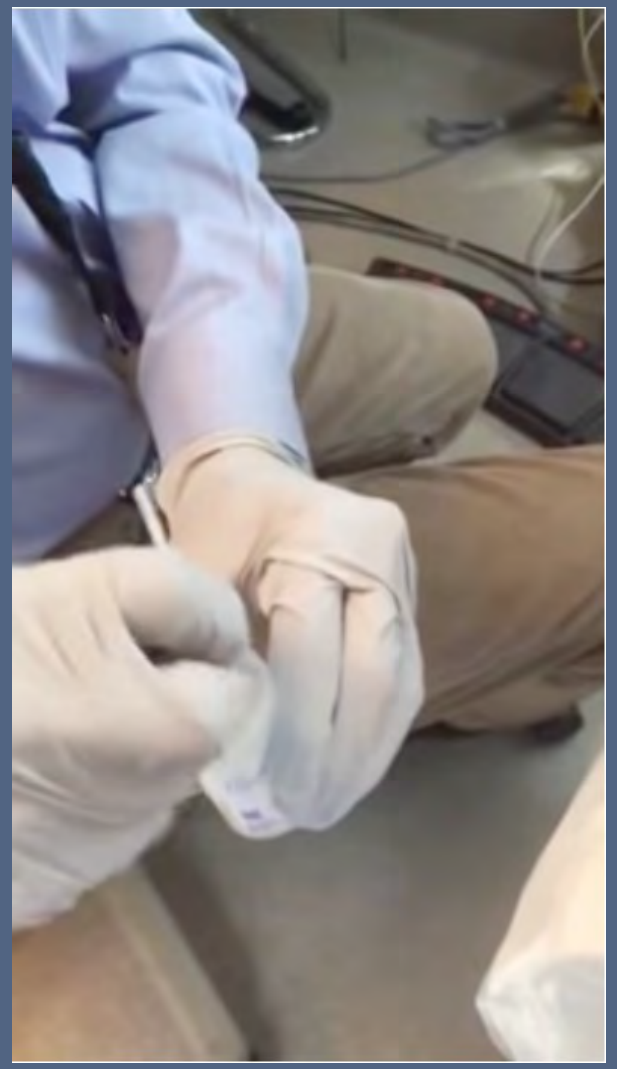
Studies	Sensitivity	Specificity	PPV	NPV
Moscicki 2016	55-93%	32.81%	26-57%	82-88%
Ramos-Cartagena 2020	95.8%	31.3%	45.5%	92.6%
Chiao 2020	77%	67%	45%	
Sambursky	96%	48%	24%	99%
Heard 2015	91%	44%	12%	98%

Sensitivity, Specificity, PPV and NPV for HR HPV to predict anal HSIL

Obtaining Anal Cytology/HPV







https://www.youtube.com/watch?v=YyzmLYFc7Yc (Jeff Logan – How to Perform anal Cytology)

But… should we screen??

Lessons from the cervix – anal assumptions

- High Grade Squamous Intraepithelial Lesions (HSIL) is the anal cancer precursor lesion
- Natural history of HPV, HSIL, and anal cancer is similar to cervical HPV, HSIL, and cervical cancer
- Hypothesized that:
  - *Screening at risk populations-> Identification of anal HSIL -> treatment of anal HSIL -> prevent progression of anal cancer*

High Resolution Anoscopy (*Identification*)

- Office-based procedure for examination of the anus, anal canal and perianus using a colposcope with 5% acetic acid and Lugol's solution
- Adapted from cervical colposcopy
- Tools, terminology, lesion descriptions and patterns validated for anal canal
- Differences from cervical colposcopy? Yes
  - Long learning curve

HRA

- Synthetic polyester swab
- Anoscopes – flat end 15mm
- Forceps ≤ 3mm
  - Flat-end baby Tischler
- Colposcope
  - Focal length 250-300mm
  - Direct view
  - Magnification (≥)
  - Angled eyepieces
  - Side-arm or overhead

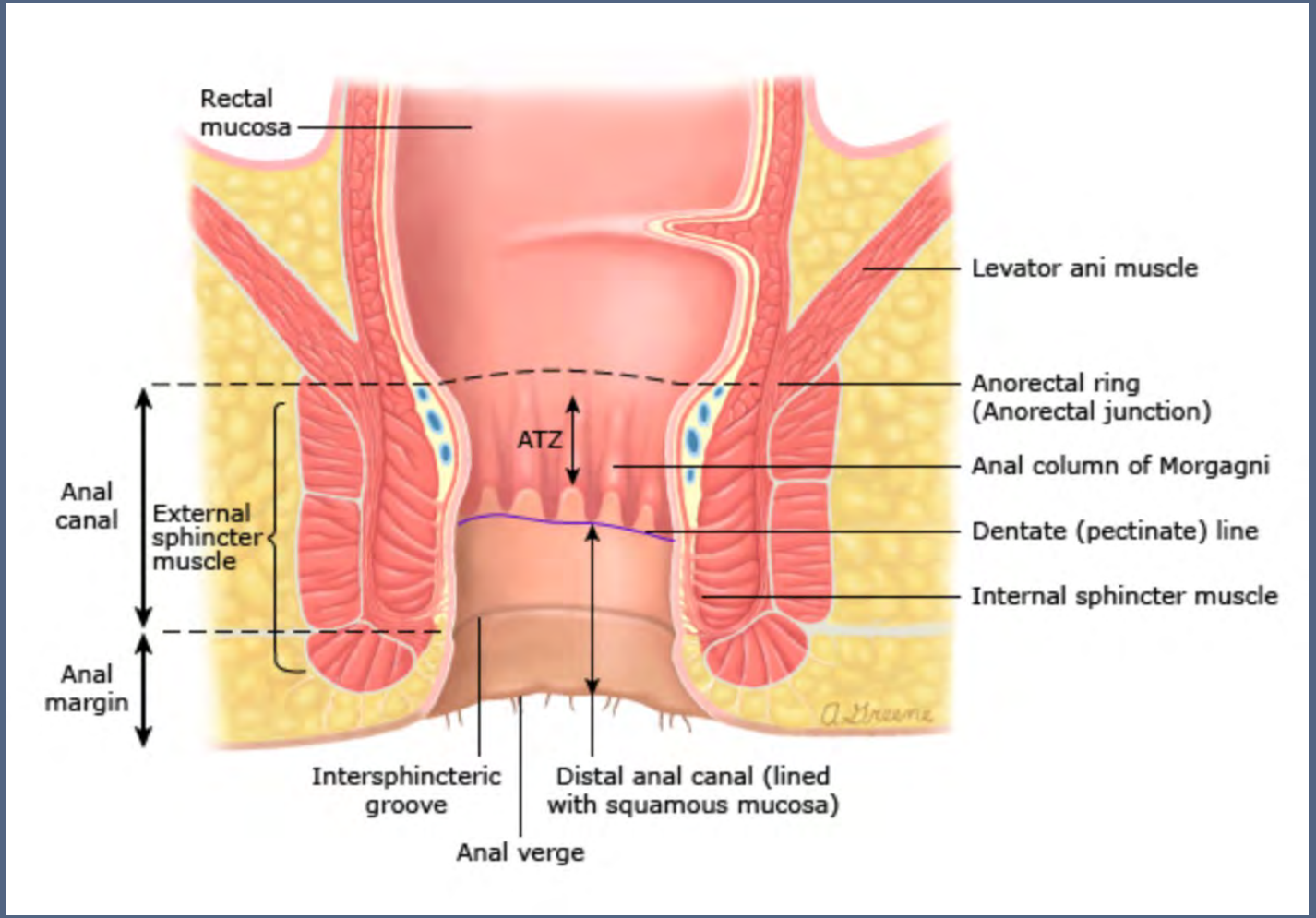
Cervical Colposcopy

- Cytobrush & spatula
- Specula
- Forceps – large & small
  - Variety of sizes and cups
- Colposcope
  - Focal length 300-350mm
  - Direct or videoscope
  - Magnification (low field ok)
  - Straight-on eyepieces
  - Center, side-arm, overhead

Slide from N. Jay

Anal Cancer – Transformation Zone

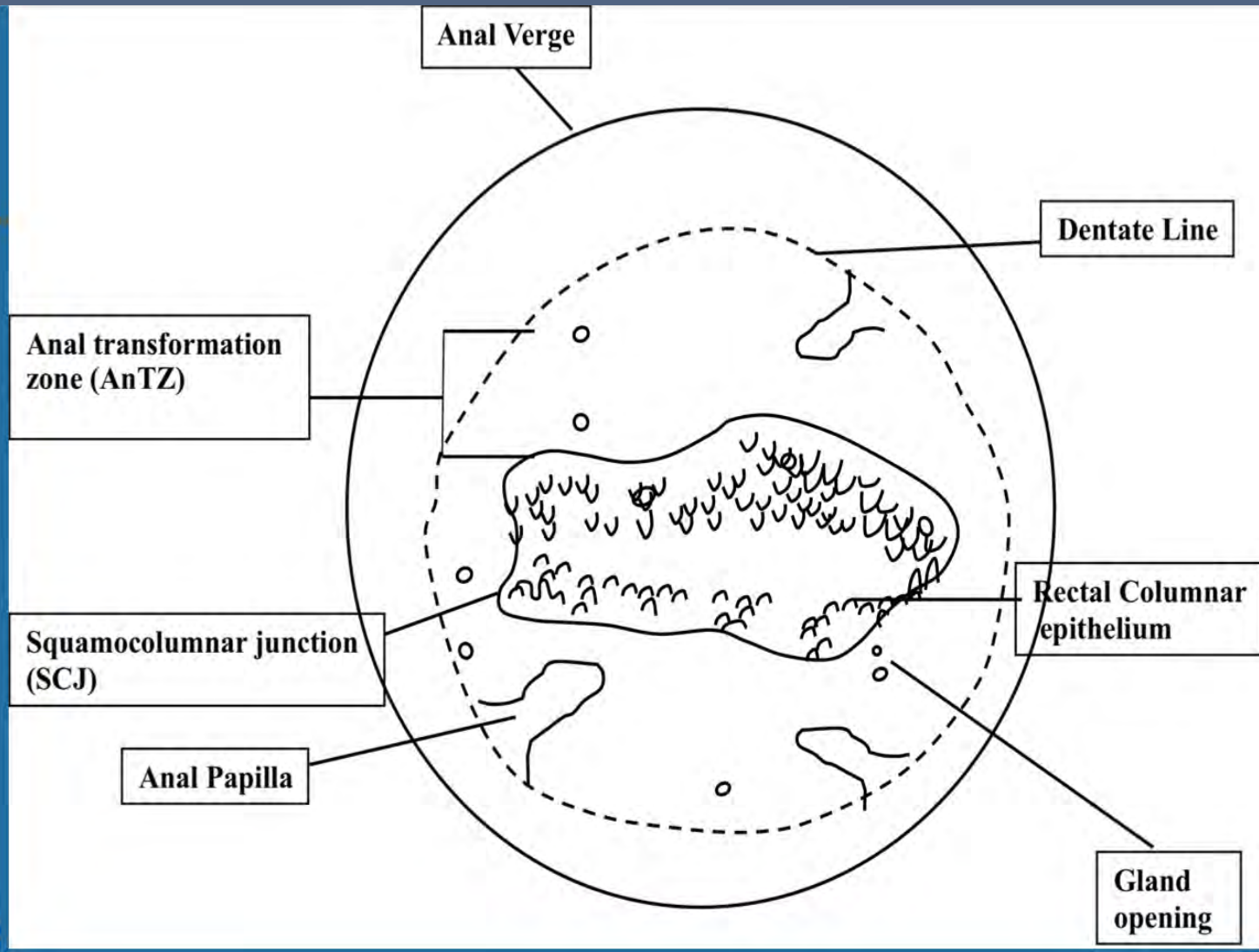
- Morphologically analogous to the cervical transformation zone
- Region of squamous metaplasia
- ”Immature” squamous metaplasia
  - Leading edge at SCJ
  - Most susceptible to HPV



Terminology

- Rectal/columnar (larger view)
- SCJ (harder to find)
- AnTZ (less features)
- Dentate Line
- Verge
- Perianus = anal margin

  5 cm (anterior midway to introitus)



Slide from N. Jay

HRA View of the SCJ

- Anal squamous epithelium abuts the rectal columnar epithelium
- Thin white line of metaplasia
- Only seen with acetic acid and metaplasia
- Need manipulation to see in its entirety
- There is always an SCJ
- Close to the verge in women

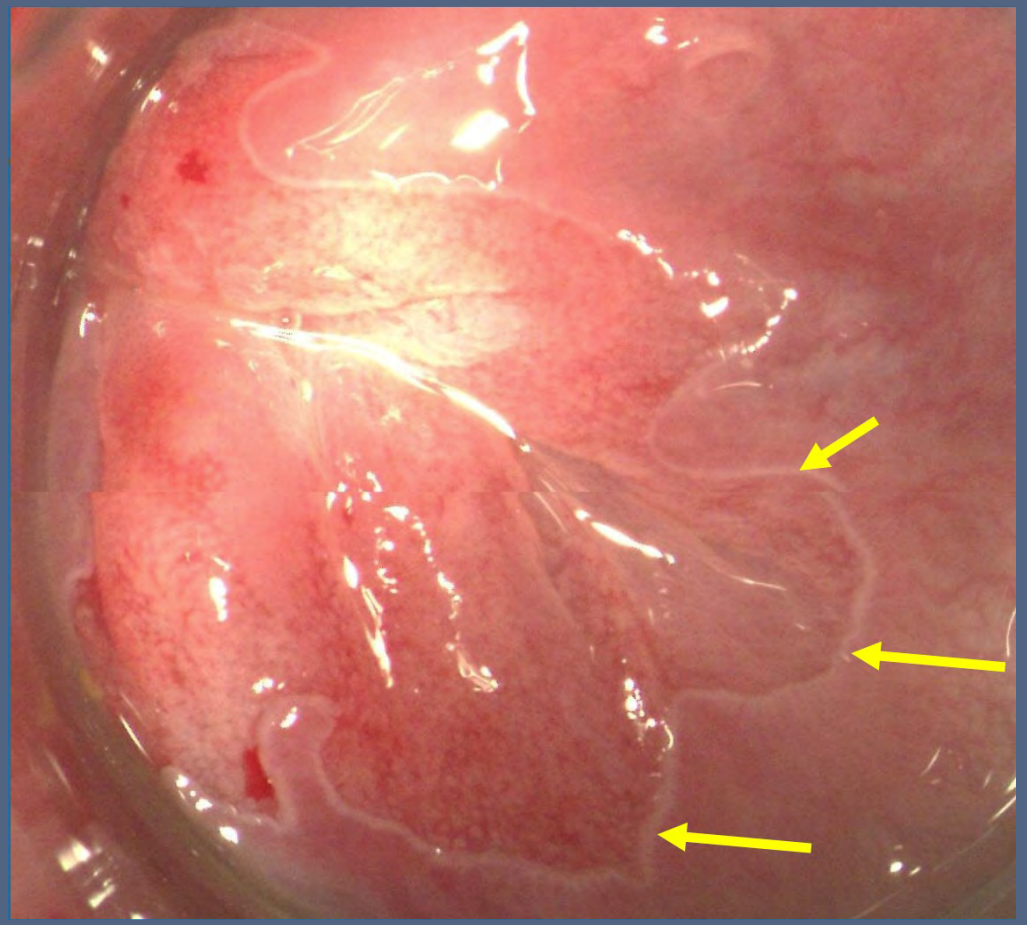
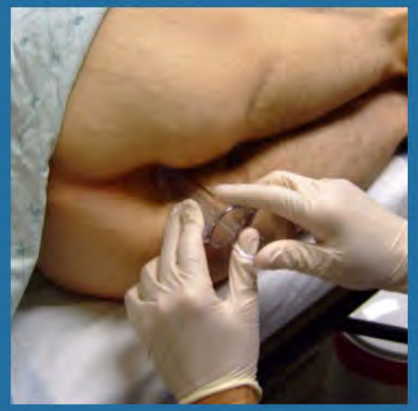


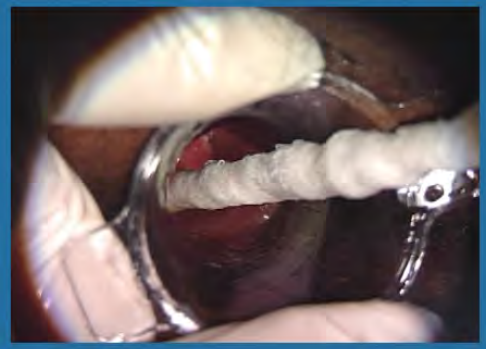
Photo from N Jay

HRA Exam Steps

1) Position – lateral or prone.

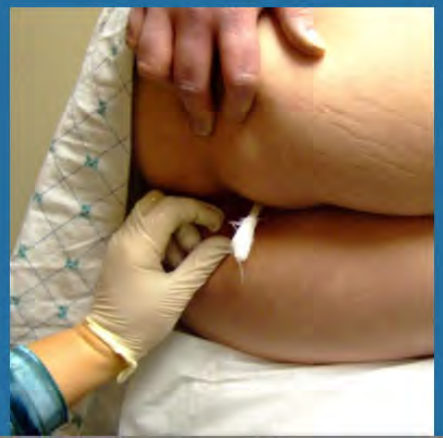


2) Insert Q-tip wrapped in gauze soaked in 5% acetic acid through anoscope.



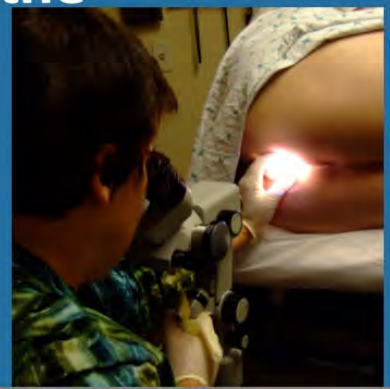
3) Remove anoscope leaving swab & gauze inside. Soak for 1-2 minutes.

3a) inspect perianus



4) Remove gauze and re-insert anoscope.

5) Observe through colposcope slowly withdrawing the anoscope until the SCJ is seen.

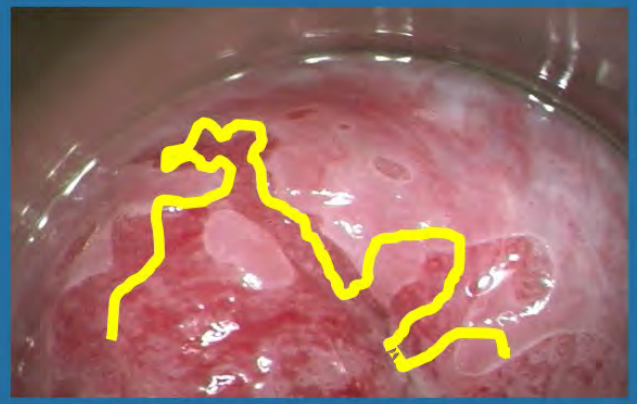


Slide from N. Jay

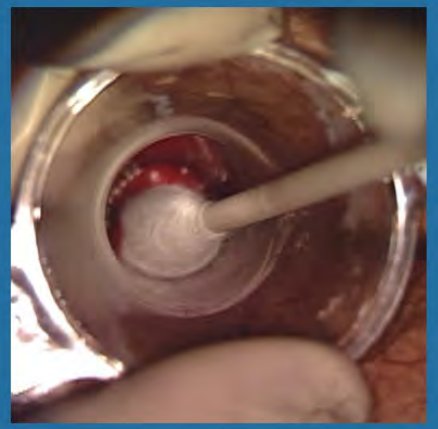
HRA Exam (con't)

Slides N. Jay

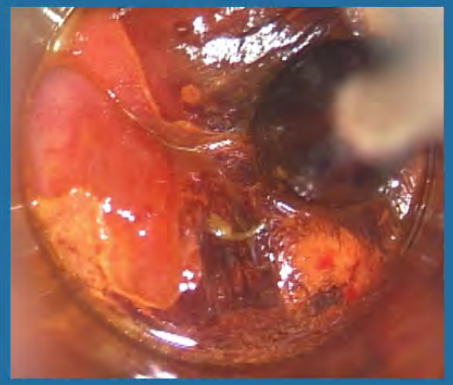
5) Examine entire SCJ



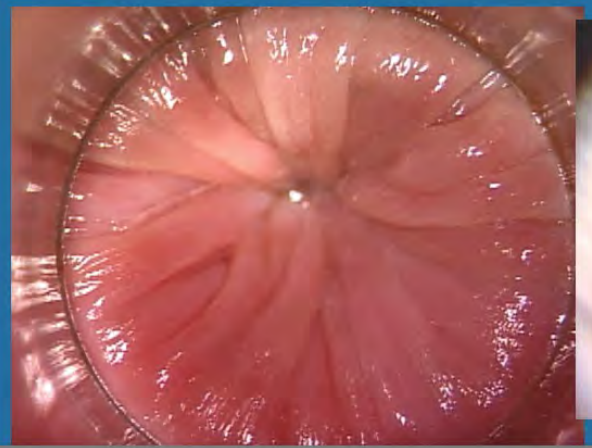
6) Reapply acetic acid liberally throughout exam.

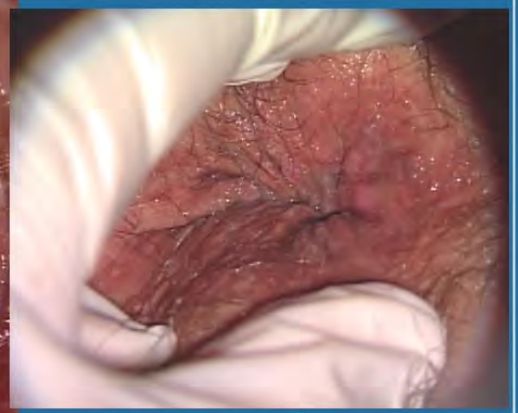


7) Apply Lugol's solution after acetic acid w/cotton swabs



8) Observe distal canal & verge as anoscope is withdrawn, then perianus.



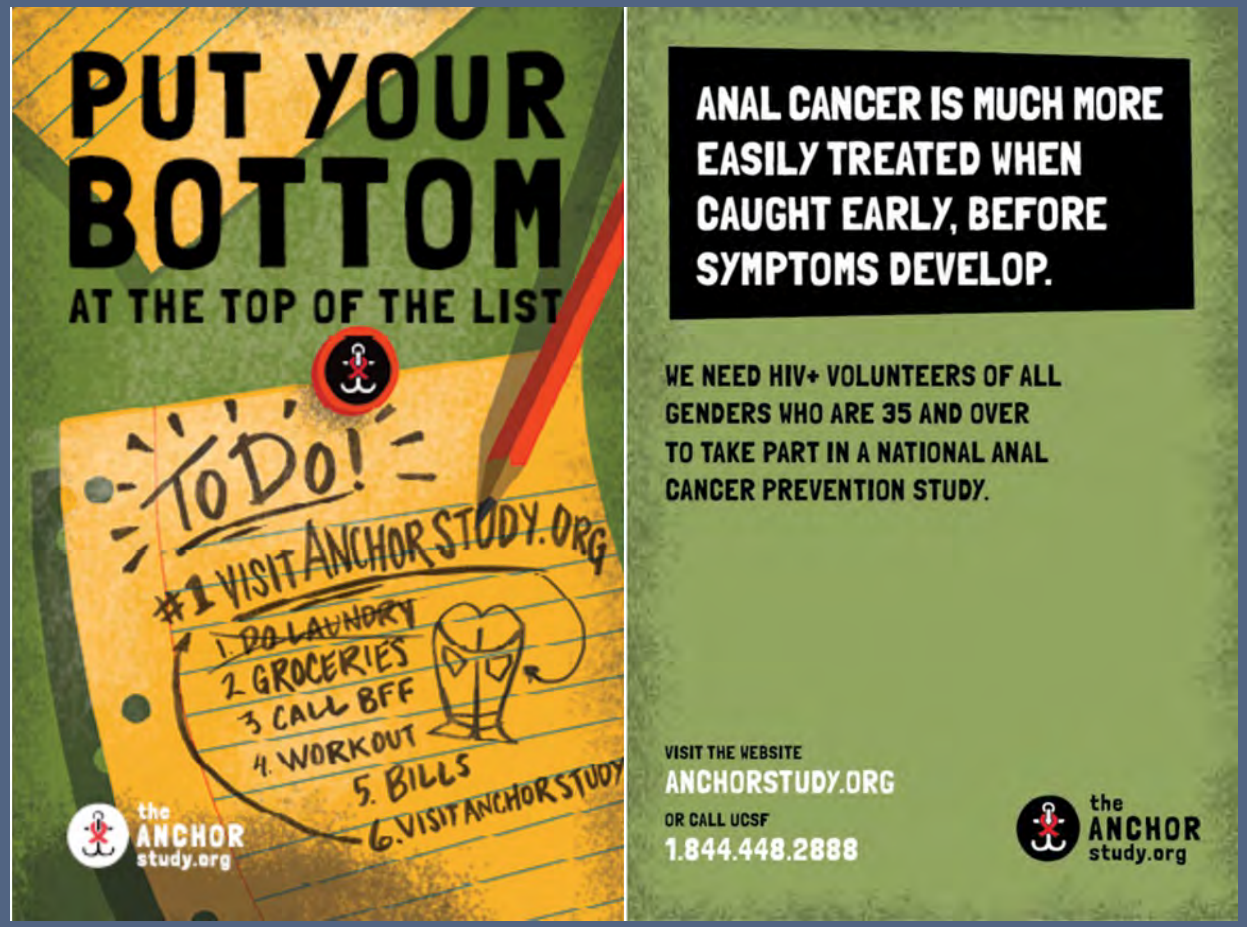


Lessons from the cervix – anal assumptions

- High Grade Squamous Intraepithelial Lesions (HSIL) is the anal cancer precursor lesion
- Natural history of HPV, HSIL, and anal cancer is similar to HPV, HSIL, and cancer
- Hypothesized that:
  - *Screening at risk individuals -> Identification of anal HSIL -> treatment of anal HSIL -> prevent progression of anal cancer*

Does treatment work to prevent cancer??

The ANCHOR Study



- Anal Cancer HSIL Outcomes Research
- Enrolled patients over 35 years of age with HIV and confirmed anal HSIL
- Randomized to treatment versus expectant management

The ANCHOR Study - Results

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer

J.M. Palefsky, J.Y. Lee, N. Jay, S.E. Goldstone, T.M. Darragh, H.A. Dunlevy, I. Rosa-Cunha, A. Arons, J.C. Pugliese, D. Vena, J.A. Sparano, T.J. Wilkin, G. Bucher, E.A. Stier, M. Tirado Gomez, L. Flowers, L.F. Barroso, R.T. Mitsuyasu, S.Y. Lensing, J. Logan, D.M. Aboulafia, J.T. Schouten, J. de la Ossa, R. Levine, J.D. Korman, M. Hagensee, T.M. Atkinson, M.H. Einstein, B.M. Cracchiolo, D. Wiley, G.B. Ellsworth, C. Brickman, and J.M. Berry-Lawhorn, for the ANCHOR Investigators Group*

The ANCHOR Study - Results

- Patients enrolled September 24, 2014 through August 5, 2021
  - Screened 10,723 total patients
  - HSIL confirmed
    - 4257/7729 men (55.1%)
    - 860/1822 women (47.2%)
    - 188/280 transgender persons (67.1%)
    - 17 patients received an anal cancer diagnosis at baseline
- 4459 enrolled patients
  - Median followup of 25.8 months

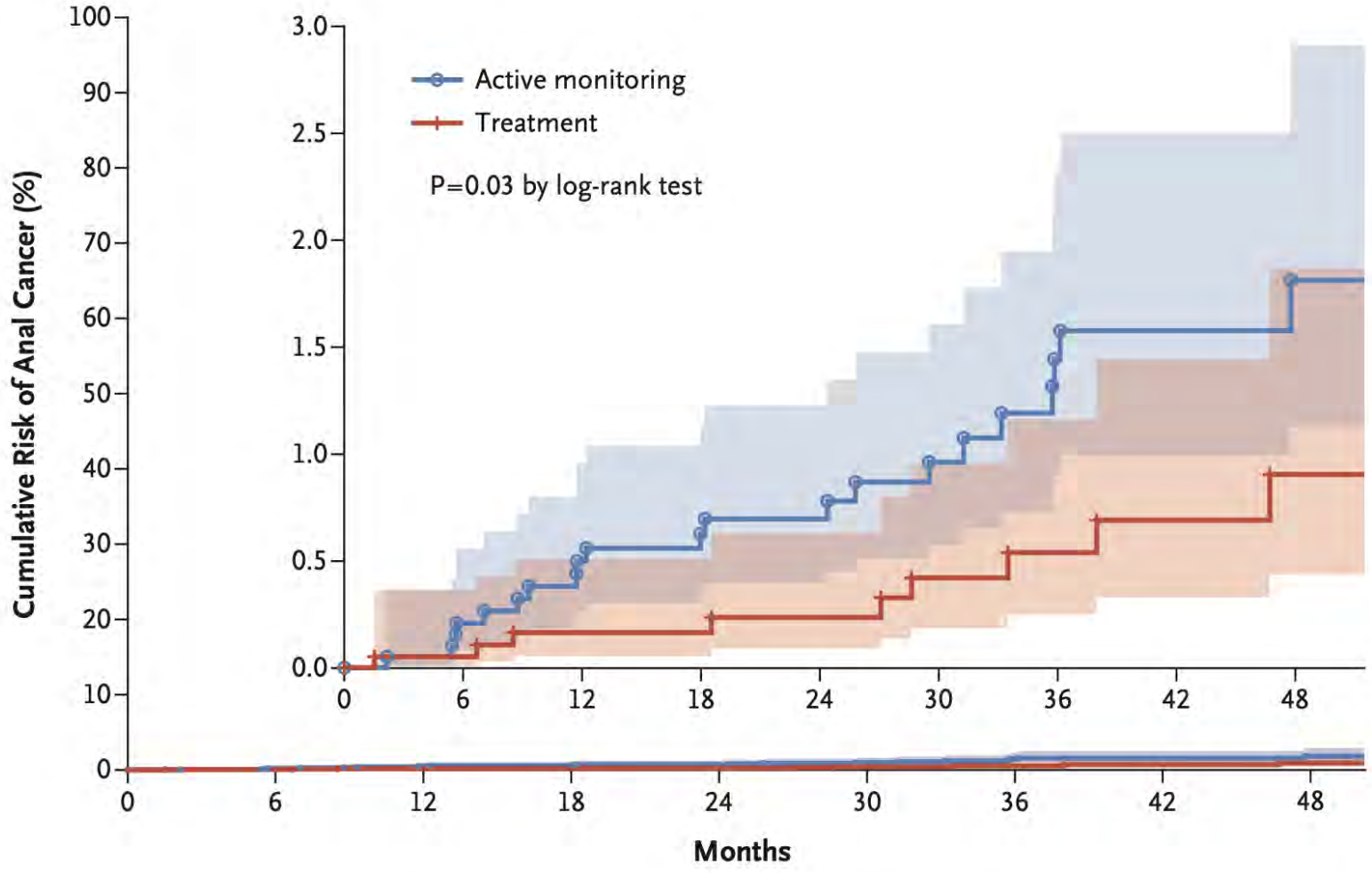
Palefsky. NEJM 2022

Types of Treatment

- No specific treatment for HPV
  - Patient-applied topical: imiquimod and 5% fluorouracil cream
  - Clinician-applied topical: 85% trichloroacetic acid, cryotherapy
  - Clinician-applied ablation: infrared coagulation (4.8%), electrocautery (86.2%), laser
  - Surgical excision

Progression to Cancer

- Cumulative progression to cancer at 48 months was 0.9% in the treatment arm and 1.8% in the monitoring arm
  - 57% reduction in anal cancer (95% CI 6% to 80%, p=0.029)
- Cancer incidence in the treatment arm was 173/100,000 PY of follow-up compared to 402/100,000 PY in the AM monitoring arm
  - 185/100,000 PY (95% CI: 115-298) for lesions less than or equal to 50% size
  - 1047/100,000 PY (95% CI: 608-1803) >50 size
  - Hazard ratio 5.26, 95% CI: 2.54-10.87



No. at Risk									
Active monitoring	2219	1856	1671	1459	1238	992	758	572	407
Treatment	2227	1871	1655	1473	1224	989	753	557	409

Figure 2. Kaplan–Meier Curve of the Time to Progression to Anal Cancer.

The inset shows the data on an expanded y axis. The shaded areas represent 95% confidence intervals.

- 9 cancers diagnosed in treatment group
- 22 cancers diagnosed in active monitoring
- Overall reduction in rate of cancer 57%

Take home points from the ANCHOR study

- Treating anal HSIL can prevent invasive anal cancer
- Almost all participants had office-based electrocautery, primarily hyfrecation
- Operating room for extensive biopsying, disease too bulky to treat in office
- Treatment for HSIL is improving but even better treatments are needed
- Careful follow-up critical as patients tend to recur despite method of treatment

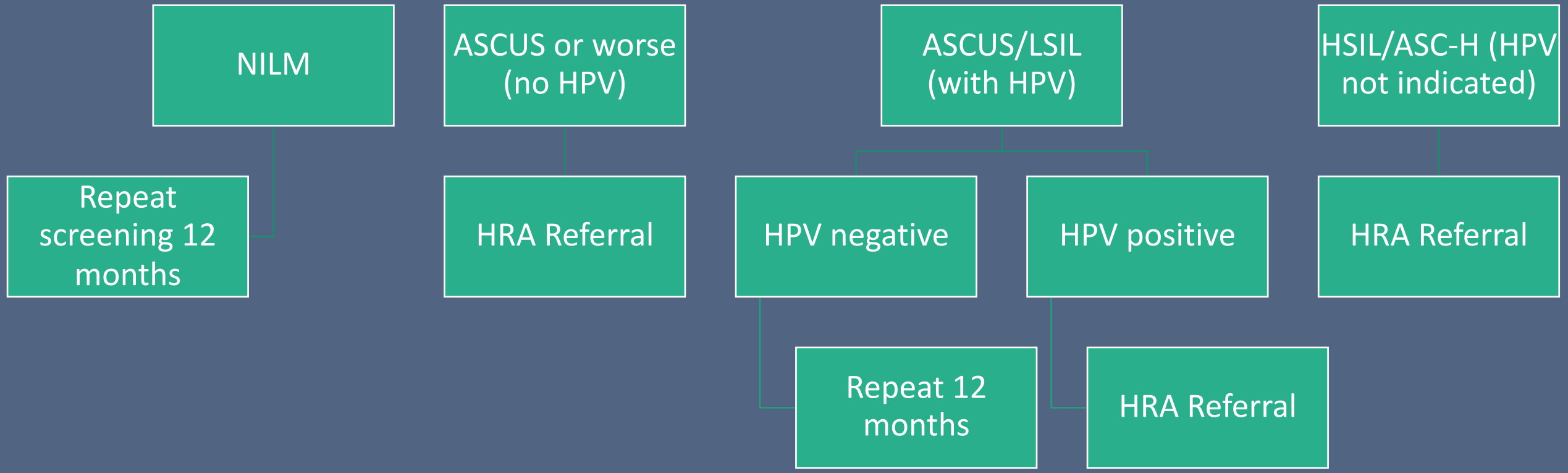
Should we screen?

- High risk patient populations
- Able to identify precancerous lesions
- Effective treatment
- Reduction of anal cancer…

OBGYNs – YES YOU SHOULD!


BREAKING NEWS
NEW GUIDELINES
IJC
INTERNATIONAL JOURNAL of CANCER
uicc
SPECIAL REPORT
Open Access
International Anal Neoplasia Society's consensus guidelines for anal cancer screening
Elizabeth A. Stier, Megan A. Clarke, Ashish A. Deshmukh, Nicolas Wentzensen, Yuxin Liu, I. Mary Poynten, Eugenio Nelson Cavallari, Valeria Fink, Luis F. Barroso ... See all authors
First published: 31 January 2024 | https://doi.org/10.1002/ijc.34850
FROM THE DESK OF RON BURGUNDY

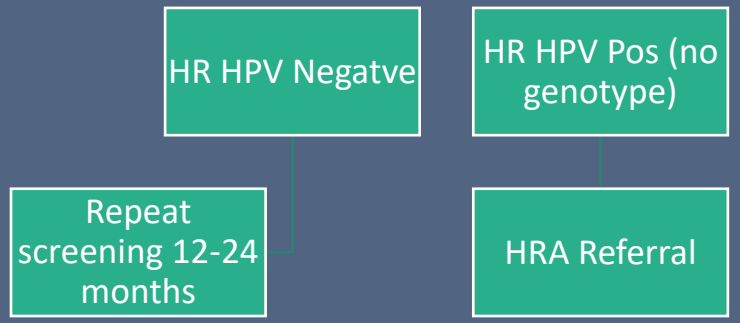
Management of Results – Cytology (+/- HPV)



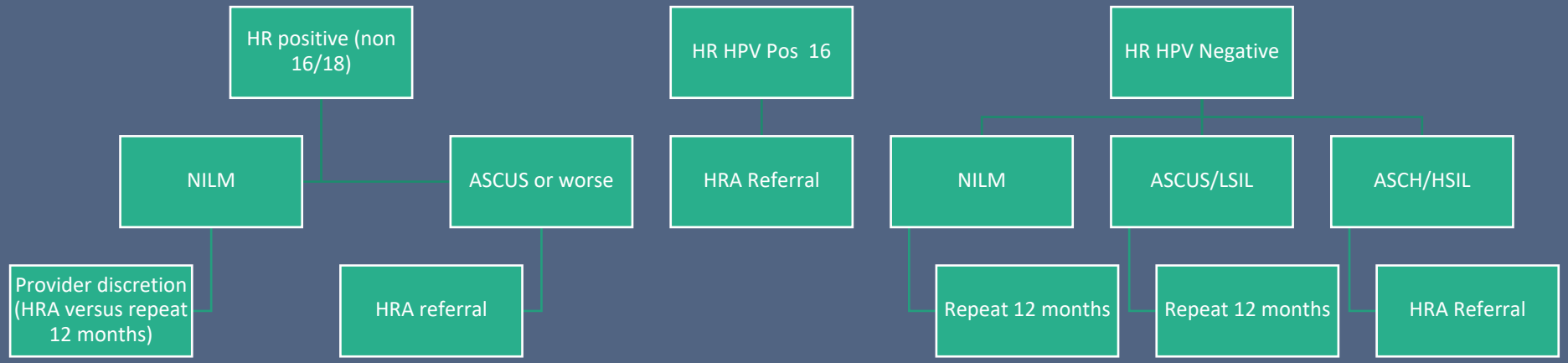
Stier. Int J Cancer 2024

Management of Results – HR HPV Testing

Primary HPV – No Cytology



Primary HPV – Reflex Cytology

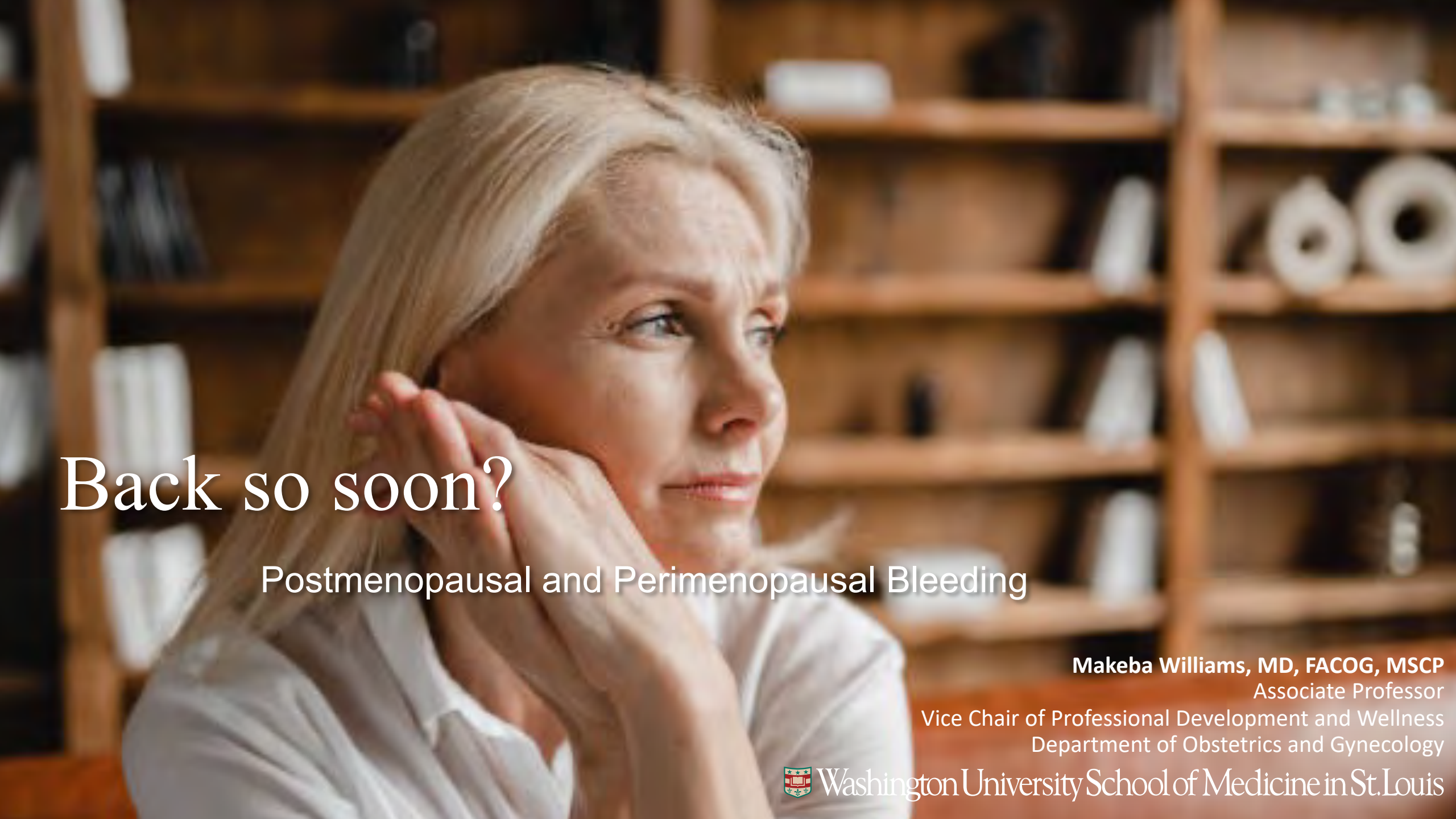


Stier. Int J Cancer 2024

Objectives

- Define anal cancer and describe the epidemiology
- Associate HPV and anal cancer
- Describe the role of an OBGYN in anal cancer screening
- Identify anal cancer screening strategies

DARE to CARE..
BACK THERE!



Back so soon?

Postmenopausal and Perimenopausal Bleeding

Makeba Williams, MD, FACOG, MSCP
Associate Professor
Vice Chair of Professional Development and Wellness
Department of Obstetrics and Gynecology
Washington University School of Medicine in St. Louis

Disclosures

Relevant Disclosures:

The Menopause Society Board of Directors

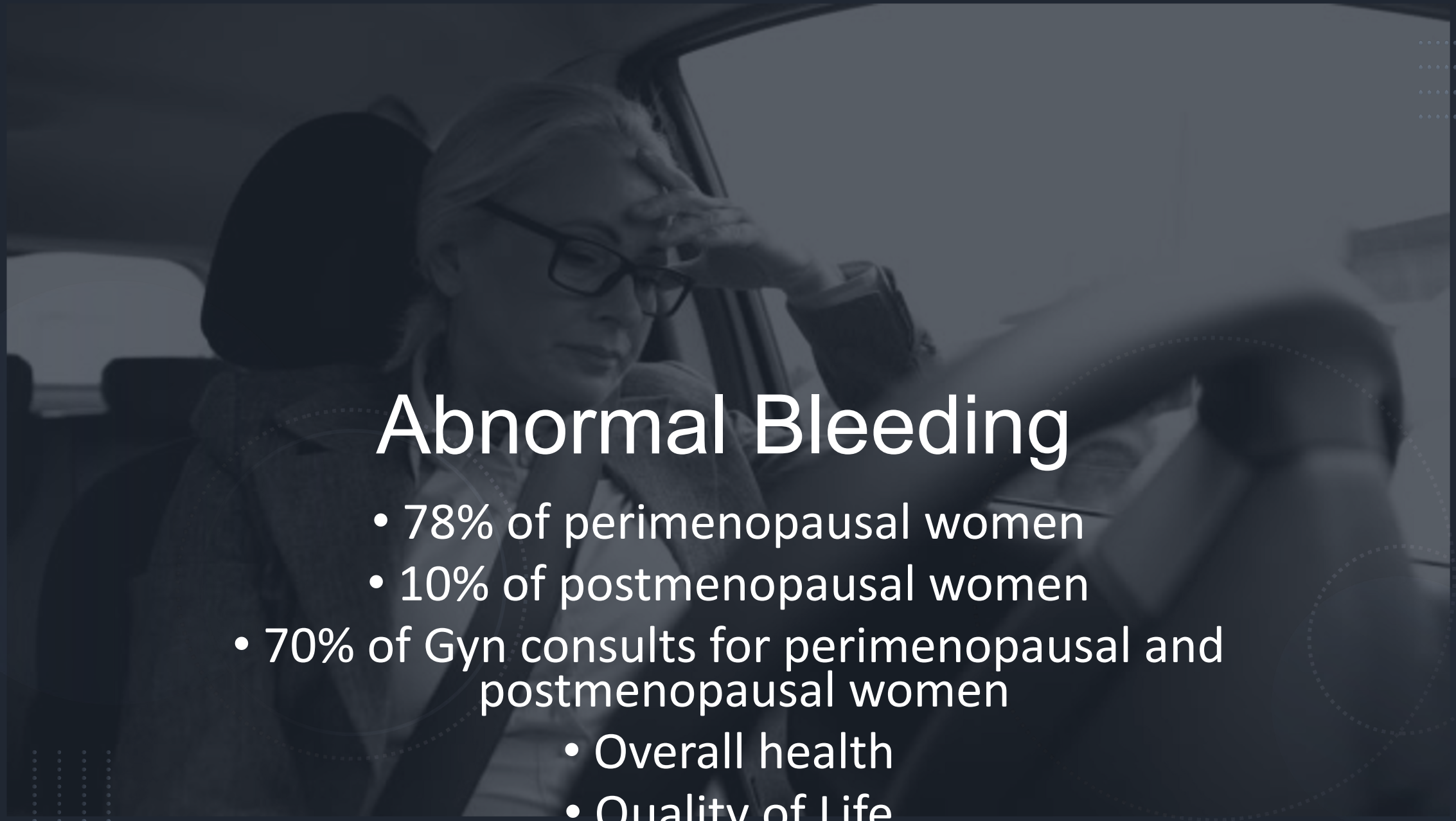
Consultant: Astellas

No conflicts of interest

References:

I will discuss clinical studies of off label use of pharmaceuticals for vasomotor symptoms.

This presentation references people born with ovaries. I may use the terms women, she, and her. These terms may not capture the diversity of all those experiencing menopause. We need more research to explore how diverse people experience menopause.



Abnormal Bleeding

- 78% of perimenopausal women
- 10% of postmenopausal women
- 70% of Gyn consults for perimenopausal and postmenopausal women
- Overall health
- Quality of Life

Learning Objectives

01

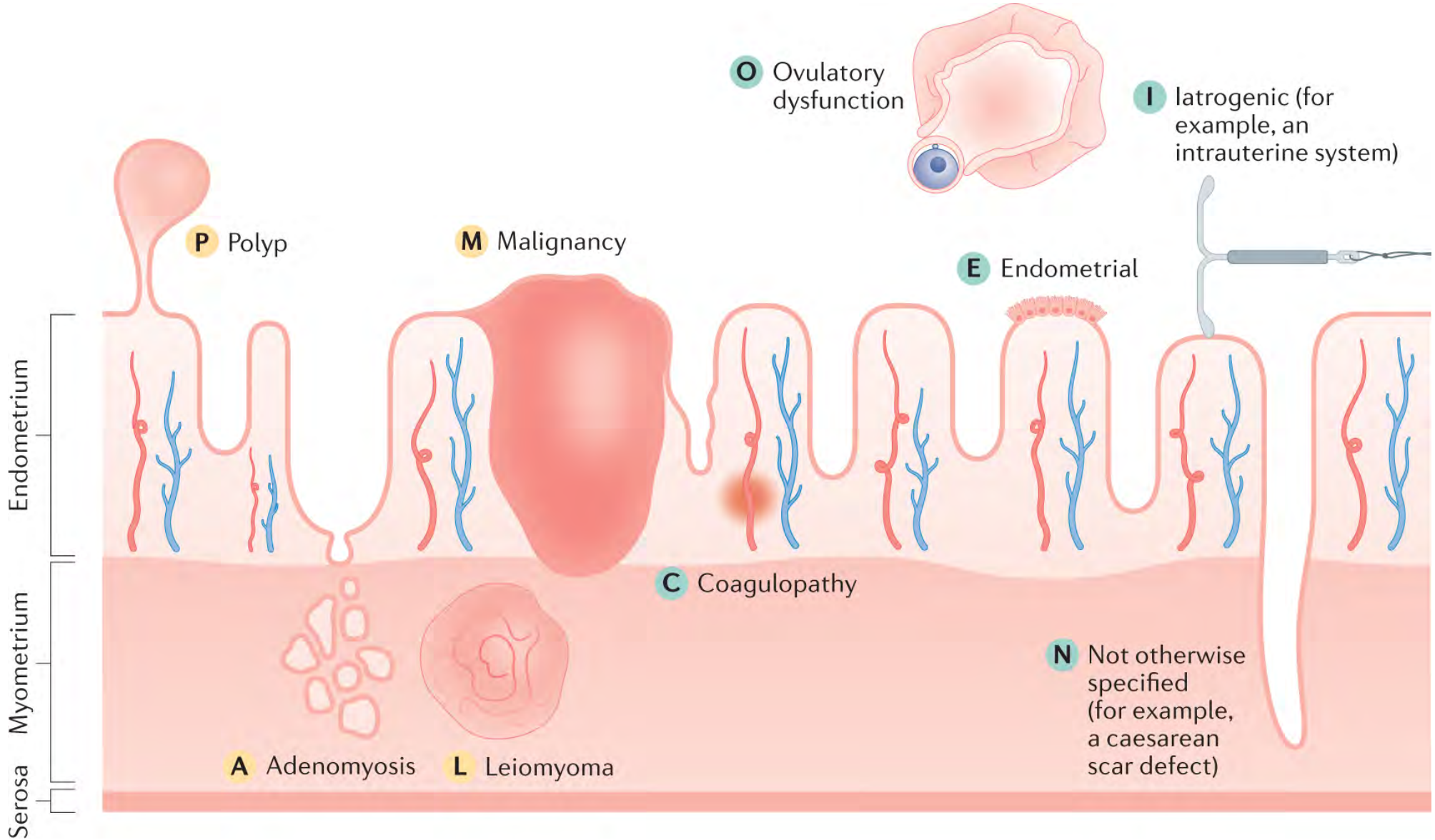
Describe the physiology and pathophysiology of perimenopausal and postmenopausal bleeding

02

Review diagnostic considerations for perimenopausal and postmenopausal bleeding

03

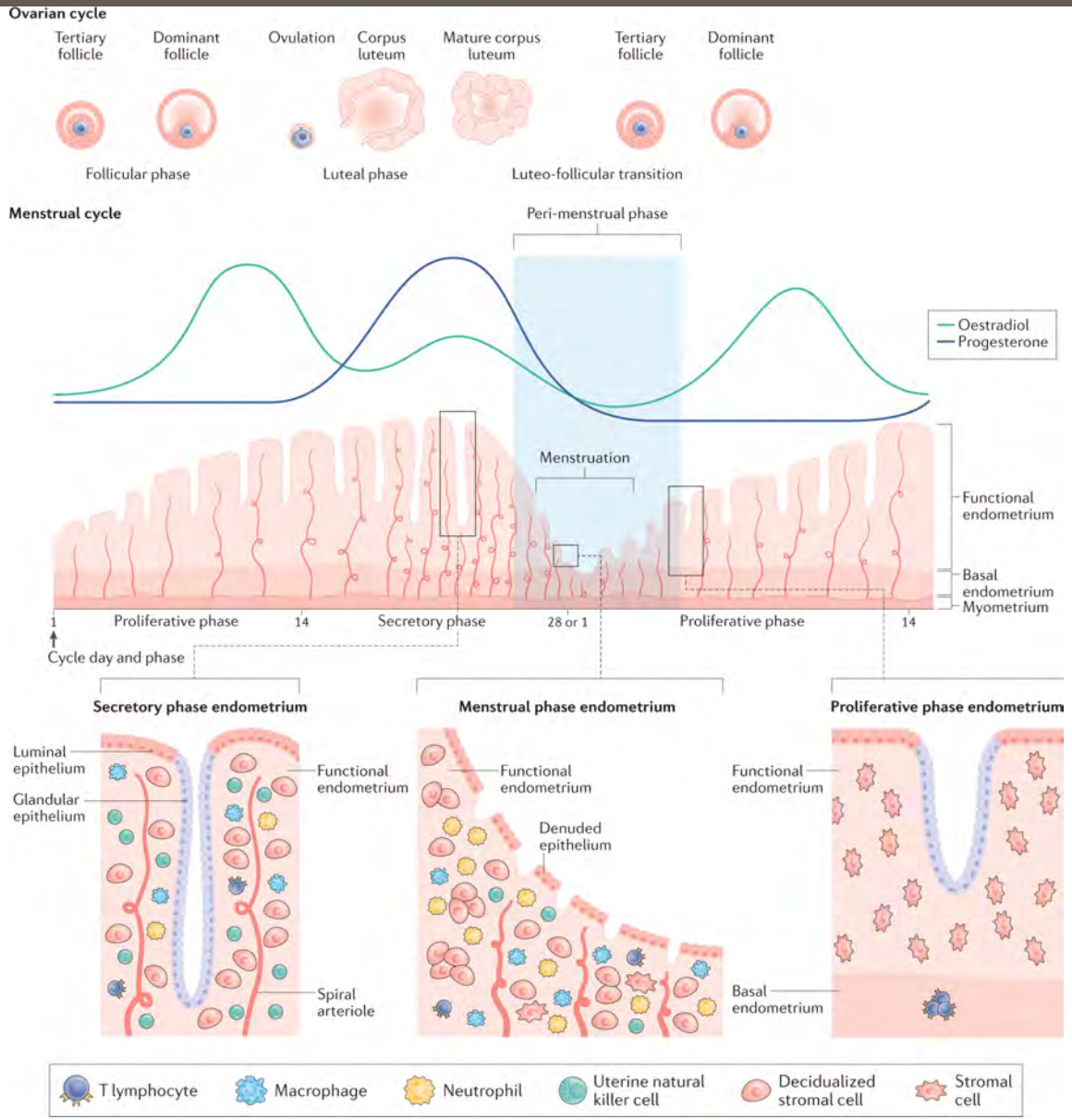
Discuss treatment options for abnormal bleeding in the menopause transition and menopause

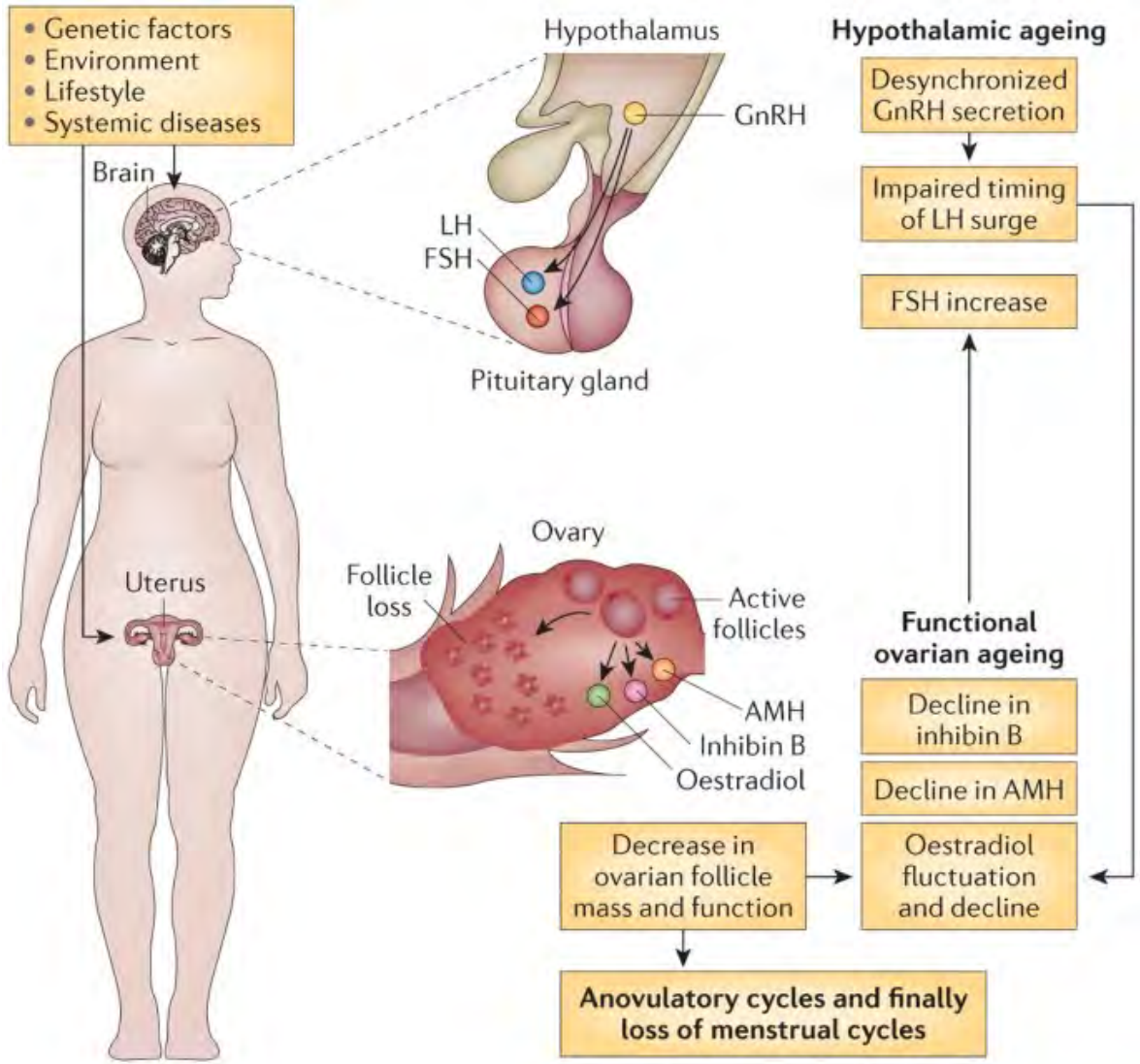


Nature Reviews Endocrinology (*Nat Rev Endocrinol*) ISSN 1759-5037 (online) ISSN 1759-5029 ()

Ovulatory Bleeding

- ORDERLY, PREDICTABLE
  - Endometrial proliferation, stromal stabilization
  - Hormone withdrawal
  - Endometrial shedding, coagulation and blood vessel repair
- Cycle resets


Ovarian cycle
Tertiary follicle
Dominant follicle
Ovulation
Corpus luteum
Mature corpus luteum
Tertiary follicle
Dominant follicle
Follicular phase
Luteal phase
Luteo-follicular transition
Menstrual cycle
Peri-menstrual phase
Oestradiol
Progesterone
Menstruation
Functional endometrium
Basal endometrium
Myometrium
1
Proliferative phase
14
Secretory phase
28 or 1
Proliferative phase
14
Cycle day and phase
Secretory phase endometrium
Menstrual phase endometrium
Proliferative phase endometrium
Luminal epithelium
Glandular epithelium
Functional endometrium
Spiral arteriole
Functional endometrium
Denuded epithelium
Functional endometrium
Basal endometrium
T lymphocyte
Macrophage
Neutrophil
Uterine natural killer cell
Decidualized stromal cell
Stromal cell



Nature Reviews | Disease Primers

Anovulatory Bleeding

UNCOORDINATED, UNPREDICTABLE

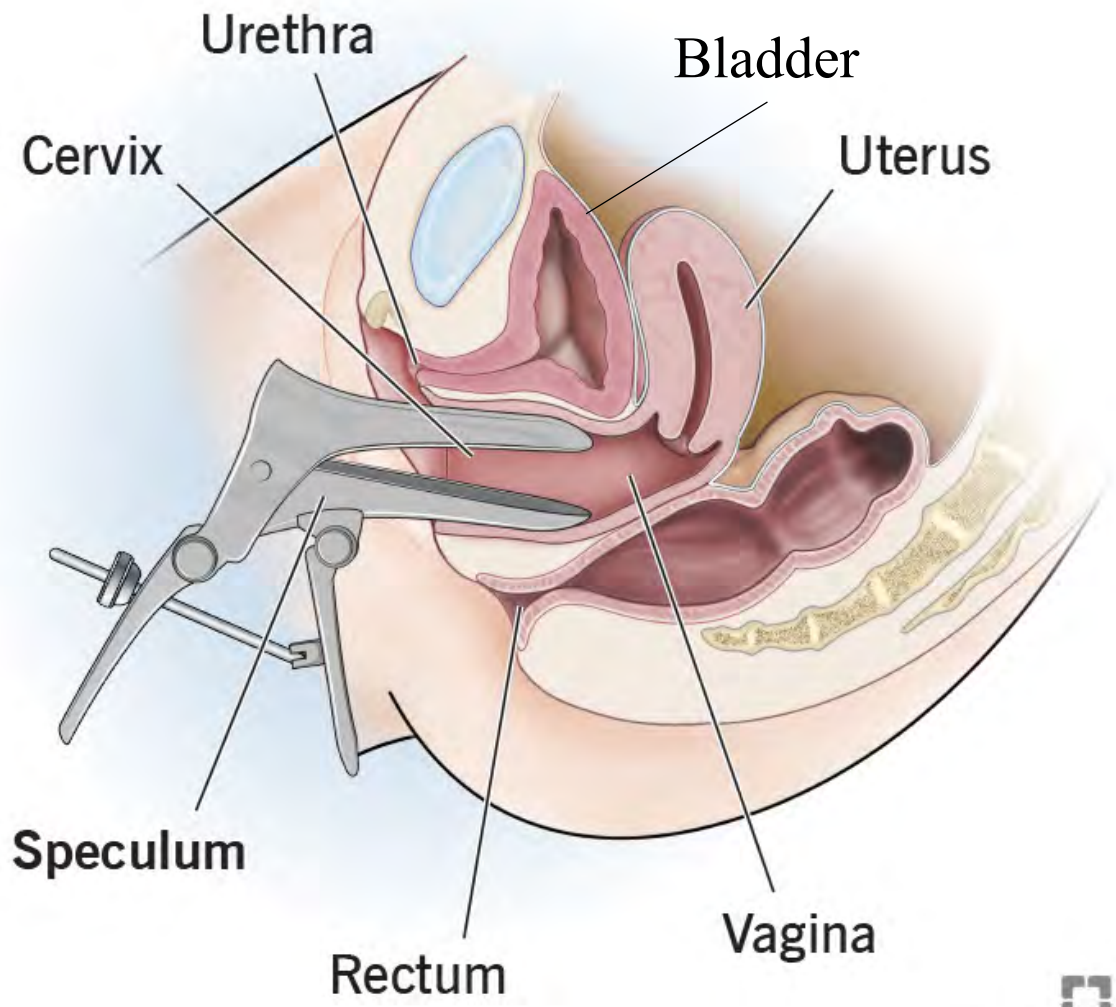
- Uncoordinated Hormone withdrawal
- Fragile endometrium, no stromal support:
- Irregular endometrial shedding, sloughing
- Erratic bleeding

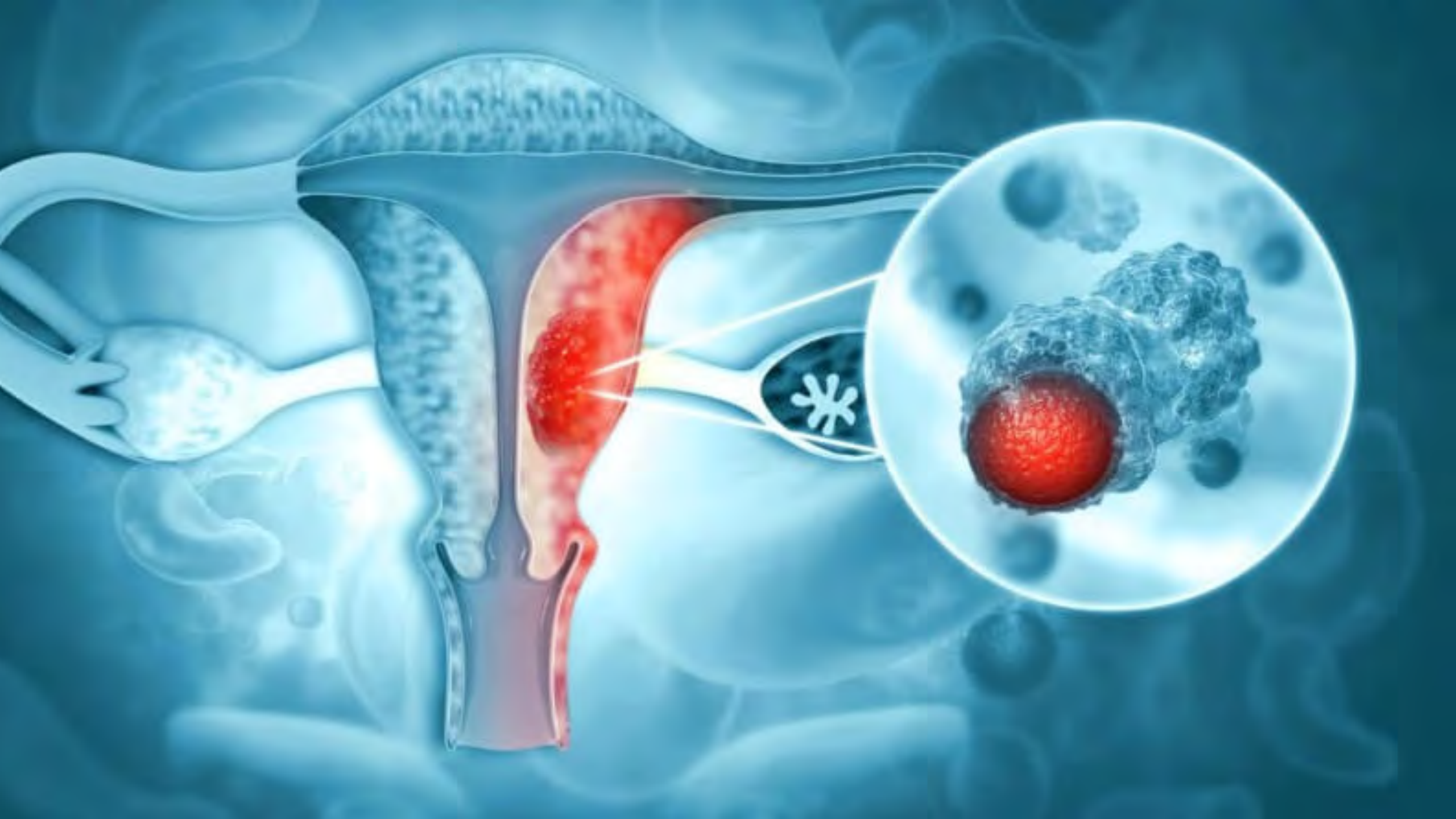
HISTORY

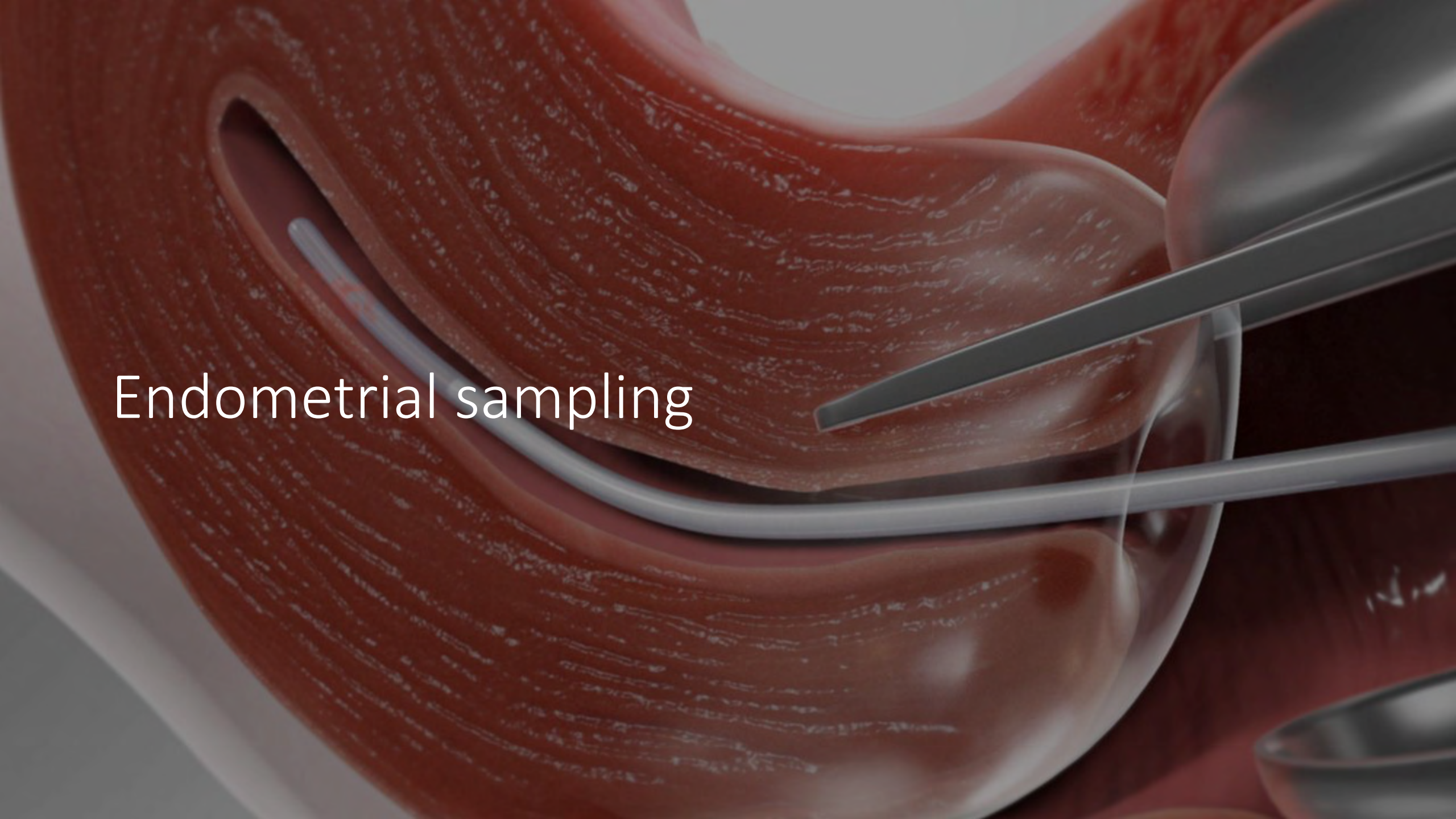
- Last or Final Menstrual Period
- Contextual factors of present bleeding
  - Onset, Duration, Frequency, volume
  - Absence of systemic symptoms such as breast tenderness, mucus, cramping, bloating, pain
- Menstrual history
  - Age at menarche
  - Age at menopause
- Gynecologic history
  - Infections
  - Abnormal Paps/HPV
- Past medical history: Obesity, PCOS, DM, Thyroid disorders, coagulopathies
- Surgical history
  - Prior pelvic procedures
- Social history
- Family history
  - Inherited mutations
- Medications
  - Hormones, Endocrine therapies, anticoagulants

Pelvic Exam

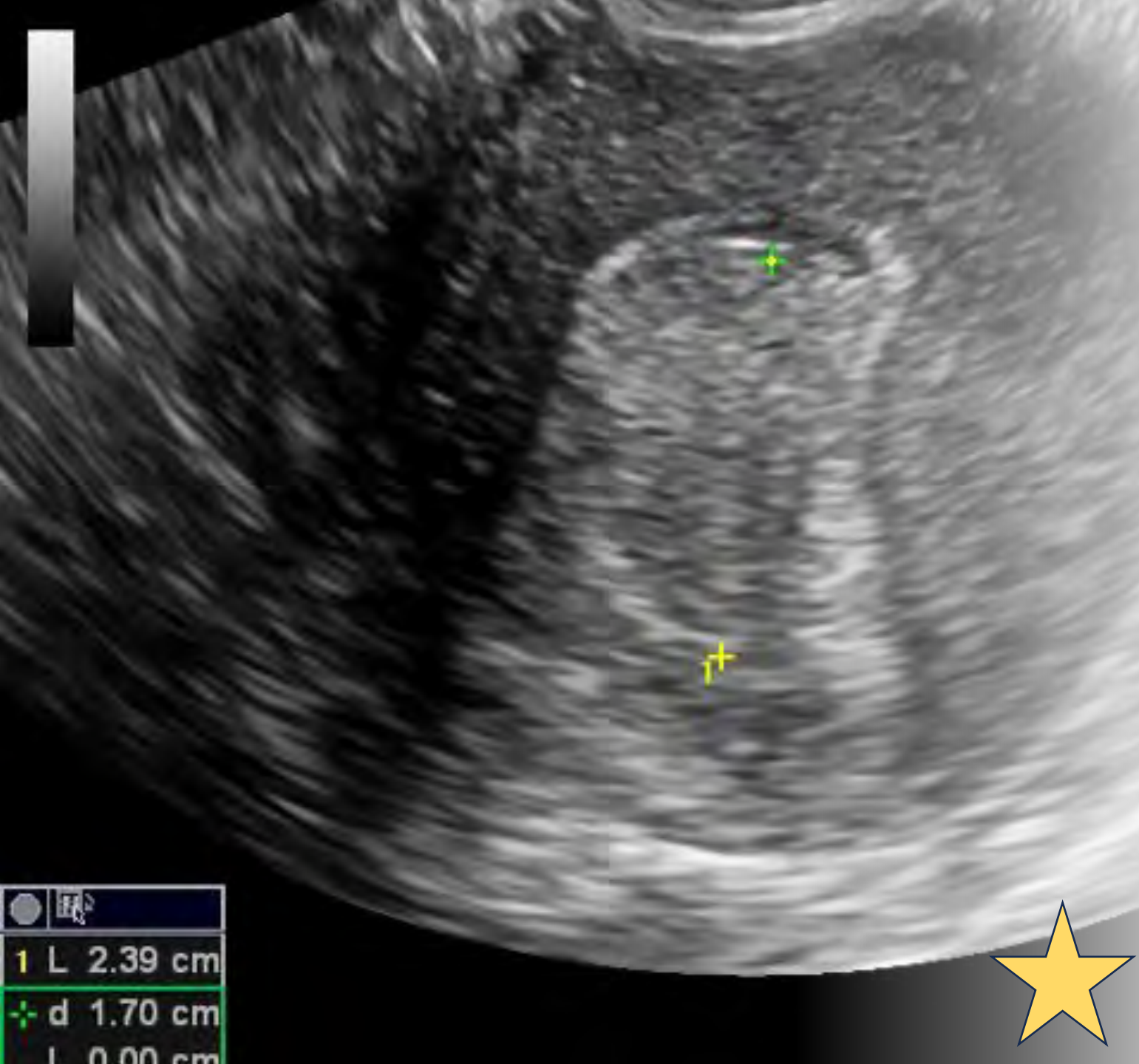
Exclude non-uterine bleeding







Endometrial sampling



Imaging

TVUS

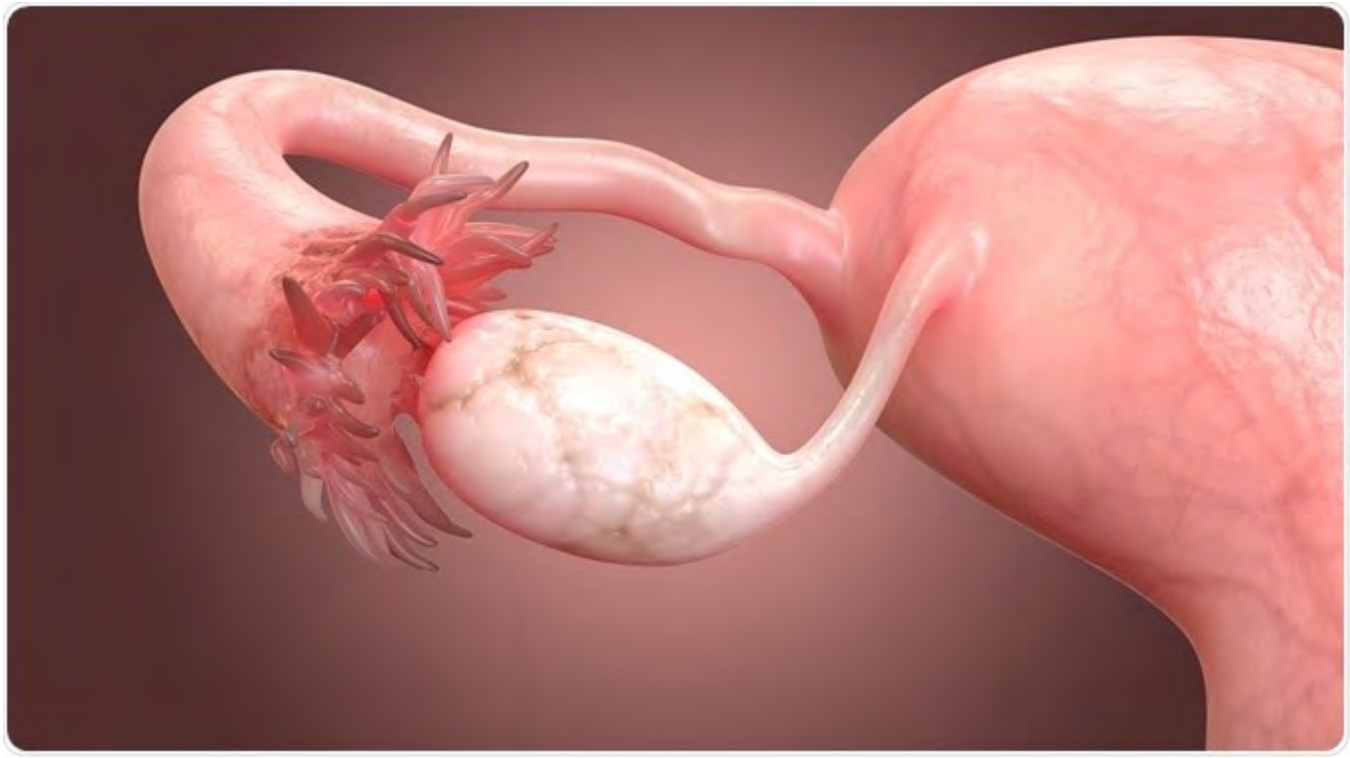
- First line assessment in low-risk women
- Measure Endometrial Thickness on long-axis views
- An endometrial thickness of ≤4 mm has a negative predictive value >99% for endometrial carcinoma
- Probability of endometrial cancer ~0.3%
- Limitations
  - Not diagnostic
  - Questionable accuracy in certain populations
  - Consider SIS or HSG

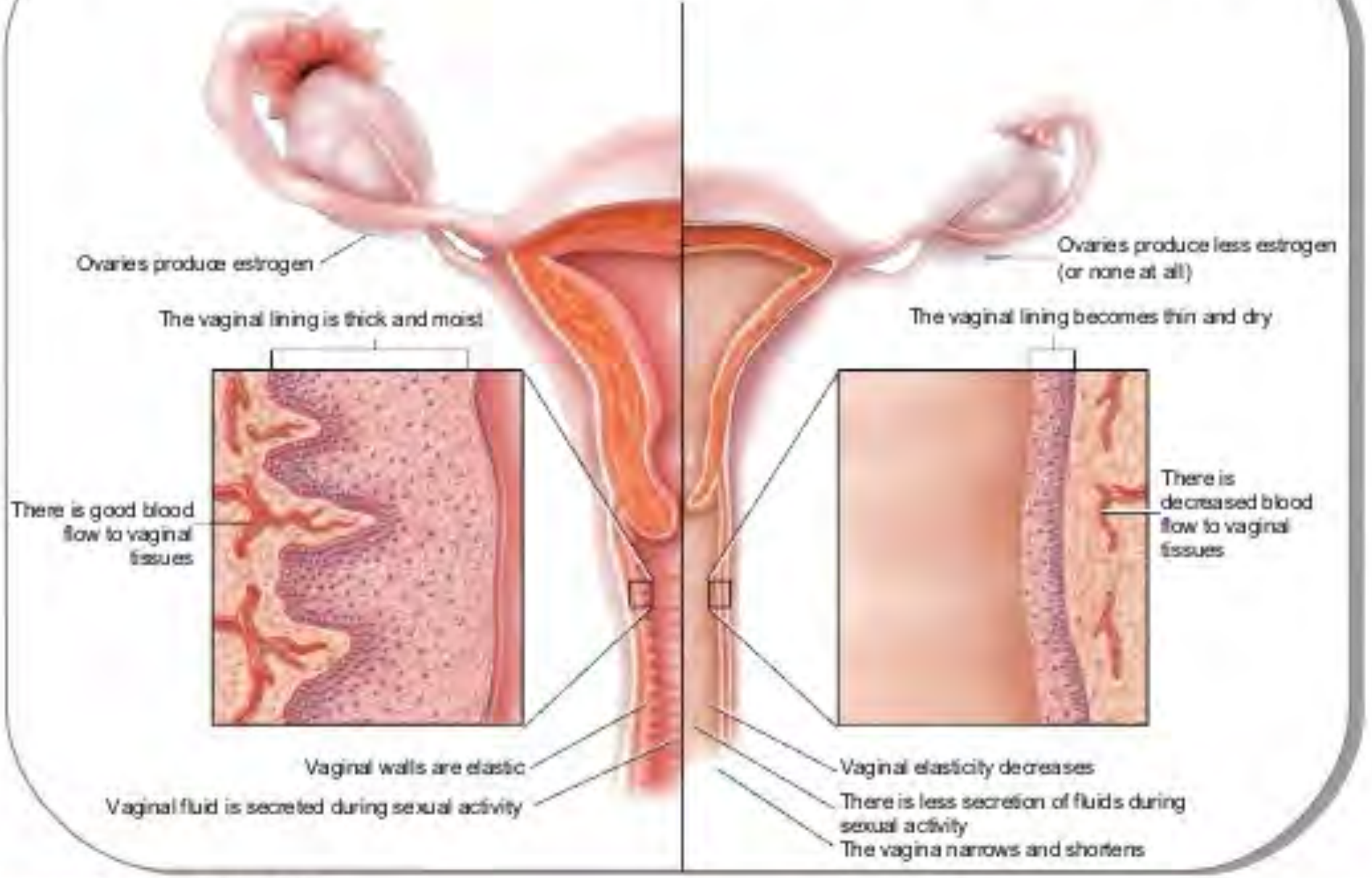
Hysteroscopy with D&C

Management

- Goal directed
  - Stop acute bleeding
  - Avoid irregular or heavy bleeding
  - Prevent complications: anemia, surgical interventions, diminished QOL
  - Contraception

Management: Anovulatory Bleeding in Perimenopause



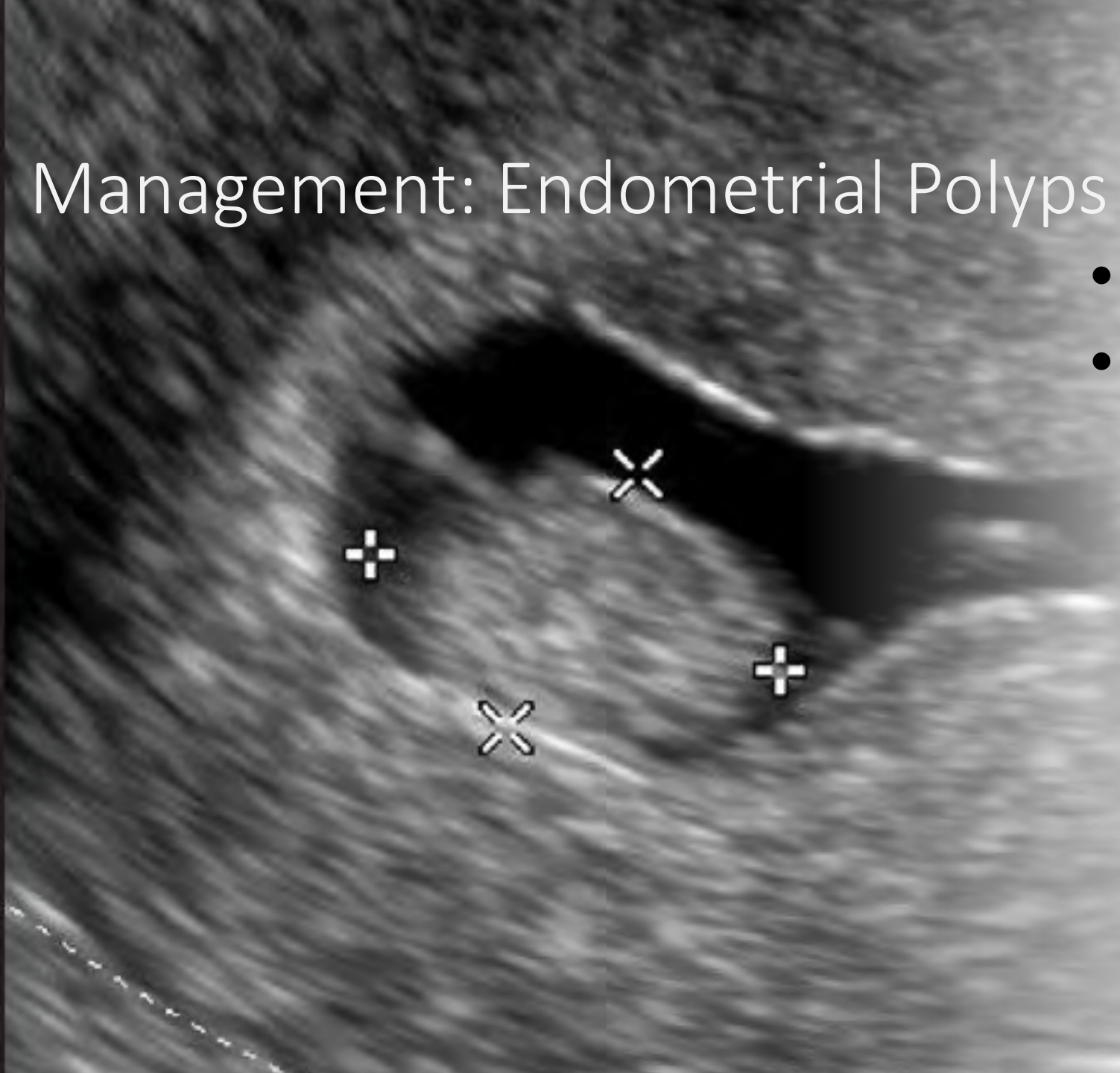


Johnston SL. *Geriatrics & Aging*. 2002;5(7):9-15.

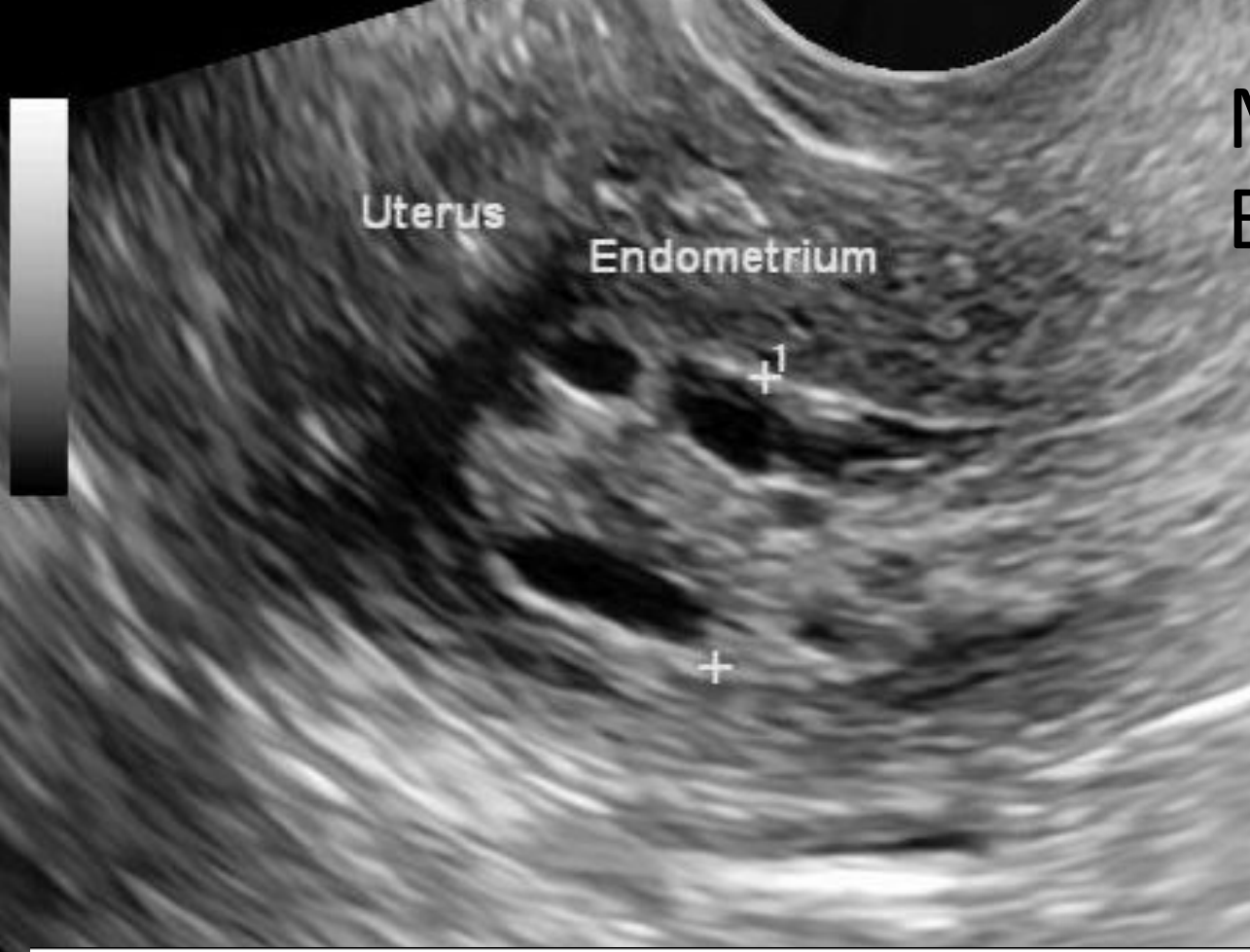
Endometrial Atrophy

- Thickness <4 mm
- Causes chronic inflammation
- Treat for chronic endometritis
- Doxycycline 100 mg BID x 10-12 days

Management: Endometrial Polyps



- Benign 99% of the time
- Surgical Excision if:
  - Symptomatic: bleeding
  - Risk factors present
    - Tamoxifen use
    - Obesity
    - Diabetes



Management: **Benign** Endometrial Hyperplasia

- D&C ± Hysteroscopy
- Hormone therapy
- Endometrial sampling
- Risk reduction strategies: weight loss
- Refer to ONCOLOGY?: EIN, Cancer

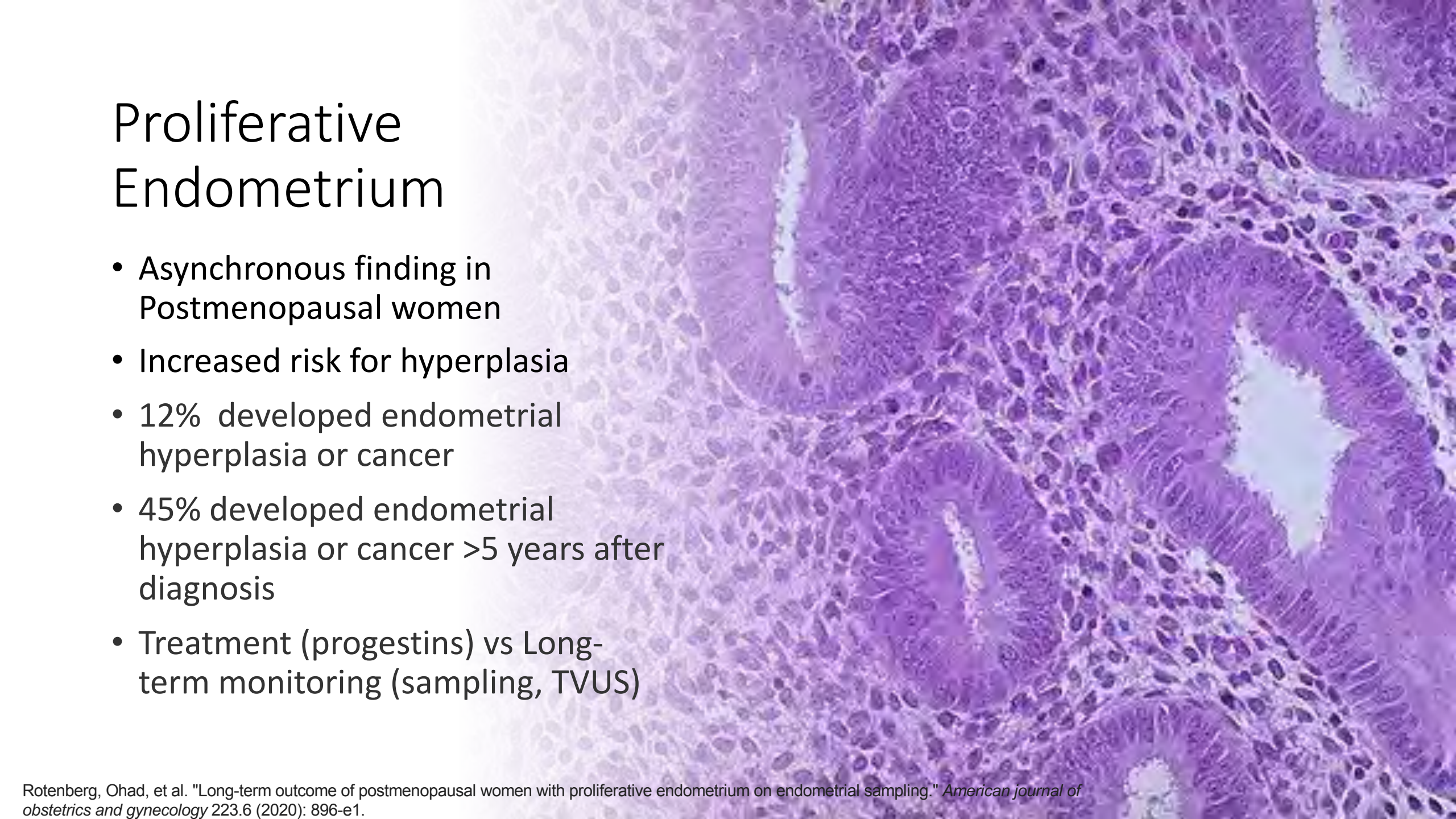
Hormonal Agent	Dosage and Length
Medroxyprogesterone acetate	10–20 mg/d (preferred) or cyclic 12–14 d/mo
Depot medroxyprogesterone	150 mg intramuscularly every 3 mo
Micronized vaginal progesterone	100–200 mg/d (preferred) or cyclic 12–14 d/mo
Megestrol acetate	80 mg twice/d (standard dose), range 40–200 mg/d
Levonorgestrel intrauterine system	52 mg in steroid reservoir over 5 y

Modified from Trimble CL, Method M, Leitao M, Lu K, Ioffe O, Hampton M, et al. Management of endometrial precancers. Obstet Gynecol 2012;120:1160–75. doi: 10.1097/aog.0b013e31826bb121

, Radiopaedia.org, rID: 30100

Proliferative Endometrium

- Asynchronous finding in Postmenopausal women
- Increased risk for hyperplasia
- 12% developed endometrial hyperplasia or cancer
- 45% developed endometrial hyperplasia or cancer >5 years after diagnosis
- Treatment (progestins) vs Long-term monitoring (sampling, TVUS)



Rotenberg, Ohad, et al. "Long-term outcome of postmenopausal women with proliferative endometrium on endometrial sampling." *American journal of obstetrics and gynecology* 223.6 (2020): 896-e1.

Management: Bleeding with Hormone Therapy Use

- No consensus guidelines
- Check the endometrial protection agent
  - Formulation
  - Compliance
- When to evaluate

Case 1

- A 63-year-old woman with well-controlled hypertension
- BMI: 25
- Social: nonsmoker, active but does not exercise
- Transdermal estrogen patch and micronized progesterone since age 49 and does not bleed while on HT
- Increased work travel in the last 4 years: misses 1 to 3 months of HT a few times a year
- Feels better while taking HT, does not experience hot flashes or mood or sleep disturbances
- Sexually active without any issues I
- In the last 6 months, when she is without her HT, she experiences sporadic spotting or bleeding but has not paid much attention to it because it stops when she restarts the HT
- Annual exam: PCP ordered TVUS and referred to GYN
  - EMS 6 mm
- Presents GYN office for HT refill

What do you do?

Case 2

- A healthy 55-year-old postmenopausal woman
- Uterine fibroids and no prior hysterectomy
- Transdermal estradiol with daily oral micronized progesterone for severe VMS with good response and strongly desires continuing
- Bothersome breakthrough bleeding

What do you do?

Diagnosing Infertility - Helping Your Patients Through The Process

Margareta D. Pisarska, MD

Director, Division of Reproductive Endocrinology and Infertility

Director, Center for Reproductive Medicine

Professor, Cedars-Sinai Medical Center

Cedars Sinai

Disclosures

- Ferring
- Natera

Objectives

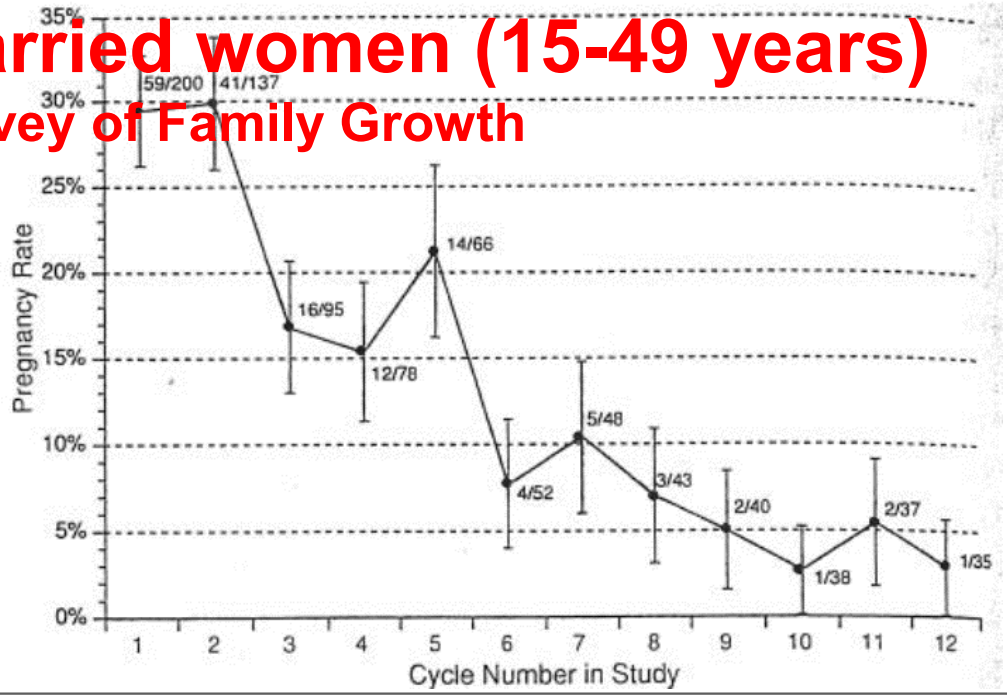
- Define Infertility
- Understand the options to improve natural fertility
- Understand the evaluation for infertility
- Some new developments in the fertility evaluation

Time Required for Conception

Time of Exposure	% pregnant
3 months	57%
6 months	72%
1 year	85%
2 years	93%

Impacts 1 in 5 (19%) married women (15-49 years)

National Survey of Family Growth



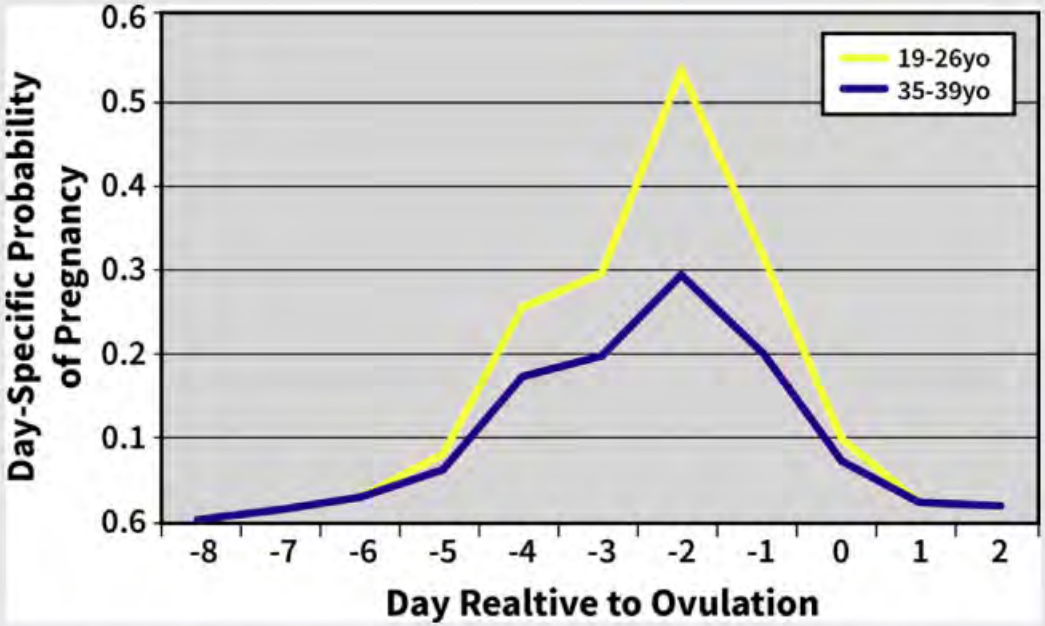
Cedars Sinai

Fertil and Steril 1996;65: 503-9
JAMA 1956,161:855
https://www.cdc.gov/reproductivehealth/infertility/index.htm#:~:text=Is%20infertility%20a%20common%20problem,year%20of%20trying%20(infertility).

New Definition of Infertility

- **“Infertility” is a disease, condition, or status characterized by any of the following:**
  - The inability to achieve a successful pregnancy based on a patient’s medical, sexual, and reproductive history, age, physical findings, diagnostic testing, or any combination of those factors.
  - The need for medical intervention, including, but not limited to, the use of donor gametes or donor embryos in order to achieve a successful pregnancy either as an individual or with a partner.
  - In patients having regular, unprotected intercourse and without any known etiology for either partner suggestive of impaired reproductive ability, evaluation should be initiated at 12 months when the female partner is under 35 years of age and at 6 months when the female partner is 35 years of age or older.

The Fertile Window



Probability of pregnancy resulting from recurrent intercourse by woman's age and cycle day. Data from Stanford and Dunson (17).

Practice Committee of the American Society for Reproductive Medicine and the Society for Reproductive Endocrinology and Infertility. Fertil Steril 2021.

Practice Committee of the American Society for Reproductive Medicine and the Society for Reproductive Endocrinology and Infertility. Fertil Steril 2021.

- The fertile window spans the 6 day interval ending on the day of ovulation
- Peak fecundability occurs within 2 days before ovulation
- The likelihood of success decreases with increasing age

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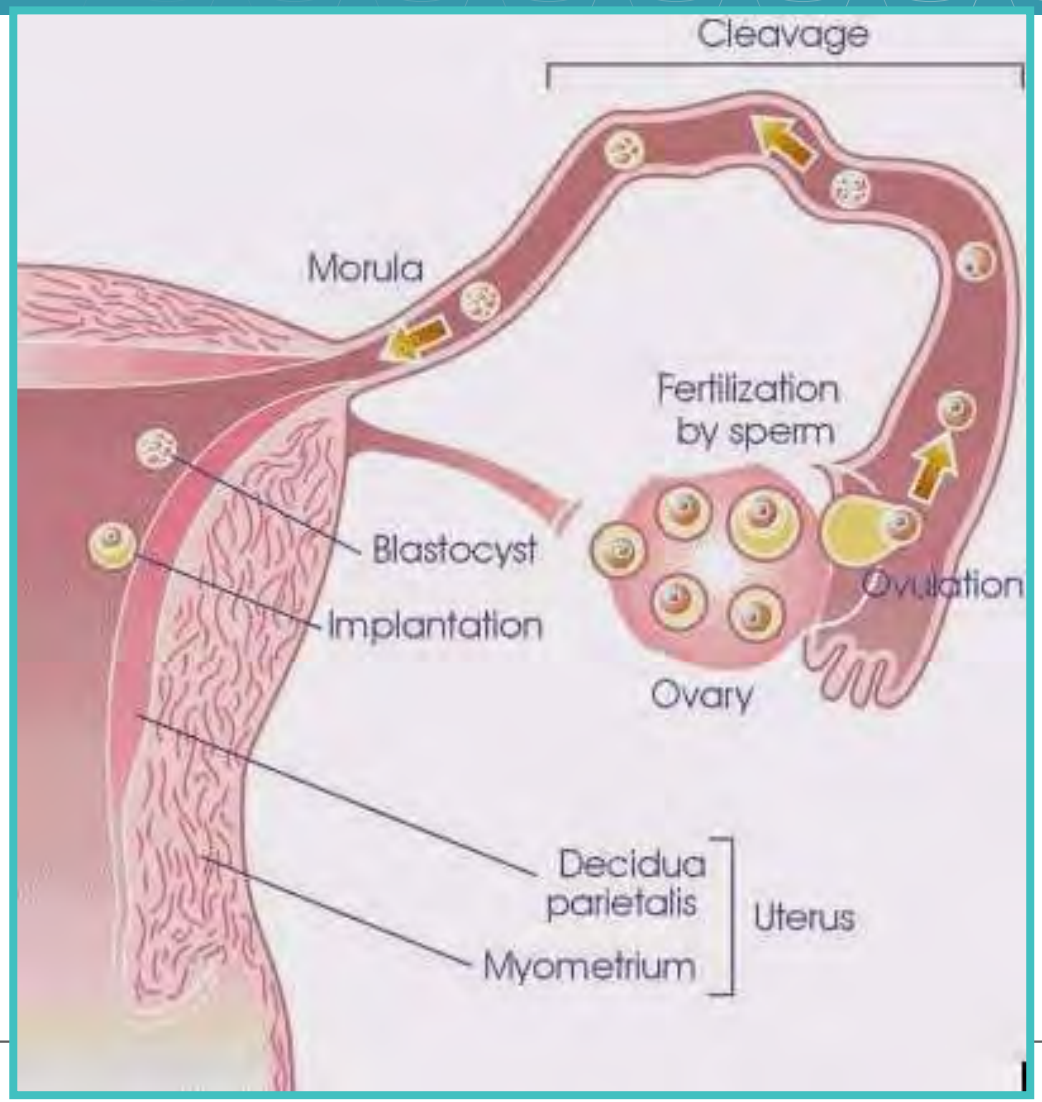
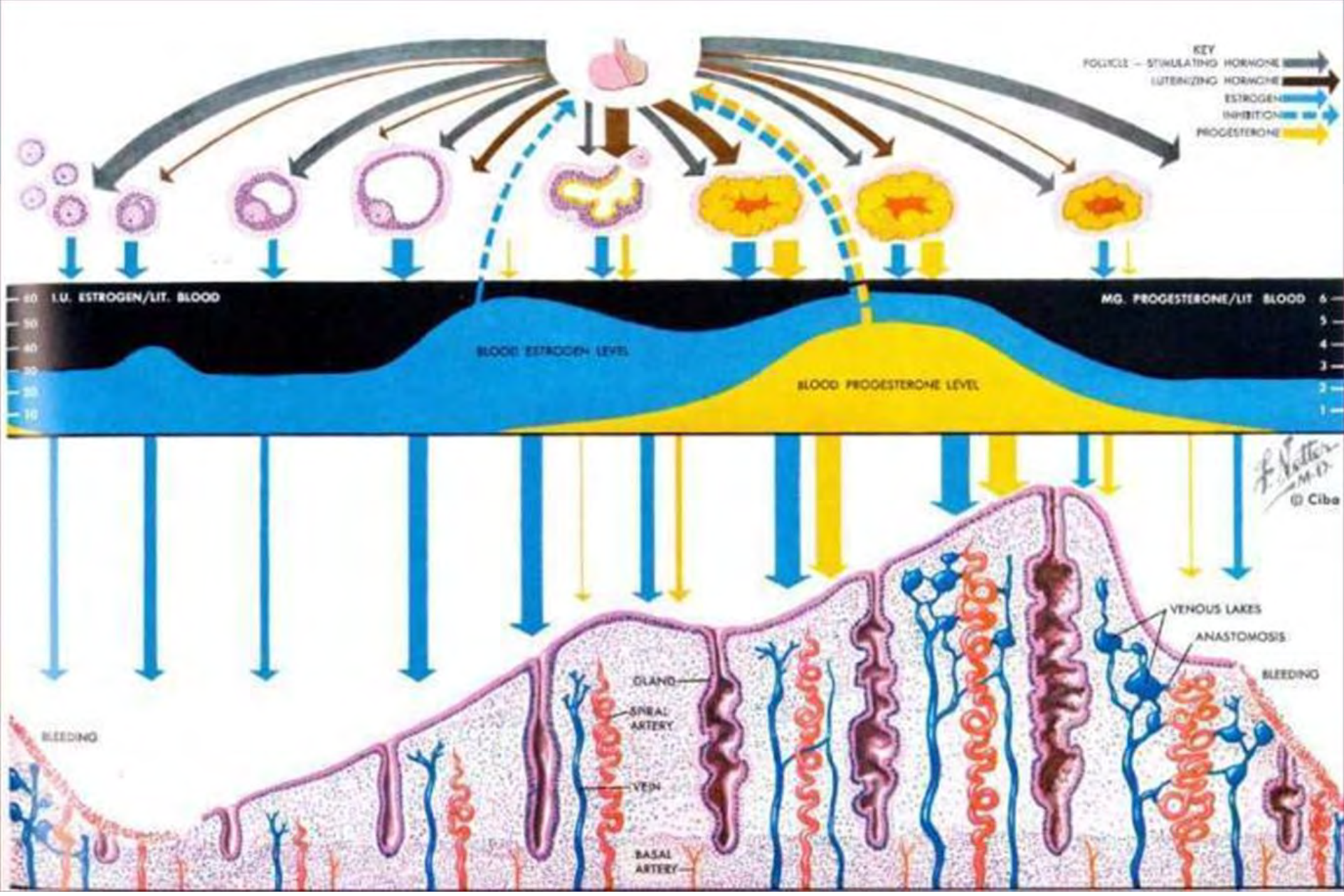
Wilcox NEJM 1995
Dunson DB, Hum Reprod 1999
Stanford JB, Am J Epidemol 2007
ASRM Practice Committee, 2021

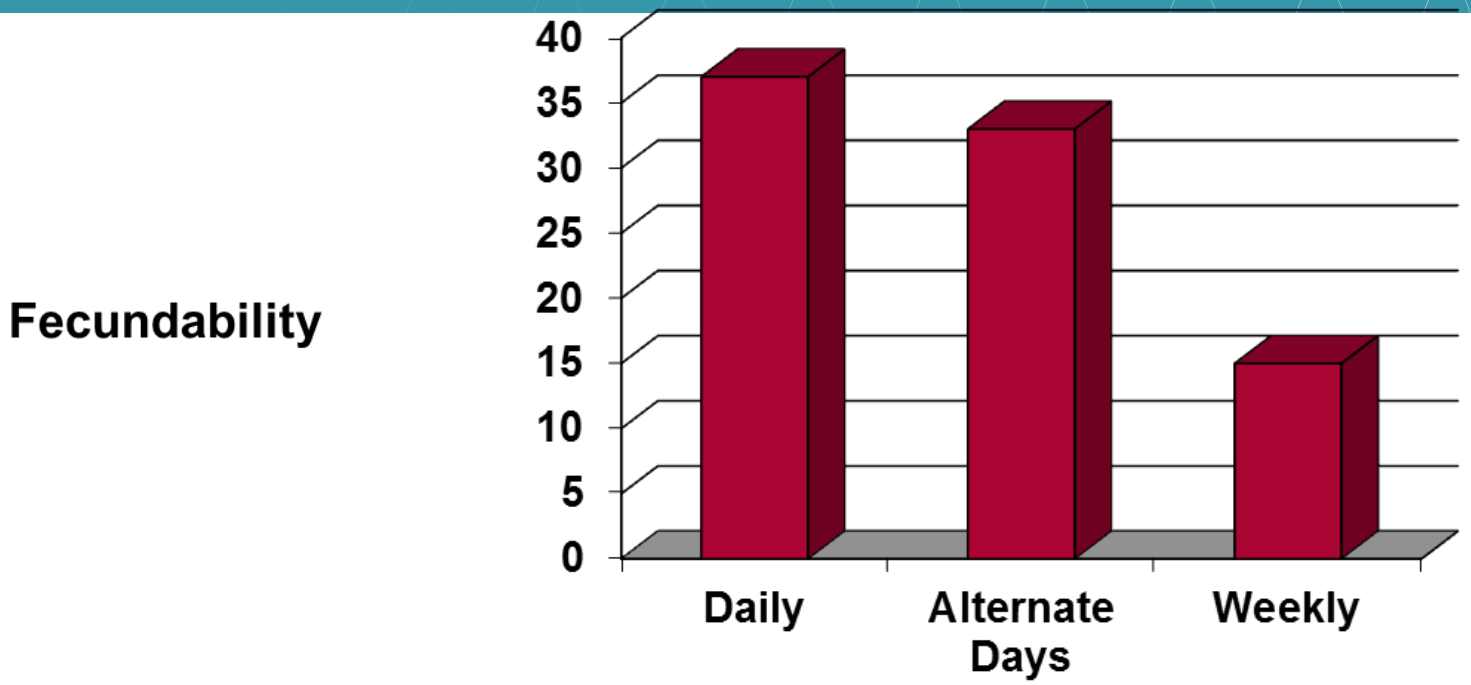
Requirements for Conception





CD 20~24
(LH +6~+10)

Natural Fertility
Frequency of Intercourse



- Reproductive efficiency increases with the frequency of intercourse and is highest when intercourse occurs every 1 to 2 days
- The stress associated with infertility can reduce sexual esteem, satisfaction, and the frequency of intercourse

Wilcox AJ, et al. NEJM 1995;333:1517–21.
Lenzi A, et al. J Endocrinol Invest 2003;26:72–6.
Andrews FM,et al. Fertil Steril 1992;57:1247–53
ASRM Practice Committee, 2021

Lifestyle Factors That May Impact Fertility - Females

- Weight - Fertility rates decrease in very thin or obese women
- Diet - Robust Data on dietary variations is lacking
  - Healthy Food Consumption may improve ovulatory dysfunction infertility
- Smoking - significantly more likely to be infertile (OR, 1.60; 95% CI, 1.34–1.91)
- Caffeine Consumption –
  - High (500 mg; >5 cups of coffee per day) decreased fertility (OR, 1.45; 95% CI, 1.03–2.04)
  - Medium (over 200 to 300 mg per day 2–3 cups per day) increase the risk of miscarriage
  - Moderate(1– 2 cups per day) no apparent adverse effects on fertility or pregnancy outcomes

Social Media - New Source of Information on Diets and Supplements for PCOS?

	Diets	Supplements
	N = 50	N = 50
Views by Uploader Credentials, (%)		
Blogger	33.5	1.8
Fitness instructor/Health coach	0.4	4.2
Healthcare professional*	33.1	1.3
Nutrition professional**	23.7	34.2
Patient	9.3	58.5
Likes by Uploader Credentials, (%)		
Blogger	44.1	2.3
Fitness instructor/Health coach	0.7	3.9
Healthcare professional*	24.2	1.7
Nutrition professional**	15.6	51.9
Patient	15.4	40.2
Quality and Reliability Scores		
DISCERN score†	3.0 ± 0.86 (0.57)	2.4 ± 0.96 (0.42)
GQS score†	3.0 ± 0.9 (0.52)	3.0 ± 0.9 (0.60)
JAMA score†	2.5 ± 0.8 (0.44)	2.8 ± 0.6 (0.56)

Poor Scores

**Healthcare professionals include physicians, nurses, advanced practitioners, and chiropractors*
***Nutritional professionals include nutritionists and registered dieticians*
†Reported values include mean ± standard deviation (Cohen Kappa statistic)

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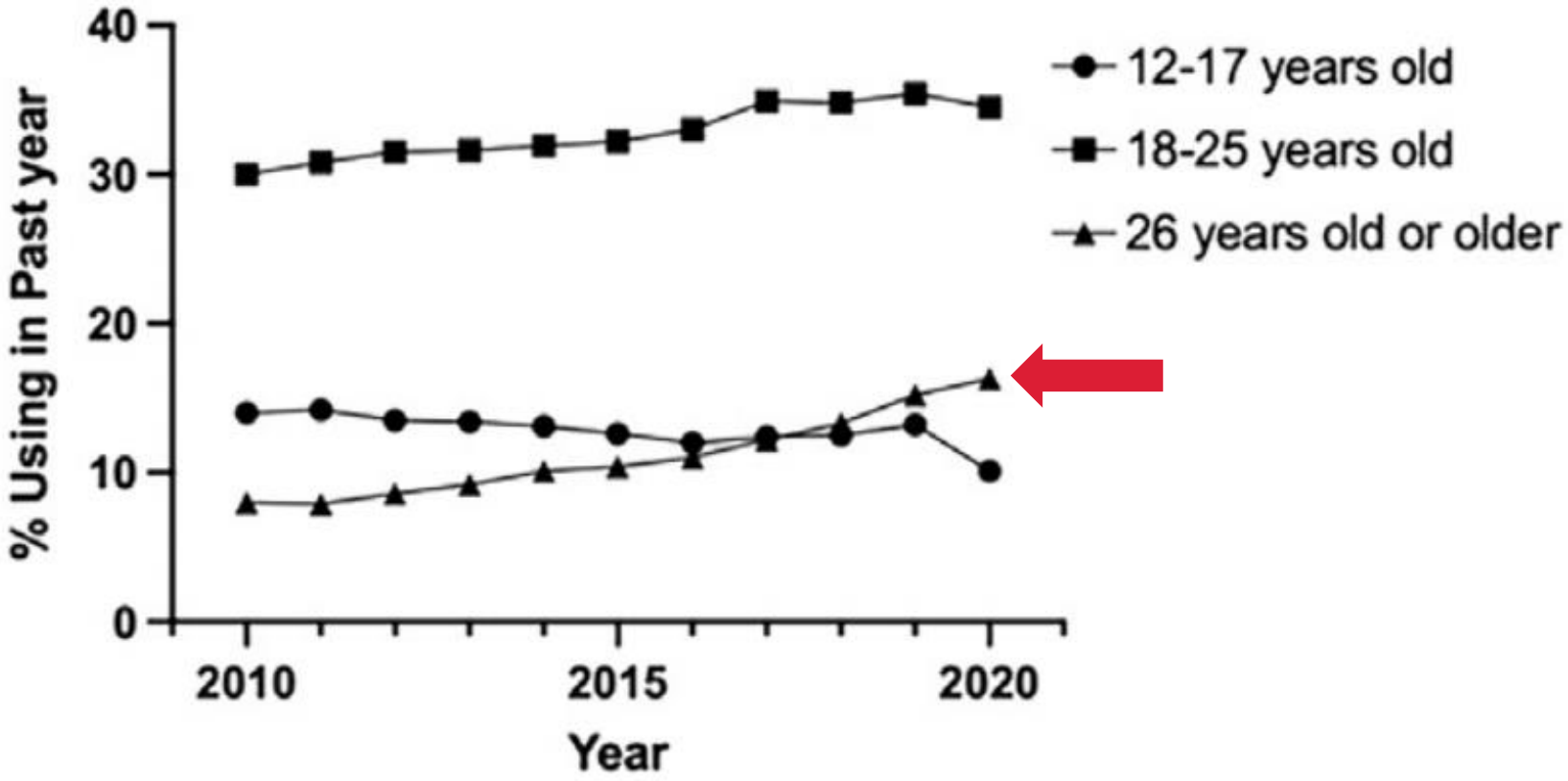
Lifestyle Factors That May Impact Fertility - Males

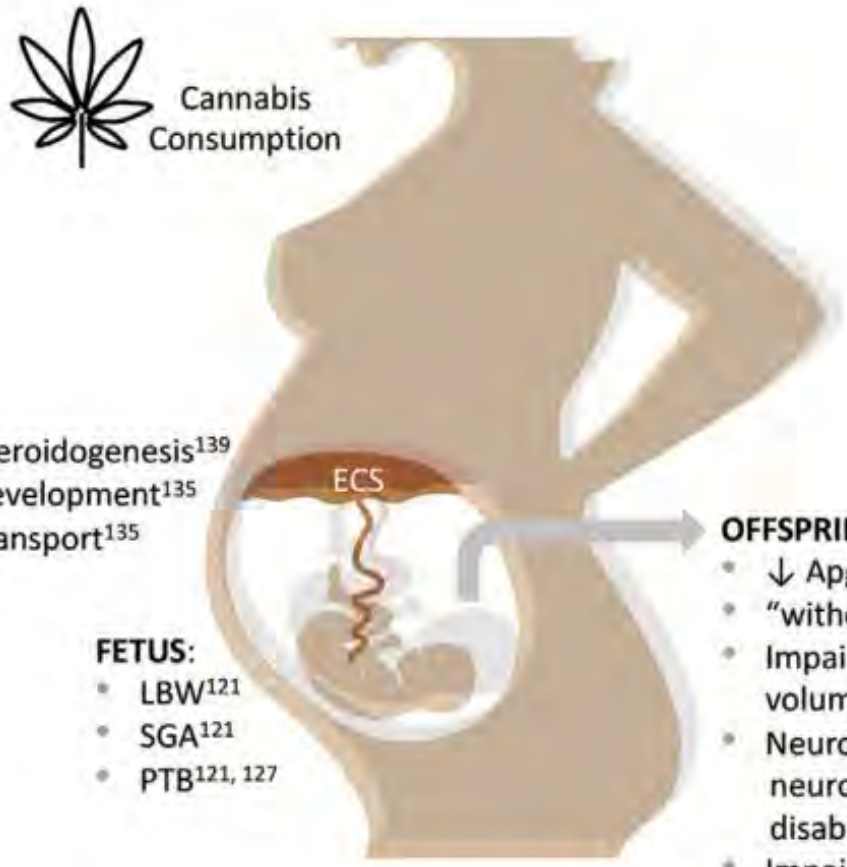
- Smoking –
  - Decreased sperm density, motility and abnormalities in sperm morphology
  - Data do not demonstrate conclusively that smoking decreases male fertility

- Alcohol – Chronic Consumption
  - Lower sperm counts, motility, morphology, seminal fluid volume
  - Lower testosterone
  - Increased risk of sexual dysfunction
  - Increased risk of ejaculatory dysfunction
  - Premature ejaculation

Cannabis Use



Cannabis Use



PLACENTA:
- Impaired steroidogenesis[139]
- Impaired development[135]
- Impaired transport[135]

FETUS:
- LBW[121]
- SGA[121]
- PTB[121, 127]

OFFSPRING:
- ↓ Apgar score, ↑ NICU admission[22, 121,123,125,126]
- "withdrawal"-like syndrome[147]
- Impaired brain development (↓ gray matter volume)[5,145,146]
- Neurobehavioral, neurocognitive and neuropsychiatric disorders (ASD, intellectual disability, learning disorders, ↑ PLE)[147-156]
- Impaired long term reproductive health[144]

ASD, autism spectrum disorder; *IUGR*, intrauterine growth restriction; *PLE*, psychotic-like experience; *PTB*, preterm birth; *SGA*, small for gestational age.

Cannabis Use - Female Reproductive Function

- Prevalence of infertility increased in users (RR, 1.7; CI 95%, 1.0–3.0)
- No association with time to pregnancy
- Alters reproductive hormones (FSH and LH)
- Ovulation
  - Delays ovulation
  - More anovulatory cycles than non-users (43% vs 15%)
  - Twice as likely to experience infertility secondary to ovulatory dysfunction
- IVF
  - 25% fewer oocytes retrieved
  - 28% fewer oocytes fertilized
- Pregnancy loss more than double
- Animal Studies – alters reproductive hormones, menstrual cycle length, ovulatory dysfunction

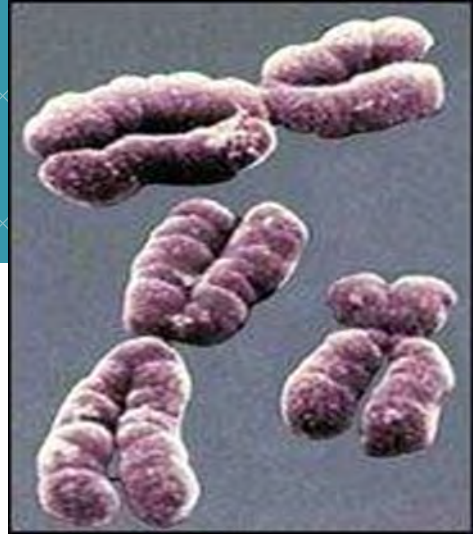
Lo. Cannabis use and reproductive health and offspring outcomes. Am J Obstet Gynecol 2022
ASRM Practice Committee Opinion 2022.

Cannabis Use - Male Reproductive Function

- Alters reproductive hormones (FSH and LH)
- 29% lower sperm counts
- Mixed reports on erectile dysfunction, orgasmic dysfunction, premature or delayed ejaculation
- Animal studies - THC can adversely affect spermatogenesis via inhibition of Leydig cell function, reduction in gonadotropins, testicular atrophy, and abnormal sperm morphology
- Alters methylation in sperm – affected genes identified are involved in early development, including neurodevelopment and cancers
- Significantly associated with sudden infant death syndrome, after adjusting for tobacco and alcohol co-use
- National Survey of Family Growth and North American Preconception Cohort Study no association to time to pregnancy

Lo. Cannabis use and reproductive health and offspring outcomes. Am J Obstet Gynecol 2022.
ASRM Practice Committee, 2021

Preconception Counseling

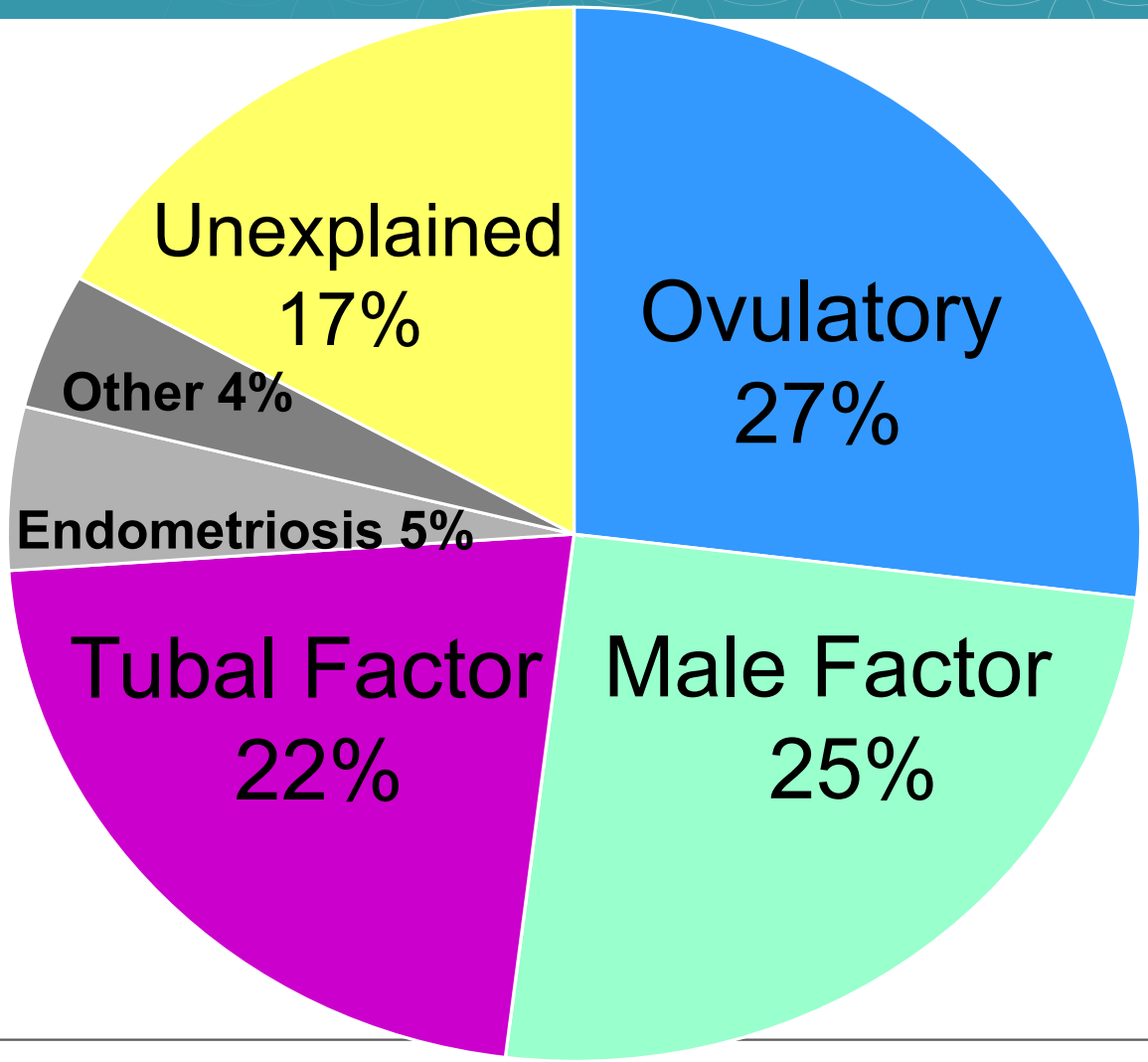


- Family Planning and Pregnancy Spacing
- Genetic Risk Factors
- Optimize Medical Conditions and review current medications
  - diabetes, hypertension, psychiatric illness, and thyroid disease
- Vaccinations
  - COVID-19
  - Influenza
  - Rubella
  - Varicella
  - Measles
- Prenatal Vitamins/ Folic Acid

Preconception Genetic Screening

- All Ethnic Backgrounds
  - Cystic Fibrosis
  - Spinal Muscular Atrophy
- African-American/Mediterranean/South East Asian
  - Hemoglobin electrophoresis (sickle cell or thalassemia)
- French Canadian/Creole - Tay Sachs disease
- Ashkenazi Jewish
  - Cystic Fibrosis, Tay Sachs disease, Canavan disease, Familial Dysautonomia, Bloom Syndrome, Fanconi anemia group C, Gaucher disease, Glycogen storage disease type 1a, mucolipidosis type IV, Niemann-Pick disease type A, DIhydrolipoamide Dehydrogenase Deficiency, Familial Hyerinsulinism, Glycogen Storage Disease Type 1a, Maple Syrup Urine Disease, Nemaline Myopathy, Usher Syndrome Type IF, Usher Syndrome Type III
- Persian Jewish
  - Pseudocholinesterase deficiency, Congenital hypoaldosteronism, Polyglandular deficiency, Hereditary inclusion body myopathy
- Family History of Developmental Delay/ Ataxia/ Fragile X Syndrome/POF/Elevated FSH
  - Fragile X premutation
- Universal Screening

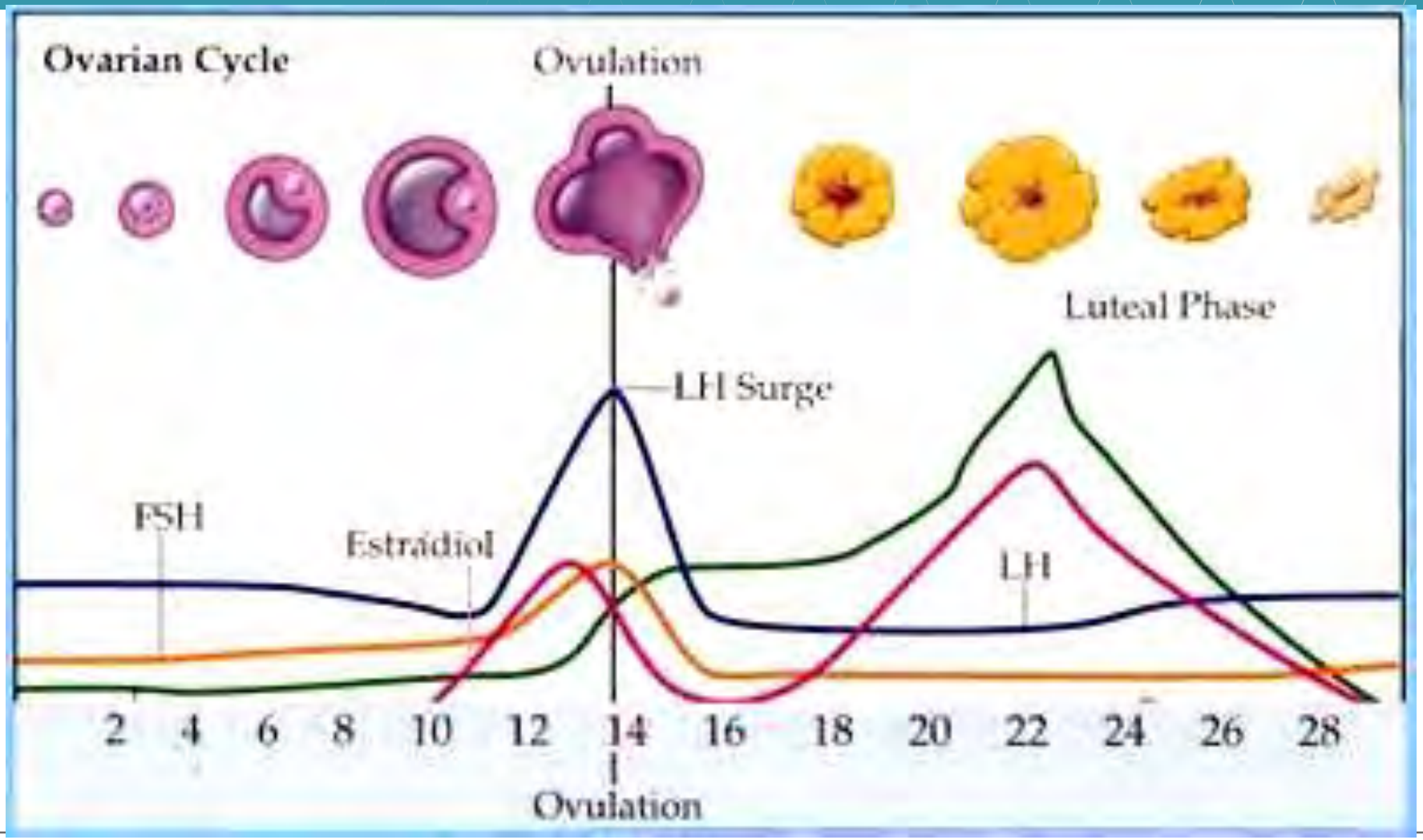
Diagnosis in Infertile Couples



Cedars Sinai

Collins, JA. Unexplained Infertility. In Keye WE, Chang RJ, Rebar RW, Soules MR (eds). Infertility: Evaluation and Treatment 1995.

Ovulation

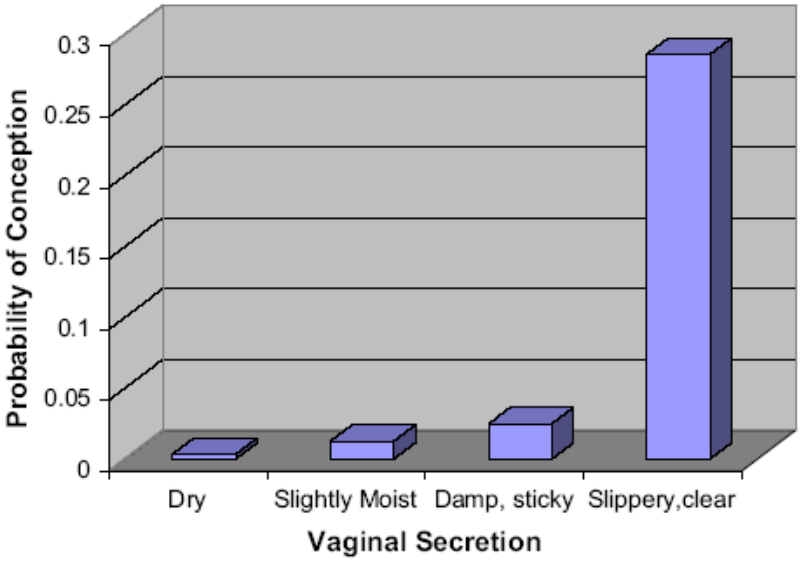

Ovarian Cycle
Ovulation
Luteal Phase
LH Surge
FSH
Estrádiol
LH
2 4 6 8 10 12 14 16 18 20 22 24 26 28
Ovulation

Natural Fertility: Menstrual History

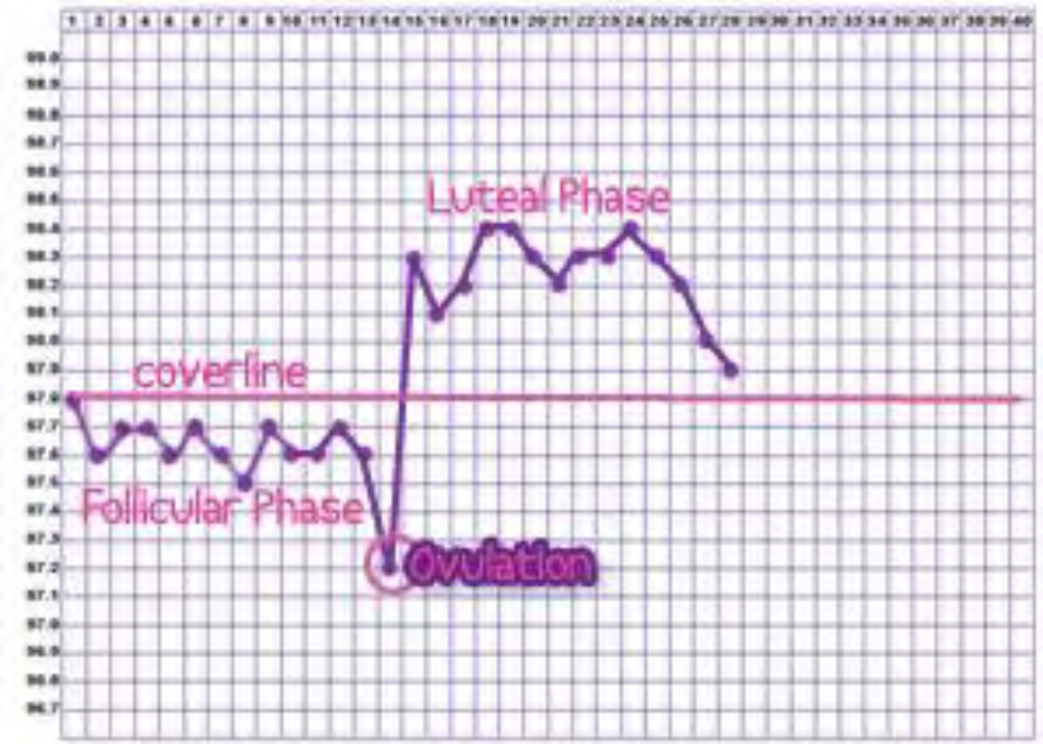
- Nonhirsute women -
  - Prevalence of ovulatory cycles with normal menstrual history is 99.5%
- Eumenorrheic women with hirsutism
  - Prevalence of regular ovulation decreases to 60%

Natural Fertility: Monitoring Ovulation

- Cervical mucus
  - Pregnancy rates at peak mucous (38%) vs. (15% to 20%)
  - More accurate than a menstrual calendar



- BBT
  - Temperature taken upon awakening
  - A biphasic pattern signifies ovulation
  - Predicts the LH surge only within 2-3 days



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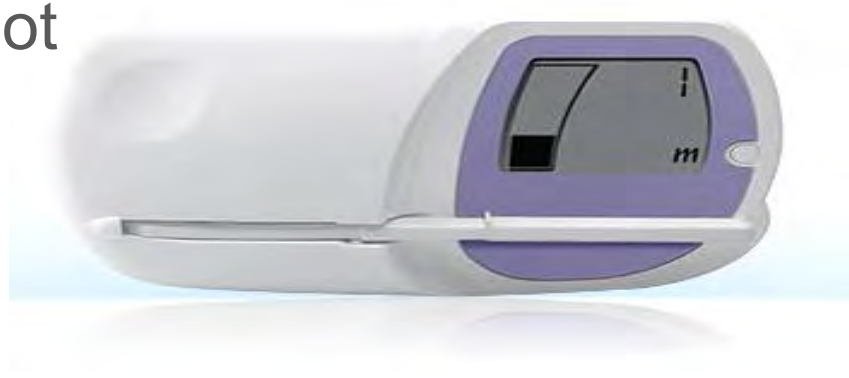
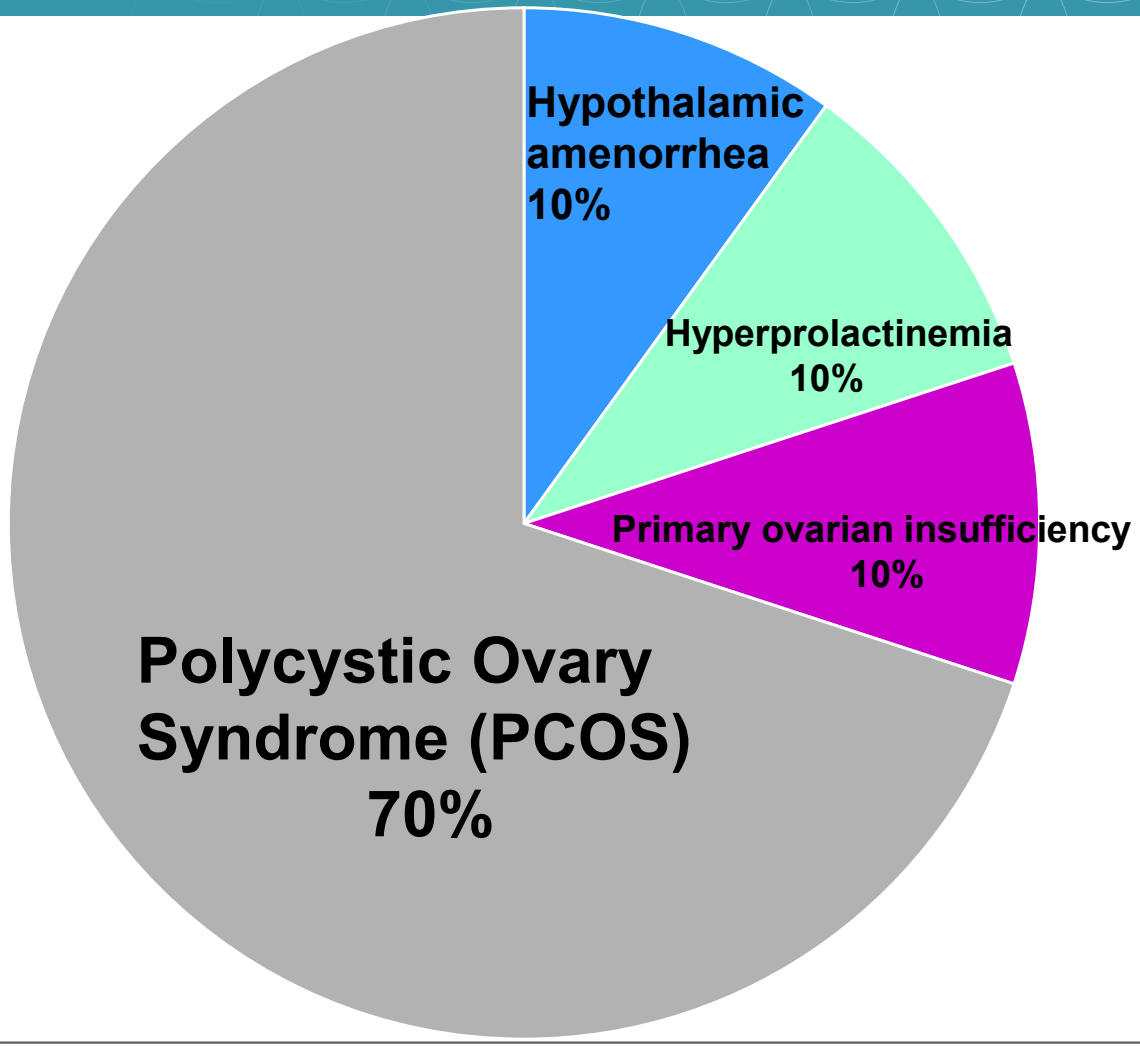
Optimizing Natural Fertility Practice Committee of the American Society for Reproductive Medicine 2021

Natural Fertility: Monitoring Ovulation

- Ovulation Detection Devices
  - may decrease the time to conception
  - ovulation may occur anytime within the 2 days thereafter
  - false-positive test results occur in approximately 7% of cycles
- App based technologies are not predictive of ovulation and may not add to traditional methods of ovulation detection
- Day 22-24 Progesterone
  - Midluteal phase > 3ng/ml



Ovulatory Dysfunction



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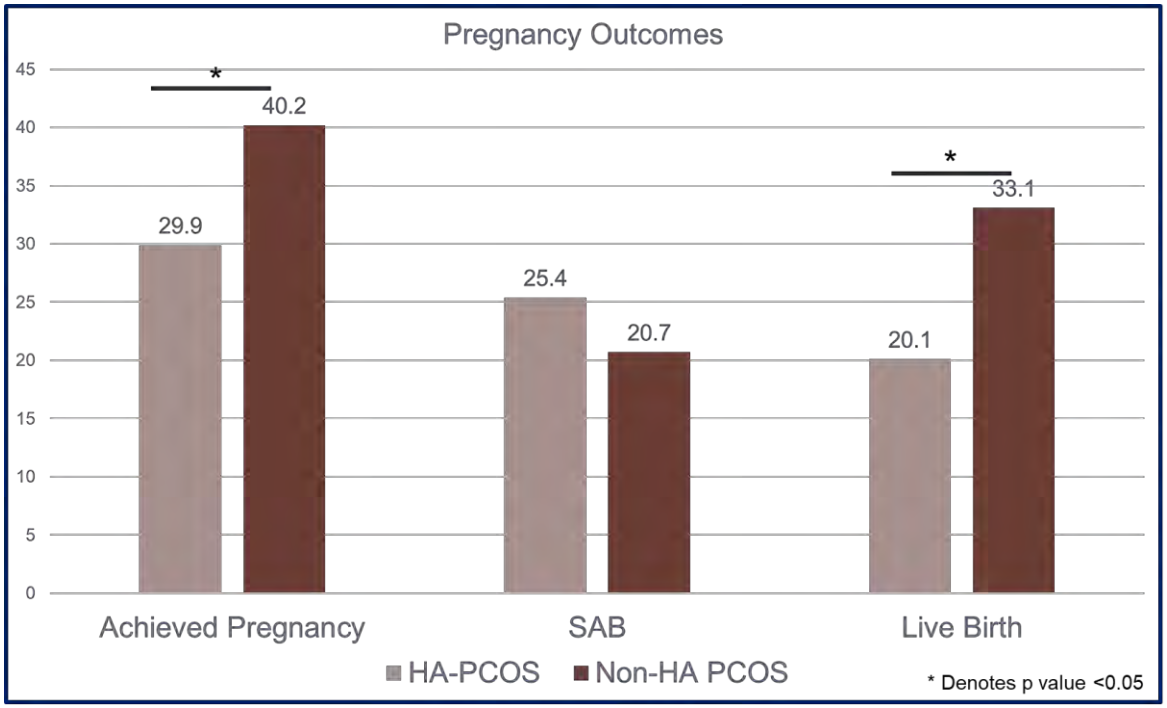
Reindollar RH, et al. Am J Obstet Gynceol 1986; 155: 531-43.

COMPARING THE PHENOTYPES OF PCOS BY NIH 1990, ROTTERDAM 2003, AND AES 2006

	Phenotypes			
Characteristics	***A***	***B***	***C***	***D***
Hirsutism/HA	√	√	√	
Ovulatory dysfunction	√	√		√
Polycystic ovaries	√		√	√
NIH1990	√	√		
Rotterdam 2003	√	√	√	√
AES 2006	√	√	√	

International Evidence Based Guideline for PCOS 2018

PCOS Phenotype Impacts Outcomes



HA-PCOS group had lower odds of live birth (OR 0.51, CI 0.34-0.76, CI 0.44-0.92)

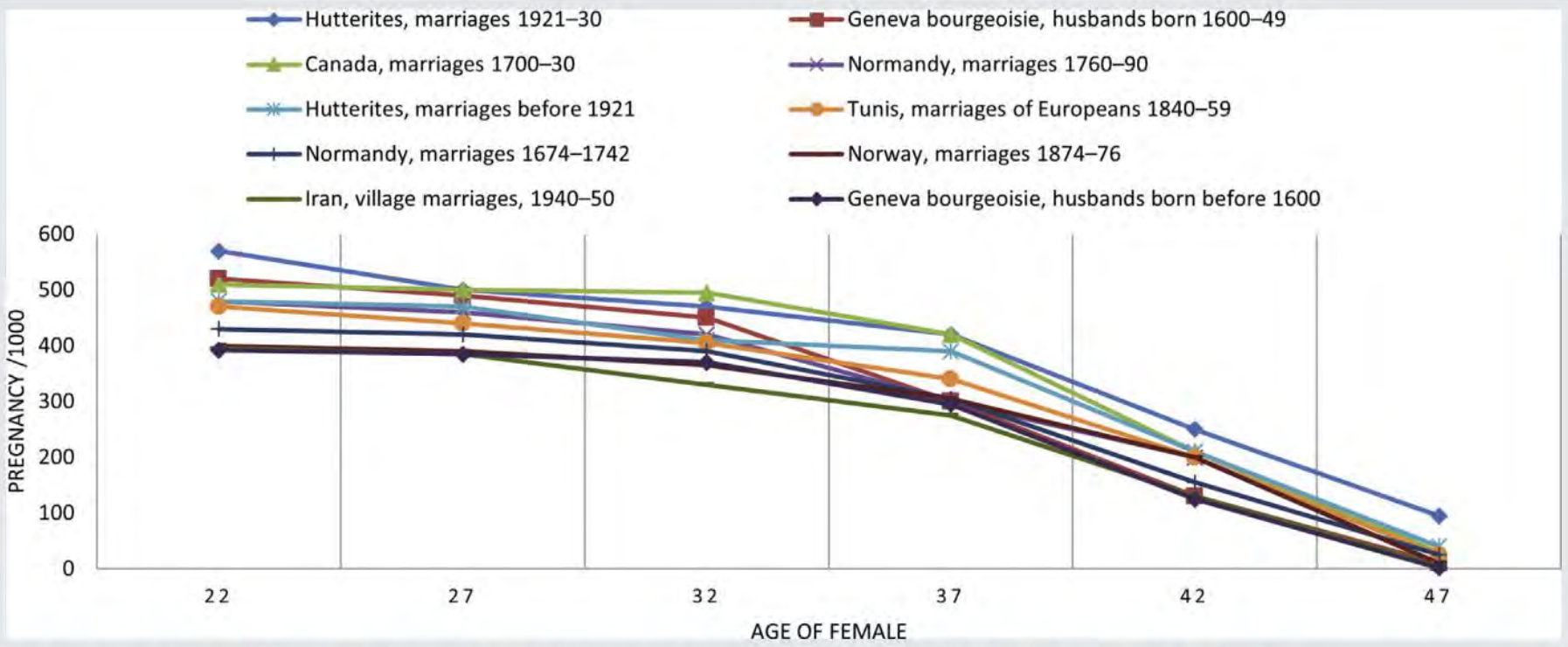
Adjusting for BMI (adjusted OR 0.74, CI 0.50-1.10 NS, CI 0.25-0.80)

Hyperandrogenemia in normally menstrual cycling women is not predictive of pregnancy outcomes.

Hyperandrogenism/Hyperandrogenemia in PCOS is predictive of pregnancy outcomes.

Chan JC, et al. Obstet Gyn submitted
Wang ET, et al, Fertil Steril 2020

Age and Fertility



Pregnancy rate (per 1,000 women) in various populations at different times in history. Modified from Larsen et al. (7).

Practice Committee of the American Society for Reproductive Medicine and the Society for Reproductive Endocrinology and Infertility. Fertil Steril 2021.

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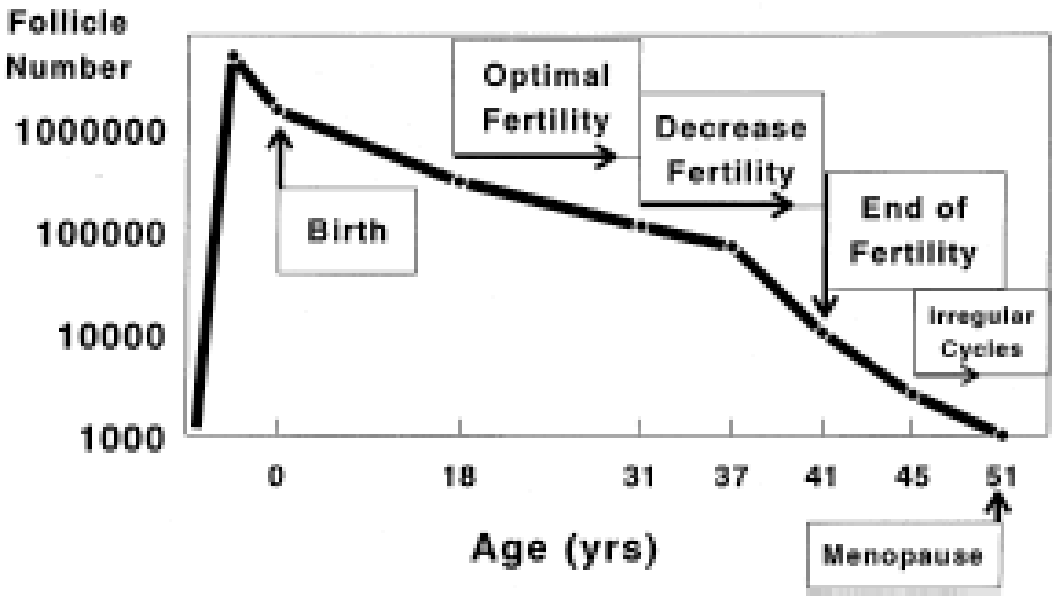
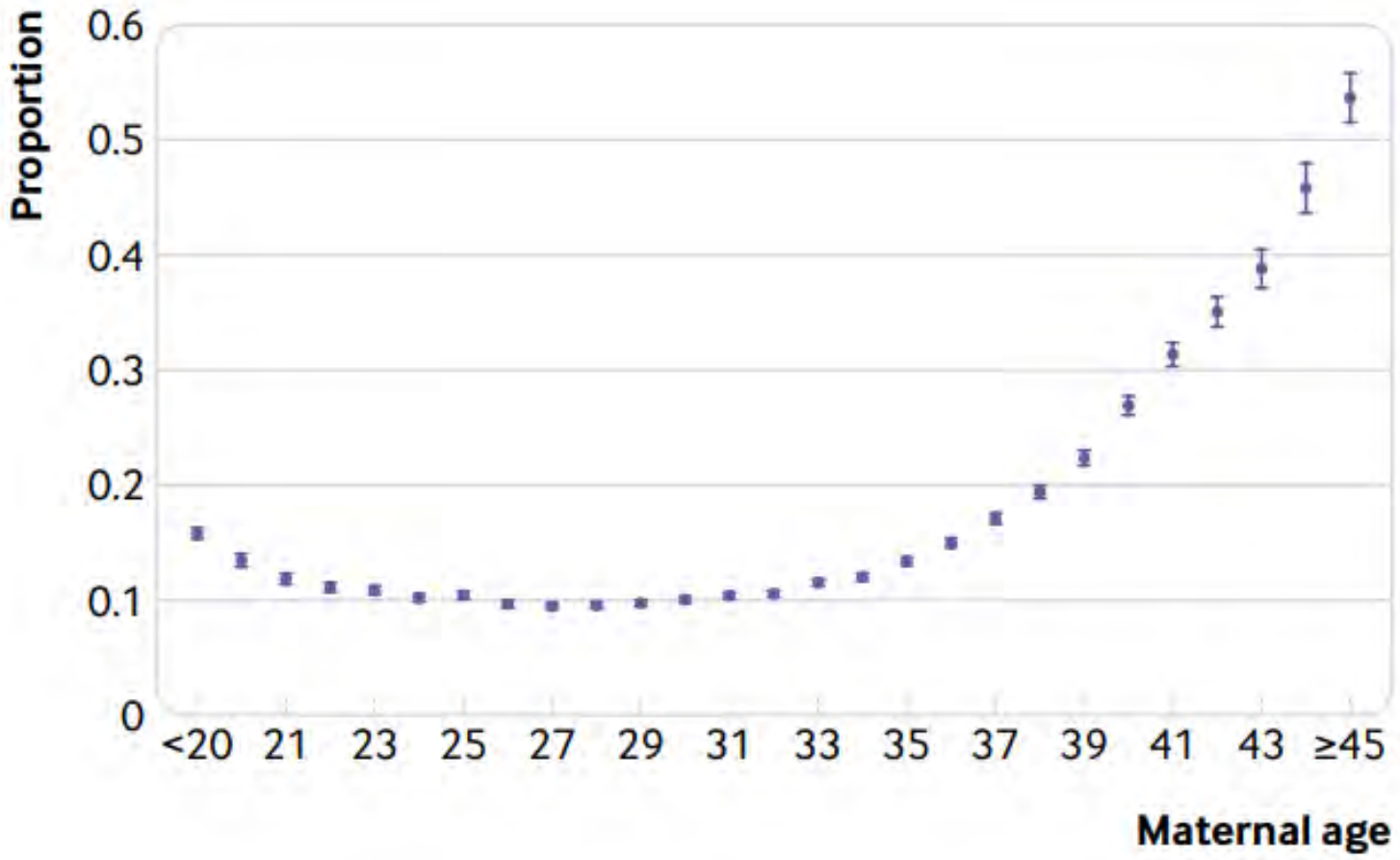
Practice Committee of the ASRM , 2021

The Declining Follicle Pool



- The human ovary has a finite number of oocytes.
- The pool of primordial follicles is formed during fetal life.
- A small number of this resting pool of primordial follicles is activated into growth daily.
- The depletion of oocytes leads to menopause.

Age Related Decline of Oocyte Quality – Miscarriage Rates

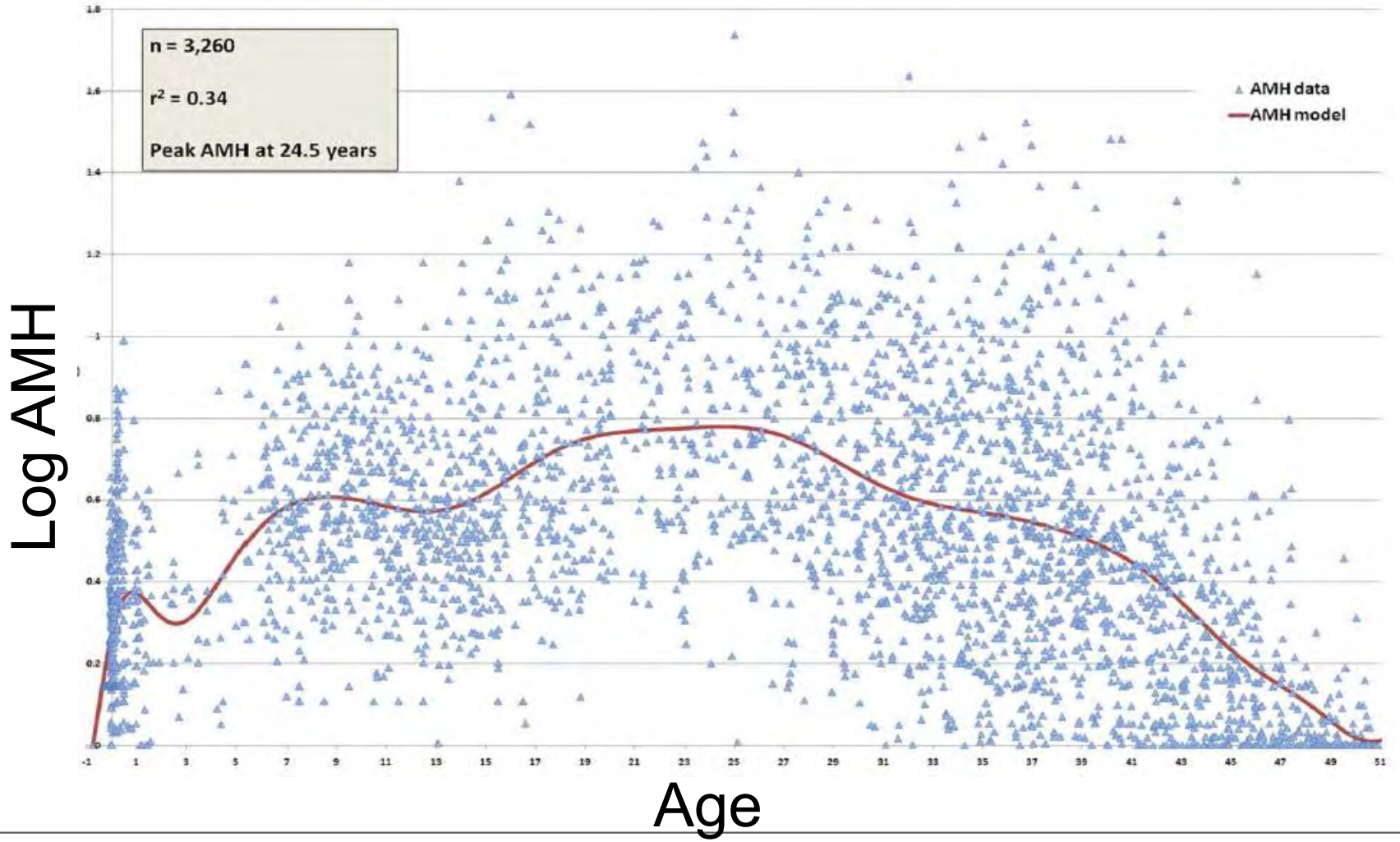


Magnus MC, et al. BMJ 2019;364:l869

Evaluation of Ovarian Age

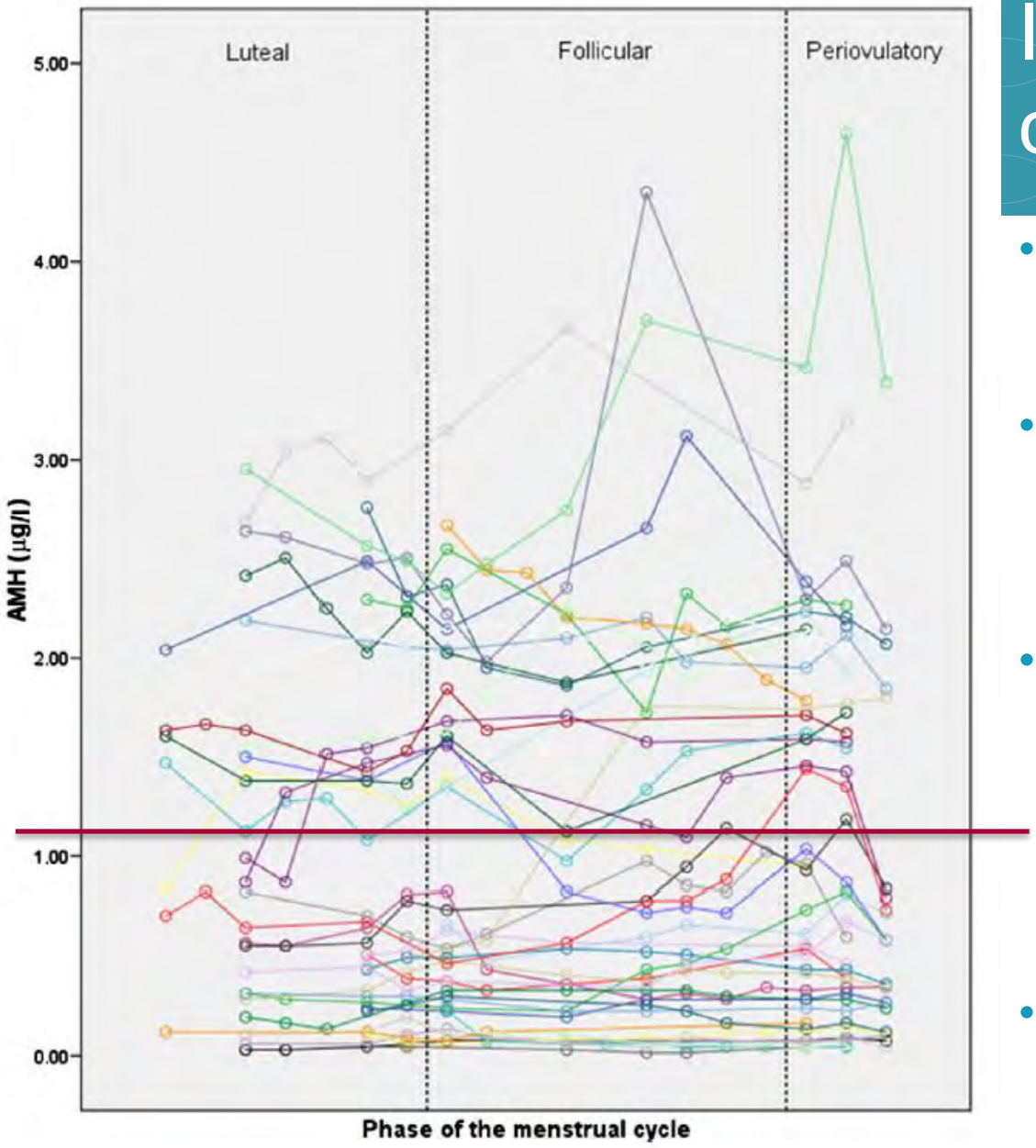
- Basal FSH and Estradiol levels
- Antral Follicle Count/ Ovarian Volume
- Antimullerian hormone (Mullerian Inhibiting Substance)

AMH values from conception to menopause



Kelsey T Plos One 2011

Is AMH cycle-dependent?



- 44 healthy women with regular cycles
- Serum AMH measured CD2-4 until 4 days post LH surge
- Individual patient plots show:
  - Low AMH stays stable
  - High AMH shows fluctuation
- If AMH <1.0 ng/dL, there is little fluctuation across the menstrual cycle

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Overbeek A Reprod Biomed Online 2012

Antral Follicle Count

Antral follicle count cutoff levels (total count)	Subjects this applied to (n)	Sensitivity	Specificity	PPV	NPV	+LR	Post-test probability
≤7	4	0.13	0.98	0.45	0.90	9.00	52.9%
≤8	13	0.47	0.95	0.54	0.93	9.33	53.8%
≤9	15	0.53	0.93	0.49	0.94	8.00	50.0%
≤10[a]	29	0.93	0.88	0.49	0.99	7.47	48.3%
≤11	40	1.00	0.79	0.37	1.00	4.80	37.5%

Note: The shift from the pretest probability (11.1%) to the post-test probability of poor response according to the antral follicle count is shown.

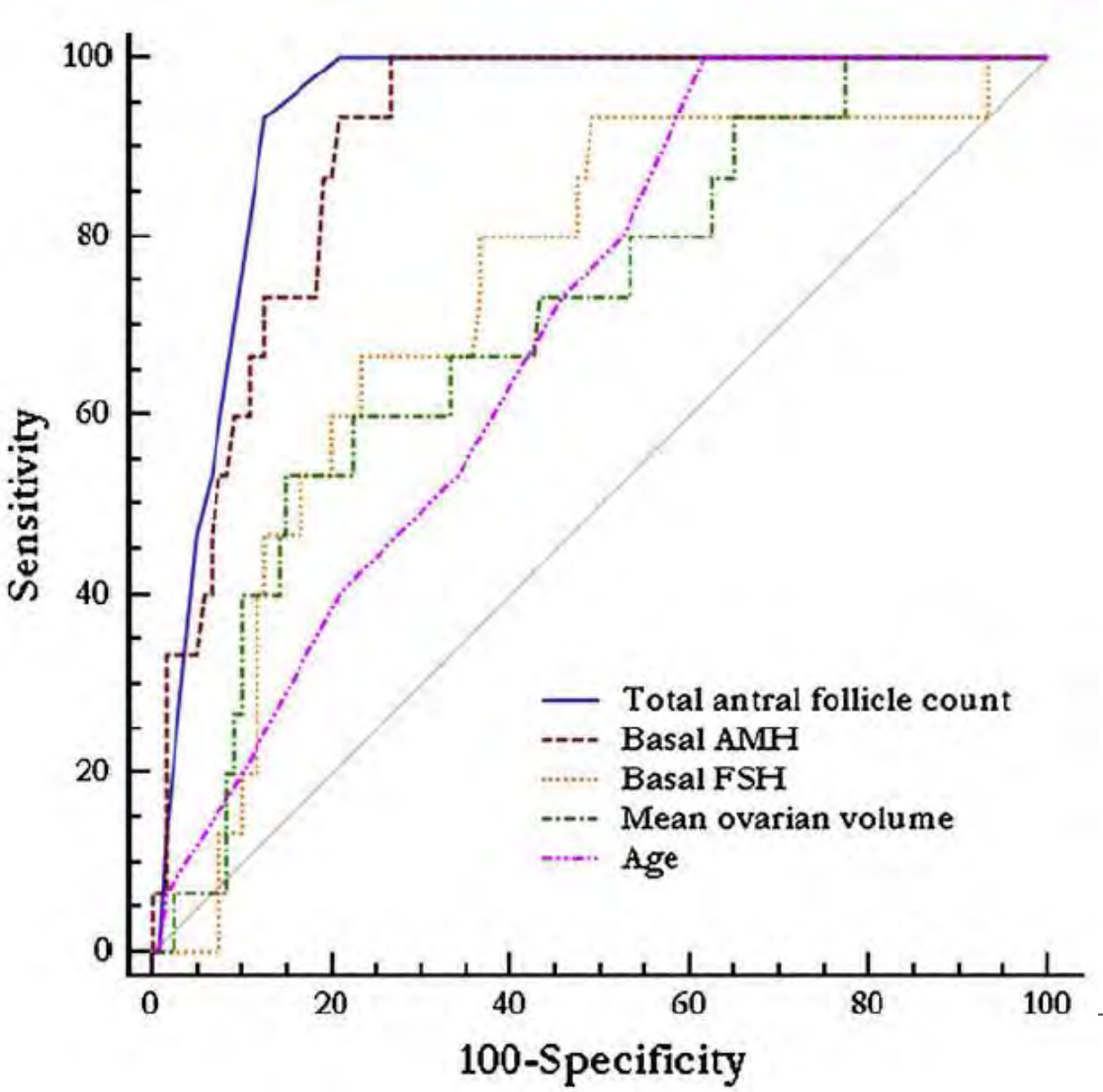
PPV = positive predictive value; NPV = negative predictive value; +LR = positive likelihood ratio.

[a] Optimum cutoff level.

Jayaprakasan. AMH and 3D US markers of ovarian reserve. Fertil Steril 2008.

Optimal value to predict good ovarian response is 10

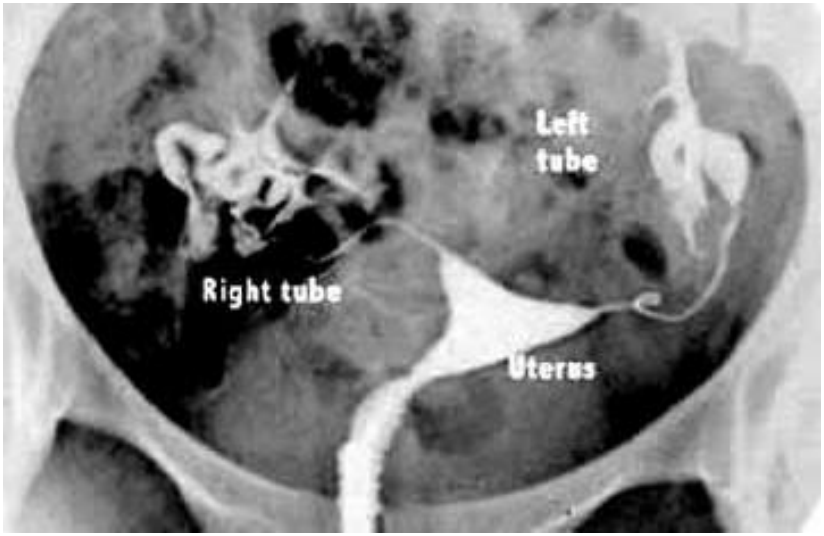
Basal Markers of Ovarian Reserve

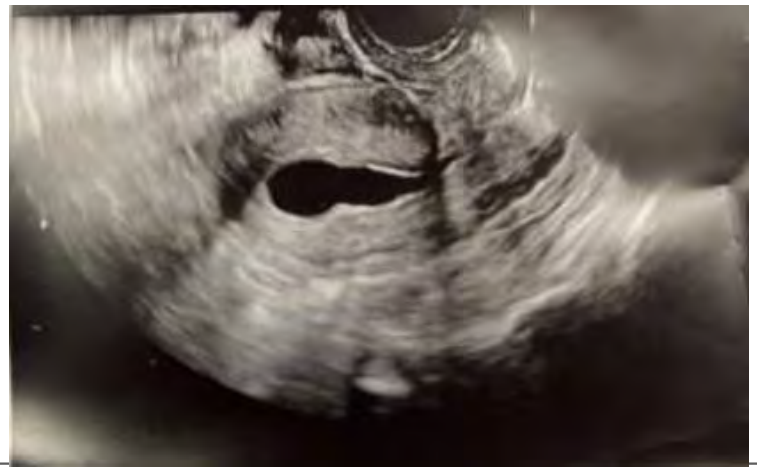


Jayaprakasan, Fertil and Steril 2010

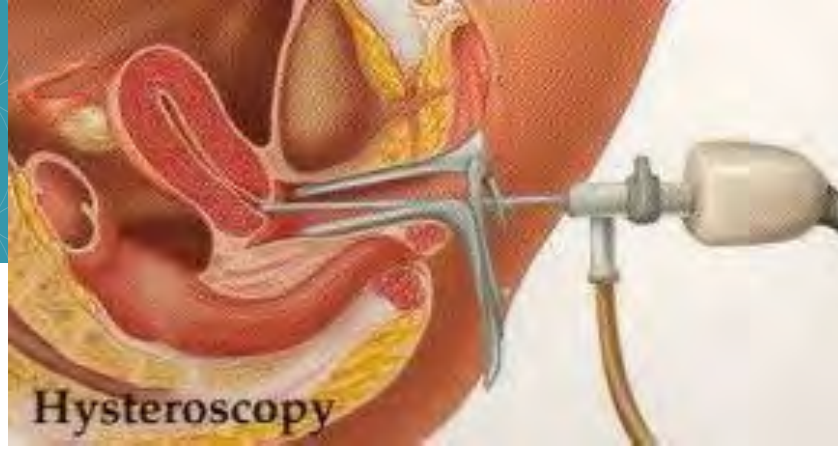
Hysterosalpingogram (HSG) and Sonohysterography

- **Hysterosalpingogram (HSG)**
- Tubal Patency
- Uterine Cavity
  - low sensitivity (50%) and positive predictive value (PPV) (30%) for intrauterine pathology.
- **Sonohysterography (SHG)**
  - defines the size and shape of the uterine cavity
  - high (>90%) PPV and negative predictive value for the detection of intrauterine pathologies (endometrial polyps, submucous myomas, synechiae)
  - hysterosalpingo-contrast sonography 76%–96% sensitivity for tubal patency

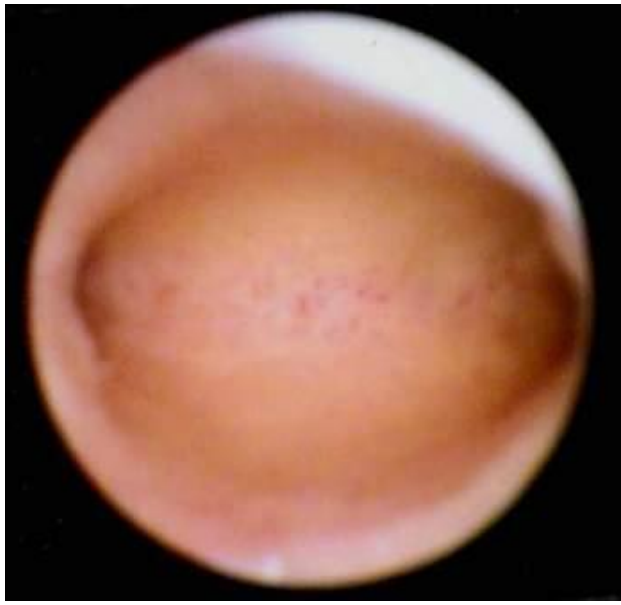




Hysteroscopy



- Definitive method for the diagnosis and treatment of intrauterine pathologies
- Sensitivity of 88% and specificity of 85% to predict tubal patency through direct visualization of fluid or air bubble flow into the tubal ostia



Endometrial Biopsy

Journal of Assisted Reproduction and Genetics (2021) 38:645–650
https://doi.org/10.1007/s10815-020-02041-9

ASSISTED REPRODUCTION TECHNOLOGIES

Clinical utility of the endometrial receptivity analysis in women with prior failed transfers

Laura E. Eisman[1] · Margareta D. Pisarska[1] · Sahar Wertheimer[1] · Jessica L. Chan[1] · Alin Lina Akopians[2] · Mark W. Surrey[2] · Hal C. Danzer[2] · Shahin Ghadir[2] · Wendy Y. Chang[2] · Carolyn J. Alexander[2] · Erica T. Wang[1]

[a] Mean, standard deviation
[b] Median (interquartile range)
[c] ≥ 1 prior failed ET compared to controls
[d] ≥ 3 prior failed ET compared to controls

Endometrial Biopsy

Table 2 Pregnancy outcomes in the subsequent FET cycle after ERA test: cases vs. controls

	≥ 1 prior failed ET $N = 131$	≥ 3 prior failed ETs $N = 20$	Controls $N = 91$	P value[a]	P value[b]
Conception (n/N (%))	92/131 (70)	12/20 (60)	70/90 (78)	0.213	0.099
Clinical pregnancy, (n/N (%))	78/130 (60)	10/20 (50)	60/90 (67)	0.315	0.161
Ongoing pregnancy/ live birth (n/N (%))	57/121 (47)	5/18 (28)	43/80 (54)	0.357	0.046

[a] ≥ 1 prior failed ET compared to controls

[b] ≥ 3 prior failed ETs compared to controls

Endometrial Biopsy

JAMA | Original Investigation

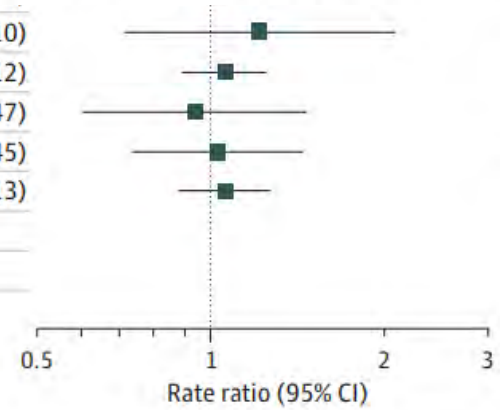
Effect of Timing by Endometrial Receptivity Testing vs Standard Timing of Frozen Embryo Transfer on Live Birth in Patients Undergoing In Vitro Fertilization

A Randomized Clinical Trial

Nicole Doyle, MD, PhD; Samad Jahandideh, PhD; Micah J. Hill, DO; Eric A. Widra, MD; Michael Levy, MD; Kate Devine, MD

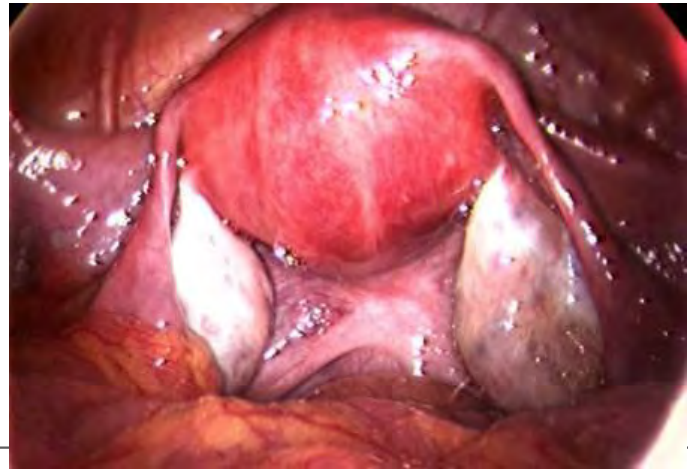
Figure 2.

					P value
Total pati					
Biochemi					.48
Biochemical pregnancy loss[b,c]	29 (9.9)	25 (8.1)	-1.8 (-2.8 to 6.4)	1.21 (0.71-2.10)	.55
Clinical pregnancy[d]	262 (68.8)	281 (72.8)	-4.0 (-10.4 to 2.4)	0.94 (0.80-1.12)	.25
Clinical pregnancy loss[c,e]	36 (13.7)	41 (14.6)	0.9 (-6.8 to 5.0)	0.94 (0.60-1.47)	.87
Total pregnancy loss[f]	65 (22.1)	66 (21.5)	-0.6 (-6.0 to 7.2)	1.03 (0.73-1.45)	.93
Live birth[g]	223 (58.5)	239 (61.9)	-3.4 (-10.3 to 3.5)	0.95 (0.79-1.13)	.38
Ectopic pregnancy	3	1			
Therapeutic abortion	1	0			
Stillbirth	2	1			



Laparoscopy

- Laparoscopy is indicated when there is evidence or strong suspicion of endometriosis, pelvic/adnexal adhesions, or significant tubal disease.
- Laparoscopy is no longer part of the initial work up for infertility.



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Optimal evaluation of the infertile female
The Practice Committee of the American Society for Reproductive Medicine 2021

Endometriosis and Infertility

- Fecundity:
  - Control population:
  - 0.15 — 0.20
  - Endometriosis population:
  - 0.02 — 0.10
- 6 – 8x more likely to have Endometriosis

The Practice Committee of the American Society for Reproductive Medicine. Endometriosis. Fertil Steril 2012

Endometriosis

nature genetics

Article

https://doi.org/10.1038/s41588-022-01254-1

Single-cell transcriptomic analysis of endometriosis

Received: 23 June 2021

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Check for updates

Marcos A. S. Fonseca[1,2,18], Marcela Haro[1,2,18], Kelly N. Wright[3,18], Xianzhi Lin[1,2,18], Forough Abbasi[1,2], Jennifer Sun[1,2], Lourdes Hernandez[1,2], Natasha L. Orr[4], Jooyoon Hong[4], Yunhee Choi-Kuaea[5], Horacio M. Maluf[6], Bonnie L. Balzer[6], Aaron Fishburn[6], Ryan Hickey[6], Ilana Cass[2,17], Helen S. Goodridge[7,8], Mireille Truong[3], Yemin Wang[4,9], Margareta D. Pisarska[10,11], Huy Q. Dinh[12,13], Amal EL-Naggar[7,14], David G. Huntsman[4,9], Michael S. Anglesio[4,15], Marc T. Goodman[5], Fabiola Medeiros[6,19], Matthew Siedhoff[3,19] & Kate Lawrenson[1,2,5,16,19]

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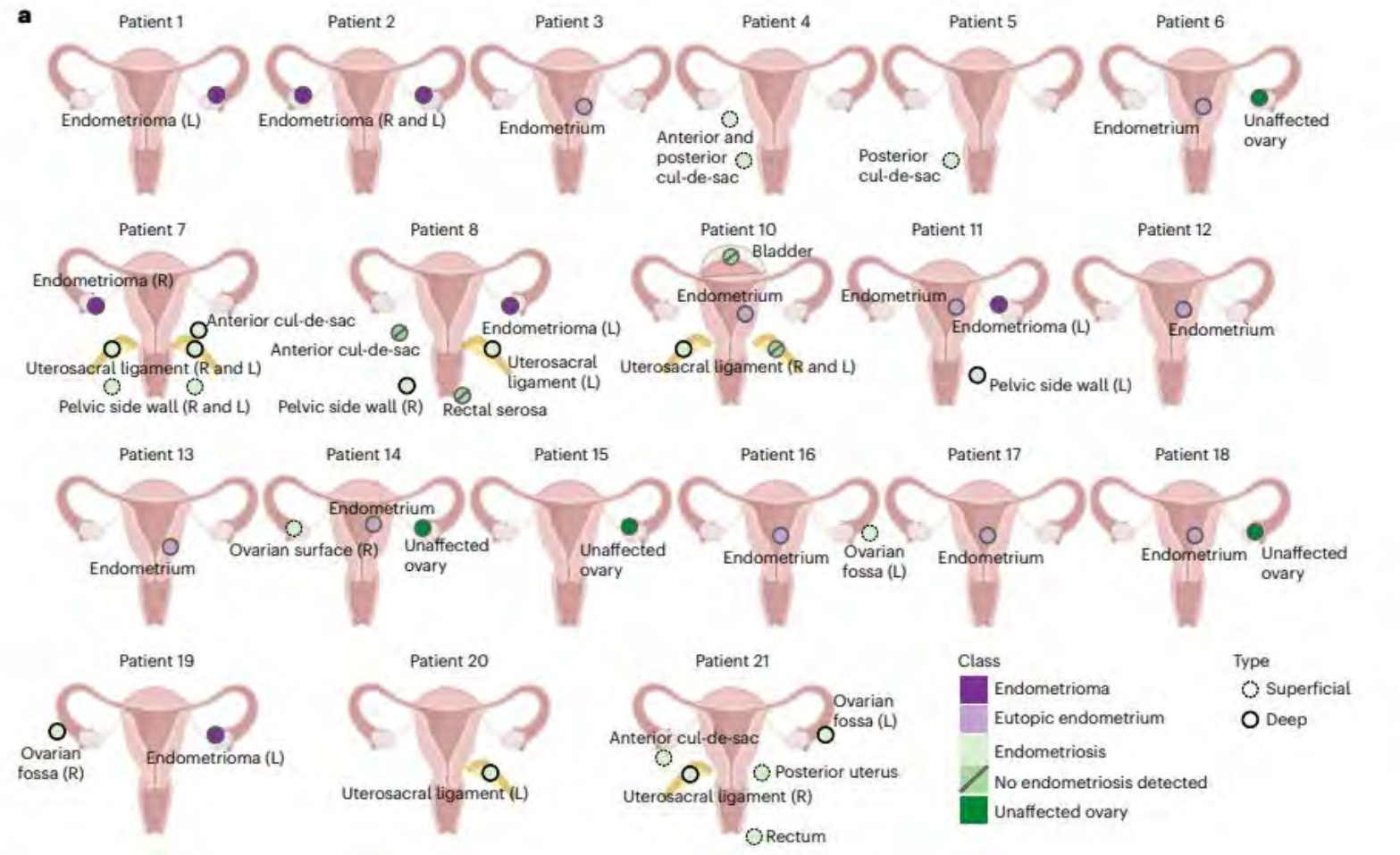
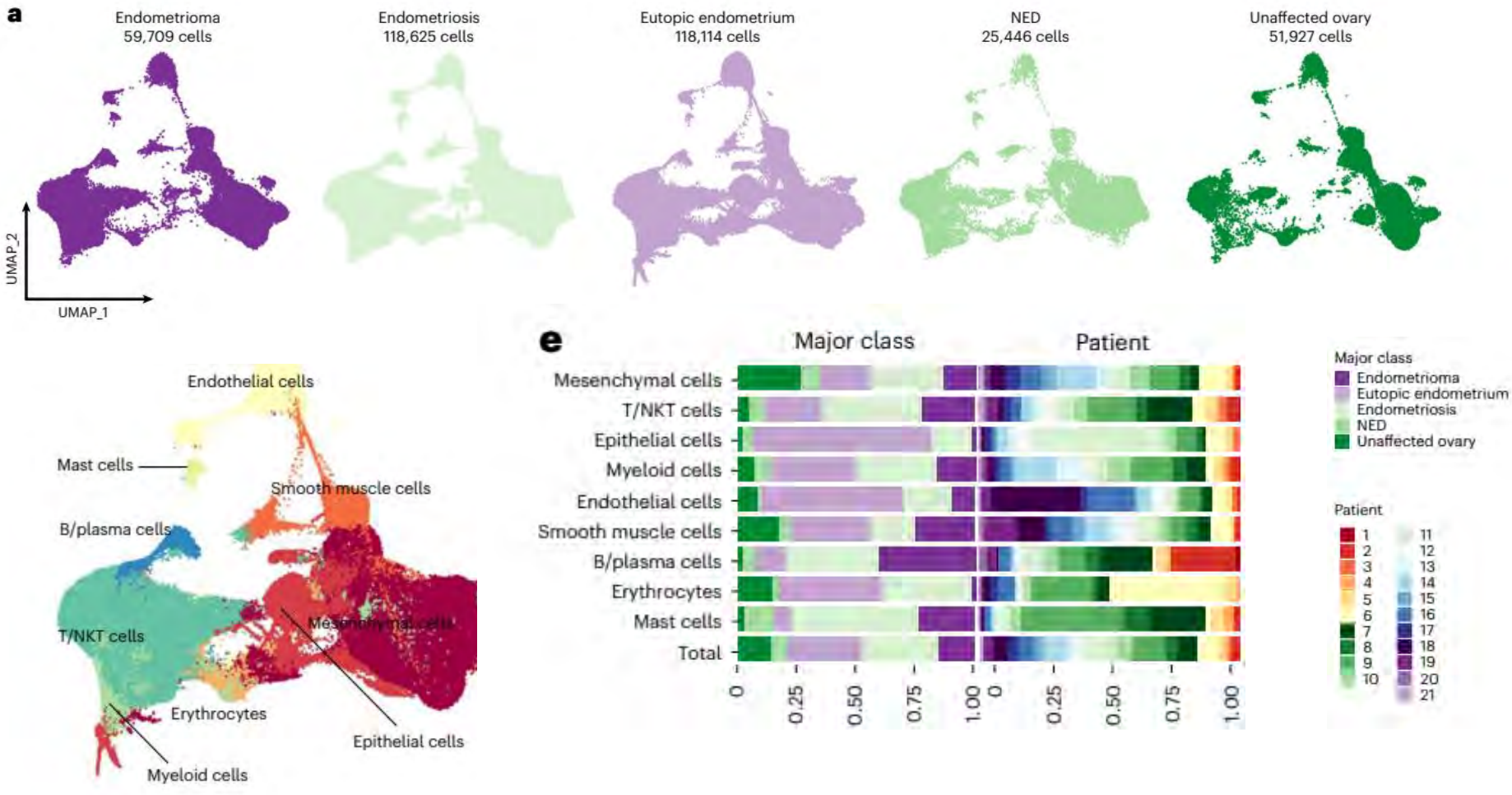
Fonseca, et al. Nat Genetics 2023

Endometriosis



Fonseca, et al. Nat Genetics 2023

Endometriosis



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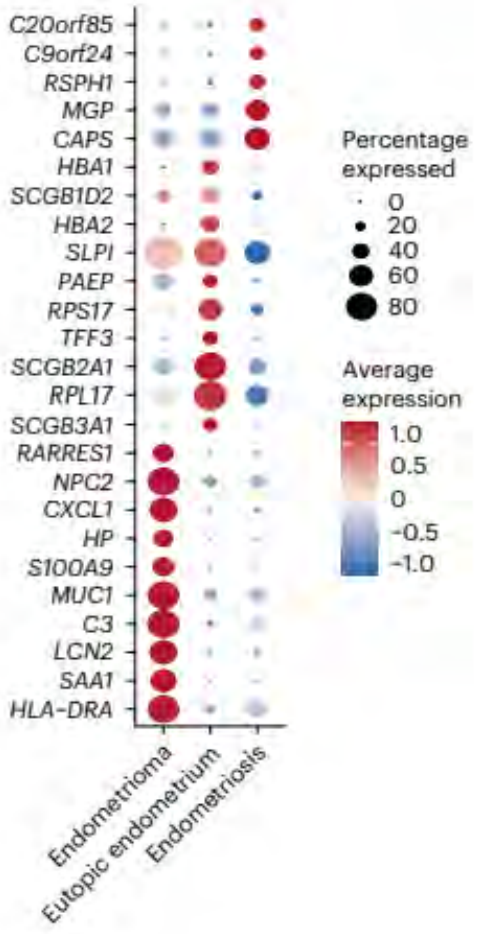
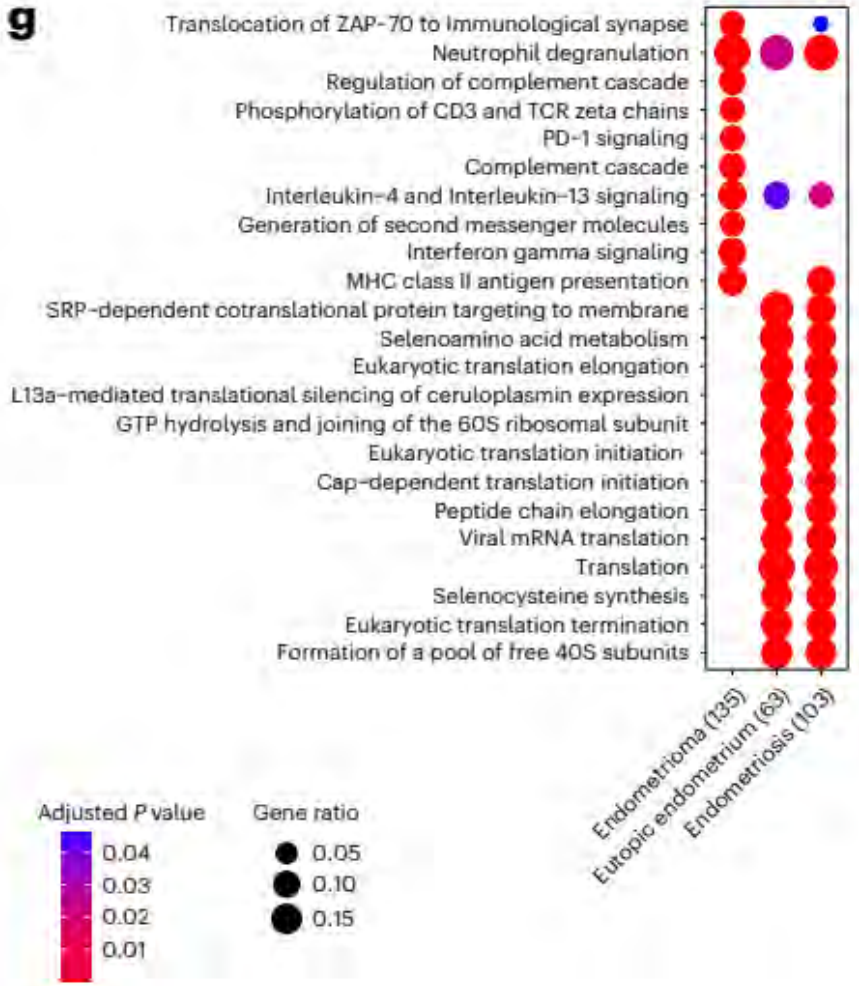
Fonseca, et al. Nat Genetics 2023

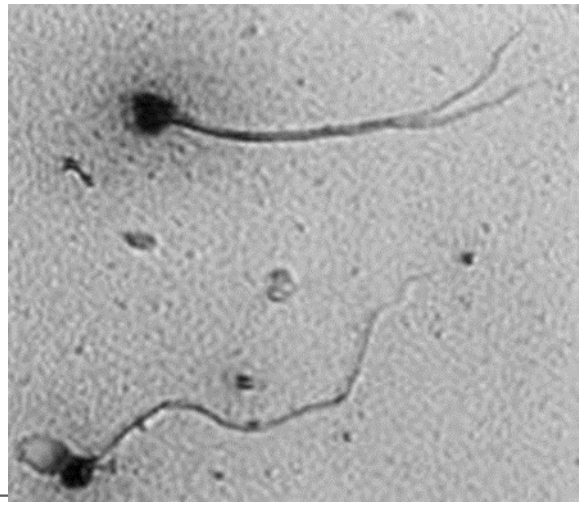
Endometriosis





Male Evaluation
Semen Analysis

- Volume ≥ 1.5 cc
- Conc. ≥ 15M/ml
- Progressive Motility > 32%
- Total Motility > 40%
- Morphology >3%



Male Evaluation – Fertile Male

Variable	Semen Measurement		
	Concentration	Motility	Morphology
	$\times 10^{-6}$/ml	%	% normal
Fertile range	>48.0	>63	>12
Indeterminate range	13.5–48.0	32–63	9–12
Univariate odds ratio for infertility (95% CI)	1.5 (1.2–1.8)	1.7 (1.5–2.2)	1.8 (1.4–2.4)
Subfertile range	<13.5	<32	<9
Univariate odds ratio for infertility (95% CI)	5.3 (3.3–8.3)	5.6 (3.5–8.3)	3.8 (3.0–5.0)

*CI denotes confidence interval.

N=696 fertile
N=765 infertile

- Extensive overlap between fertile and subfertile
- Strongest single predictor is morphology

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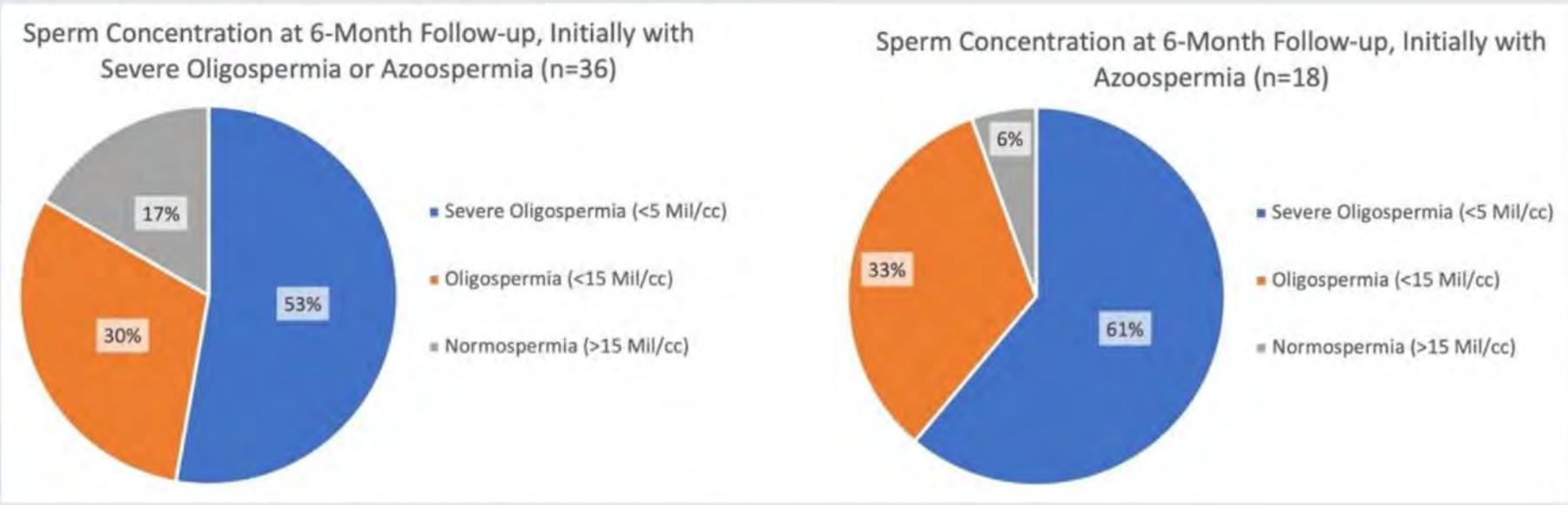
Guzick, DS, et al. New England J Med 2001; 345:1388

Male Infertility and Anabolic Steroid Use



Sperm concentration at 6-month follow-up for patients initially with severe oligospermia or azoospermia.

Ledesma. Fertility after AS use. Fertil Steril 2023.

- Subsequent fertility
- 37.5% achieved a successful subsequent pregnancy
  - 33.3% used assisted reproductive technology
  - 66.7% conceived naturally

Male Infertility and Medications

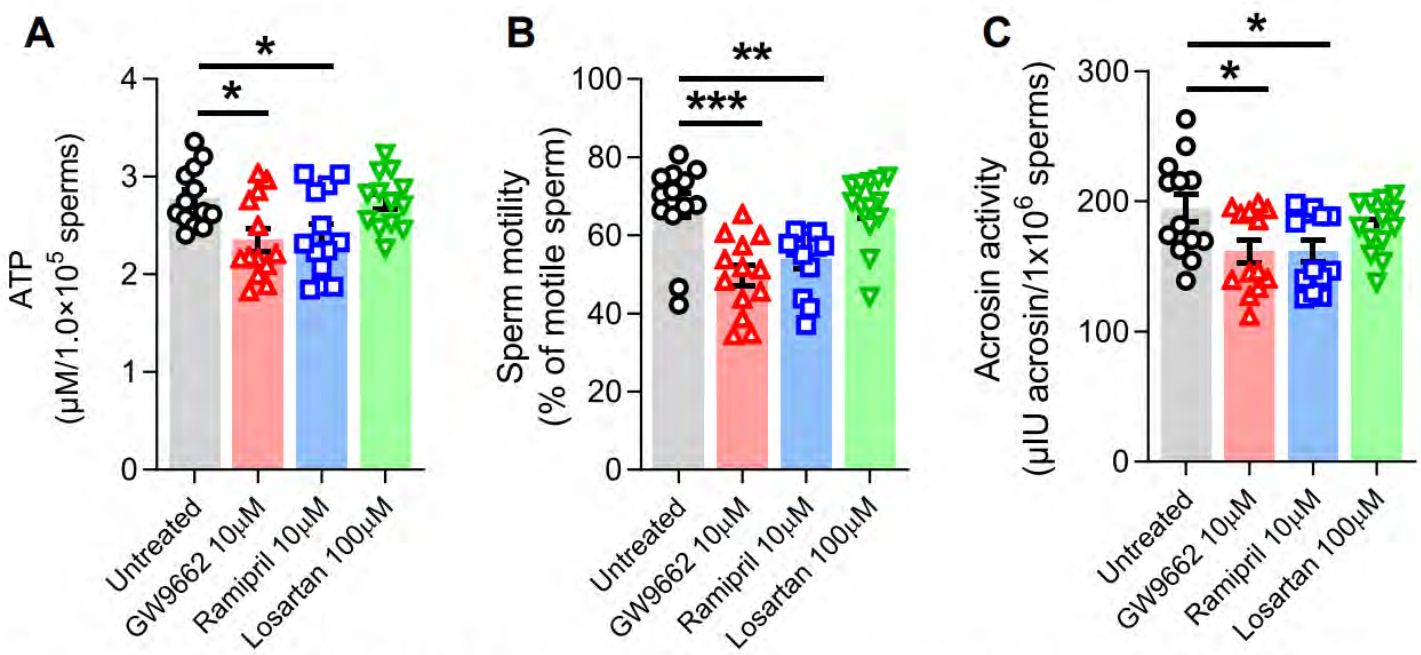


Figure 7. The metabolic and physiologic effect tACE in human sperm. Human sperm were treated for 12 h with either 10 μM GW9662 or 10 μM ramipril or 100 μM losartan and then (*A*) production of ATP, (*B*) motility, and (*C*) acrosine activity were determined as described in the Experimental procedures. Untreated samples were used as a control. Sperm representative motility video is shown in Video S2. Data are presented as means ± SEM (n = 13/group). An one-way ANOVA with Bonferroni's correction for multiple comparisons was used to analyze group comparisons. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$. tACE, testis angiotensin-converting enzyme.

Conclusion

- Initial Evaluation- conducted based on reproductive needs of the individual or couple
- Consider referral to Reproductive Endocrinology and Infertility Subspecialist
- Cannabis use does alter reproductive function, additional studies are needed.
- Social Media for healthcare information is largely created by non-healthcare professionals and overall video popularity is not correlated with video quality.
- Anabolic steroids and other medications impact sperm, even following discontinuation.

Moving towards precision medicine

- PCOS phenotyping is important - it determines pregnancy outcomes
- Endometrial biopsy for endometrial receptivity is not recommended
- Endometriosis is heterogenous and new treatments will need to be tailored to the type of disease.

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  - *Katherine Moran, MD*
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  - *Ally Kosturakis, MD*
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Helping Hand of Los Angeles, Inc.

Our patients for participating in our studies to improve outcomes!

Cedars Sinai

Disclosures

Relevant Disclosures:

The Menopause Society Board of Directors

Consultant: Astellas

No conflicts of interest

References:

I will discuss clinical studies of off label use of pharmaceuticals for vasomotor symptoms.

This presentation references people born with ovaries. I may use the terms women, she, and her. These terms may not capture the diversity of all those experiencing menopause. We need more research to explore how diverse people experience menopause.

—I wasn't expecting you so soon. Premature Menopause

Makeba Williams, MD, FACOG, MSCP
Associate Professor
Director, Midlife and Menopause Medicine
Vice Chair of Professional Development and Wellness
Department of Obstetrics and Gynecology

Learning Objectives

01

Describe the physiology and pathophysiology of premature menopause or premature ovarian insufficiency

02

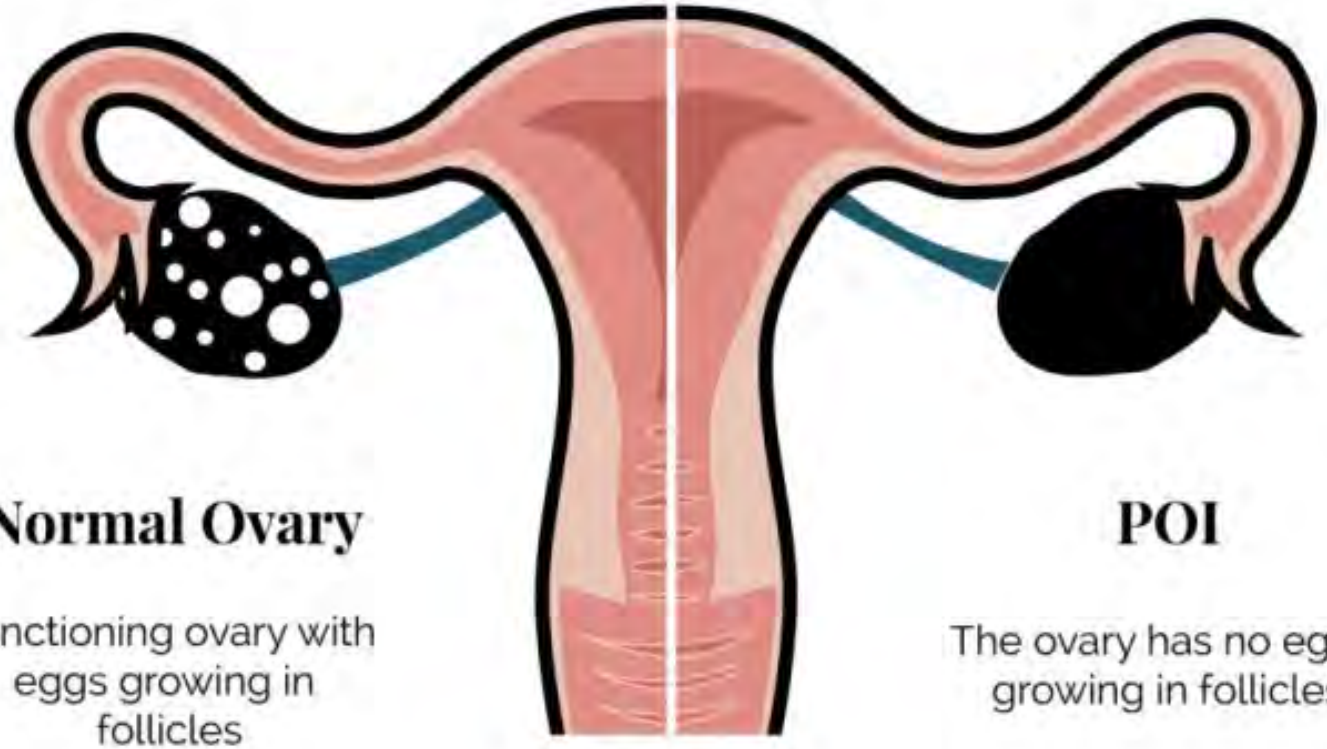
Review diagnostic considerations and management of women with premature menopause secondary to ovarian insufficiency and oophorectomy.

03

Discuss the use of hormones in women with complex medical conditions who are diagnosed with premature menopause

PREMATURE OVARIAN INSUFFICIENCY

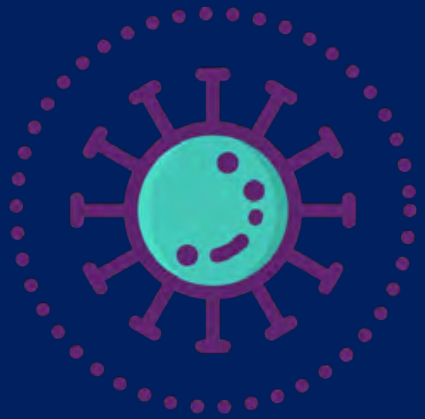
WHAT IS POI?



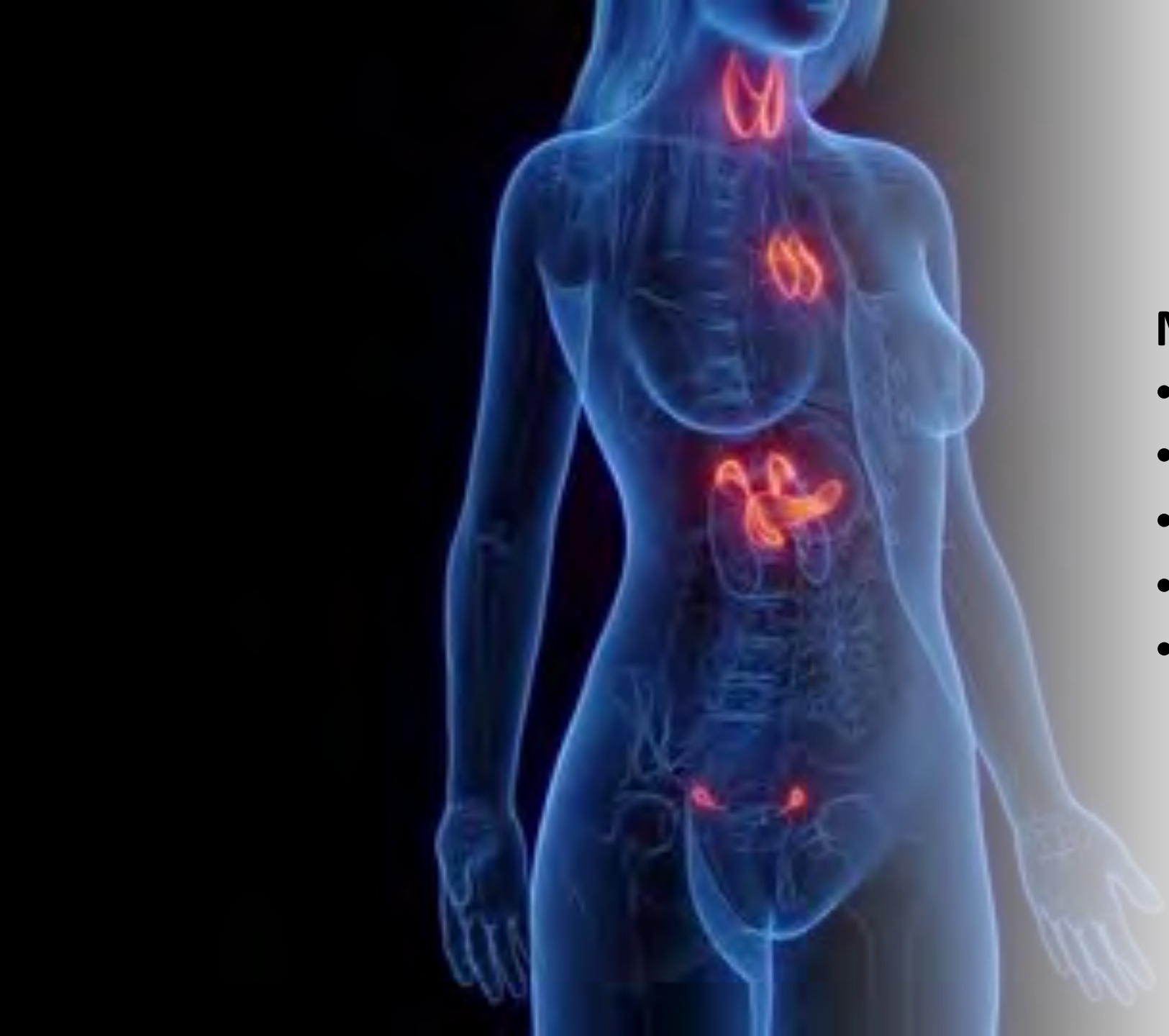
1% US population

- 1% White
- 1.4% Black
- 1.4% Hispanic
- 0.5% Chinese
- 0.1% Japanese

3.7% worldwide





Multi-organ System Impact

- CHD
- Neurocognitive
- Osteoporosis
- Sexual function
- Mortality & Morbidity

33% visit 3 physicians before diagnosis is made

Learning Objectives

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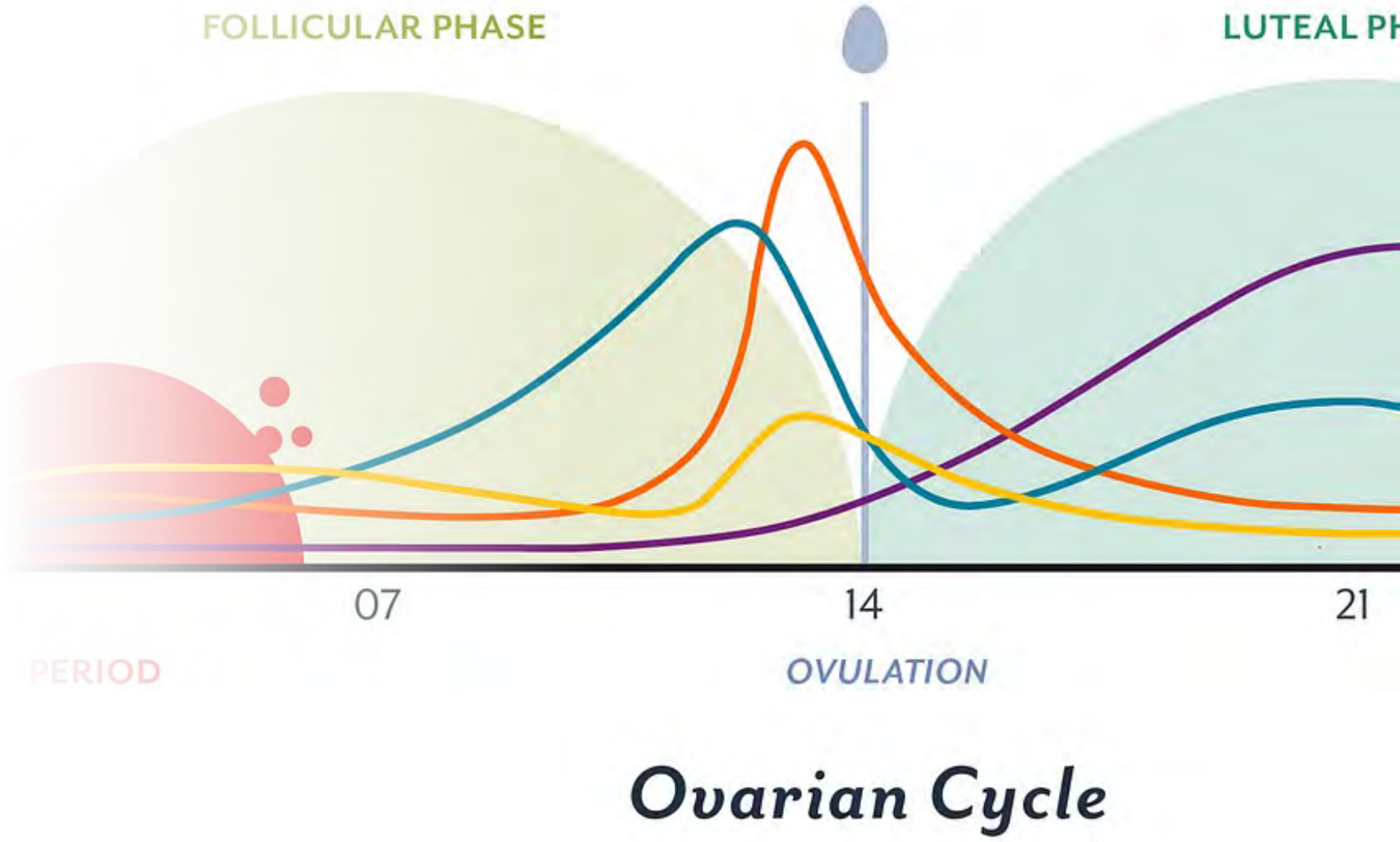
Suspicious Signs of POI

- Amenorrhea x3 months with hx of regular cycles
- Amenorrhea >6 months with hx of irregular cycles
- New onset menstrual changes, decreased ovarian reserve



Menopause Symptoms:

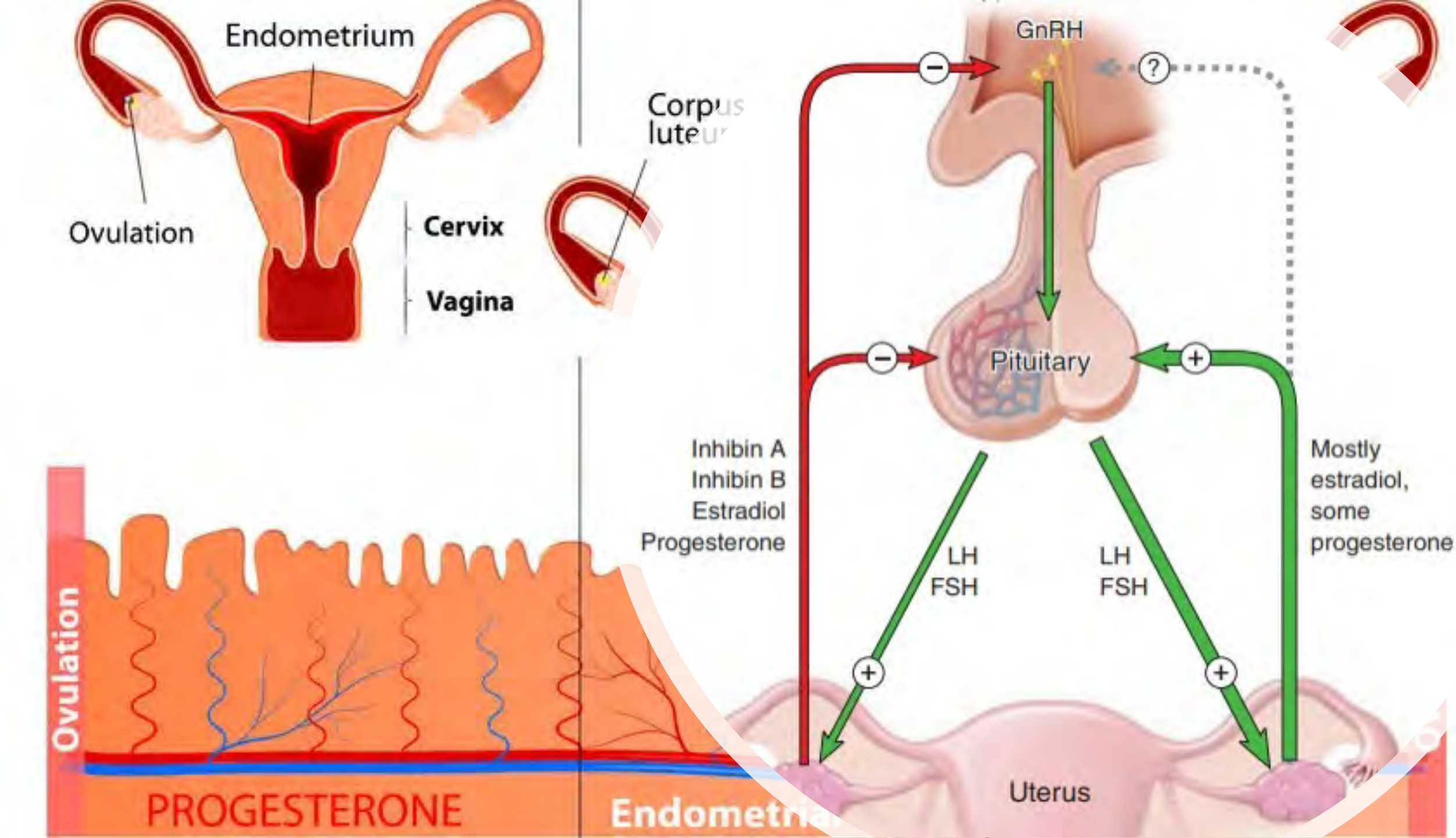
- Hot flashes/night sweats
- Sleep disruption
- Vaginal dryness

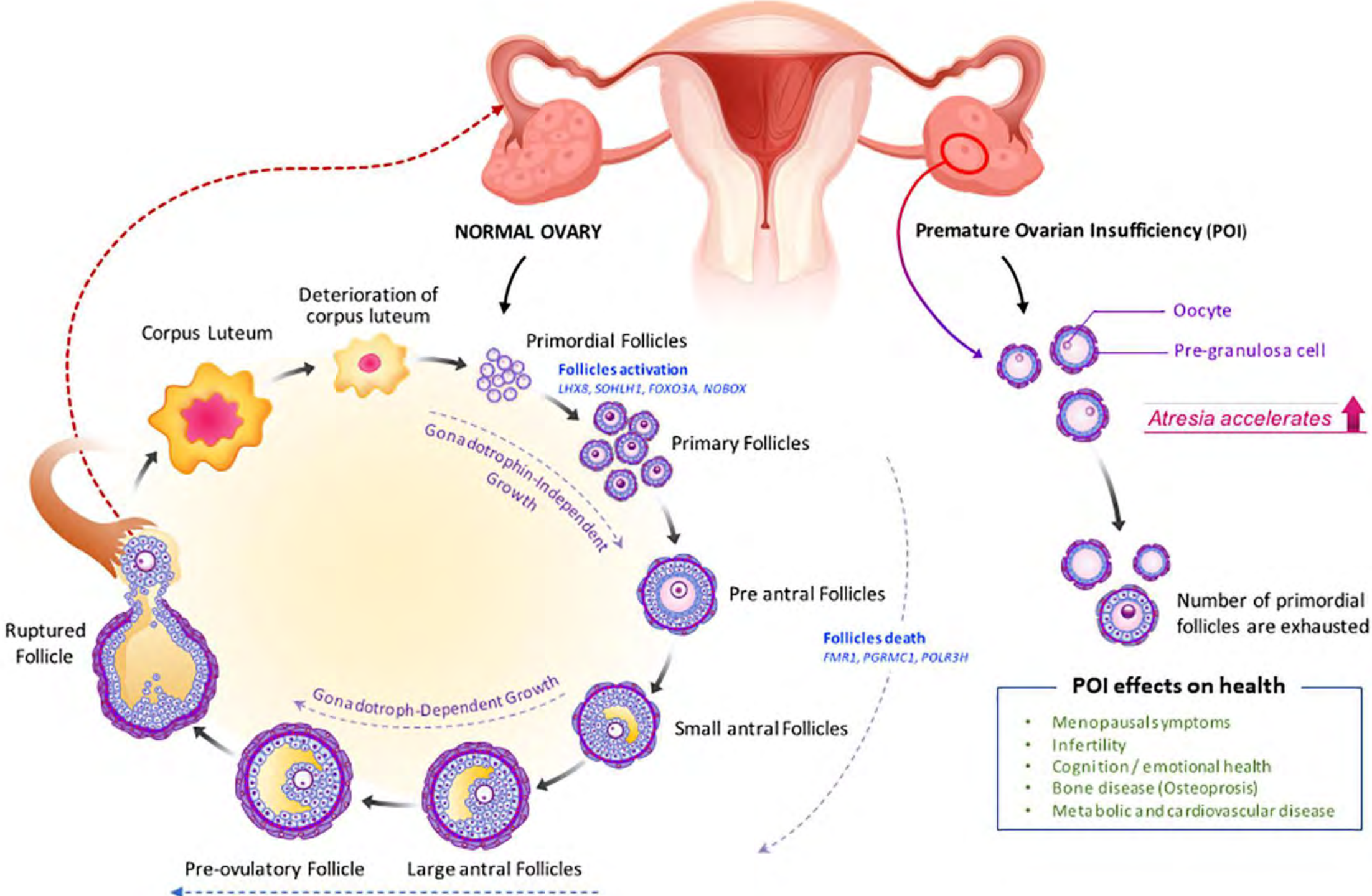
Sexual dysfunction

Depression/Anxiety

Cognitive decline

Dry eye syndrome


Endometrium
Ovulation
Cervix
Vagina
Corpus luteum
GnRH
?
Pituitary
Inhibin A
Inhibin B
Estradiol
Progesterone
LH
FSH
LH
FSH
Mostly estradiol, some progesterone
Uterus
Ovulation
PROGESTERONE
Endometrial


NORMAL OVARY
Premature Ovarian Insufficiency (POI)
Deterioration of corpus luteum
Corpus Luteum
Primordial Follicles
Follicles activation
LHX8, SOHLH1, FOXO3A, NOBOX
Primary Follicles
Gonadotrophin-Independent Growth
Pre antral Follicles
Follicles death
FMR1, PGRMC1, POLR3H
Small antral Follicles
Gonadotroph-Dependent Growth
Large antral Follicles
Pre-ovulatory Follicle
Ruptured Follicle
Oocyte
Pre-granulosa cell
Atresia accelerates
Number of primordial follicles are exhausted
POI effects on health
Menopausal symptoms
Infertility
Cognition / emotional health
Bone disease (Osteoprosis)
Metabolic and cardiovascular disease

History

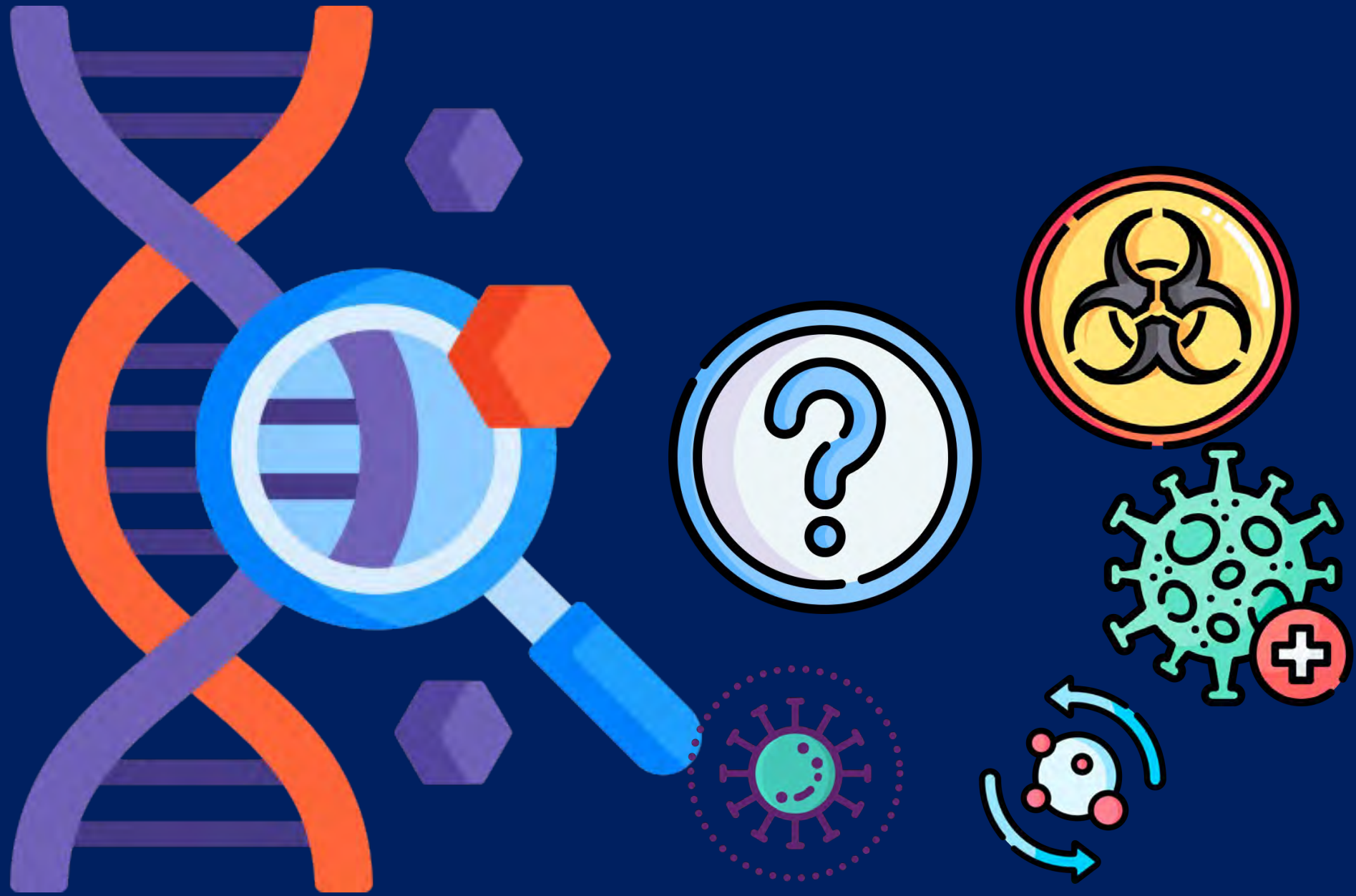
- Menstrual
- Family
  - Menstrual irregularities/Early menopause
  - Genetic disorders
  - Neurocoognitive disorders

Laboratory Evaluation

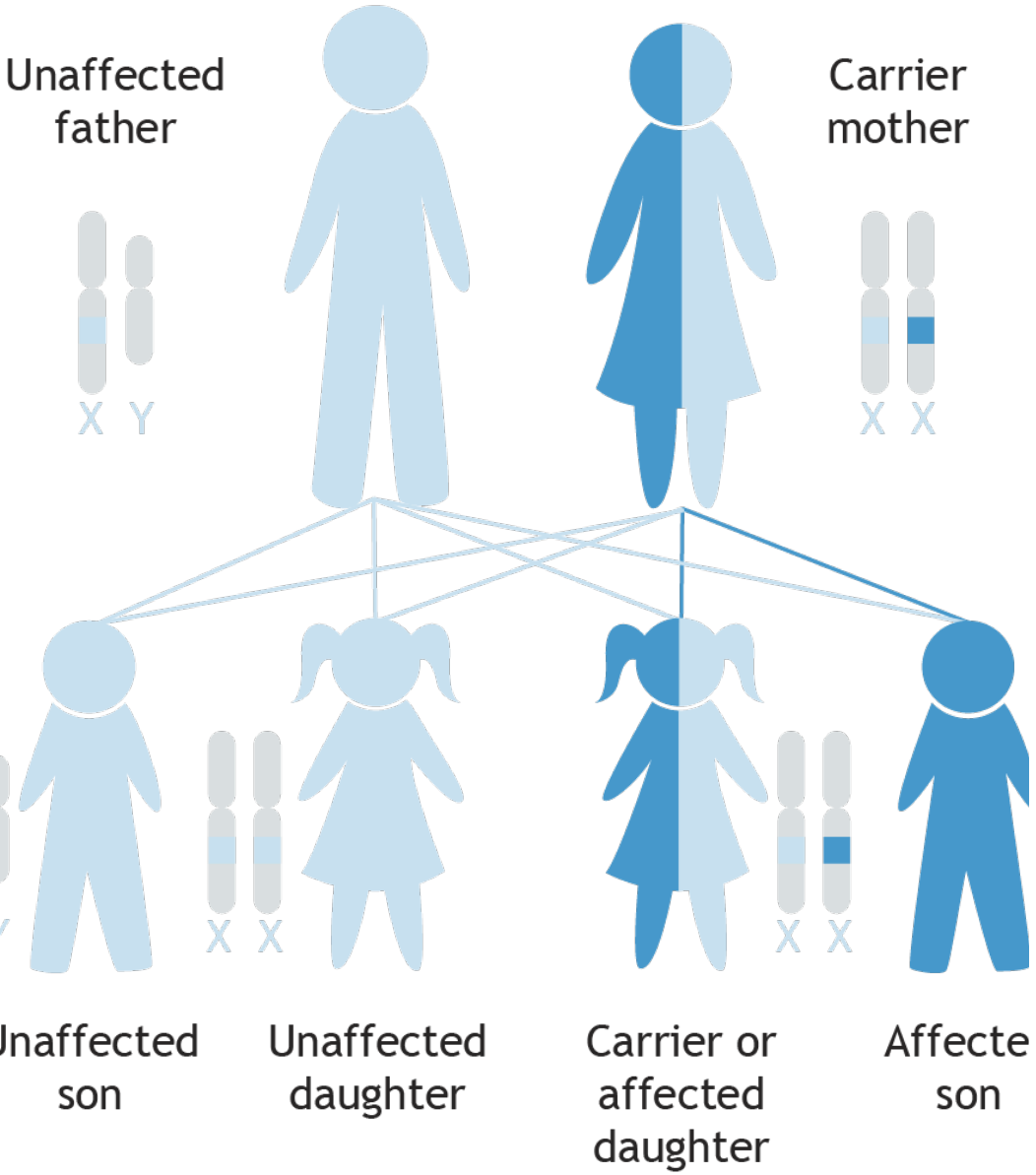
- HCG level: rule out PREGNANCY
- Thyroid function
- Prolactin levels
- Gonadotrophic function
  - FSH
    - ➢ *If elevated, repeat in 1 month with Estradiol*

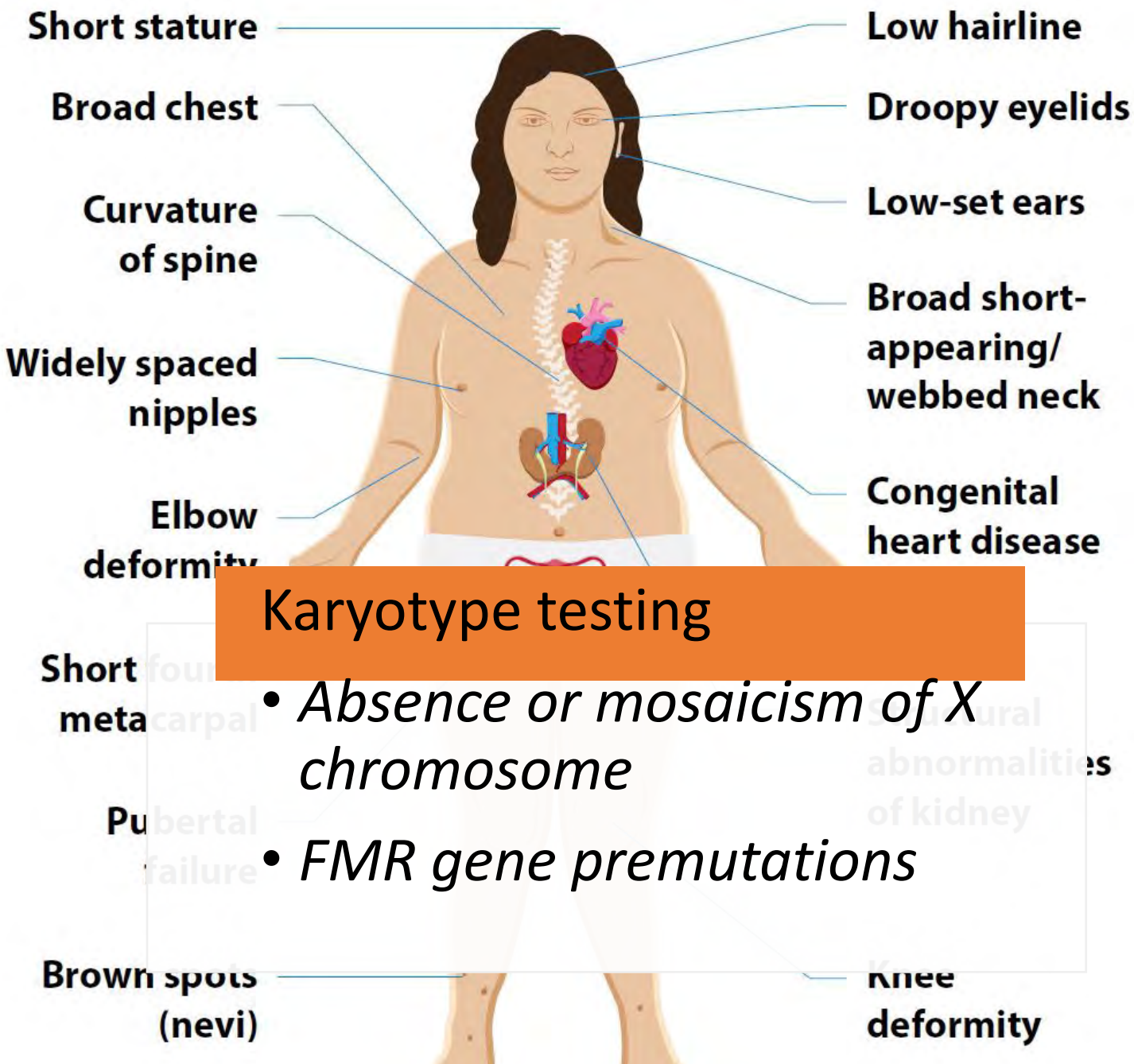






X-Linked Inheritance in Fragile X Syndrome

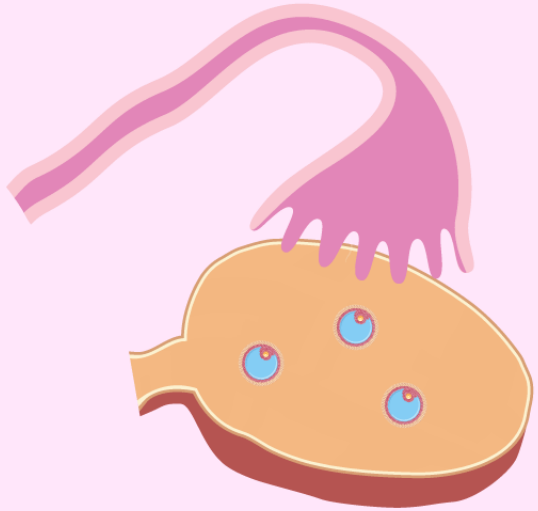




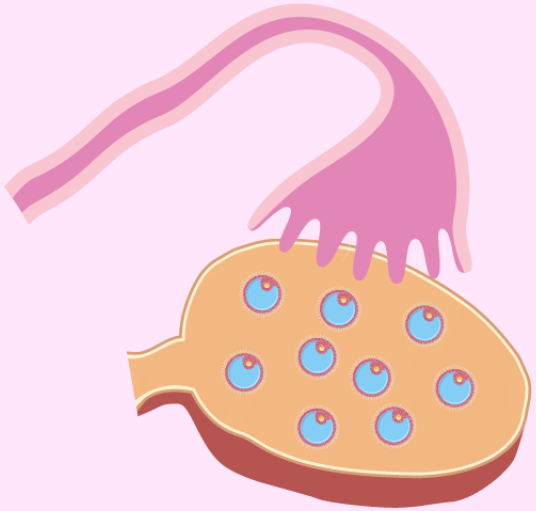
Karyotype testing

- *Absence or mosaicism of X chromosome*
- *FMR gene premutations*

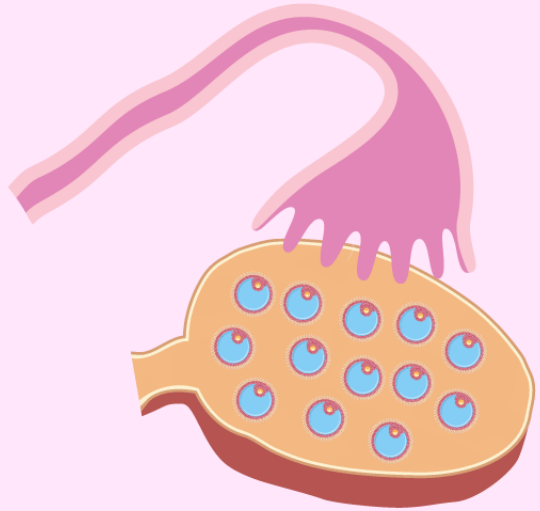

Autoimmune thyroid disease, Addison’s disease, Type I Diabetes



Low ovarian reserve



Normal ovarian reserve



High ovarian reserve

- Gonadotoxic therapies: cyclophosphamide therapy, radiation, chemotherapy, pelvic surgery
- Environmental toxins: chemicals (phthalates, bisphenols, dioxins)
- Galactosemia
- Infections: Mumps, HIV

Surgical Menopause

- Vasomotor symptoms
- Genitourinary symptoms
- Sexual dysfunction
- Cognitive impairment
- Bone loss
- Cardiovascular disease
- All cause mortality
- Cancer death

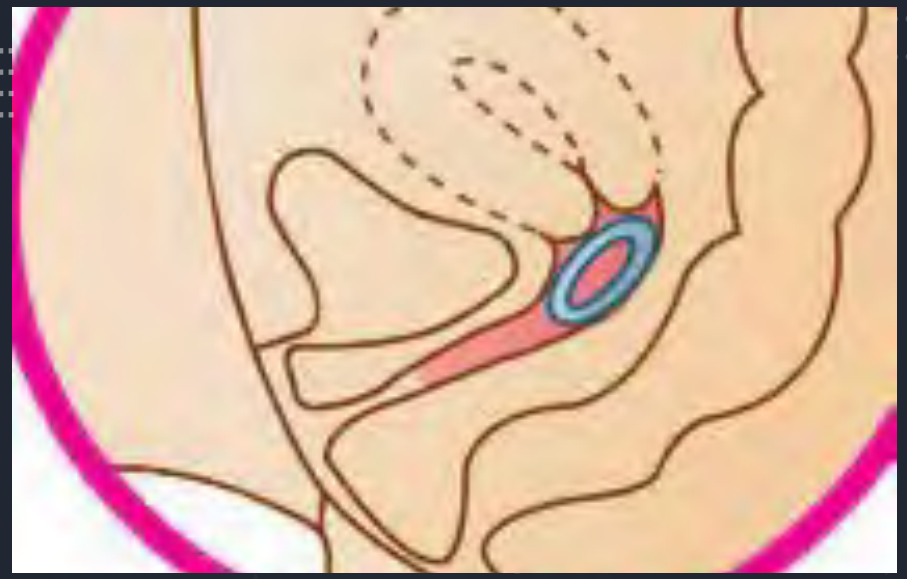

Treatment

Psychological Support


R
Hormone therapy

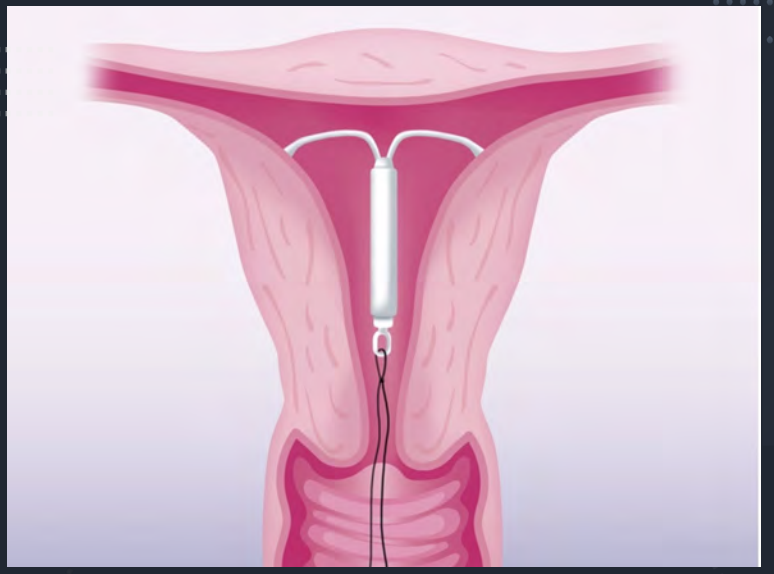
Estrogen Replacement Therapy

- Transdermal patch or Vaginal Ring 0.100 mg/day E_2 transdermal patch or 0.100 mg/day E_2 ring
- Full-dose physiologic replacement for young women
- Serum E_2 level of 100 pg/mL
  - Near normal mean E_2 level for normally cycling women of 104 pg/mL
- Avoids 1st pass liver metabolism
- Allows continuous dosing
- CVD/ thrombotic risk markers not adversely effected



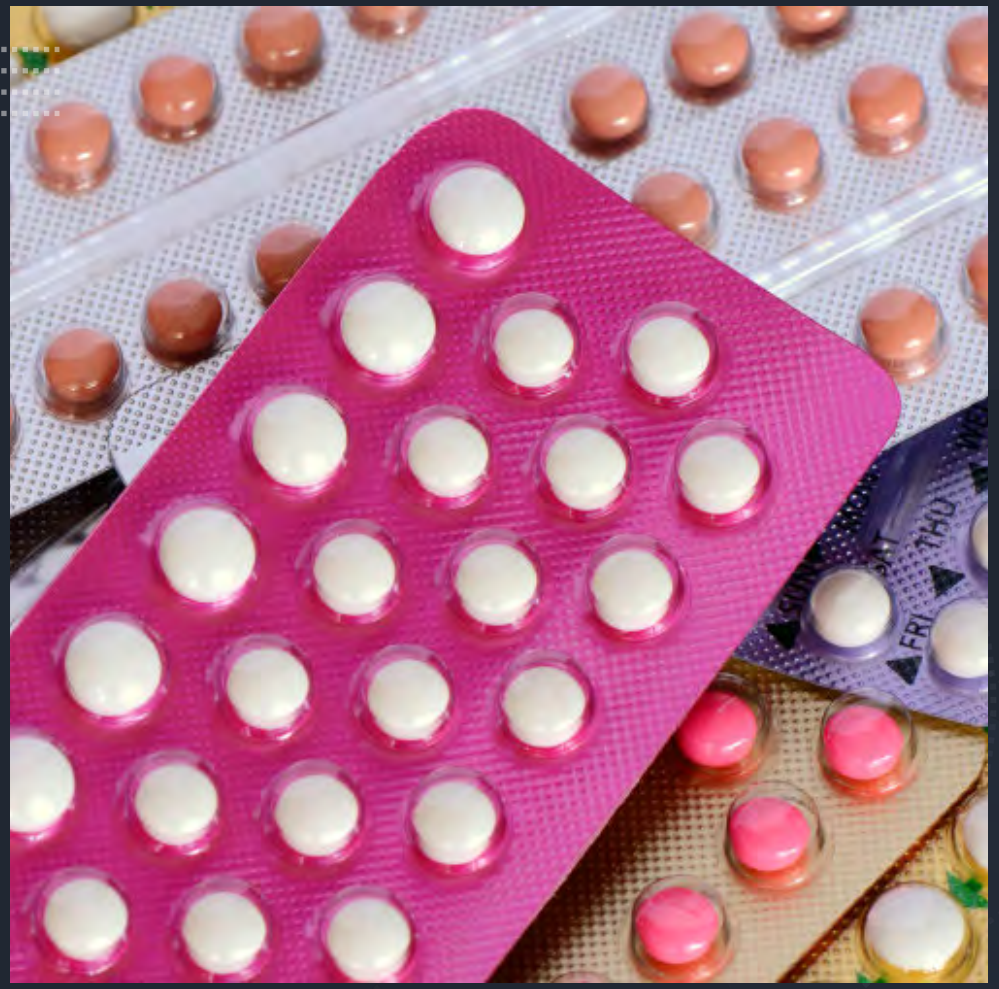
Endometrial Protection

- Medroxyprogesterone Acetate (MPA) 10 mg/d x 12 days per month
- ? Micronized progesterone
  - Not well studied for use with full Estrogen replacement doses
- Off label: Levonorgestrel IUDs
- Precautions for abnormal or breakthrough bleeding
  - ➢ Evaluate breakthrough bleeding: pregnancy test, pathology

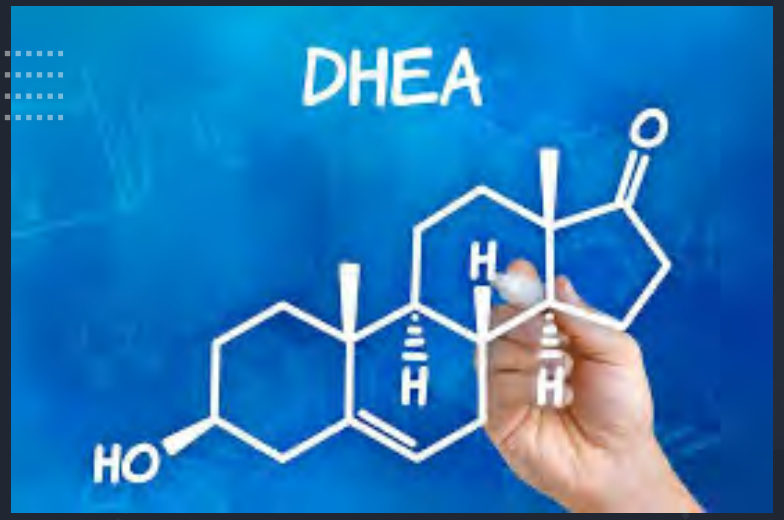


Combined Hormonal Contraception

- Use with caution
- Supraphysiologic levels of synthetic estrogen and progestin
- Increased risk of VTE, ATE, HTN, worsening lipid profiles
- Menopause symptoms with cyclical use



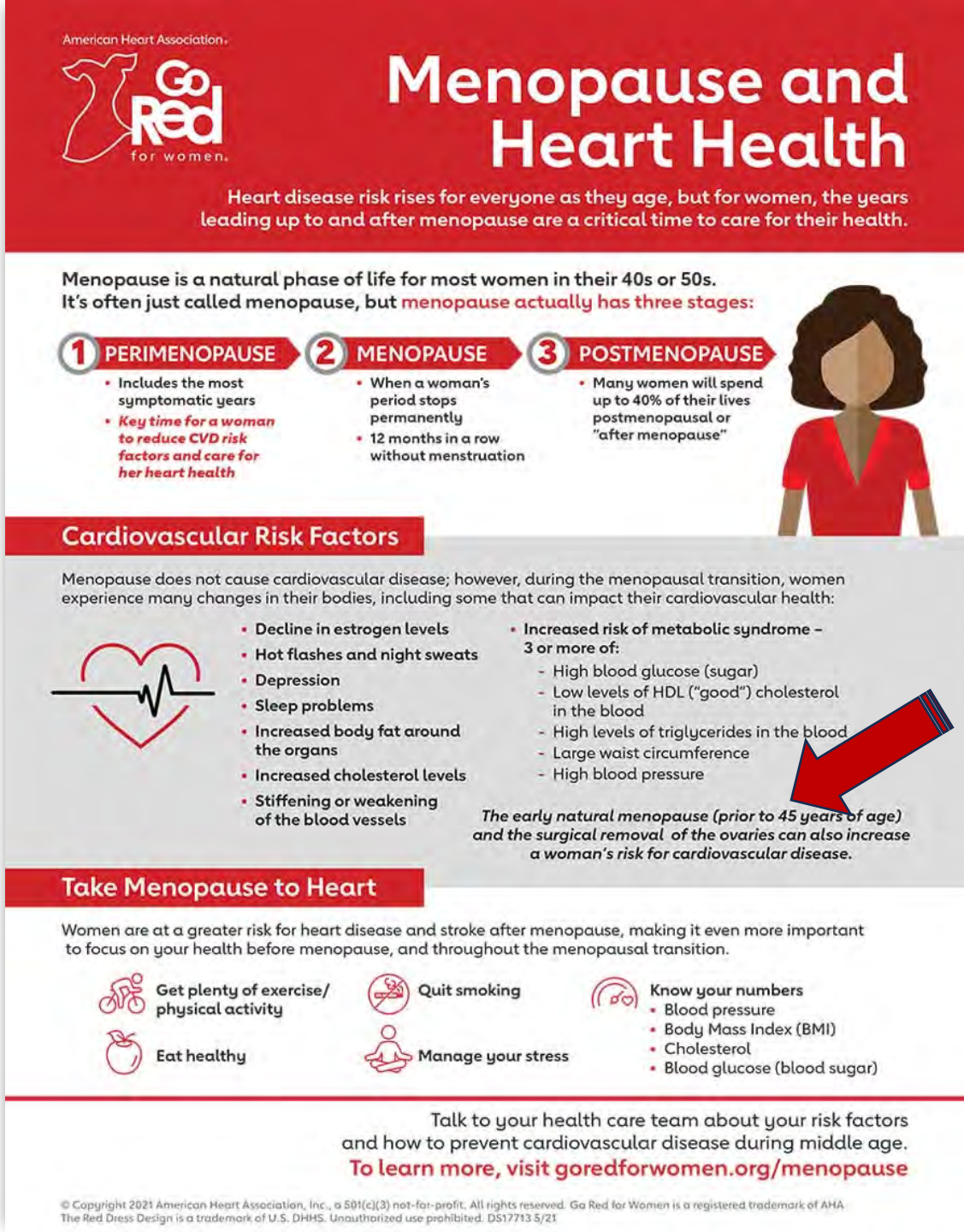
More Research Needed



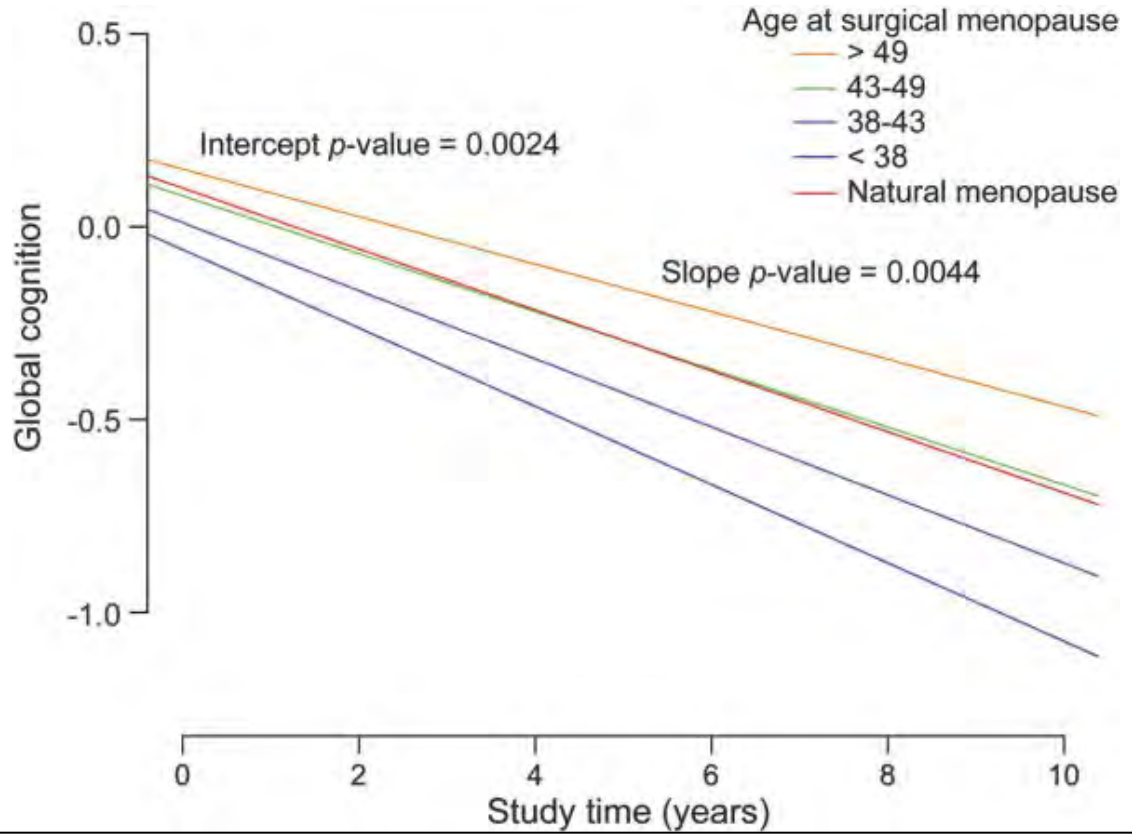
Bone Health

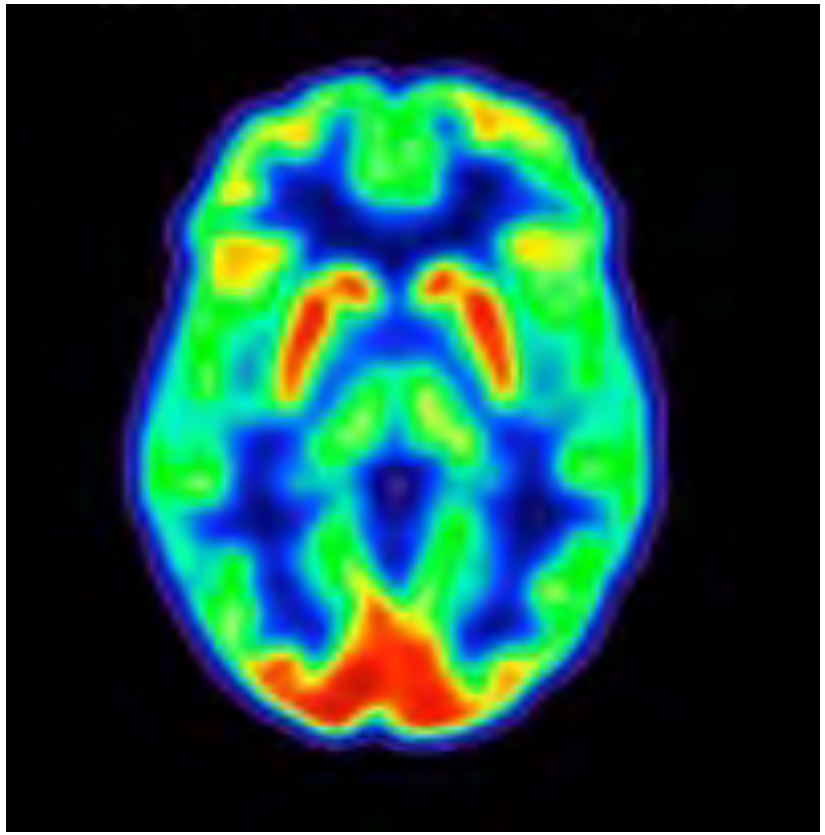
- Baseline BMD with DEXA recommended
- Calcium 1200 mg daily
  - Dietary source is preferred
  - Supplement if necessary
- Vitamin D 1000-2000 IU daily
  - maintain in normal range >30 ng/mL
- Weight bearing exercise

- Reduced Endothelial function
  - ➢Improved with 6 months of HRT
- 50% greater risk of CVD events in women with premature menopause
  - ➢Risk decreases with initiation of HRT within 1 year of menopause and maintained for 10 years
- Regular CVD risk assessments and risk reduction measures
- Lipid management
- BP management
- Early initiation of HRT at physiologic levels



Neurocognitive Health





Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women.
Bove, Riley; Secor, Elizabeth; Chibnik, Lori; Barnes, Lisa; Schneider, Julie; MD, MS; Bennett, David; De Jager, Philip; MD, PhD
Neurology. 82(3):222-229, January 21, 2014.

Fertility Loss

- AMH
- Partner with REI
- Psychological support

Emotional Health


Prevention, Nutrition,
Sleep hygiene, Weight management

Learning Objectives

01

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Discuss the use of hormones in women with complex medical conditions who are diagnosed with premature menopause

Turner Syndrome

Photo courtesy of TSGA TURNER SYNDROME GLOBAL ALLIANCE

Risk Factors

- Growing up in a dioxin superfund neighborhood
- Gonadotoxic chemotherapy
- Radiation therapy
- Ovarian suppression with leuprolide

Treatment considerations

- HRT
- Bones
- Psychology
- Fertility
- Sexual function
- Mood

TUESDAY

HOW TO DEVELOP A CULTURE OF SAFETY AND QUALITY IN THE OR

Jaime Arruda, MD

Clinical Director for Robotic Surgery
Professor Clinical Medicine, Ob/Gyn

DISCLOSURES

- Consultant and Study PI for Eximis Surgical
- Consultant Medtronics

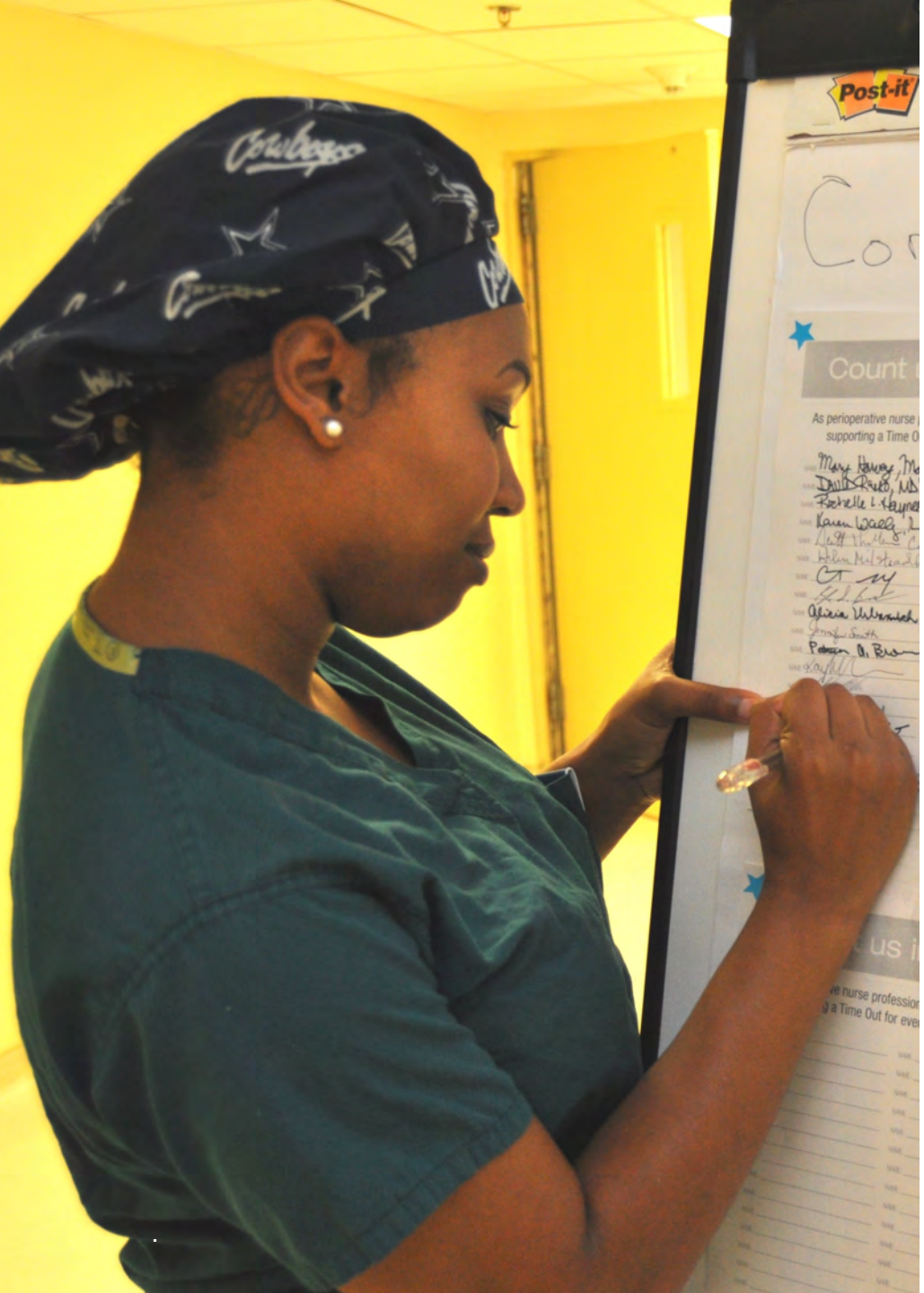
THERE WILL BE NO AVIATION SAFETY REFERENCES IN THIS TALK…

OBJECTIVES

- Review the role of each **team member** in contributing to safety in the operating room
- Consider improvements in **communication** which can make the OR a safer place – preoperative “time-out”, surgical “debrief”
- Understand strategies to improve **surgical site infections**
- **Track quality measures** in your operating room and use them in a constructive way

SURGICAL TEAM

- **Surgical tech (scrub tech):** prepares room, passes instruments/supplies, assist at bedside, clean-up
- **Scrub nurse:** as above with some extended skills depending on hospital credentials
- **Circulating nurse:** completes non-scrubbed tasks in the room, documentation, passes supplies onto surgical field, responsible for initiating the time-out/debrief
- **First assist**: bedside assistance, suction/irrigation, suture passing, open and close
- **Medical student:** operate and assist under the direct supervision of resident and attending
- **Resident:** operate and assist under supervision of attending
- **Attending surgeon:** responsible for the primary operation of the case
- **Anesthesia team:** sedation and airway management, pain management, positioning
- **Ancillary staff:** perfusion team, industry representatives, proctors, etc.



SURGICAL TEAM TIMEOUT

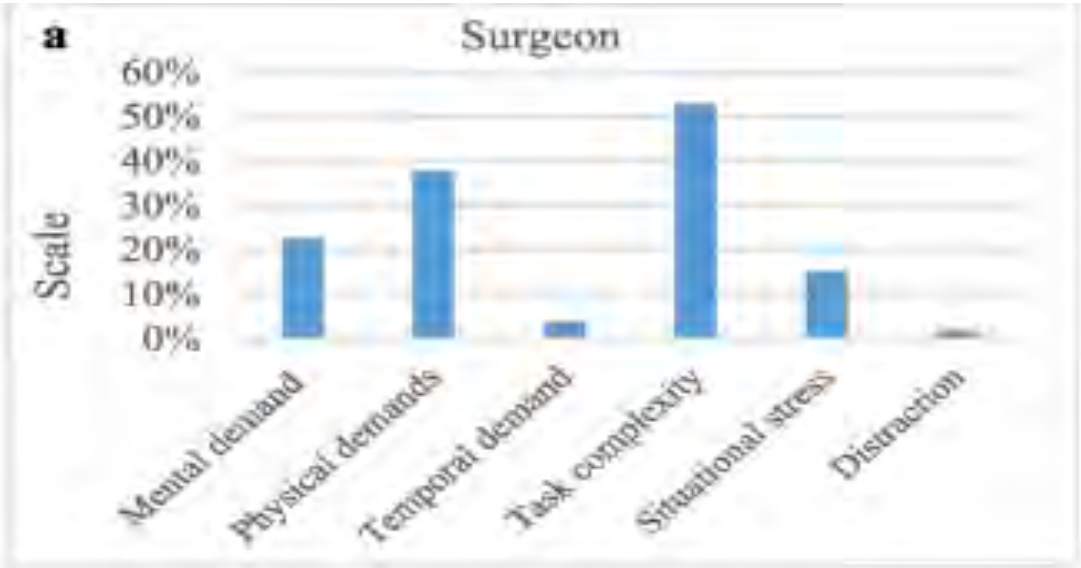
- **Patient identification timeout:** circulating nurse and anesthesia team verify patient and procedure with the patient AWAKE.
- **Surgical timeout:** performed with the entire surgical team in the room after the prep/drape
  - Patient name and identifier (MRN, DOB)
  - Procedure Name
  - Procedure site verification
  - Allergies
  - Preoperative antibiotic
  - VTE prophylaxis
  - Specimens
  - Fire risk
  - Discharge plan and location

SURGICAL TIMEOUT

- **Vanderbilt** prospective study of 166 observed "Time out" procedures for non-emergent cases in 2016
- "Time out" was initiated 100% of the time
- Average duration of a "time out" was 60.8 seconds
- 6% of the time, the "time out" was interrupted for a safety concern
  - 40% due to Medication discrepancy (e.g. incorrect antibiotic)
  - 40% related to procedural clarification (e.g. consent not matching the stated procedure)
  - 20% due to postoperative plan discussion (e.g. patient going home, ICU, floor)
- 10% of the time, at least one member of the operating room team was actively distracted during the time out
- 1.3% of the time, the timeout was performed AFTER the surgical incision had been made

SURGICAL TEAM WORKLOAD

- Perception of workload in the operating room is not divided equally!
- Study by Totonchilar et al (2023) evaluated 346 surgical team members over 76 cases (a total of 409 questionnaires) on the different types of demands in the OR:
  - **Mental demands** – how mentally fatiguing was the procedure? (endo or cancer cases)
  - **Physical demands** – how physically fatiguing was the procedure? (large fibroid uterus)
  - **Temporal demands** – how hurried or rushed was the pace of the procedure? (crash c-section)
  - **Task complexity** – how complex was the procedure? (difficult laparoscopy)
  - **Situational stress** – how anxious did you feel while performing the procedure? (working with a difficult attending)
  - **Distractions** – how distracting was the operating room environment? (getting paged from the PACU)


a
Surgeon
Scale
60%
50%
40%
30%
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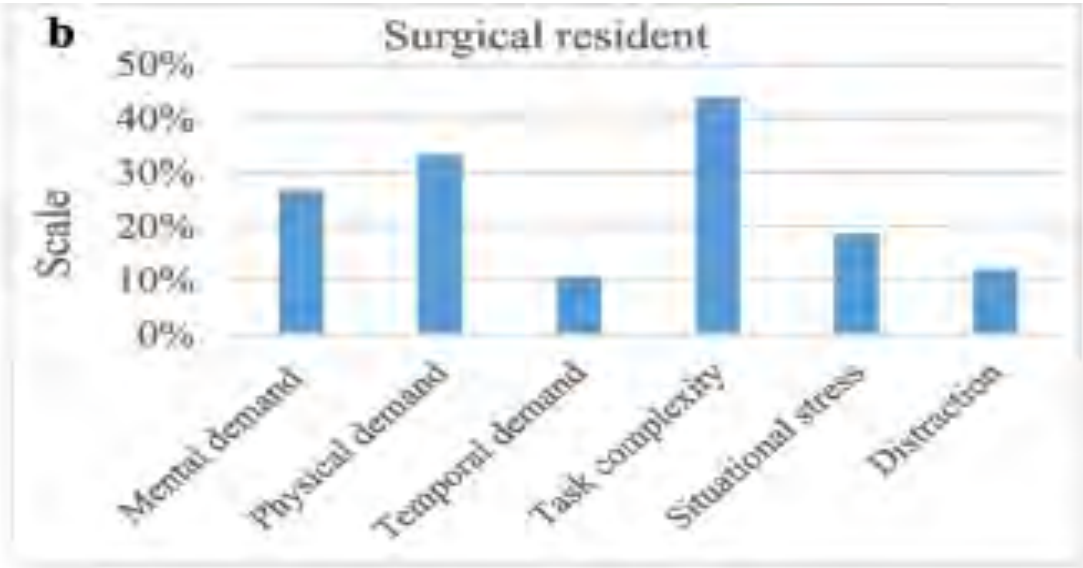
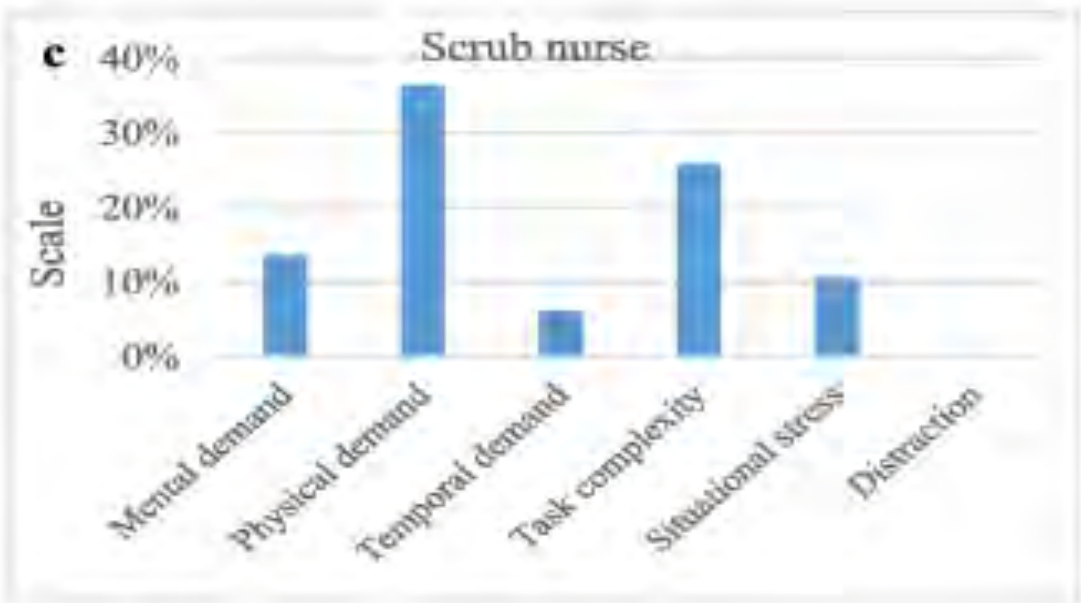
10%
0%
Mental demand
Physical demands
Temporal demand
Task complexity
Situational stress
Distraction


b
Surgical resident
Scale
50%
40%
30%
20%
10%
0%
Mental demand
Physical demand
Temporal demand
Task complexity
Situational stress
Distraction


c
Scrub nurse
Scale
40%
30%
20%
10%
0%
Mental demand
Physical demand
Temporal demand
Task complexity
Situational stress
Distraction


d
Circulating nurse
Scale
35.%
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25.%
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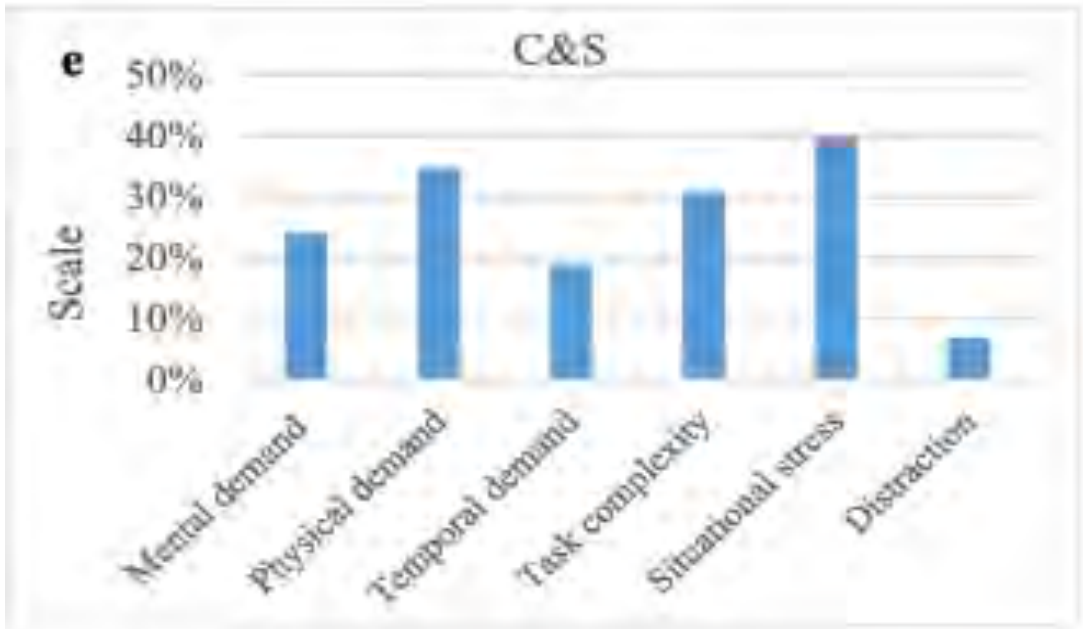
0.%
Mental demand
Physical demand
Temporal demand
Task complexity
Situational stress
Distraction


e
C&S
Scale
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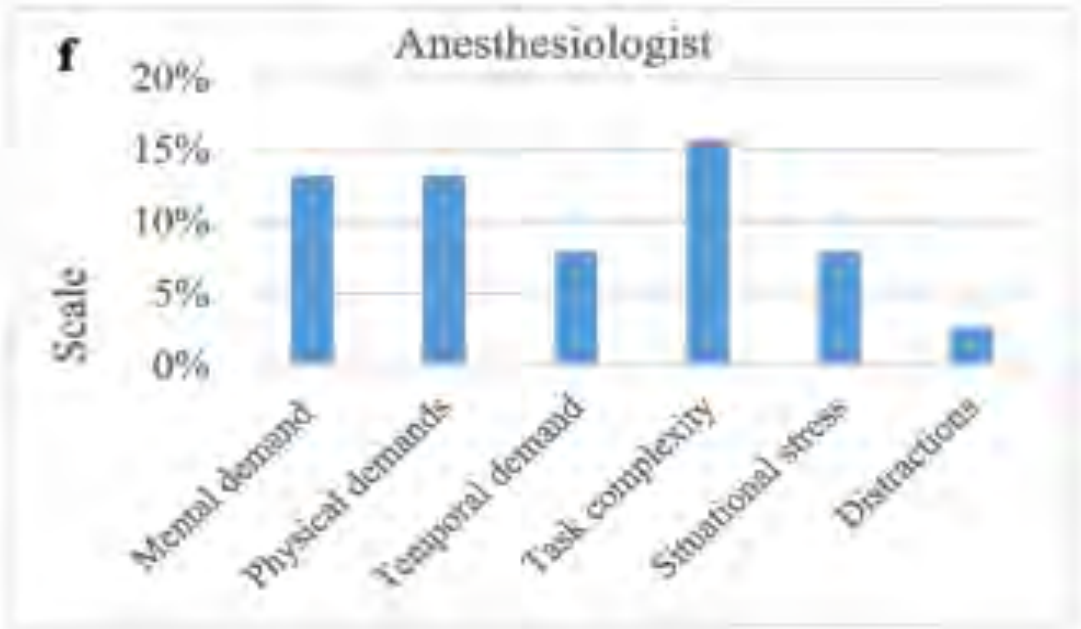
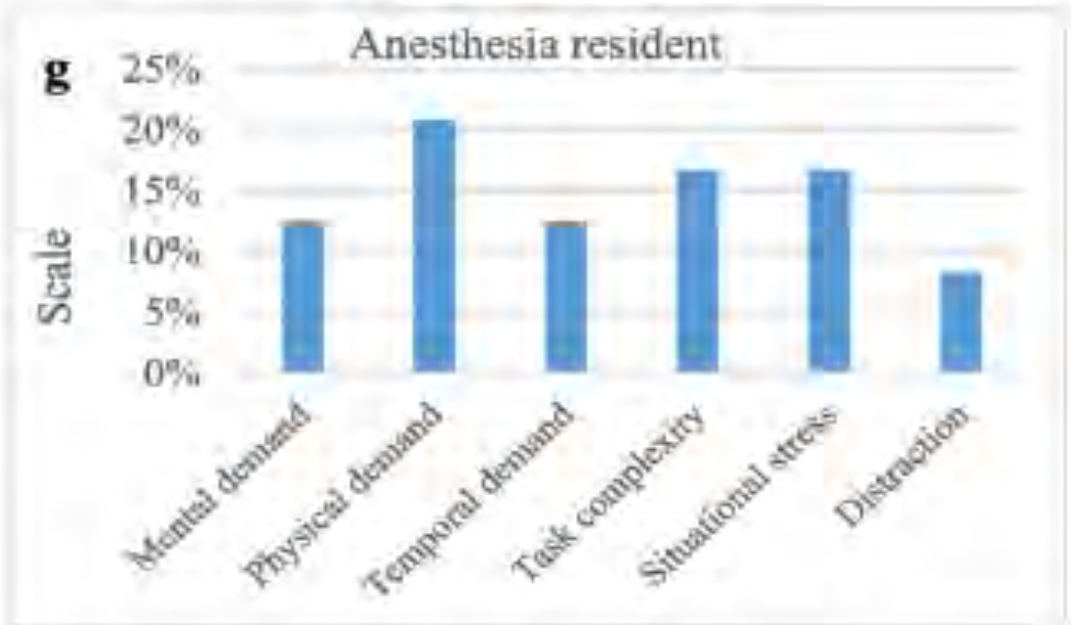
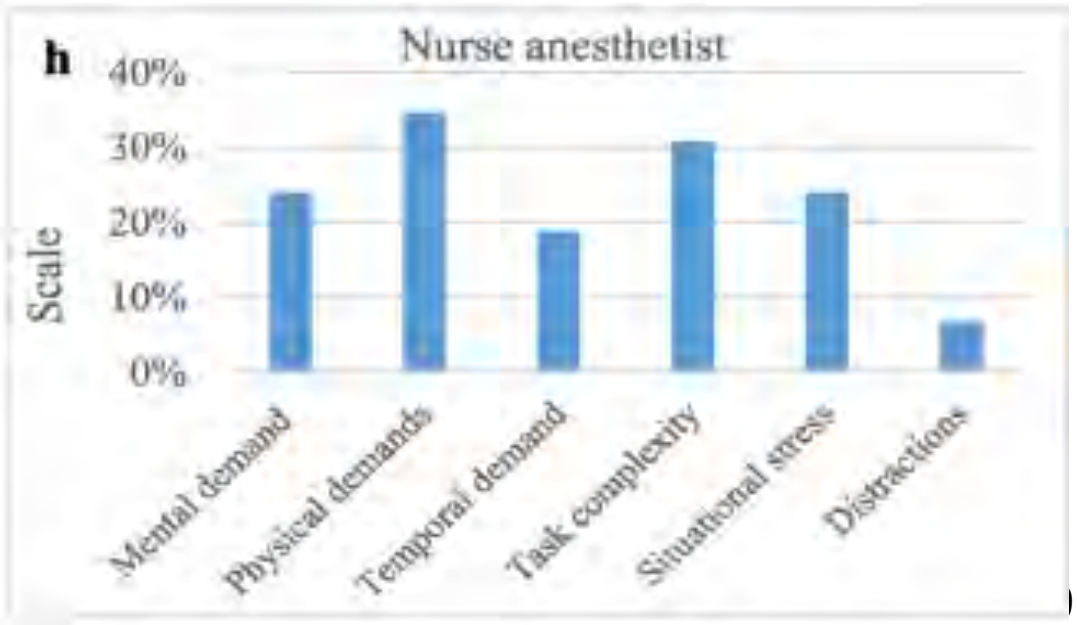
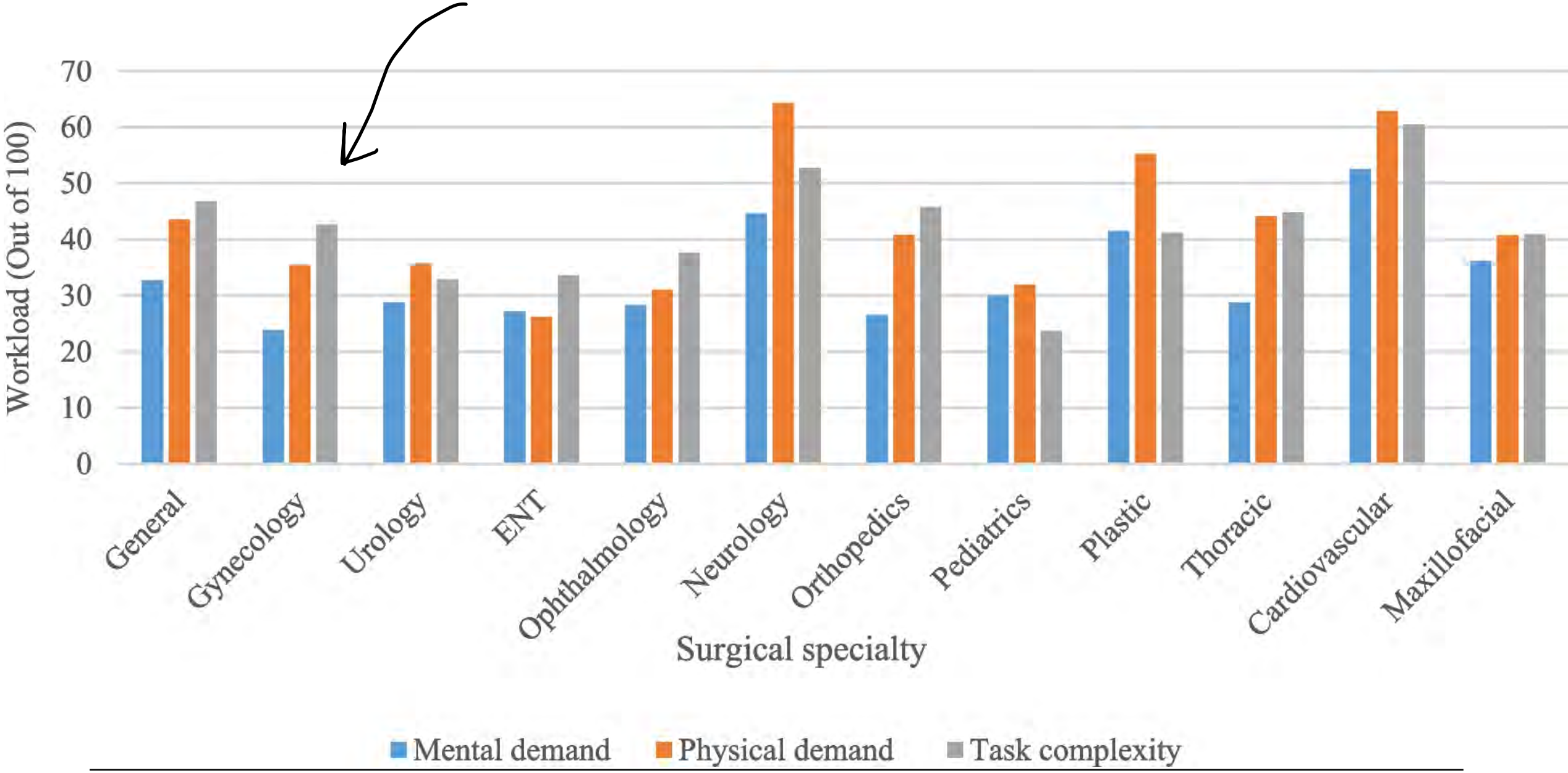
Mental demand
Physical demand
Temporal demand
Task complexity
Situational stress
Distraction


f
Anesthesiologist
Scale
20%
15%
10%
5%
0%
Mental demand
Physical demands
Temporal demand
Task complexity
Situational stress
Distractions


g
Anesthesia resident
Scale
25%
20%
15%
10%
5%
0%
Mental demand
Physical demand
Temporal demand
Task complexity
Situational stress
Distraction


h
Nurse anesthetist
Scale
40%
30%
20%
10%
0%
Mental demand
Physical demands
Temporal demand
Task complexity
Situational stress
Distractions


70
60
50
40
30
20
10
0
Workload (Out of 100)
General
Gynecology
Urology
ENT
Ophthalmology
Neurology
Orthopedics
Pediatrics
Plastic
Thoracic
Cardiovascular
Maxillofacial
Surgical specialty
Mental demand
Physical demand
Task complexity

Technique	Cases	Mental demand (Mean±sd)	Physical demand (Mean±sd)	Temporal demand (Mean±sd)	Task complexity (Mean±sd)	Situational stress (Mean±sd)	Distraction (Mean±sd)	Total workload (Mean±sd)
Open	300	34.46 ± 25.50	45.58 ± 26.89	24.31 ± 22.89	45.50 ± 26.46	30.86 ± 24.34	24.68 ± 16.61	34.23 ± 16.91
MIS	96	26.61 ± 22.63	28.17 ± 23.77	21.45 ± 22.05	31.61 ± 25.79	25.62 ± 27.14	26.82 ± 18.56	26.71 ± 17.28
Combined	13	40.76 ± 17.77	38.84 ± 23.81	20 ± 17.91	40.76 ± 28.27	24.23 ± 15.39	30 ± 24.57	32.43 ± 15.42
Total surgeries	409	32.82 ± 24.86	41.28 ± 27.06	23.50 ± 22.50	42.09 ± 26.94	29.42 ± 24.87	25.35 ± 17.37	32.41 ± 17.21

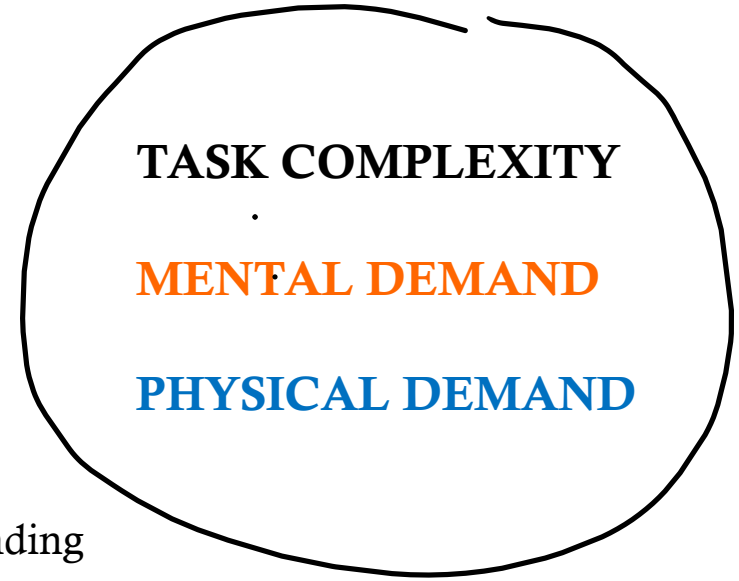
SURGICAL TEAM WORKLOAD

- The "workload" of different members of the surgical team is influenced by specialty, technique (open, MIS), role and surgical duration.
- Ob/Gyn surgeons' workload was most influenced by **TASK COMPLEXITY**, **PHYSICAL DEMAND** and **MENTAL DEMAND.**
- Open surgery was both **physically demanding** with **high task complexity** for surgeons.
- MIS surgery had **high task complexity** for surgeons.
- Circulating nurse and scrub nurse may be more distress by **TIME** and **SITUATIONAL STRESS.**
- Trainees in the OR may be distressed by **DISTRACTIONS**, even when not perceived by more experienced members of the team.

Totonchilar et al , "Eximaning workload variations among different surgical team roles, specialties, and techniques: a mulitcenter cross-sectional descriptive study." Periop Med 2024;2/30/24

HOW CAN WE REDUCE THE STRESS FOR EACH OF THESE TEAM MEMBERS?

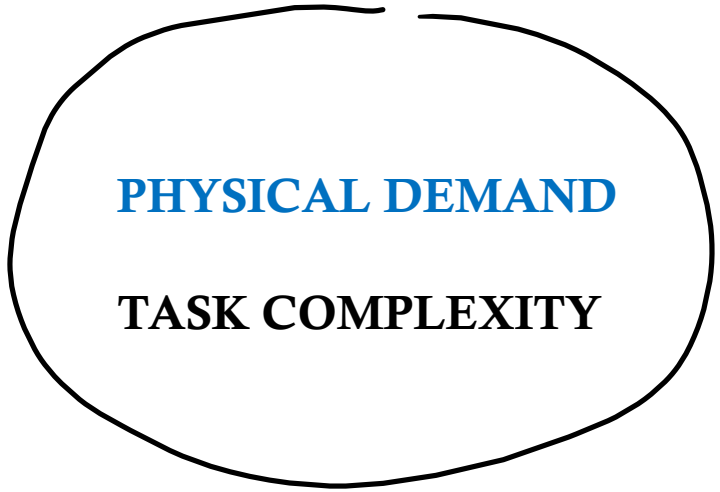
STRATEGIES TO IMPROVE SURGICAL TEAM WORKLOAD



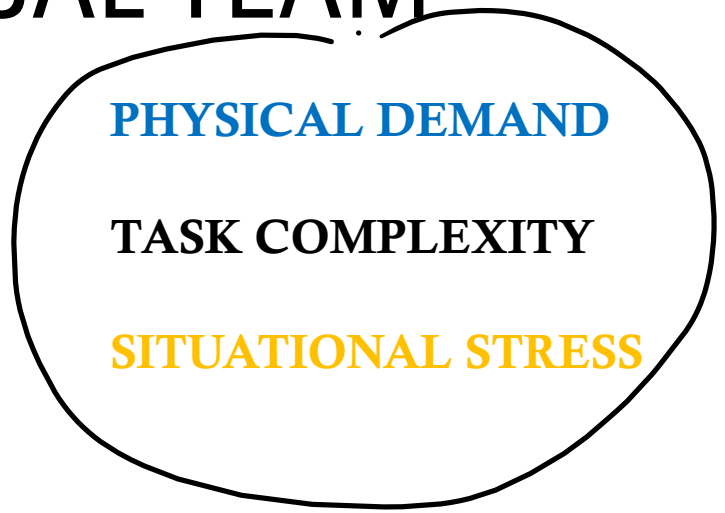
- **Surgeon**:
  - Improve ergonomics to **reduce physical stress**
    - Lower the laparoscopy screen to eye level and directly across the table
    - Remain seated (for hysteroscopy, robotic and vaginal surgery)
    - Make everybody the same height (stepstool, lower or raise the table)
    - Use a "princess pad" (padded mat) underfoot to reduce strain from standing
  - Recognize when the **mental demand** of a case is overwhelming
    - Ask your circulating nurse to let you know when a certain time is reached
    - Take a biobreak
    - Call consultant
    - Move focus to another area

STRATEGIES TO IMPROVE SURGICAL TEAM WORKLOAD

- **Scrub nurse**:
  - Technological and organization advancements (voice-activated call for equipment)
  - Optimize preference card (reduce amount of instrumentation needed)
  - Take breaks at non-urgent parts of the case.



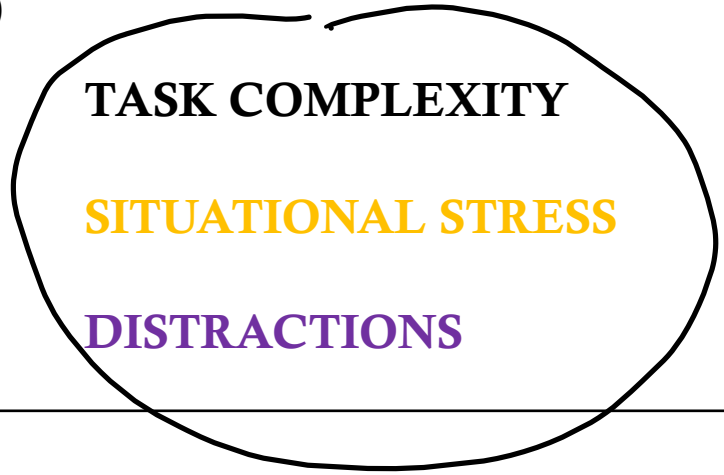
STRATEGIES TO IMPROVE SURGICAL TEAM WORKLOAD



- **Circulating nurse**:
  - Streamline protocols (reduce situational stress)
    - Send every pathology specimen separately labeled
    - Decide as an institution what you are going to use as a prep solution
    - Always place the foley on the sterile field
  - Prepopulate EMR (reduce time consuming documentation and potential for medical errors)
    - Link the diagnosis/indication for surgery with the pathology specimen so it appears on the specimen request
  - Respect the time-out and debrief (reduce stress and specimen/procedural errors)
    - Make it the culture in the OR that everyone stops and participates when the circulator leads the time-out

STRATEGIES TO IMPROVE SURGICAL TEAM WORKLOAD

- **Trainee**:
  - Turn off the music (reduce distractions)
  - Develop a system for coverage when scrubbed in (who covers consults and floor calls, reduce distractions)
  - Set goals and agree on communication of when to take over (allow trainee to operate to their potential without overwhelming their mental stress)
  - Encourage simulation/practice (build confidence)

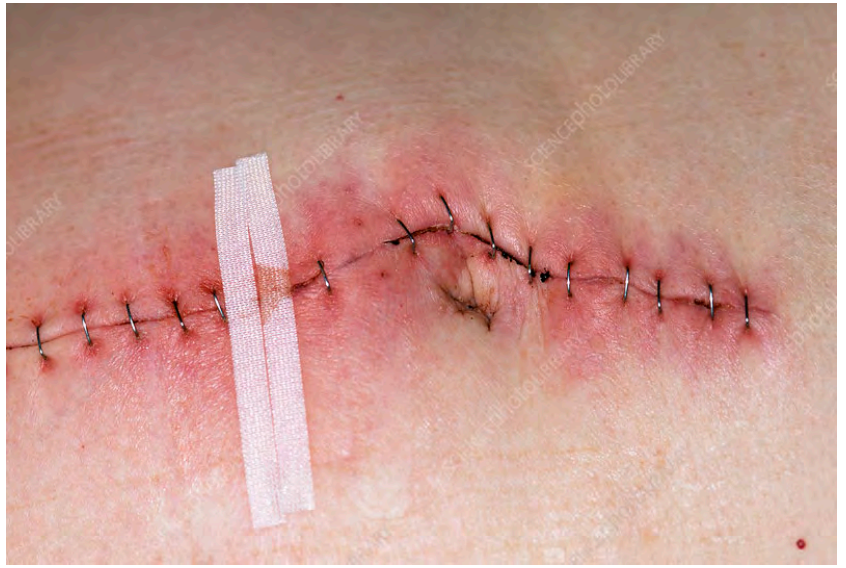


THE "DEBRIEF"

- Similar to the "time-out" but at the completion of the case before the Attending surgeon has left the room.
- Surgical pause involving all members of the team.
- Review the **procedure performed.**
- Review the **specimens** in detail (fresh or permanent, need for frozen, what you'd like them called.)
- Review any case-related issues and **complications.**
- Review any **drains** left in place.
- Review if the **surgical count** was correct.
- Empower any member of the team to speak up if there is a safety issue during the case.

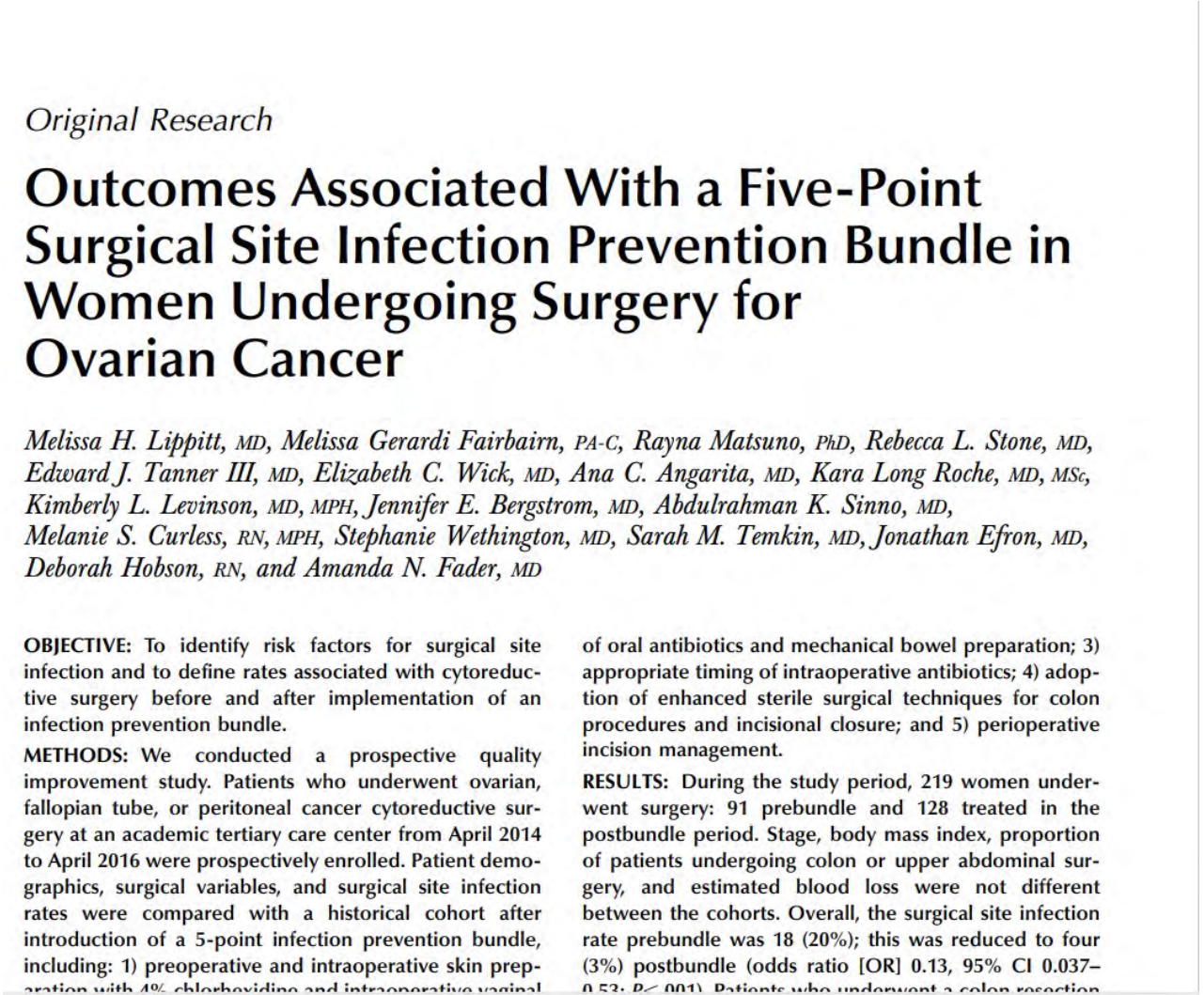
SURGICAL SITE INFECTION

- Surgical complications are a major source of medical harm and cost in the United States with an estimated yearly cost of $25 billion per year.
- 25% of all hospital acquired infections in the US are surgical site infections.
- SSI's contribute to increase length of hospital stay, decreased quality of life, increased readmissions, increased repeat procedures, excess morbidity and mortality.
- CDC reports hysterectomy-associated SSI rates of 0.9-1.7% including:
  - Superficial skin infections (e.g. cellulitis)
  - Deep skin infections (e.g. wound abscess)
  - Organ space infections (e.g. peritoneal or vaginal cuff abscess)



SSI PREVENTION

- Study of patients undergoing cytoreductive surgery for ovarian cancer from 2014-2016 at JHU.
- Identified a 20-33% risk of infection in these cases.
- Implemented a 5-point SSI reduction bundle.
- **Reduced the overall SSI rate from 20% pre-bundle to 3% post-bundle** (odds ratio 0.13, 95% CI 0.037-0.53, P<.001)
- **Reduced the colon resection SSI rate from 33% to 7%.**
- **Reduced the SSI-related hospital readmission from 13% to 3%.**



Original Research

Outcomes Associated With a Five-Point Surgical Site Infection Prevention Bundle in Women Undergoing Surgery for Ovarian Cancer

Melissa H. Lippitt, MD, Melissa Gerardi Fairbairn, PA-C, Rayna Matsuno, PhD, Rebecca L. Stone, MD, Edward J. Tanner III, MD, Elizabeth C. Wick, MD, Ana C. Angarita, MD, Kara Long Roche, MD, MSc, Kimberly L. Levinson, MD, MPH, Jennifer E. Bergstrom, MD, Abdulrahman K. Sinno, MD, Melanie S. Curless, RN, MPH, Stephanie Wethington, MD, Sarah M. Temkin, MD, Jonathan Efron, MD, Deborah Hobson, RN, and Amanda N. Fader, MD

OBJECTIVE: To identify risk factors for surgical site infection and to define rates associated with cytoreductive surgery before and after implementation of an infection prevention bundle.

METHODS: We conducted a prospective quality improvement study. Patients who underwent ovarian, fallopian tube, or peritoneal cancer cytoreductive surgery at an academic tertiary care center from April 2014 to April 2016 were prospectively enrolled. Patient demographics, surgical variables, and surgical site infection rates were compared with a historical cohort after introduction of a 5-point infection prevention bundle, including: 1) preoperative and intraoperative skin preparation with 4% chlorhexidine and intraoperative vaginal of oral antibiotics and mechanical bowel preparation; 3) appropriate timing of intraoperative antibiotics; 4) adoption of enhanced sterile surgical techniques for colon procedures and incisional closure; and 5) perioperative incision management.

RESULTS: During the study period, 219 women underwent surgery: 91 prebundle and 128 treated in the postbundle period. Stage, body mass index, proportion of patients undergoing colon or upper abdominal surgery, and estimated blood loss were not different between the cohorts. Overall, the surgical site infection rate prebundle was 18 (20%); this was reduced to four (3%) postbundle (odds ratio [OR] 0.13, 95% CI 0.037–0.53; P< .001). Patients who underwent a colon resection

Fader et al, "Outcomes associated with a five-point surgical site infection prevention bundle in women undergoing surgery for ovarian cancer", Obstet Gynecol, v130, n4, October 2017

SSI PREVENTION BUNDLE

1. Preoperative and intraoperative skin preparation with 4% chlorhexidine (abdominal and vaginal)
2. Oral antibiotics in patients undergoing mechanical bowel prep
3. Appropriate timing of antibiotics
4. Enhanced sterile surgical techniques for colon procedures and incisional closure
5. Perioperative incision management

CHG VAGINAL PREP

- 2-4% CHG vaginal prep substantially lowers the bacterial count after vaginal preparation when compared to iodine.
- Some increase in vaginal irritation.
- Consider vaginal cuff irrigation at completion of case.
- ACOG recommends either CHG or iodine.

Chlorhexidine Versus Iodine for Vaginal Preparation Before Hysterectomy: A Randomized Clinical Trial

Austin M Hill [1], Rachel N Pauls [1], Jack Basil [2], Tiffanie Tam [1], Eunsun Yook [3], Abigail Shatkin-Margolis [1], Steven Kleeman [1], Jennifer Yeung [1], Emily Aldrich [1], Catrina C Crisp [1]

Affiliations + expand

PMID: 34333502 DOI: 10.1097/SPV.0000000000001066

Abstract

Objective: The American College of Obstetricians and Gynecologists does not provide a recommendation regarding the preferred vaginal preparation solution. We intended to compare the effectiveness of chlorhexidine versus iodine in decreasing vaginal bacterial counts.

Methods: In this institutional review board-approved study, participants undergoing total hysterectomy via vaginal or laparoscopic approach were randomized to 4% chlorhexidine or 10% iodine for presurgical vaginal preparation. Swabs were collected from the vaginal mucosa before, then 30, 60, and 90 minutes after preparation. Our primary outcome was the number of positive cultures (≥5,000 bacteria) at 90 minutes. The secondary outcomes included the presence of selected pathogens, postoperative complications, and infections. The sample size of 71 per arm was calculated using $\alpha P = 0.05$, 80% power, and anticipating a 22% difference in positive cultures.

Results: Between May 2018 and August 2019, 85 participants were randomized. The average age was

Hill et al, "Chlorhexidine versus iodine for vaginal preparation before hysterectomy: a randomized clinical trial." Female Pelvic Med Reconstr Surg, 2022 Feb 1;28(2):77-84.

ORAL ANTIBIOTICS WITH BOWEL PREP

- Commonly used for endometriosis or cancer cases
- One bottle “MiraLax” powder (238 g) and four tablets bisacodyl “Docolax” (5 mg tablets)
- Nine tablets Neomycin sulfate (500 mg tablets)
- Twelve tablets Erythromycin (250 mg tablets)
- Begin 24 hours before surgery with a clear liquid diet

INTRAOPERATIVE ANTIBIOTICS

- IV Cephazolin 1-3 g (weight based)
- IV Metronidazole 500 mg
- Administer within 30 minutes of procedure start
- Re-dose cephazolin when indicated (every 3 hours, blood loss >1500 cc, or both)
- Skin and vaginal CHG prep

ENHANCED STERILE TECHNIQUE FOR INTESTINAL RESECTION AND WOUND CLOSURE

- Gown and glove change by surgical team after intestinal surgery or bowel resection
- "Clean closure tray" for wound closure
  - New suction and bovie cautery
  - Gown and glove change
  - Separate instruments for wound closure (switch just before closing the fascia)

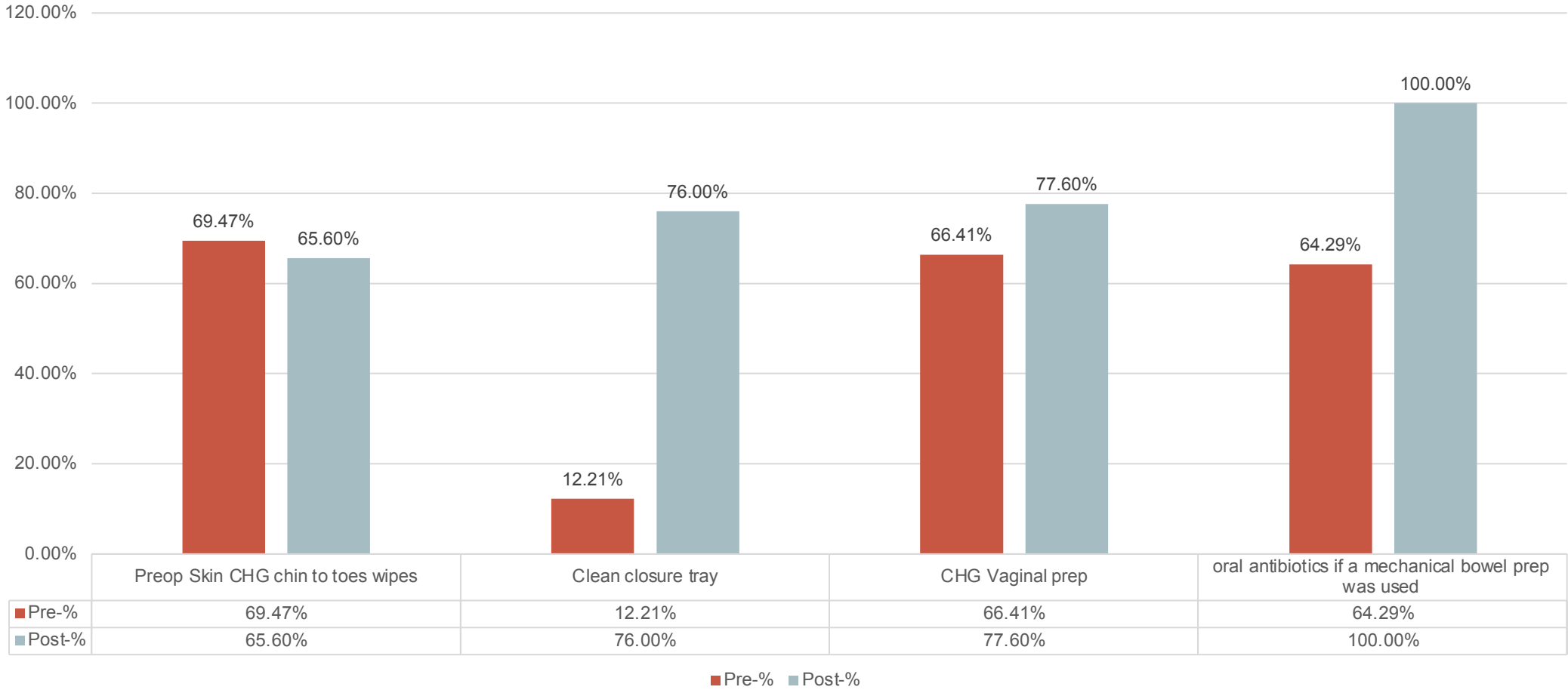
POSTOPERATIVE WOUND CARE

- Remove surgical dressing on postoperative day #1
- Enhanced attention to wound care by physician and nursing staff
  - Daily cleaning of wound and surrounding skin
  - Daily shower if possible
- Strict glycemic control (blood glucose <180 mg/dL)

UNIVERSITY OF COLORADO EXPERIENCE WITH SSI REDUCTION BUNDLE

1. Defined "Perfect Care" for hysterectomy perioperative care (input from surgeons, nursing, anesthesia, infection control team, hospital admin and quality)
2. Head-to-toe CHG wipe in the pre-operative area
3. CHG skin and vaginal preparation intraoperative
4. Oral Antibiotics with mechanical bowel prep
5. Added Metronidazole to pre-op antibiotics
6. Clean Closure tray

HYST SSI Prevention bundle components- compliance pre and post bundle implementation



	Preop Skin CHG chin to toes wipes	Clean closure tray	CHG Vaginal prep	oral antibiotics if a mechanical bowel prep was used
Pre-%	69.47%	12.21%	66.41%	64.29%
Post-%	65.60%	76.00%	77.60%	100.00%

Pre-implementation data collection period: 4/2021 through 9/2021
Post-implementation data collection period: 7/2022 through 12/2022

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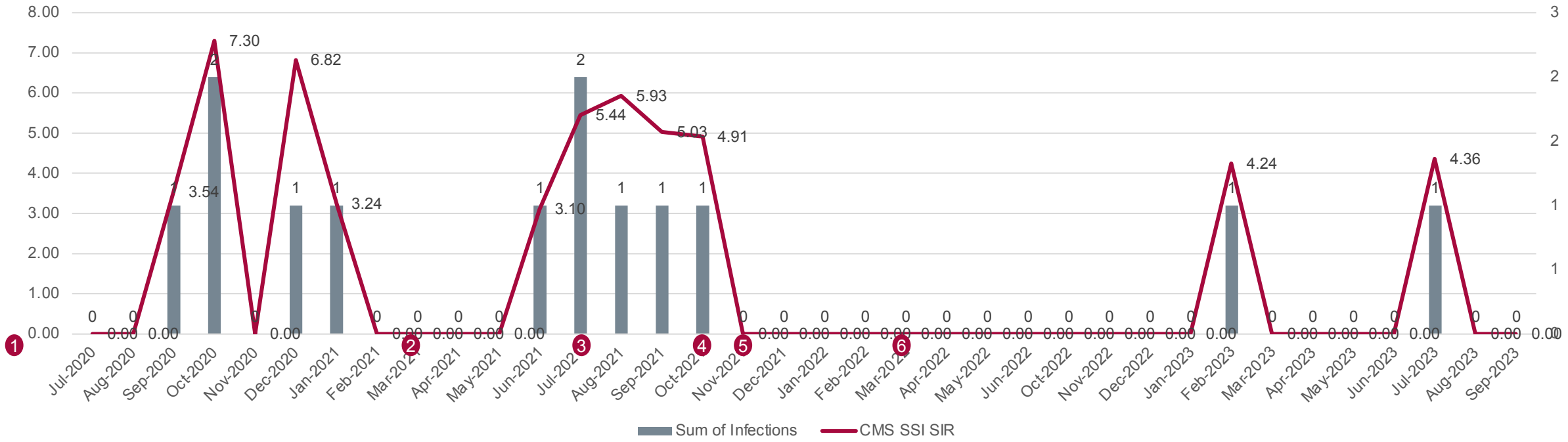
UCH Surgical Site Infections (SSI): CMS Reportable SSI



Actions/Tactics

1. Defined Perfect Care (May 2020)
2. Collaborative case review launched (March 2021)
3. Clean closure tray implementation (July 2021)
4. Real-time chart review for perfect care element fallouts (October 2021)
5. Transitioned to CHG solution for vaginal prep (November 2021)
6. Add Metronidazole to preoperative IV antibiotics for hysterectomy patients (March 2022)

Source: System HAI Report - Power BI

Timeline: 7-2021 through 9/2023

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HOW DO WE GIVE QUALITY FEEDBACK TO SURGEONS?

SURGEON FEEDBACK – GRANULAR SCOPE

- We maintain a **surgical quality dashboard** with individual surgeon and department quality metrics.

  - Data is confidential.
  - Data access is at the discretion of the surgeon or their division leader.
  - Compliance with the elements of the SSI prevention bundle, time-out, debrief, etc.
  - Quality nurse who investigates each SSI and performs a chart review for bundle element fallouts (ie. Was the patient allergic to CHG and thus received an iodine-based prep? Was it an error in nursing documentation?)
  - Developing an app for surgeons to access their own data as well as departmental metrics.

QUALITY FEEDBACK – LARGER SCOPE

- Present the SSI bundle compliance and SSI rates (whole department) to the Hospital and System Quality meetings quarterly.
- Celebrate the improvements - other departments have adopted the Ob/Gyn SSI bundle elements.
- Ongoing education to surgeons (faculty, APPs and residents), nurses and OR staff to keep momentum going.
- Make changes in the SSI bundle as new data emerges to continue to improve care.
- Support from the department and the hospital is integral to making this a success.

CONCLUSIONS

- Surgeons can and do have a significant role in improved communication with operating room staff.
- Operating room team behaviors (such as “time out” and “debrief”) can have an impact on patient safety outcomes.
- Initiation of components of a surgical site infection bundle can reduce SSI and re-admission rates.
- Sharing the quality data with surgeons and staff (in a non-putative way) can impact compliance and success of safety interventions.

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QUESTIONS?

University of Colorado **Anschutz Medical Campus**

Vulvar and Vaginal Dysplasia: Management and Updates

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University of Colorado

Disclosures

- Conflict of Interest
  - No financial relationships or conflict of interest to disclose

- Special thanks to Dr. Christine Conageski

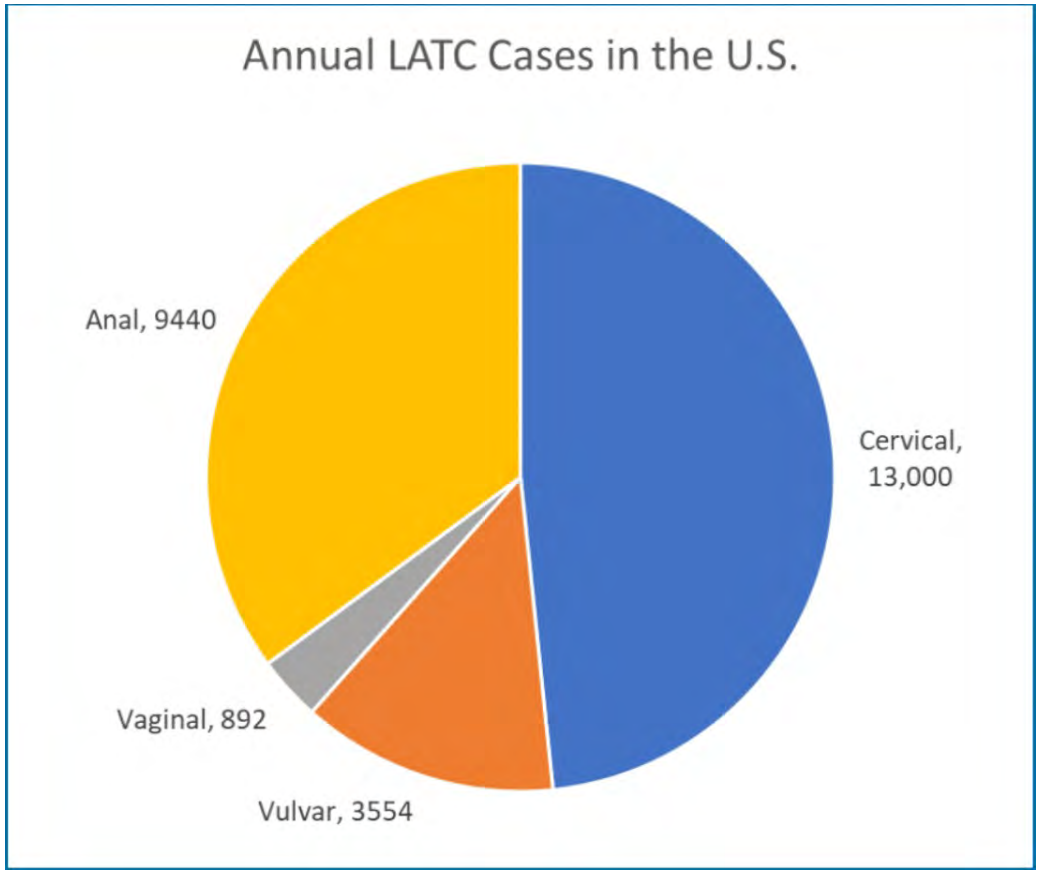
Objectives

1. Review epidemiology and pathogenesis of vulvar and vaginal dysplasia

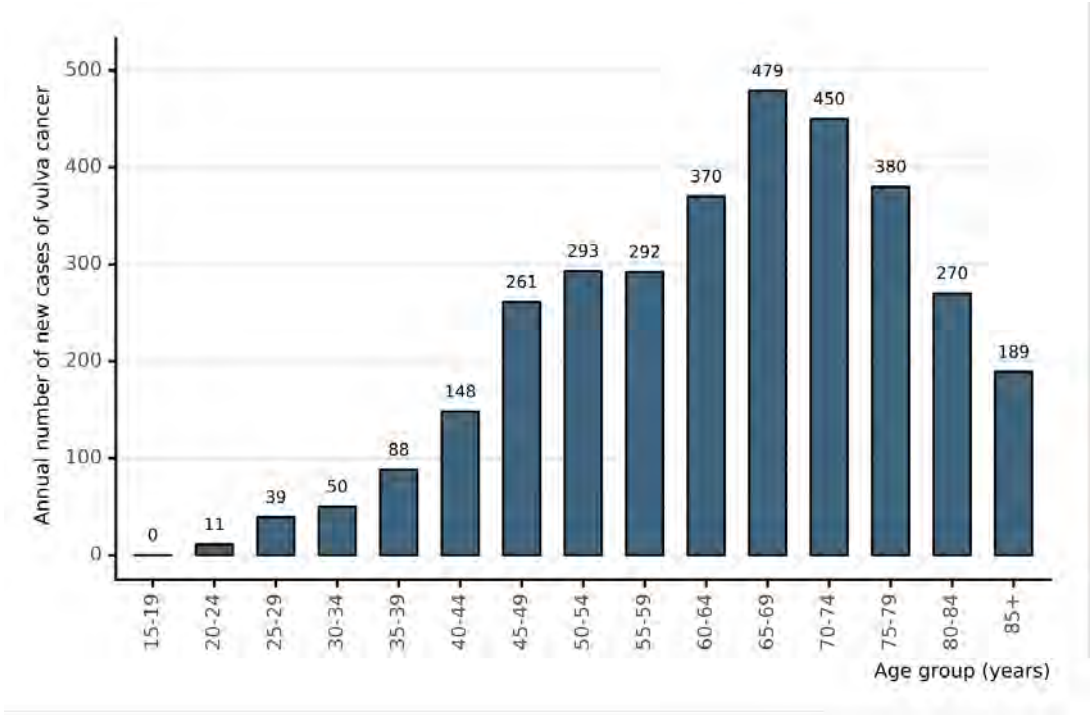
2. Discuss current strategies and updates in the management of vulvar and vaginal dysplasia

Lower Ano-Genital Tract Cancers (LATC)

- Squamous cell carcinoma accounts for 80-90%
- High rates of HPV-positivity
- Risk of LATC increases with age



Vulvar Cancer in USA



- Annual number of new cases: 6900
- Cumulative risk (%) at age 75: 0.03%
- Annual number of deaths: 1630

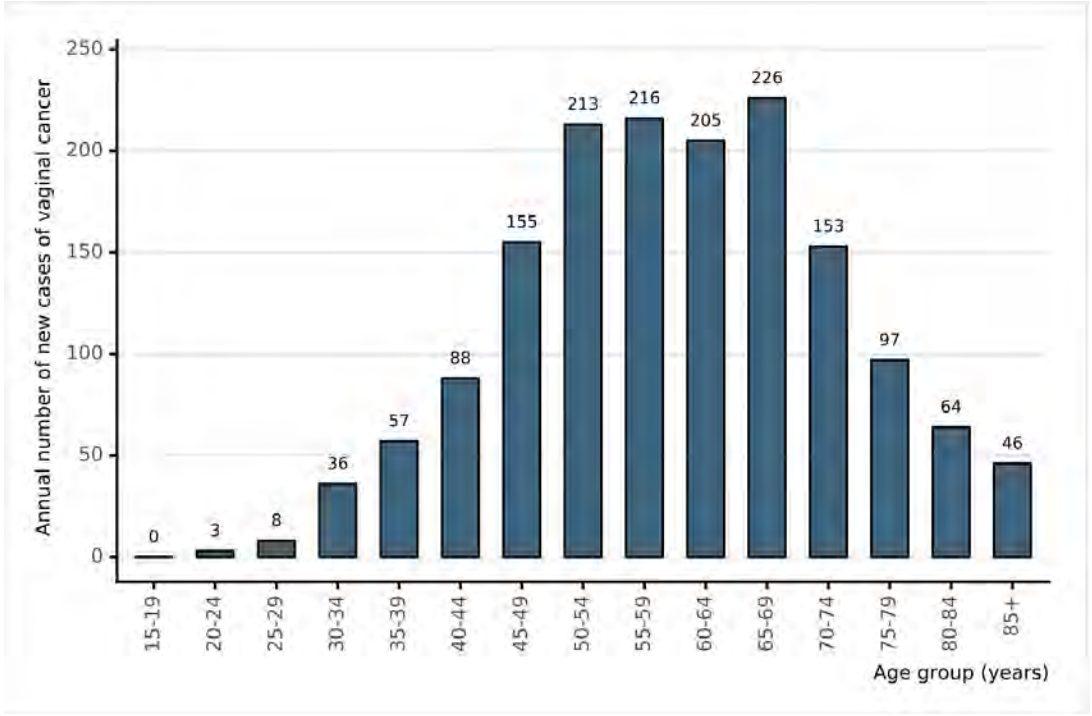
Vulvar Cancer

- HPV-associated vulvar cancers:
  - Have warty and basaloid patterns
  - Are typically undifferentiated
  - Found in younger women with similar risk factors for cervical cancer
  - Have higher overall survival rates and lower risk of recurrence than non-HPV associated vulvar cancers
- HPV independent vulvar cancers:
  - Primarily driven by inflammatory precoursors
  - Usually multifocal
- Melanoma
  - Have the worst prognosis

Risk Factors: Vulva

Family Health History	Prior Health History
• Rare genetic conditions (WHIM), Fanconi anemia • Primary immune deficiencies	• HPV infections (especially 16/18) • Genital condyloma • Anogenital tract dysplasia or cancer • Solid organ transplant recipient • Lichen sclerosus, Paget's disease, lichen planus • ESR

Vaginal Cancer in USA



- Annual number of new cancer cases: 8650
- Cumulative risk at 75 years old: 0.02%
- Annual number of deaths: 1870

Vaginal cancer

- Primary vaginal cancer: 1-2% of all gynecologic cancers
- 90% squamous cell in origin
  - Most commonly HPV-related
  - Other types: clear cell adenocarcinomas and melanoma
- Incidence rates have been stable over time

- Risk of vaginal cancer increases for patients with history of:
  - CIN 3/AIS (SIR 18.5)
  - Cervical cancer (SIR 8)
  - DES Exposure (SIR 40.7)
- Risk remains increased even after hysterectomy

Risk Factors: Vagina

Hormonal	Family Health History	Prior Health History
• DES exposure in utero (OR 1.9)	• Rare genetic conditions (WHIM), Fanconi anemia • Primary immune deficiencies	• HPV infection • Genital condyloma • Anogenital tract dysplasia or cancer • Solid organ transplant recipient

Lessons from the cervix

- High Grade Squamous Intraepithelial Lesions (HSIL) is the vulvar/vaginal precursor lesion
- Natural history of HPV, HSIL, and vulvar cancer is similar to cervical HPV, HSIL, and cervical cancer

- Hypothesize that:
  - Identification of HSIL -> treatment of HSIL -> prevent progression to lower genital tract cancer

Different from the cervix: Screening

- There are no studies of screening for vaginal or vulvar cancers in average risk patients
- No guidelines for screening for vulvar cancer in any patient population
- ASCCP recommends against screening for vaginal cancer after hysterectomy for benign disease

- ** ASCCP **does recommend** screening with vaginal cytology after hysterectomy for cervical dysplasia or cancer

Prevention and Risk Reduction

HPV vaccination

The single most powerful prevention against lower anogenital tract cancers

HPV Vaccination: Vulva/Vagina

- 100% effective against VAIN 2+/VIN 2+ without prior HPV exposure
- 79% effective against VAIN2+/VIN 2+ with prior HPV exposure

- Epi studies from Denmark demonstrate a decrease in vulvar/vaginal cancers post-introduction of HPV vaccine

Garland SM, 2007; Rasmussen, 2020; Bertoli 2020

Treatment of Cancer Precursors: Average-Risk People

- Little data regarding treatment of VaIN, VIN
- Extrapolated from cervical studies
- Systematic review of 3,322 cases
  - 9% HSIL VIN progressed to cancer if untreated
  - 3% HSIL VIN progressed to cancer if treated

Treatment is recommended for all vulvar and vaginal HSIL lesions

American College of Obstetrics and Gynecology (ACOG)	European College for the Study of Vulval Disease (ECSVD)
ASCCP	European Federation for Colposcopy (EFC)
European Society of Gynaecological Oncology (ESGO)	International Society for the Study of Vulvovaginal Disease (ISSVD)
Society of Gynecology Oncology (SGO)	

Treatment of Vulvar and Vaginal HSIL

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HSIL of the Vulva

Acceptable treatment modalities:

- Surgical excision
- Ablation (CO_2 laser, argon beam, cavitational ultrasonic surgical aspiration)
- Electrosurgical excision
- Medical Therapy: imiquimod
  - ? Utility: 5-FU, Cidofovir, Photodynamic therapy (eg aminolevulinic acid)

Factors influencing treatment decisions

- Management plans must be individualized by patient
- Important variables to consider in making management plan:
  - Histologic features on biopsy
  - Distribution of disease
    - Size
    - Location
  - Patient's risk of progression
    - Age
    - Immunosuppression

Consider importance of preservation of normal anatomy, symptom relief, maintenance of quality of life and sexual function

Vulvar HSIL may be associated with invasive cancer

Risk of occult cancer from wide local excision of vulvar HSIL surgical specimen is 11-22%

Pretl, J Gyn Onc, 2017; Thuis, Int J Gyn Onc, 2000; Husseinzadeh, Gyn Onc, 1999; Modesitt, Ob Gyn, 1998

Surgical excision Vulvar HSIL

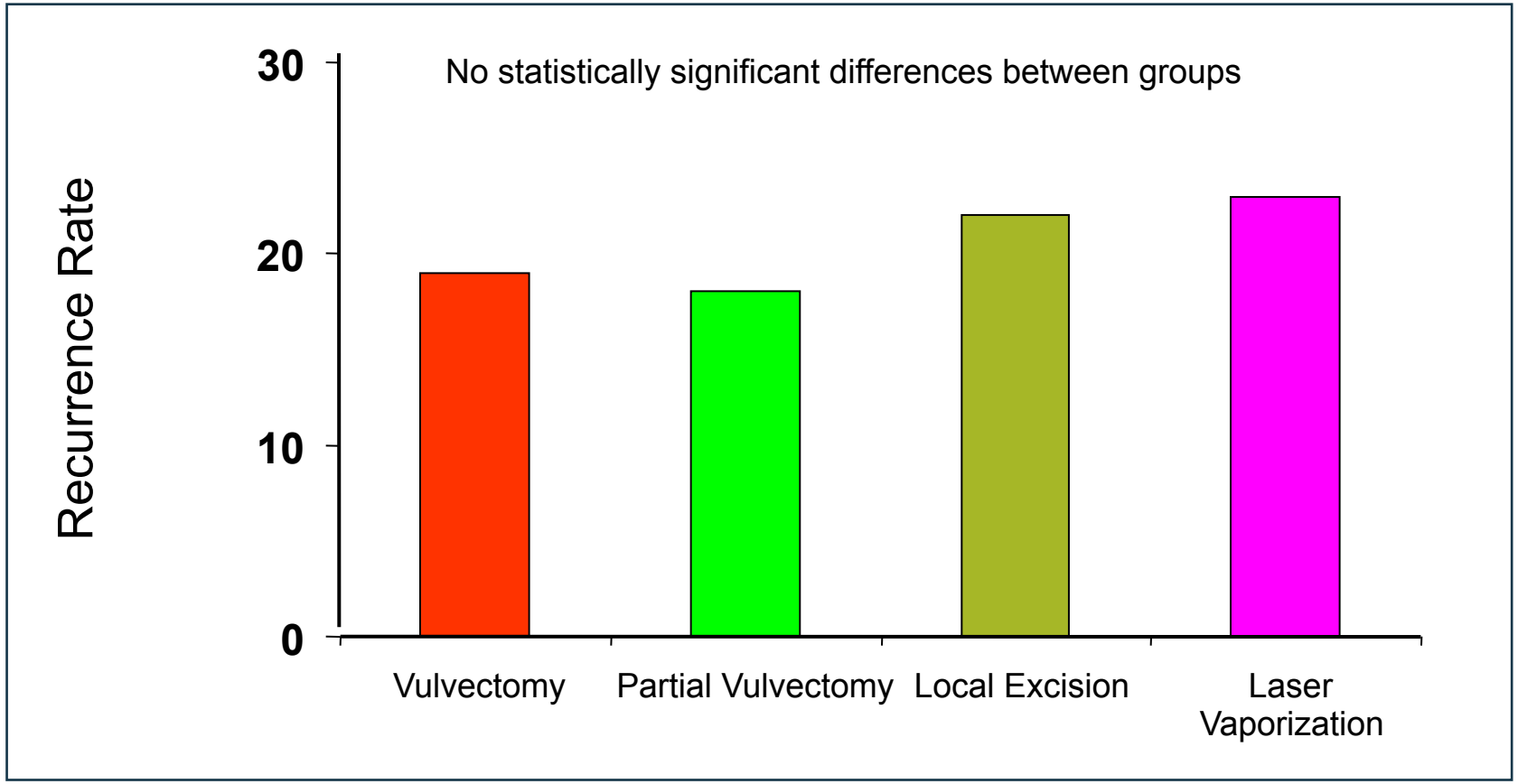
- Margins– 1cm if able
- Depth
  - Hair bearing areas to 2.7 mm
  - Non-hair bearing = 0.1 to 1.9 mm (average = 0.5 +/- 0.2 mm)

Risk of Recurrence

- Ranges from 6 to 50% post treatment
- 50% recurrence reported within 16.9 months post-surgery
- Influential factors:
  - Margin status
  - Duration of follow-up
  - VIN type
  - Patient factors
    - Multifocal disease
    - Immunosuppression
    - Smoking

Recurrence After Treatment

(mean follow-up 39 months)



Gynecologic Oncology. 2005; 97: 645-651

Margin Status

	Recurrence	No Recurrence	P-value
Number	22	37	
Average age (yr)	42	47	0.23
Positive margins	18 (82%)	21 (57%)	0.05
Negative margins	3 (14%)	15 (41%)	0.03

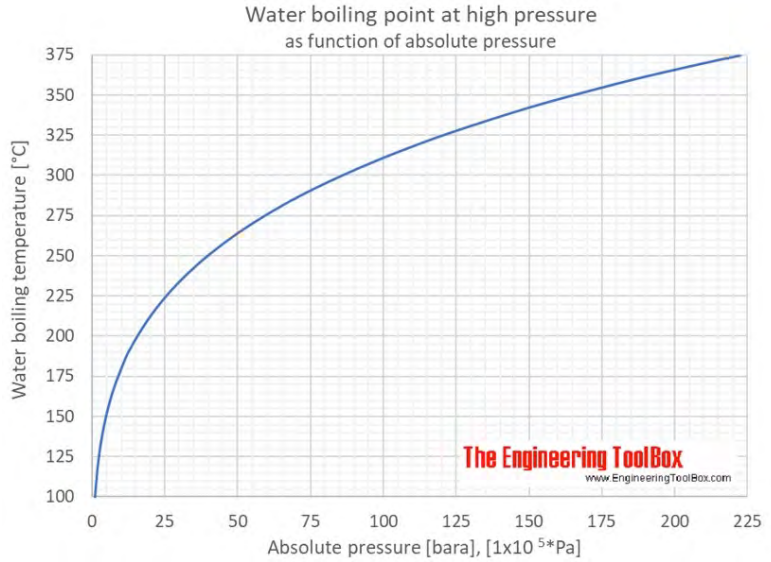
Median Time to recurrence:
Positive margins 22 months
Negative margins 44 months

Vulvar Ablative Techniques: CUSA

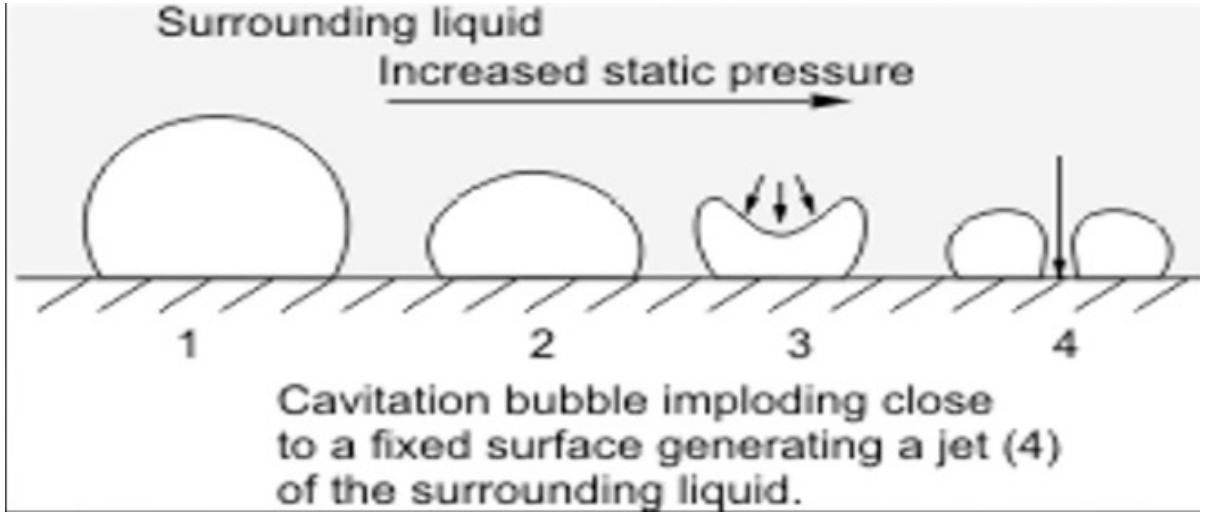
- Cavitational ultrasonic surgical aspiration
- Generates ultrasonic waves in the range of 23 kHz to produce tissue cavitations
- Tissue fragmentation is accomplished by a hollow titanium tip that vibrates up to 23,000 times per second
- An irrigating fluid is delivered through the handpiece to create an emulsion while suction is provided through another portal to aspirate tissue and provide a clean operative site

CUSA Principle

- High speed mechanical waves can be used in non-elastic media, such as water, to create a cavitation effect
- Cavitation is the process of boiling a liquid (vapour formation) as a result of pressure reduction rather than heat addition
- Tissues with weak intracellular bonds and high water content, such as tumors and lipomas, are easy to fragment, whereas tissues with strong intracellular bonds, such as nerves and vessel walls, resist fragmentation.



CUSA Principle



- The ultrasonic aspirator has

two rupturing effects at the tissue interface:

- SUCTION EFFECT: couples tissue to the tip and forces impacted tissue to vibrate, accelerate, and decelerate with the tip, eventually fragmenting away from nonaffected tissues.
- CAVITATION: rapidly oscillating tip produces localized pressure waves, which cause vapor pockets around cells in tissues with high water contents; the collapse of these pockets causes the tissue cells to rupture.

Vulvar Ablative Techniques: CO2 Laser

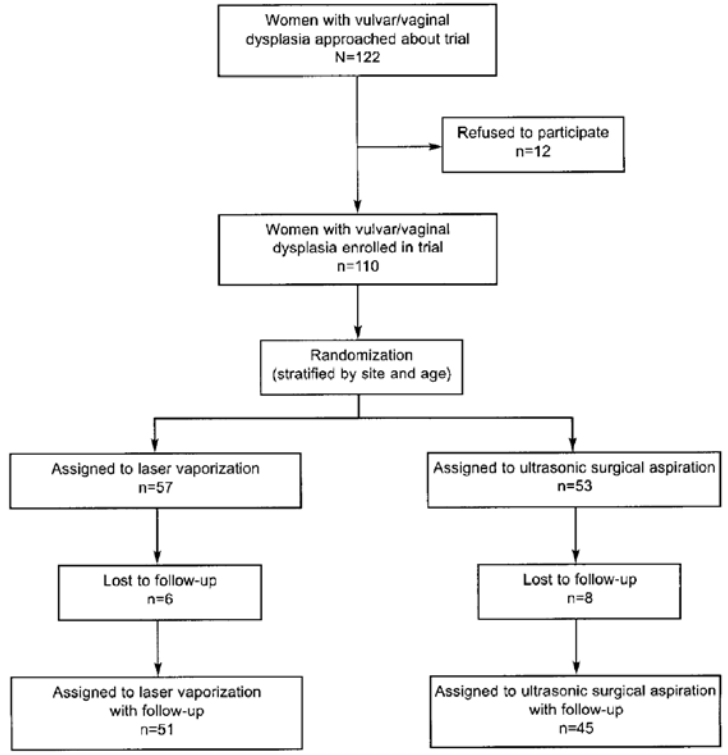
- 10,600 nanometer wavelength laser
- Heat injury
- Ablation of epidermis and dermis to the basement membrane
- Causes inflammatory healing response

- Challenges:
  - Special credentialling
  - Equipment
  - Fire risk

CUSA versus CO2 Laser

- Randomized control trial, single-site
  - 96 women completed 1 year of followup

	Laser (N=51)	CUSA (N=45)	Relative Risk (95% CI)
No evidence of dysplasia	38 (74.5%)	34 (75.6%)	0.96 (0.64-1.50)
Presence of dysplasia (bx)	13 (25.5%)	11 (24.4%)	



- Recurrence higher in VIN than VaIN patients

CUSA vs. CO2 Laser

- *Pain decreased in patients treated by ultrasonic surgical aspiration*
- *Presence of scarring significant reduced compared to CO2 laser treatment*

Table 2. Adverse effects and Visual Analog Scale Pain Scores by Treatment Group

	Laser (n=51)	USA (n=45)	P*
VAS pain scale (mm)	35.1±4.9	20.7±4.3	.032†
VAIN	46.5±5.8	36.7±6.6	
VIN	23.6±5.8	7.6±5.9	
Presence of scarring (VIN only)	6/22 (27)	0/20 (0)	.012
Infection (yeast, UTI, other)	8 (16)	5 (11)	.513
VAIN	5	3	
VIN	3	2	
Dysuria, burning	6 (12)	6 (13)	.817
VAIN	0	1	
VIN	6	5	
Adhesions	2 (4)	2 (4)	.898
VAIN	1	2	
VIN	1	0	
Abnormal discharge	6 (12)	2 (4)	.195
VAIN	3	1	
VIN	3	1	
Other	3 (5.9)	2 (4.4)	.75
Eschar	2	2	
Vaginal petechiae	1		

USA, ultrasonic surgical aspiration; VAS, visual analog scale; VAIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; UTI, urinary tract infection.
Data are n, n (%), or mean±standard error of the mean.
* Chi-square test for proportions.
† Independent samples *t* test.

Topical Therapy: Imiquimod treatment of vulvar HSIL

- Systematic review with 162 patients
  - Complete response rate → 51%
  - Partial response rate→ 25%
  - Recurrence rate →16%
  - Side effects mostly site inflammation
    - Mild to moderate erythema or erosions

Mahto M, et al. Int J STD AIDS 2010; 21:8.

Followup after Treatment

- Patients should be seen on a regular basis for clinical assessment
  - Biopsy any suspicious areas
- Life long surveillance is likely recommended
- Follow up modulated according to risk of recurrence (type of lesion, patient's age, and immunological conditions)

HPV-associated HSIL: Risk of Progressive Disease

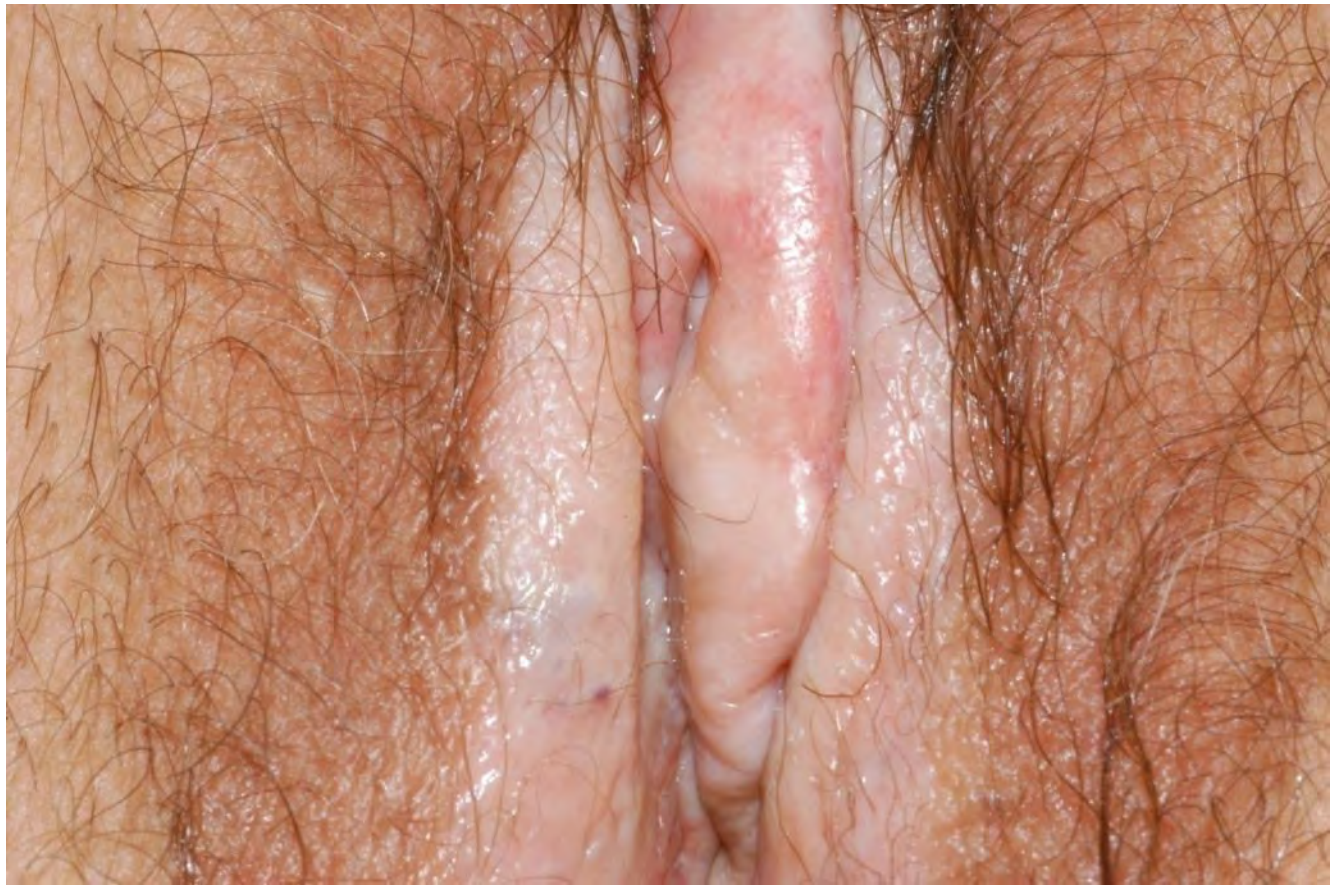
- Untreated HSIL → significant invasive potential
  - Particularly in women over 30[1]
- Untreated vulvar HSIL progression to invasive cancer ≥10% per year
  - Only about 2% for CIN 3[2]
- Lifetime risk of invasive vulvar cancer after treatment for HSIL = 3% to 6%
  - Only 0.3% to 0.4% for CIN 3[1]

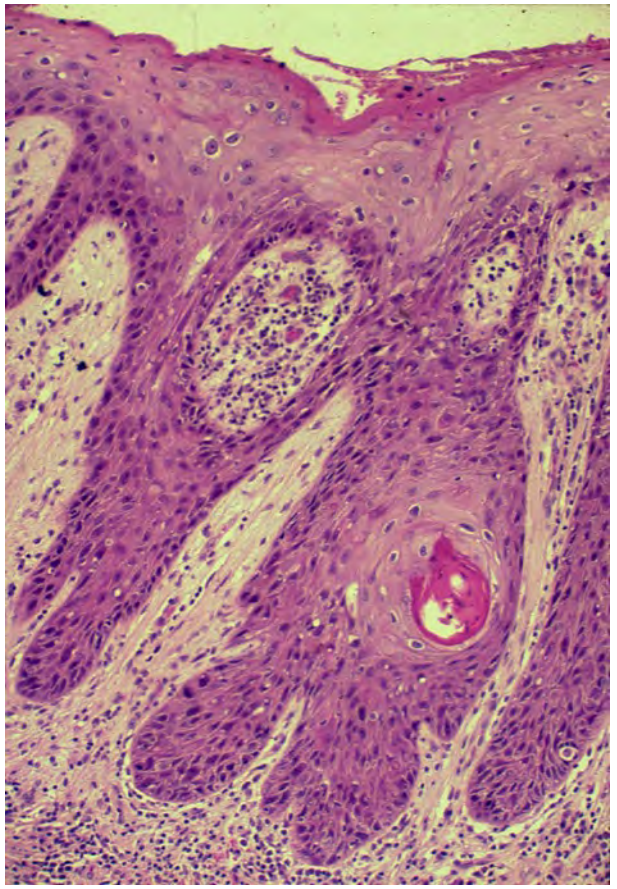
1. Jones RW et al. *Obstet Gynecol* 2005; 106: 1319–26
2. 2.Jones RW. *Eur J Gynaecol Oncol* 2001; 22: 393–402

Differentiated VIN

ISSVD 1986	ISSVD 2004	LAST 2012
VIN 1	Flat condyloma or HPV effect	LSIL
VIN 2	VIN, usual type a.VIN, warty type b.VIN, basaloid type c.VIN, mixed (warty/basaloid) type	HSIL
VIN 3		
Differentiated VIN	VIN, differentiated type	

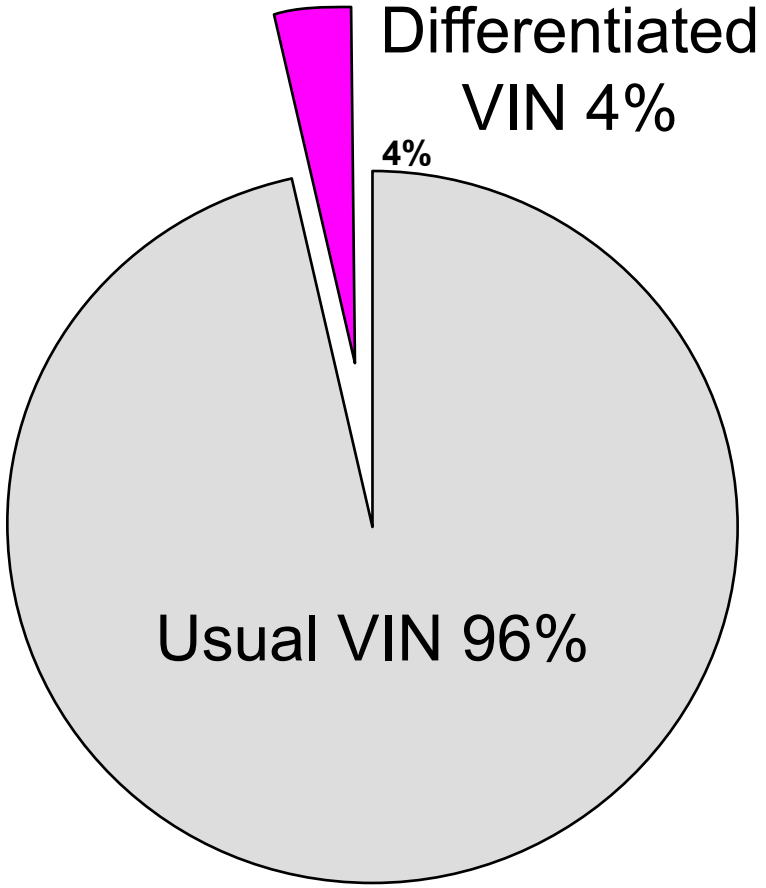
VIN differentiated





T Wright, MD collection

dVIN diagnosed infrequently compared to vulvar HSIL (Usual VIN)



European Journal of Cancer. 2009; 45: 851-856

dVIN prevention: Treatment of Lichen Sclerosus

- Prospective study of LS treated with high potency topical steroids (HPTS):
  - N = 507
  - Followup 4.7 years
  - Compliant group: 0 with VIN 2+
  - Partially compliant/non-compliant – 7 (4%) with VIN 2+ (3 cancers)
  - P < 0.001

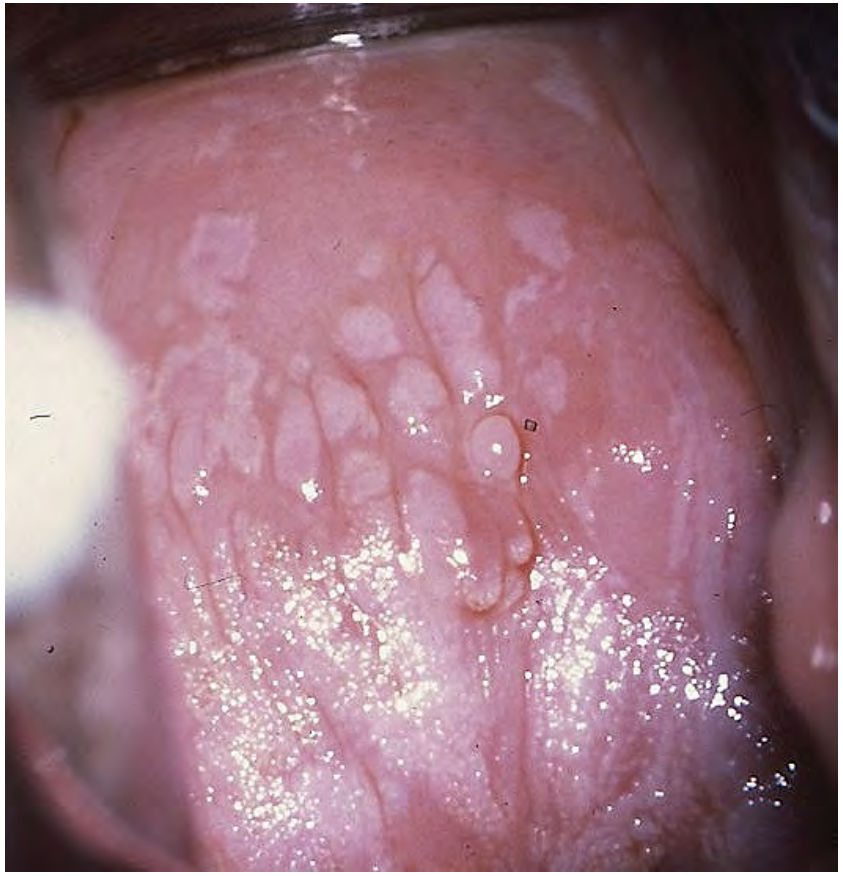
- ACOG endorses British Association of Dermatologist guidelines:
  - 3 months of medium to high potency steroids
  - Individualize use of of long term maintenance therapy

Vaginal Dysplasia

How is VaIN Diagnosed?

- Most diagnosed on colposcopy for abnormal Pap (> 80%)
- Colposcopy of the vagina after diagnosis of other anogenital lesions
- Lesion found on pelvic exam
- > 90% asymptomatic but may report postcoital bleeding or unusual vaginal discharge

Treatment of Vaginal LSIL



C Conageski, MD collection

- No management guidelines for VaIN at ASCCP Consensus Conference
- Progression risk smaller than cervical LSIL - be conservative
- Treatment of all low grade disease almost impossible
- Studies support the observational approach to Vulvar - LSIL

Treatment of VaIN

- Excision: Vaginectomy or partial vaginectomy
  - Local excision
  - Electrosurgical loop excision
- Ablative techniques
  - Carbon dioxide (CO2) laser, CUSA
  - Photodynamic therapy
  - Electrocoagulation

VaIN Excisional Therapy

- Provide specimen for histopathological evaluation and diagnosis; may effectively rule out cancer

- Wide local excision associated with lowest risk recurrence
  - Limited by applicability due to high prevalence of multifocal disease
  - Success rates 66 to 80%
- Partial upper vaginectomy
  - Treatment of choice for high grade VaIN at the apical part or in the region of the vaginal cuff scar

- Total vaginectomy: NOT Recommended

VaIN Ablative Therapy

- Depth of destruction
  - General thickness less than 1 mm
  - Mean thickness of the total epithelium was 0.4 mm
  - Thickness did not differ between grades of VaIN

- Laser depth 1 – 1.5 mm
  - Larger spot sizes and the superpulse mode are used to avoid deep penetration and the conduction of excessive heat.

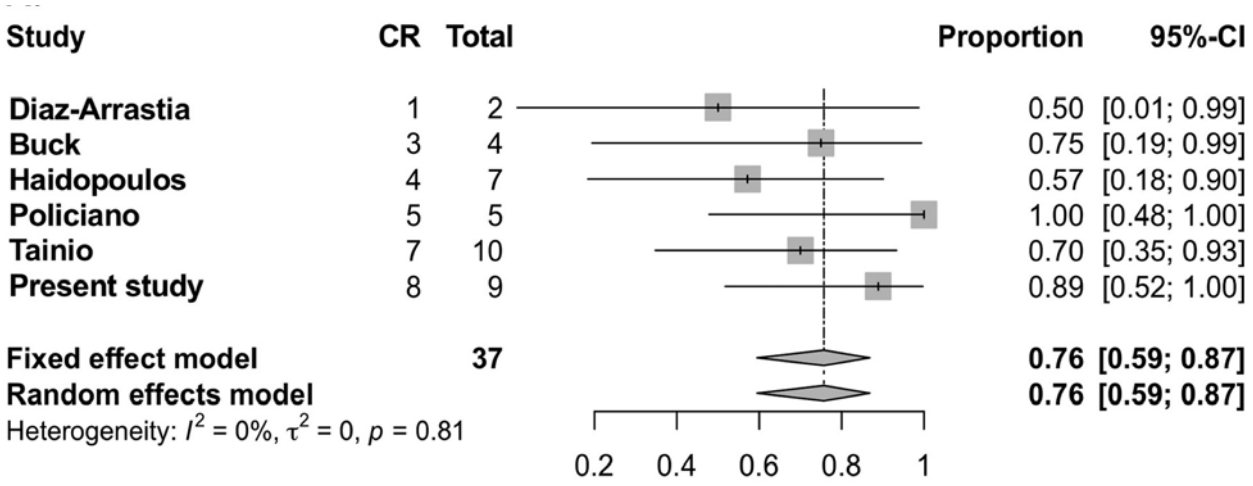
VaIN Ablative Therapy

- CUSA is a safe and effective option for treatment of VaIN
  - Allow exact removal of epidermal or mucosal lesions without thermal or mechanical damage to surrounding structures or underlying stroma.

- Prospective study
  - 92 patients underwent CUSA for VaIN
  - Median follow up 4.5 years
  - Cure rate 80.4%
  - No adverse events

VaIN Medical Therapy: Imiquiod

- Mechanism of Action:
  - Immune response modifier
  - Induces cytokines, simulates natural killer cells
  - Promote maturation and activity of Langerhans cells
  - Increases effectiveness of T-cell mediate response
- Metanalysis (5 articles, 29 women)
  - Complete response (histologically proven clearance of VaIN): 0.76
  - Response rates (rate of patients who showed CR or any response): 0.89



VaIN Treatment: 5-FU

- Cure rates from 62.5 – 86%
- Limited by side effects: vaginal discharge, burning, pain or ulcers and therefore reduced compliance
- Would NOT use this as first line

Choice of Therapy

- Individualized based on patient characteristics, extent of disease, number of lesions, location of lesions

- Recurrence rates
  - Topical treatment 20-62.5%
  - Laser ablation 26.4%
  - Excision 32.7%
  - Radiotherapy 0%

Kim MK 2018

Questions?

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THANK YOU

What's new and on the horizon in contraception?

Cara Clure, MD, MSCS

Assistant Professor, Division of Complex Family Planning, Department of OB/GYN

University of Colorado Anschutz Medical Campus

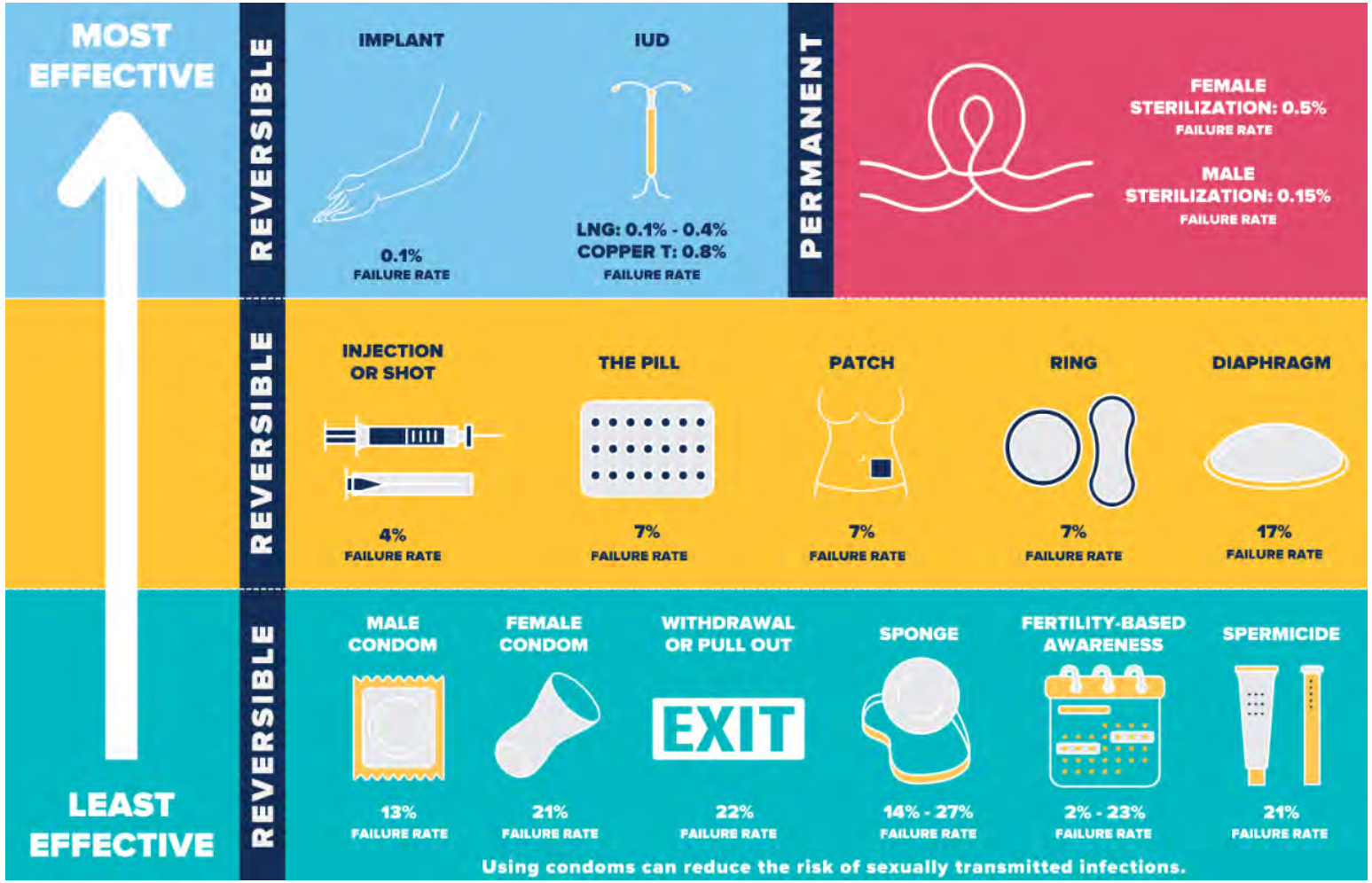
Disclosures

- None
- Will discuss brand names as pertinent for new contraceptive methods

Objectives

1. Review updates and recent research on contraception.
2. Describe novel contraceptive methods and technologies in development.
3. Discuss contraceptive provision in the current landscape of reproductive health care.

Contraceptive options



Newest options!

Annovera™
(segesterone acetate and ethinyl estradiol vaginal system)
Delivers 0.15 mg/0.013 mg per day

2019 | 2020 | 2021 | 2022 | 2023 | 2024

OB-GYN & Family Planning
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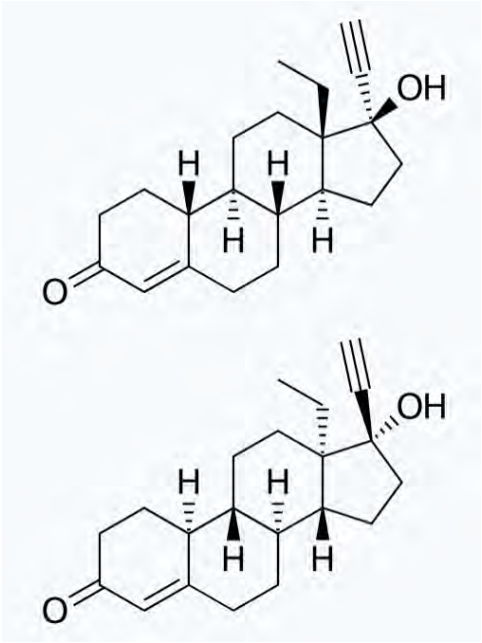
Over-the-counter progestin-only pill

- Norgestrel 0.075 mg daily (Opill®)
- FDA approved July 2023 with planned availability in early 2024
- No age restrictions
- 28 pill pack, no placebo pills

Allen and Bartz, *Obstet Gynecol* 2024

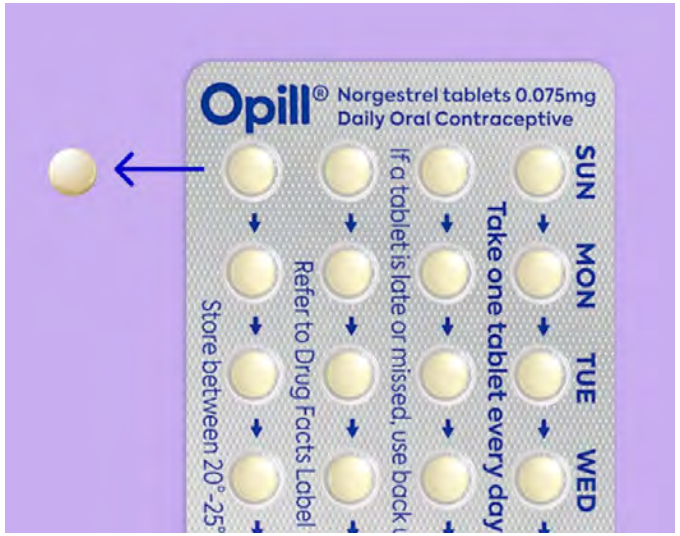
Norgestrel

- Synthetic 2nd generation progestin
- Racemic mixture of active levonorgestrel (LNG) and inactive dextronorgestrel
  - Half as potent as LNG
- Weak androgenic activity
- Available in combined OCP



Over-the-counter progestin-only pill

- Current breast cancer is only absolute contraindication
- Relative contraindications:
  - Benign or malignant liver tumors
  - Severe cirrhosis
  - Acute liver disease
  - Positive antiphospholipid antibodies
  - Past breast cancer
  - Malabsorptive bariatric surgery
  - Drug-drug interactions



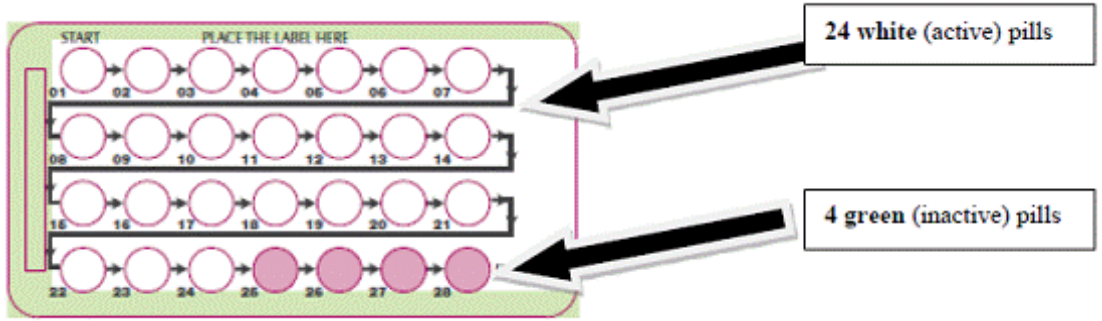
Allen and Bartz, *Obstet Gynecol* 2024

How does the Opill® compare to other POPs?

- Norethrindrone 0.35 mg (Micronor®)
  - 1st generation progestin

- Drospirenone 4 mg (Slynd®)
  - 4th generation, derived from spironolactone

Slynd®
(drospirenone) tablets, 4 mg



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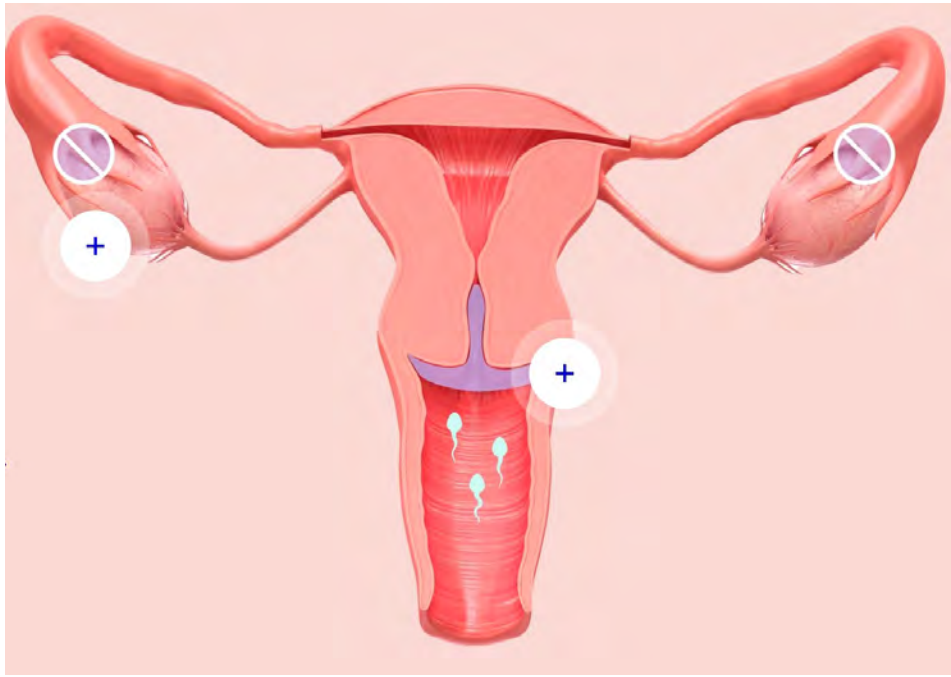
Mechanism of action

- OTC POP
  - Primary = thickens cervical mucus
  - Secondary = ovulation suppression (50-66%)
- DRSP only pill is similar except for higher ovulation suppression (99+%)
- NET only pill does not reliably suppress ovulation



Glasier et al, *Contraception* 2022
Archer et al, *Contraception* 2015

Over-the-counter progestin-only pill

- Recommended to take at the same time/within 3 hours
  - Small study showed no changes in cervical mucus by 6 hours of missing OTC POP
- If late or miss a pill, need back-up for 48 hours
  - NET only pill: same
  - DRSP only pill: given long half-life, back-up is only needed if 2+ tabs are missed

Glasier et al, *Contraception* 2023

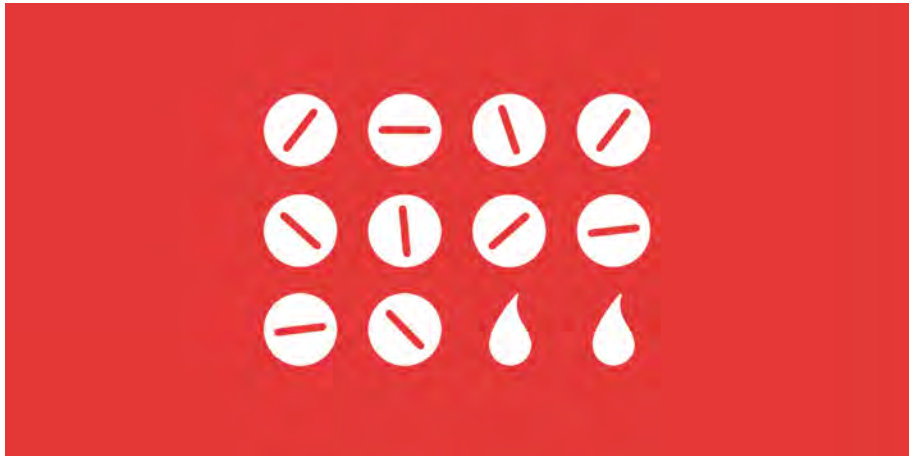
Contraceptive efficacy

- OTC POP: Pearl Index 4.4 (95% CI, 1.9-8.8)
- Perfect use of POPs – 99.5%, typical use – 95%
- DRSP only pill typical use – 98%

Allen and Bartz, *Obstet Gynecol* 2024
Zuniga et al, *Contraception* 2022

Bleeding profiles

- OTC POP: 48% BTB/spotting, up to 1/4 were amenorrheic
- DRSP only pill: 30% BTB/spotting, <5% prolonged bleeding, up to 1/3 amenorrheic
- NET only pill: 70% BTB/spotting, 33-50% prolonged bleeding



FDA Drug Label: Norgestrel
Archer et al, *Contraception* 2015
Kovacs, *Hum Reprod 1996*

OTC POP: side effects

- 17.4% discontinued due to side effects
  - 2/3 were due to bleeding
- Headache
- Breast tenderness
- GI side effects
- Acne

Comparison

DRSP only pill:

- Highest ovulation suppression
- 24hr delayed intake window (t1/2 = 30+hr)
- Anti-androgenic
- High cost without insurance coverage*

OTC pill:

- Decent ovulation suppression
- 3hr delayed intake window (t1/2 = 12 hr)
- Not yet available

NET only pill:

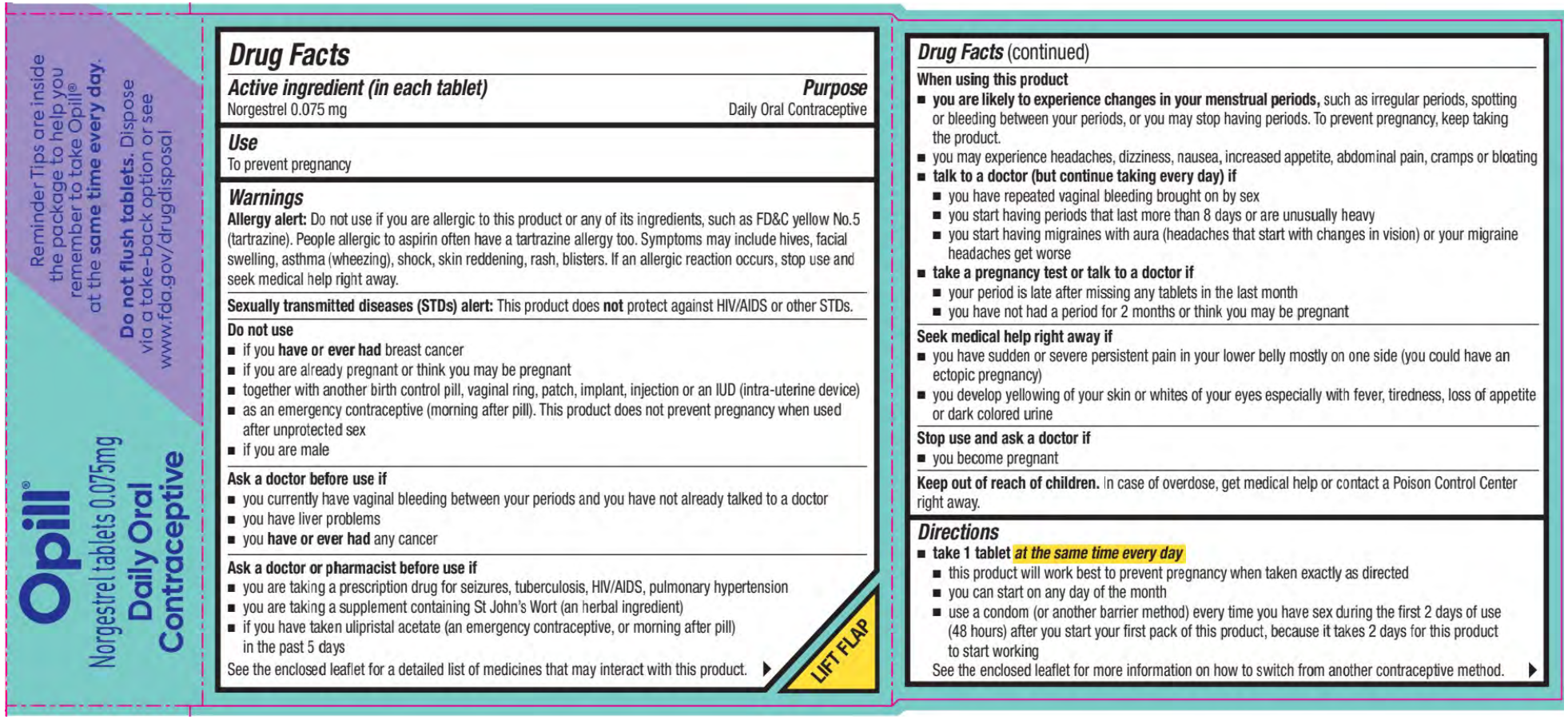
- Inconsistent ovulation suppression
- 3hr delayed intake window (t1/2 = 9 hr)
- Most bleeding side effects
- Cheap

*Fall 2023: improved CO Medicaid coverage with no PAT needed

Take home points: progestin-only pills

- DRSP only pill is the most forgiving, anti-androgenic pill with high ovulatory suppression and good bleeding profile
- But over a 1/3 of OCP users have missed pills due to issues with getting their next supply, making the OTC pill important!

OTC approval



Reminder Tips are inside the package to help you remember to take Opill® at the **same time every day**.

Do not flush tablets. Dispose via a take-back option or see www.fda.gov/drugdisposal

Opill®

Norgestrel tablets 0.075mg

Daily Oral Contraceptive

Drug Facts

Active ingredient (in each tablet) — ***Purpose***

Norgestrel 0.075 mg — Daily Oral Contraceptive

Use

To prevent pregnancy

Warnings

Allergy alert: Do not use if you are allergic to this product or any of its ingredients, such as FD&C yellow No.5 (tartrazine). People allergic to aspirin often have a tartrazine allergy too. Symptoms may include hives, facial swelling, asthma (wheezing), shock, skin reddening, rash, blisters. If an allergic reaction occurs, stop use and seek medical help right away.

Sexually transmitted diseases (STDs) alert: This product does **not** protect against HIV/AIDS or other STDs.

Do not use

- if you **have or ever had** breast cancer
- if you are already pregnant or think you may be pregnant
- together with another birth control pill, vaginal ring, patch, implant, injection or an IUD (intra-uterine device)
- as an emergency contraceptive (morning after pill). This product does not prevent pregnancy when used after unprotected sex
- if you are male

Ask a doctor before use if

- you currently have vaginal bleeding between your periods and you have not already talked to a doctor
- you have liver problems
- you **have or ever had** any cancer

Ask a doctor or pharmacist before use if

- you are taking a prescription drug for seizures, tuberculosis, HIV/AIDS, pulmonary hypertension
- you are taking a supplement containing St John's Wort (an herbal ingredient)
- if you have taken ulipristal acetate (an emergency contraceptive, or morning after pill) in the past 5 days

See the enclosed leaflet for a detailed list of medicines that may interact with this product. ▶

LIFT FLAP

Drug Facts (continued)

When using this product

- **you are likely to experience changes in your menstrual periods,** such as irregular periods, spotting or bleeding between your periods, or you may stop having periods. To prevent pregnancy, keep taking the product.
- you may experience headaches, dizziness, nausea, increased appetite, abdominal pain, cramps or bloating
- **talk to a doctor (but continue taking every day) if**
  - you have repeated vaginal bleeding brought on by sex
  - you start having periods that last more than 8 days or are unusually heavy
  - you start having migraines with aura (headaches that start with changes in vision) or your migraine headaches get worse
- **take a pregnancy test or talk to a doctor if**
  - your period is late after missing any tablets in the last month
  - you have not had a period for 2 months or think you may be pregnant

Seek medical help right away if

- you have sudden or severe persistent pain in your lower belly mostly on one side (you could have an ectopic pregnancy)
- you develop yellowing of your skin or whites of your eyes especially with fever, tiredness, loss of appetite or dark colored urine

Stop use and ask a doctor if

- you become pregnant

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **take 1 tablet *at the same time every day***
  - this product will work best to prevent pregnancy when taken exactly as directed
  - you can start on any day of the month
  - use a condom (or another barrier method) every time you have sex during the first 2 days of use (48 hours) after you start your first pack of this product, because it takes 2 days for this product to start working

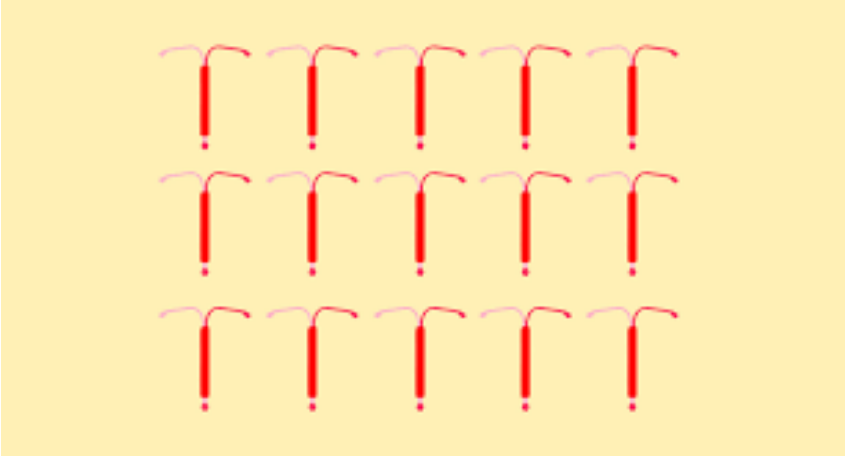
See the enclosed leaflet for more information on how to switch from another contraceptive method. ▶

OTC approval

- ACCESS study of >1200 users
  - >99% correctly self-selected if they were appropriate users
  - 93% adherence to daily use
    - No difference in adolescents or individuals with low health literacy
  - 97% used back-up if a pill was missed
- Modeled data suggests potential to reduce up to 34,000 unintended pregnancies per year
- Zena® combined oral contraceptive pill seeking approval

Extended use of LARCs

- Offering when appropriate is patient centered
- Avoids barriers to accessing contraceptive care



Dethier et al, *Contraception* 2022

Extended use of IUDs

- 8-year approval for 52 mg LNG IUD obtained in 2022
  - Year 7 (478 users): 1 ectopic, 1 implantation 4 days post-removal
  - Year 8 (343 users): 0 pregnancies
  - Amenorrhea rates 39% at years 7 & 8
- Mean LNG levels 119 pg/mL at 8.5 years (58.6 pg/mL at 3 years with 13.5 mg LNG IUD)
- Trials are ongoing up to 10 years

Creinin et al, *Am J Obstet Gynecol* 2022
Dethier et al, *Contraception* 2022

Extended use of IUDs

- 52 mg LNG IUD likely effective beyond 8 years to 10 years, can offer with joint decision making due to limited data
- Extended use not recommend for the 19.5 mg or 13.5 mg LNG IUD
- Good data supporting 12 years for 380 mm^2 copper IUD with some evidence up to 15 years

Dethier et al, *Contraception* 2022

Extended use of ENG implant

- Data for extended use up to 5 years
- Limited data in patients with class 3 obesity (BMI >40)
  - Association between lower ENG levels and higher BMI
- Caution in patients using CYP3A4 inducers
- Nexplanon® extension trial is underway looking at up 5 years to support an updated FDA label

Ali et al, *Hum* Reprod 2016
Lazorwitz et al, *Contraception* 2019

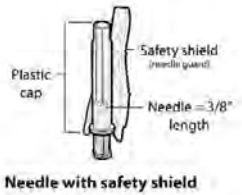
Extended use of LARC

- Safe, effective, and desirable for many patients
- Need to shift thinking away from ”expiring” devices
- Pharmacokinetic and prospective trials are ongoing for extended use

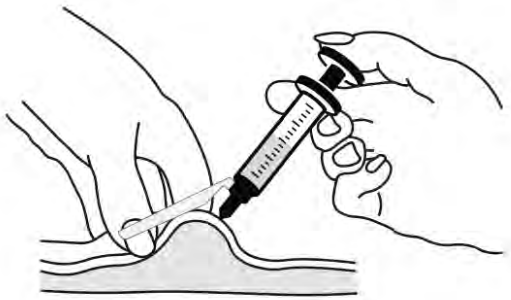
DMPA-SQ

- 104 mg subcutaneous injection every 13-15 weeks
- Self-administration is off-label
- Pre-filled syringe, need rx for other supplies
- Patient education materials are available online (bedsider.org, Reproductive Health Access Project)


Prefilled syringe

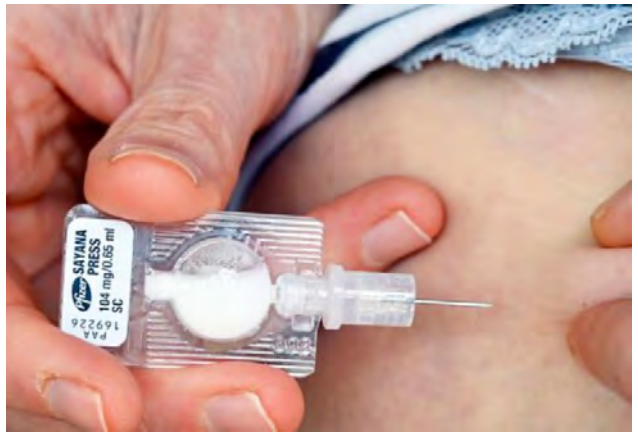


Needle with safety shield



Kohn et al, *Contraception* 2022

DMPA-SQ



- Long history of use globally
- Sayana Press®
  - Created for easy self-administration
  - Not approved or available in the US

Kohn et al, *Contraception* 2022

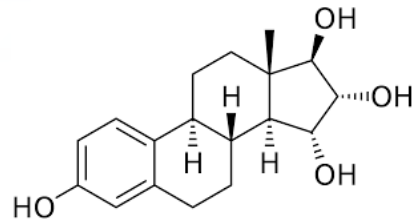
DMPA-SQ

- Increasing data that self-administration is safe, effective, and can improve continuation rates (10-30% higher)
- Renewed interest during COVID-19 pandemic, but availability is still limited

Kohn et al, *Contraception* 2022

Novel contraceptive methods

- Enhance existing methods
- Use new delivery systems
- Alter hormonal composition
- Use multipurpose prevention technologies (MPT)
- Create novel agents and targets



Haddad et al, *Clinic Obstet Gynecol* 2021

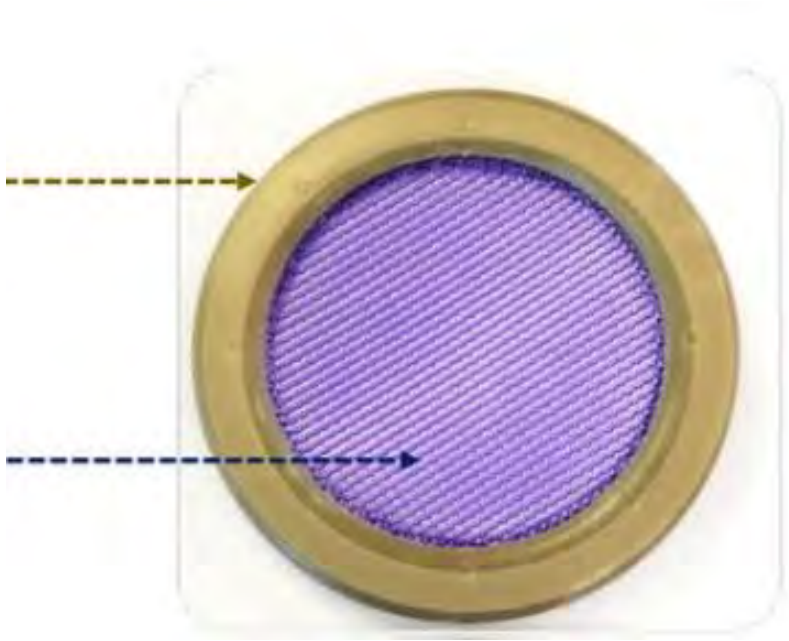
Nonhormonal ring

- Ovaprene®
- “One size fits most” ring inserted at the end of menses and removed at the start of next menses
- Phase 3 contraceptive efficacy trial started

Del Priore et al, *J Reprod Med* 2009

Nonhormonal ring

- Spermiostatic, silicone ring
  - Ferrous gluconate – immobilizes sperm
  - Ascorbic acid – increases cervical mucus
  - Polyglycolide – increases vaginal pH
- Physical barrier
  - Non-braided, fluid-permeable mesh barrier



Del Priore et al, *J Reprod Med* 2009

Contraception in development

- IUD with NSAID reservoir
- Microneedle patch
- Monthly pill
- Six-month injectable
- Non-hormonal vaginal capsule to thicken vaginal mucus
- Hormonal contraceptives for sperm-producing people

Current landscape

- 19 million pregnancy-capable individuals live in “contraceptive deserts”
- Detrimental effects on contraceptive access:
  - COVID-19 pandemic
  - Legislative restrictions
- In current environment of restricted access to abortion care, increased access to contraception is vital

Summary

- Understanding the differences in new methods can help guide their use
- While the OTC pill itself is not novel, the approval is important for access
- Increasing data support extended LARC use and self-administration of DMPA-SQ
- New developments are on the horizon!

Questions?

Preconception genetic carrier screening and PGT

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Cedars Sinai

cedars-sinai.org

Disclosures

- *Ferring*
- *Natara*

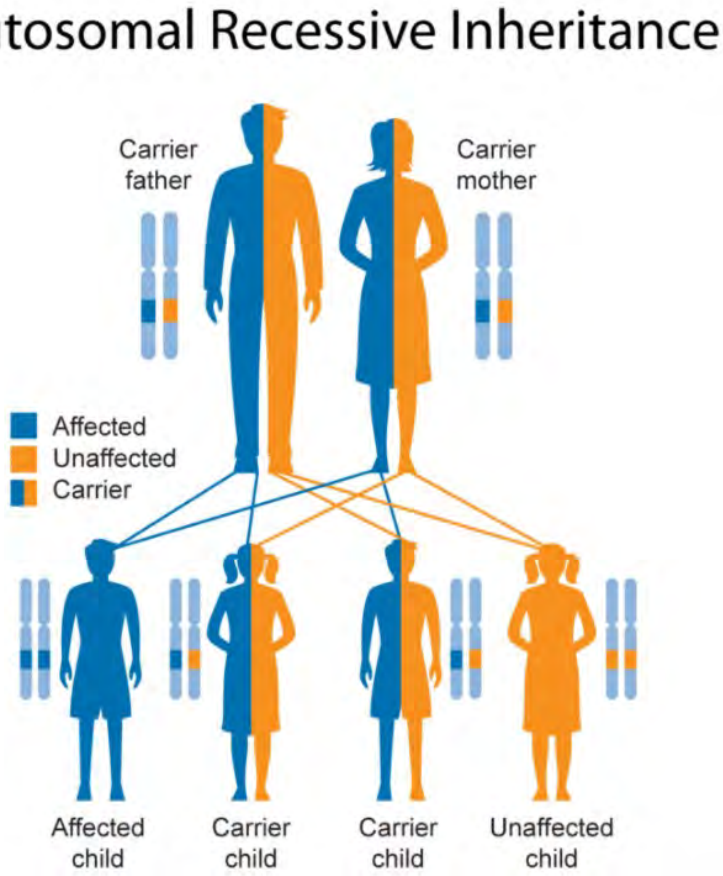
Objectives

- *Address preconception genetic carrier screening*
- *Preimplantation Genetic Testing*
- *Prenatal Genetic Screening and Testing*
- *Utilization of genomics and technologies for pregnancy well being*

Carrier screening – identification of autosomal recessive disorders

Cross: Aa x Aa

	A	a
A	AA	Aa
a	Aa	aa



Carrier screening for genetic conditions ACOG 2017

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 691 • March 2017
(Reaffirmed 2020)

(Replaces Committee Opinion Number 318, October 2005; Committee Opinion Number 432, May 2009; Committee Opinion Number 442, October 2009; Committee Opinion Number 469, October 2010; Committee Opinion Number 486, April 2011)

Committee on Genetics

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Genetics in collaboration with committee members Britton Rink, MD; Stephanie Romero, MD; Joseph R. Biggio Jr, MD; Devereux N. Saller Jr, MD; and Rose Giardine, MS.

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Carrier Screening for Genetic Conditions

- *Carrier screening to all couples, regardless of their race/ethnicity (ie, pan-ethnic carrier screening)*
  - *cystic fibrosis (CF)*
  - *spinal muscular atrophy (SMA)*
- *Carrier screening based on certain races/ethnicities*
  - *alpha thalassemia*
  - *Hb beta chain-related hemoglobinopathy (sickle cell disease)*
  - *Tay-Sachs disease*
  - *Canavan disease*
  - *familial dysautonomia*

ACOG Committee Opinion- Carrier Screening for Genetic Conditions No. 691, March 2017

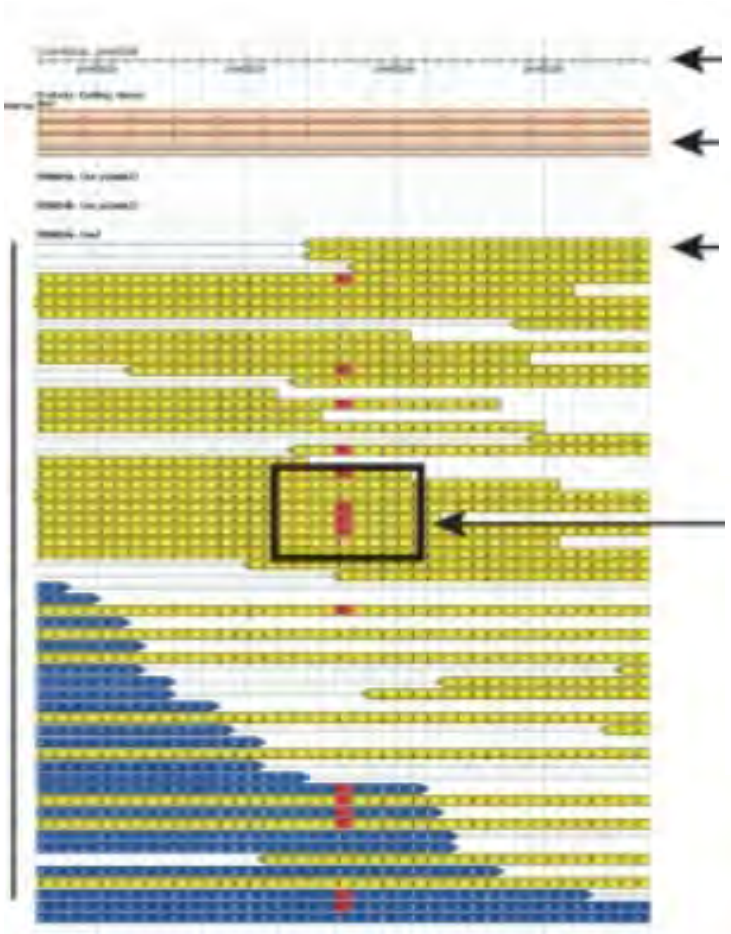
Preconception genetic carrier screening ACMG 2021

- *Clinical utility is measured by the fact that individuals or couples are informed and may alter reproductive decision making because of the carrier screening results.*
- *Clinical utility is represented by its ability to provide individuals an opportunity to discuss their risks and consider reproductive options that are available pre-pregnancy, during pregnancy, or after birth. Availability of reproductive options may depend on various socioeconomical, legal, and cultural factors in different regions.*
- *Examples of reproductive options include:*
  - *In vitro fertilization with preimplantation genetic testing for monogenic conditions*
  - *Use of donor gamete/embryo*
  - *Adoption*
  - *Prenatal diagnosis using chorionic villus sampling or amniocentesis followed by a decision to either prepare for an affected child including special care after birth or terminate the pregnancy*
  - *A decision not to have children*

Gregg AR, et al. ACMG Professional Practice and Guidelines Committee Genetics in Medicine (2021) 23:1793–1806; https://doi.org/10.1038/s41436-021-01203-

Next generation sequencing

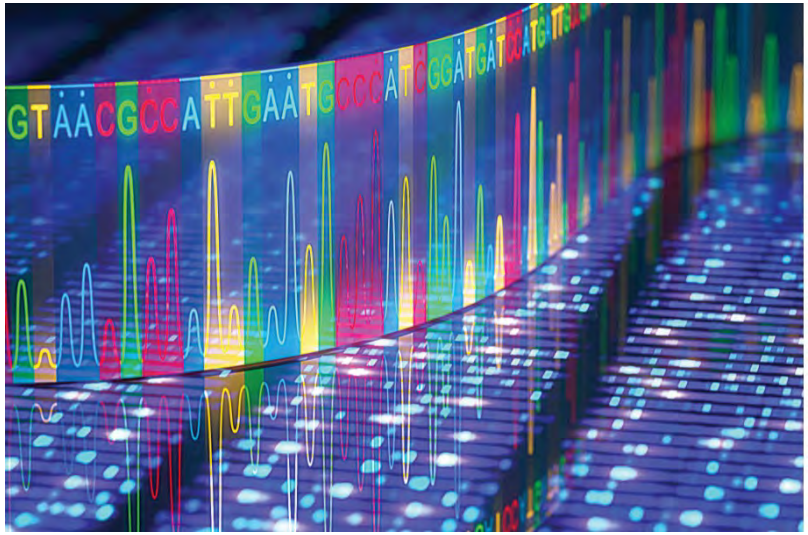
- *NGS platforms perform sequencing of millions of small fragments of DNA in parallel.*
- *Bioinformatics analyses are used to piece together these fragments by mapping the individual reads to the human reference genome.*
- *Each of the three billion bases in the human genome is sequenced multiple times, providing high depth to deliver accurate data and an insight into unexpected DNA variation.*
- *NGS can be used to sequence entire genomes or specific areas of interest, including all 22 000 coding genes (a whole exome) or small numbers of individual genes.*



Sam Behjati and Patrick S Tarpey Arch Dis Child Educ Pract Ed. 2013 Dec; 98(6): 236–238.

Next Generation Sequencing for carrier screening - 2021

- *low cost*
- *high throughput identification of sequence variants across many genes simultaneously*
- *Allows equitable opportunities for patients to learn their reproductive risks using next-generation sequencing technology*
- *An improved understanding of this risk allows patients to make informed reproductive decisions*
- *Reproductive decision making is the established metric for clinical utility of population-based carrier screening*
- *Standardization of the screening approach will facilitate testing consistency*



Cedars Sinai

Gregg AR, et al. ACMG Professional Practice and Guidelines Committee Genetics in Medicine (2021) 23:1793–1806; https://doi.org/10.1038/s41436-021-01203-

Carrier Screening for Genetic Conditions American College of Medical Genetics and Genomics (ACMG) 2021

- *ACMG Goals*
  - *Develop carrier screening that is ethnic and population neutral and more inclusive of diverse populations to promote equity and inclusion*

Tables 1-4*

Public Database gnomAD v 2.0.2[49]; 415 autosomal recessive	+	Carrier frequency in gnomAD at least 1/200 for six ancestral populations where Pathogenic and Likely Pathogenic variants were considered[50]	**86 genes**

Table 5*

Carrier frequency known to be at least 1/200 however not captured in gnomAD v 2.0.2	or	Genes with at least a 1/200 carrier frequency of pathogenic or likely pathogenic variants in a subpopulation that has at least 1% representation in the US including US territories.	**9 genes**

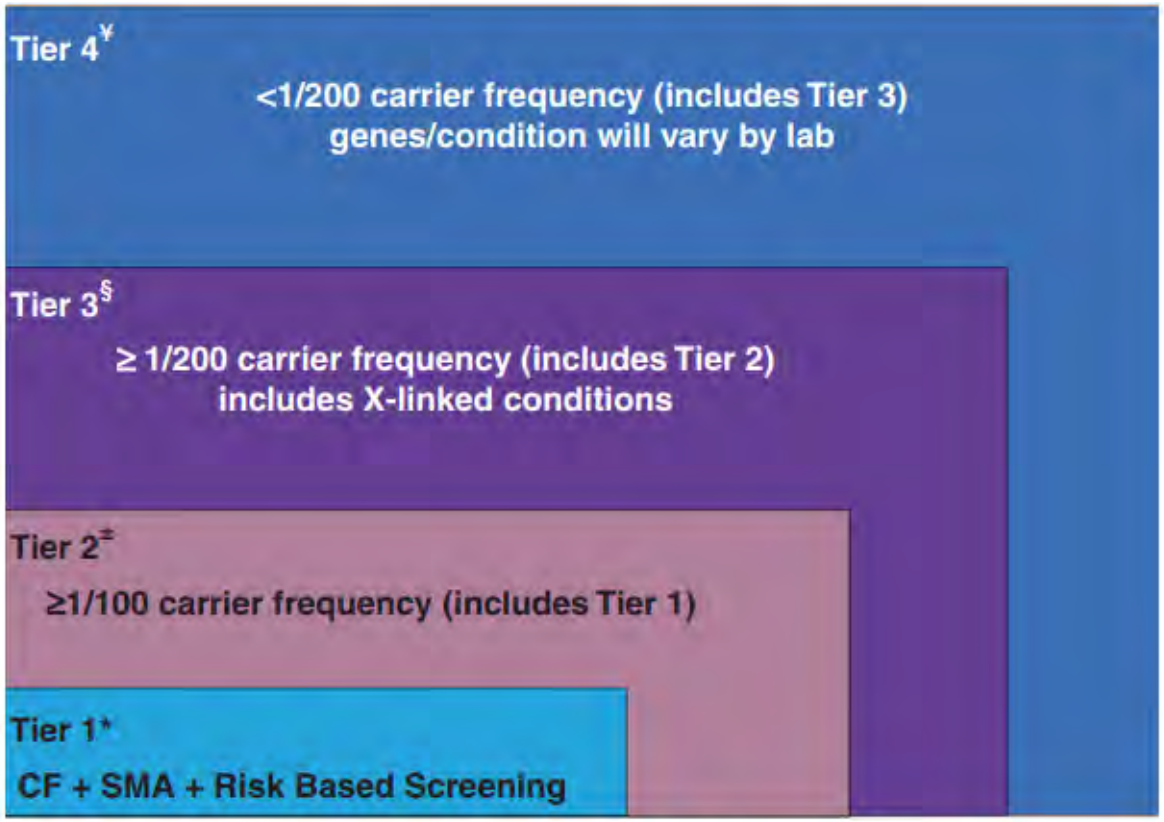
Table 6*

X-linked phenotypes (N=355) were identified in the OMIM database (November 30, 2020)[55] (Table S2)	+	Prevalence of the OMIM phenotypes (Table S2) were determined using OMIM[55], Orphanet[63], MedlinePlus[64]; prevalence required was at least 1/40,000	**16 genes**

***All conditions included with at least moderate severity[5,65]**

Gregg AR et al. ACMG Professional Practice and Guidelines Committee Genetics in Medicine (2021) 23:1793–1806; https://doi.org/10.1038/s41436-021-01203-

Preconception genetic carrier screening ACMG



Tier 4 screening should be considered for a pregnancy that stems from a known or possible consanguineous relationship (second cousins or closer) or when a family or personal medical history warrants.

All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening which tests for 112 genetic conditions

Limiting the carrier frequency to ≥1/100 creates missed opportunities to identify couples at risk for serious conditions

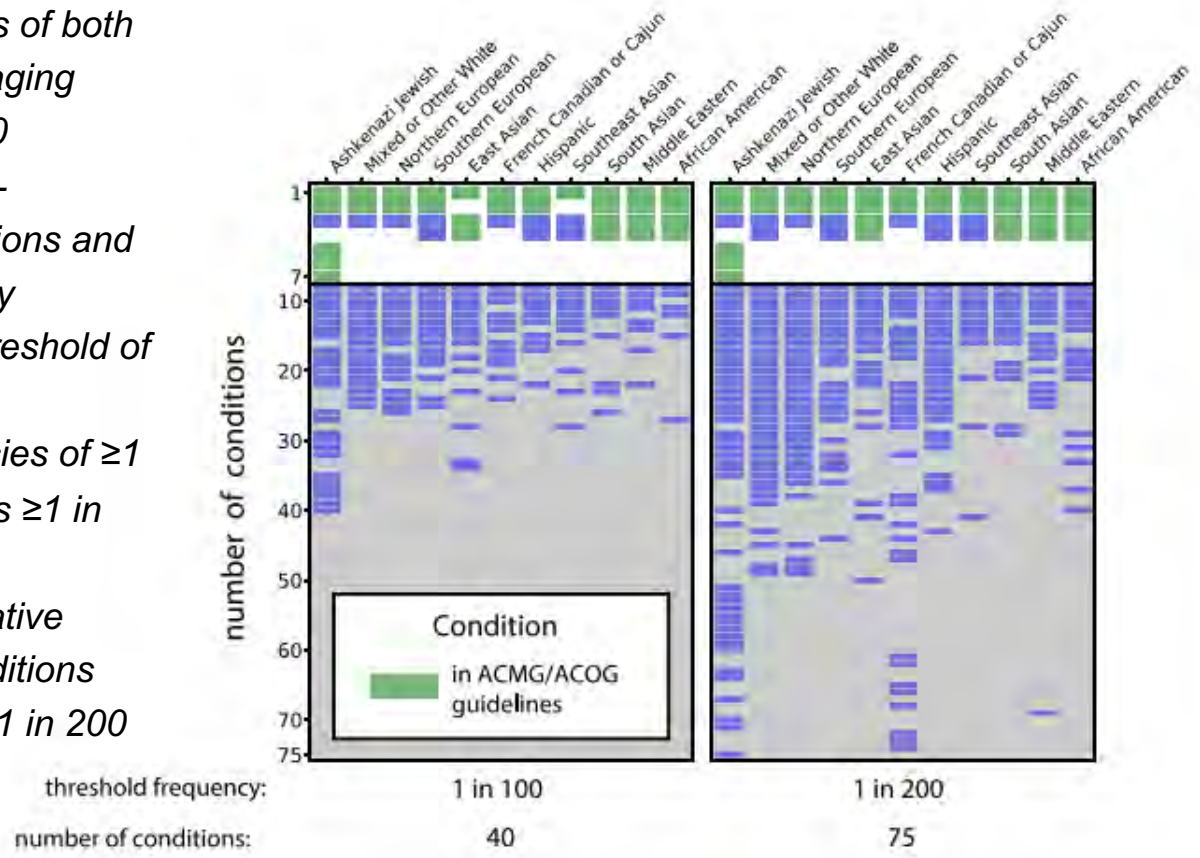
Carrier screening for two common conditions using a carrier frequency threshold of 1/100 may not be equitable across diverse populations.

Cedars Sinai

Gregg AR et al. ACMG Professional Practice and Guidelines Committee Genetics in Medicine (2021) 23:1793–1806; https://doi.org/10.1038/s41436-021-01203-

Carrier screening panel that supports equity across diverse populations

- *Using evidence-based interpretations of both ACOG and ACMG criteria and leveraging carrier frequency data from >460,000 individuals across 11 ethnicities (self-reported) which identified 176 conditions and applied criteria from ACOG frequency threshold of ≥1 in 100 and ACMG threshold of ≥1 in 200.*
- *Forty conditions had carrier frequencies of ≥1 in 100 and 75 had carrier frequencies ≥1 in 200*
- *Following severity criteria a conservative equitable panel consisting of 37 conditions and a more permissive panels and ≥1 in 200 consists of 74 conditions.*



Taber, et al. Genetics in Medicine (2022) 24, 201–213

Cedars Sinai

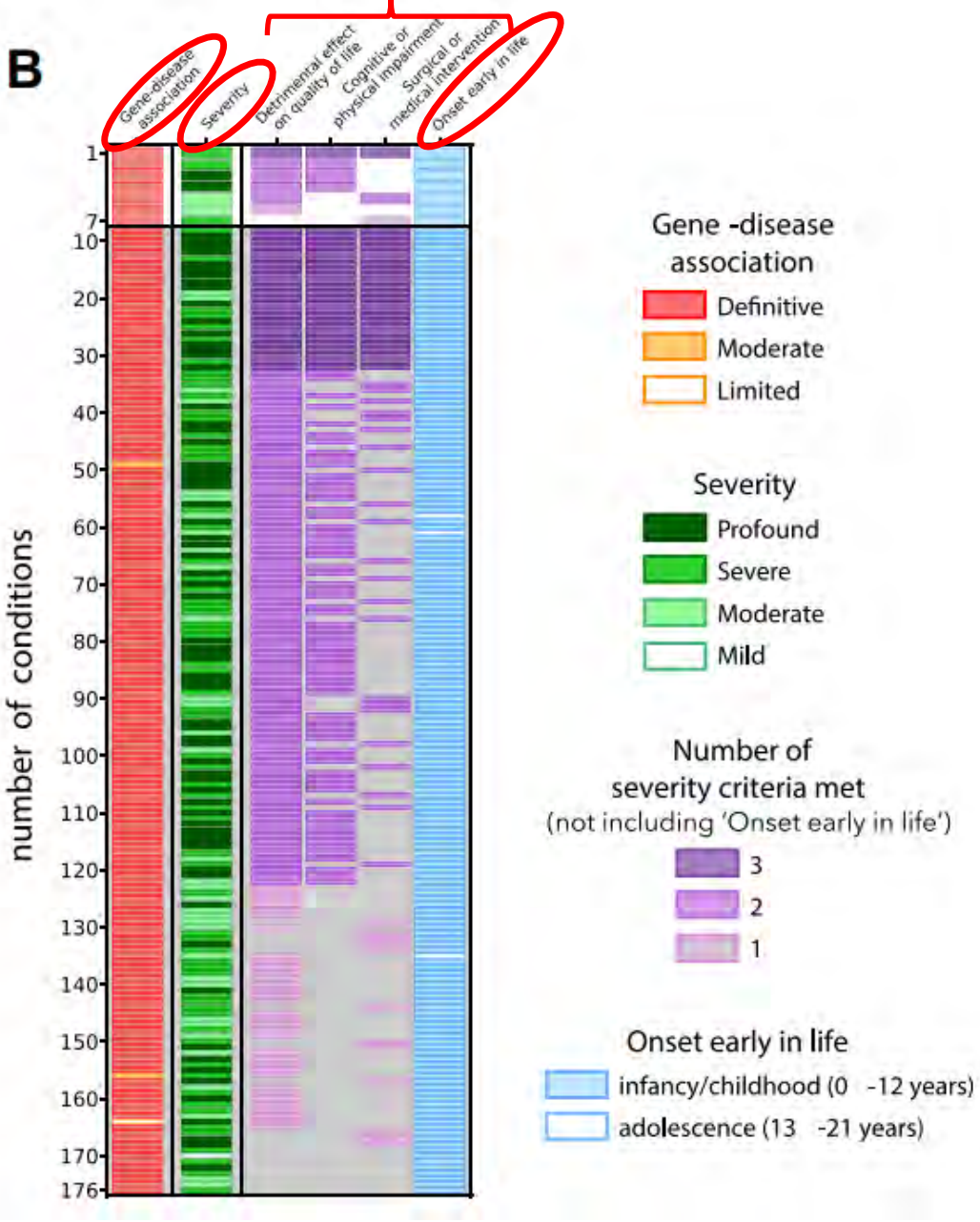
176 Panel

Moderate or higher gene–disease association – 175 of 176 conditions (99.4%) Captures 99.8% of carriers and >99.9% of ARCs compared with a 176-condition panel

Moderate severity - 175 of 176 conditions (99.4%)

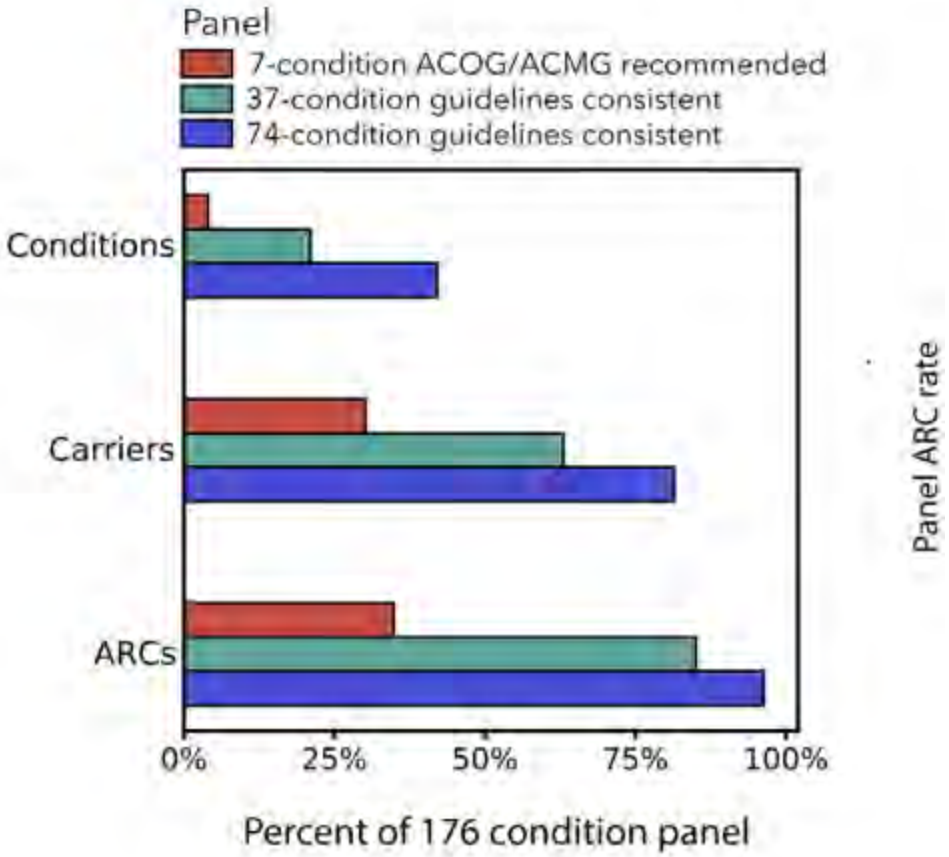
ACOG severity criterion, 165 of 176 - Captures 94.2% of carriers and 92.3% of ARCs

Age of onset (infancy/childhood) - 165 of 176 conditions (93.8%)



Taber, et al. Genetics in Medicine (2022) 24, 201–213

Carrier screening panel that supports equity across diverse populations



- *Compared to the 176 conditions panel*
  - *37 conditions panel would capture 63.0% of carriers and 84.6% of ARCs*
  - *74 conditions panel would capture 81.4% of carriers and 96.6% of at risk couples (ARCs)*

Taber, et al. Genetics in Medicine (2022) 24, 201–213

Genetic carrier screening – Impact on decision making (3 studies)

- *47% - screening was to spare a future child a life with a severe disorder*
- *Higher anxiety in high-risk and pregnant respondents*
- *100% would opt for the test again*
- *Reproductive decision making was more common when patients received results **before an established pregnancy** (62–77%).*
  - *The most common decisions were*
    - *59% in vitro fertilization with preimplantation genetic diagnosis*
    - *20% diagnostic test during pregnancy*
    - *7.7% use of a donor gamete*
    - *5.1% consider adoption*
- ***Testing during pregnancy***
  - *16-36% had an affected fetus of those performing diagnostic testing*
  - *40-67% discontinued their pregnancy*

Ivy van Dijke, et al European Journal of Human Genetics (2021) 29:1252–1258;
Ghiossi, C. E., et al. J. Genet. Couns. 27, 616–625 (2018).
Johansen Taber, K. A.,et al Genet. Med. 21, 1041–1048 (2019)
Gregg AR, et al ACMG Professional Practice and Guidelines Committee Genetics in Medicine (2021) 23:1793–1806

Carrier screening ACMG – Recommendations Tier 3 or Tier 4

- *Carrier screening (Tier 3) is optional and can be performed at any time*
- *Preconception screening is recommended over prenatal screening*
  - *less stressful on patients with positive screening*
  - *allows for the full complement of reproductive decision making*
- *If done in pregnancy, concurrent partner testing should be offered*
- *When a reproductive partner has changed, carrier screening should be readdressed*
- *Carrier screening is not a test for all genetic conditions*
  - *will not identify de novo variants in the offspring*
  - *does not replace newborn screening*
- *When Tier 1 or Tier 2 carrier screening was performed in a prior pregnancy, Tier 3 screening should be offered*
- *Consanguineous couples should have Tier 4 screening*
- *If family history warrants, additional genes may be considered*
- *Negative test reduces but does not eliminate the risk of an affected child*

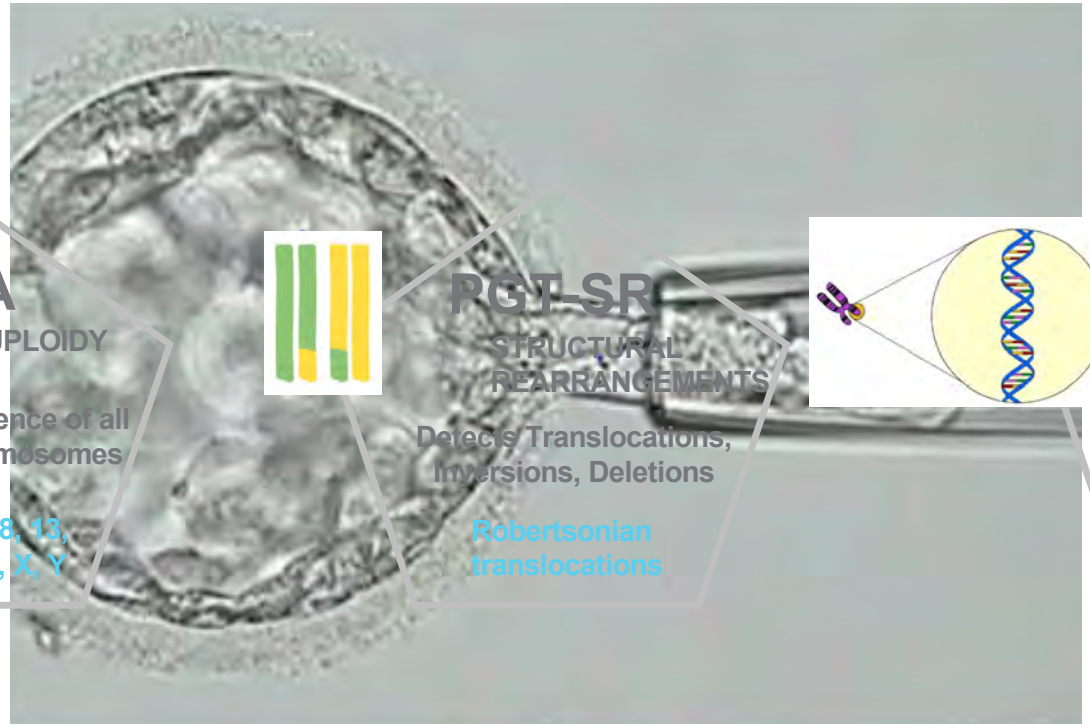
Gregg AR et al. ACMG Professional Practice and Guidelines Committee Genetics in Medicine (2021) 23:1793–1806; https://doi.org/10.1038/s41436-021-01203-

Carrier screening- Greater Expanded Panel (176 plus)

- *Larger panels that include ACOG and ACMG criteria should be considered*
  - *More ethnically inclusive panel*
  - *Moderate or higher gene–disease association – 175 of 176 conditions (99.4%)*
  - *Moderate to severe disease severity - 175 of 176 conditions (99.4%)*
  - *ACOG severity criterion*
    - *Determinantal effect on quality of life*
    - *Cognitive or physical impairment*
    - *Surgical or medical intervention*
  - *Onset early in life*

Taber, et al. Genetics in Medicine (2022) 24, 201–213

Preimplantation genetic testing
PGT-A, PGT-SR, PGT-M



PGT-A
ANEUPLOIDY

Screens for presence of all 23 pairs of Chromosomes

Trisomy 21,18, 13,
Monosomy 7, X, Y

PGT-SR
STRUCTURAL REARRANGEMENTS

Detects Translocations, Inversions, Deletions

Robertsonian translocations

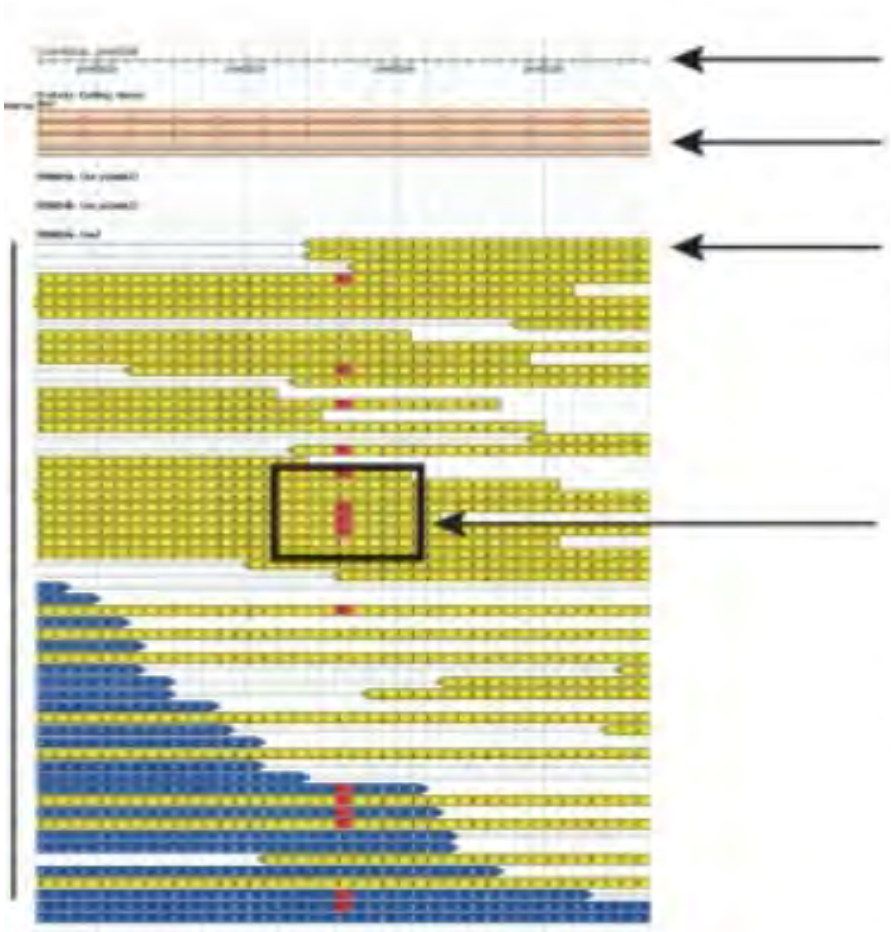
PGT-M
MONOGENIC

Used to detect known Inherited Disorders

Cystic Fibrosis, Tay Sachs, Sickle Cell, BRCA

Preimplantation genetic testing platforms

- *NGS allows for direct reading of sequenced DNA fragments and their quantification based on sequence read numbers*
- *whole chromosome aneuploidy (PGT-A)*
- *medium size deletions or insertions in chromosomes (PGT-SR)*
- *detection of single gene disorders (PGT-M)*



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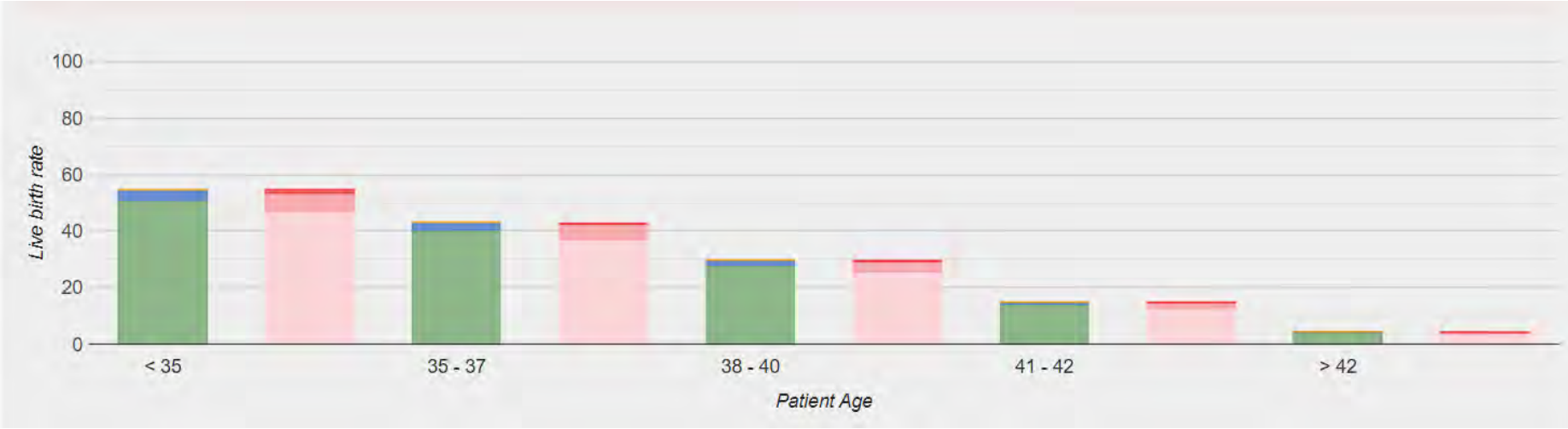
ESHRE PGT Consortium good practice recommendations for the detection of structural and numerical chromosomal aberrations† ESHRE PGT-SR/PGT-A Working Group 2020
Sam Behjati and Patrick S Tarpey Arch Dis Child Educ Pract Ed. 2013 Dec; 98(6): 236–238.

PGT-A to improve IVF outcomes –live births

National assisted reproductive technology (ART) surveillance systems (SART)

Data 2019

293, 672 Total Cycles



PGT-A - Time to pregnancy and advanced reproductive age > 37 yo

- *Analysis of data from national assisted reproductive technology (ART) surveillance systems*
- *PGT-A is not associated with improved rates of clinical pregnancy or live birth after fresh autologous blastocyst transfer among women aged <37 years*
- ***PGT-A of embryos appeared to improve the likelihood of having a live birth among women >37 years***
- *Cycles that were intended for PGT-A were more likely to reach embryo transfer in all age groups, but more significantly in women aged >37*
- *RCT that focused on women with advanced maternal age (38-41 years old) demonstrated a significantly higher live birth rate with PGT-A group per cycle (36% vs 21.9%, P<031) and a lower miscarriage rate (2.7% vs 39%, P<0007)*

Chang et al. Fertil Steril. 2016; 105(2): 394–400.
Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology Fertil Steril 2018;109:429–36.

Live birth with and without PGT-A for < 38 yo (RCT)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Live Birth with or without Preimplantation Genetic Testing for Aneuploidy

J. Yan, Y. Qin, H. Zhao, Y. Sun, F. Gong, R. Li, X. Sun, X. Ling, H. Li, C. Hao, J. Tan, J. Yang, Y. Zhu, F. Liu, D. Chen, D. Wei, J. Lu, T. Ni, W. Zhou, K. Wu, Y. Gao, Y. Shi, Y. Lu, T. Zhang, W. Wu, X. Ma, H. Ma, J. Fu, J. Zhang, Q. Meng, H. Zhang, R.S. Legro, and Z.-J. Chen

- *20 and 37 years of age*
- *three or more good-quality blastocysts*
- *Good Prognosis*

Table 3. Cumulative Live-Birth Rate and Secondary Outcomes.*

Outcome	PGT-A Group (N=606)	Conventional-IVF Group (N=606)	Absolute Difference (95% CI)	Rate Ratio (95% CI)
Primary outcome				
Cumulative live-birth rate — no. (%)†	468 (77.2)	496 (81.8)	−4.6 (−9.2 to −0.0)	0.94 (0.89 to 1.00)
Singleton	462 (76.2)	478 (78.9)	−2.6 (−7.3 to 2.1)	0.97 (0.91 to 1.03)
Twin	6 (1.0)	18 (3.0)	−2.0 (−3.5 to −0.4)	0.33 (0.13 to 0.83)
Secondary outcomes				
Cumulative biochemical pregnancy — no. (%)	526 (86.8)	571 (94.2)	−7.4 (−10.7 to −4.2)	0.92 (0.89 to 0.96)
Cumulative clinical pregnancy — no. (%)	505 (83.3)	556 (91.7)	−8.4 (−12.1 to −4.7)	0.91 (0.87 to 0.95)
Cumulative ongoing pregnancy — no. (%)	479 (79.0)	514 (84.8)	−5.8 (−10.1 to −1.5)	0.93 (0.88 to 0.98)
Birth weight				
Singleton				
No. of observations	462	478		
Mean weight — g	3417±488	3449±488	−32 (−95 to 30)	
Twin				
No. of observations	12	36		
Mean weight — g	2500±714	2605±420	−105 (−444 to 235)	
Cumulative pregnancy loss — no./total no. (%)				
Biochemical	31/526 (5.9)	41/571 (7.2)	−1.3 (−4.2 to 1.6)	0.82 (0.52 to 1.29)
Clinical	46/526 (8.7)	72/571 (12.6)	−3.9 (−7.5 to −0.2)	0.69 (0.49 to 0.98)
First trimester	37/526 (7.0)	60/571 (10.5)	−3.5 (−6.8 to −0.1)	0.67 (0.45 to 0.99)
Second trimester	9/526 (1.7)	12/571 (2.1)	−0.4 (−2.0 to 1.2)	0.81 (0.35 to 1.92)
Good birth outcome — no. (%)‡	378 (62.4)	385 (63.5)	−1.2 (−6.6 to 4.3)	0.98 (0.90 to 1.07)
Features of live births				
Duration of pregnancy — wk	39.2±1.7	39.1±1.6	0.0 (−0.2 to 0.2)	
No. of embryos transferred	1.2±0.4	1.3±0.6	−0.2 (−0.2 to −0.1)	
No. of embryo-transfer procedures	1.1±0.4	1.3±0.5	−0.1 (−0.2 to −0.1)	
Interval since randomization — mo	12.5±2.0	12.4±2.3	0.1 (−0.2 to 0.4)	
Frozen embryos				
No. of unused embryos	5.2±3.2	5.5±2.9	−0.3 (−0.6 to 0.1)	
No. of unused embryos in women without a live birth	4.4±2.8	4.9±2.9	−0.4 (−1.2 to 0.3)	

Yan, et al N Engl J Med 2021;385:2047-58

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Live birth with and without PGT-A for < 38 yo (RCT)

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Table S3. The rates of pregnancy, pregnancy loss and live birth after the first embryo transfer between PGT-A and IVF.

Outcome	PGT-A group (N=576)	IVF group (N=594)	Absolute Difference (95%CI)	Rate Ratio for PGT-A vs. IVF (95%CI)
Primary outcome: live birth-no. (%)	382/576 (66.3)	369/594 (62.1)	4.2 (-1.3, 9.7)	1.07 (0.98, 1.16)
Singleton	376/576 (65.3)	357/594 (60.1)	5.2 (-0.4, 10.7)	1.09 (0.99, 1.19)
Twin	6/576 (1.0)	12/594 (2.0)	-1.0 (-2.4, 0.4)	0.52 (0.19, 1.36)
Secondary outcomes				
Biochemical pregnancy-no. (%)	451/576 (78.3)	462/594 (77.8)	0.5 (-4.2, 5.3)	1.01 (0.95, 1.07)
Clinical pregnancy-no. (%)	422/576 (73.3)	427/594(71.9)	1.4 (-3.7, 6.5)	1.02 (0.95, 1.09)
Ongoing pregnancy-no. (%)	393/576 (68.2)	384/594 (64.6)	3.6 (-1.8, 9.0)	1.06 (0.97, 1.15)
Pregnancy loss-no./total no. (%)				
Biochemical pregnancy loss	26/451 (5.8)	33/462 (7.1)	-1.4 (-4.6, 1.8)	0.81 (0.49, 1.33)
Clinical pregnancy loss	39/451 (8.7)	55/462 (11.9)	-3.3 (-7.2, 0.7)	0.73 (0.49, 1.07)
First trimester	30/451 (6.7)	44/462 (9.5)	-2.9 (-6.4, 0.7)	0.70 (0.45, 1.09)
Second trimester	9/451 (2.0)	11/462 (2.4)	-0.4 (-2.3, 1.5)	0.84 (0.35, 2.00)

No adjustment was made for multiplicity of secondary outcomes. 95% CIs should not be used to infer definitive treatment outcomes.

- *No difference even after the first IVF cycle*

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Yan, et al N Engl J Med 2021;385:2047-58

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Table S2. Live birth rate after each embryo transfer cycle.

Outcome	PGT-A group (N=606)	IVF group (N=606)	Absolute Difference (95% CI)	Rate Ratio for PGT-A vs. IVF (95%CI)
Live birth after 1st embryo transfer-no. (%)	382/576 (66.3)	369/594 (62.1)	4.2 (-1.3, 9.7)	1.07 (0.98, 1.16)
Live birth after 2nd embryo transfer-no. (%)	74/119 (62.2)	106/192 (55.2)	7.0 (-4.2, 18.2)	1.13 (0.93, 1.36)
Live birth after 3rd embryo transfer-no. (%)	2/5 (40.0)	19/49 (38.8)	1.2 (-43.8, 46.3)	1.03 (0.33, 3.19)
Live birth conceived naturally-no.	10	2	-	-

No adjustment was made for multiplicity of secondary outcomes. 95% CIs should not be used to infer definitive treatment outcomes.

- *More women in the conventional-IVF group underwent a second or third embryo-transfer cycle:*
  - *Second Cycle -192 women in the conventional-IVF group and 119 in the PGT-A group*
  - *Third Cycle - 49 women in the conventional-IVF group and 5 in the PGT-A group*

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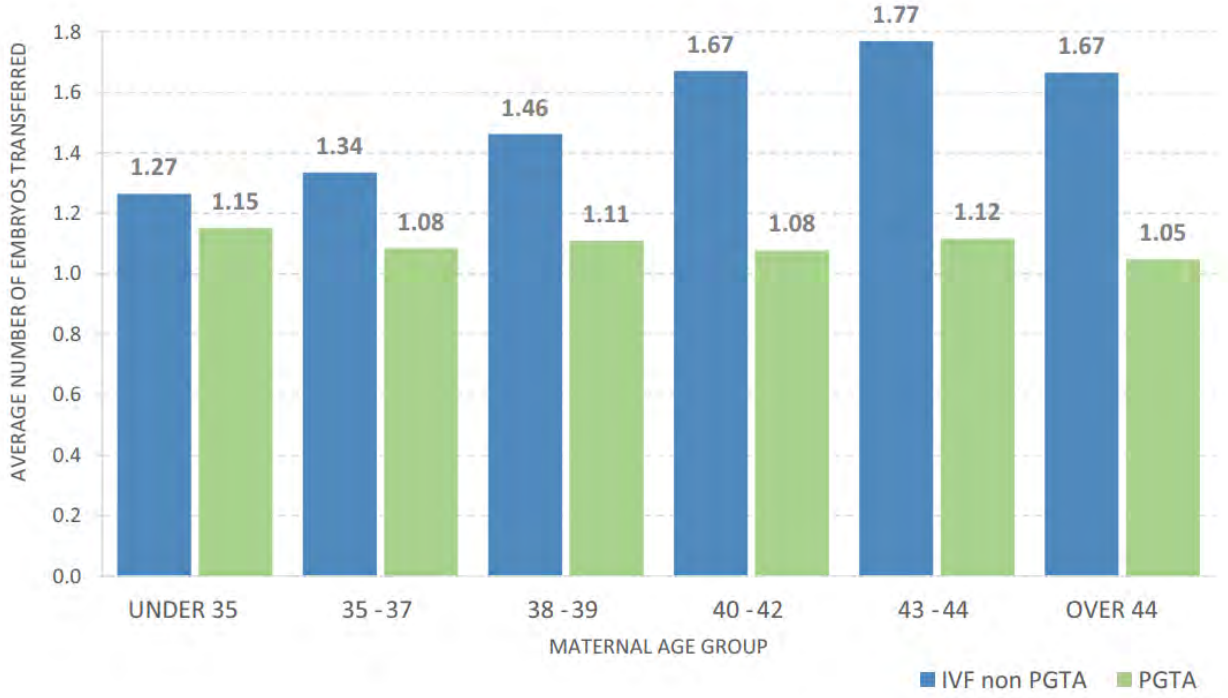
Yan, et al N Engl J Med 2021;385:2047-58

PGT-A Retrospective Cohort Study
2464 PGT-A, 190,010 cycles



- *Fewer embryos are required to achieve a pregnancy following PGT-A compared to regular IVF*

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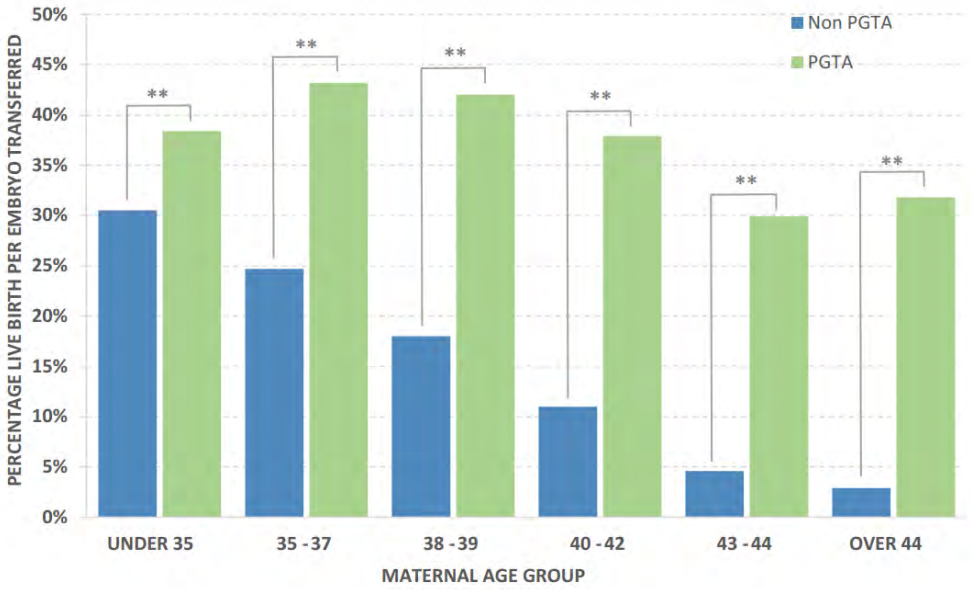
Sanders et al Journal of Assisted Reproduction and Genetics (2021) 38:3277–3285

PGT-A Retrospective Cohort Study
2464 PGT-A 190,010 cycles



- *PGT-A versus non PGT-A*
  - *Live birth rates were significantly higher in all age groups*
  - *Mostly single embryo transfers (SET)*
  - *Less number of transfers per live birth , particularly if over 40 years*

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Sanders et al Journal of Assisted Reproduction and Genetics (2021) 38:3277–3285

PGT-A: Recommendations

- ***Recommendations***
  - *Shortened time to pregnancy and increased success for women over 37 yo*
  - *Potential benefit in select populations of younger reproductive age women*
  - *Selection of embryo for elective single embryo transfer – Decrease risk of multiple gestations*
  - *Beneficial if proceeding with PGT-M or PGT-SR*
  - *Potential benefit for long term fertility preservation*
  - *Cost benefit – minimize number of frozen embryo transfer cycles?*
- ***Considerations***
  - *Would embryos that don't survive to the stage of biopsy for genetic testing lead to successful pregnancies*
  - *Are false positive test results possible (mosaicism 3-20%) that could lead to a healthy genetically normal pregnancy?*
- ***Counseling is necessary for shared decision making for PGT***

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Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology Fertil Steril 2018;109:429–36. 2018; Practice Committee and Genetic Counseling Professional Group (GCPG) of the American Society for Reproductive Medicine. Fertil Steril 2020;114:246-54

Genetics and Pregnancy – Purpose

- *Prenatal testing for chromosomal abnormalities are designed to provide an accurate assessment of a patient's risk of carrying a fetus with a chromosomal disorder.*
- *Testing for chromosomal abnormalities should be an informed patient choice based on adequate and accurate information.*
- *All patients should be offered both screening and diagnostic tests, and all patients have the right to accept or decline testing after counseling.*

ACOG Practice Bulleting Screening for Fetal Chromosomal Abnormalities. 2018
Photo: https://www.theguardian.com/world/2021/aug/03/hopes-uk-trial-will-allay-pregnant-womens-covid-vaccine-concerns

Pregnancy – Genomic testing capabilities

- *Recommendations*

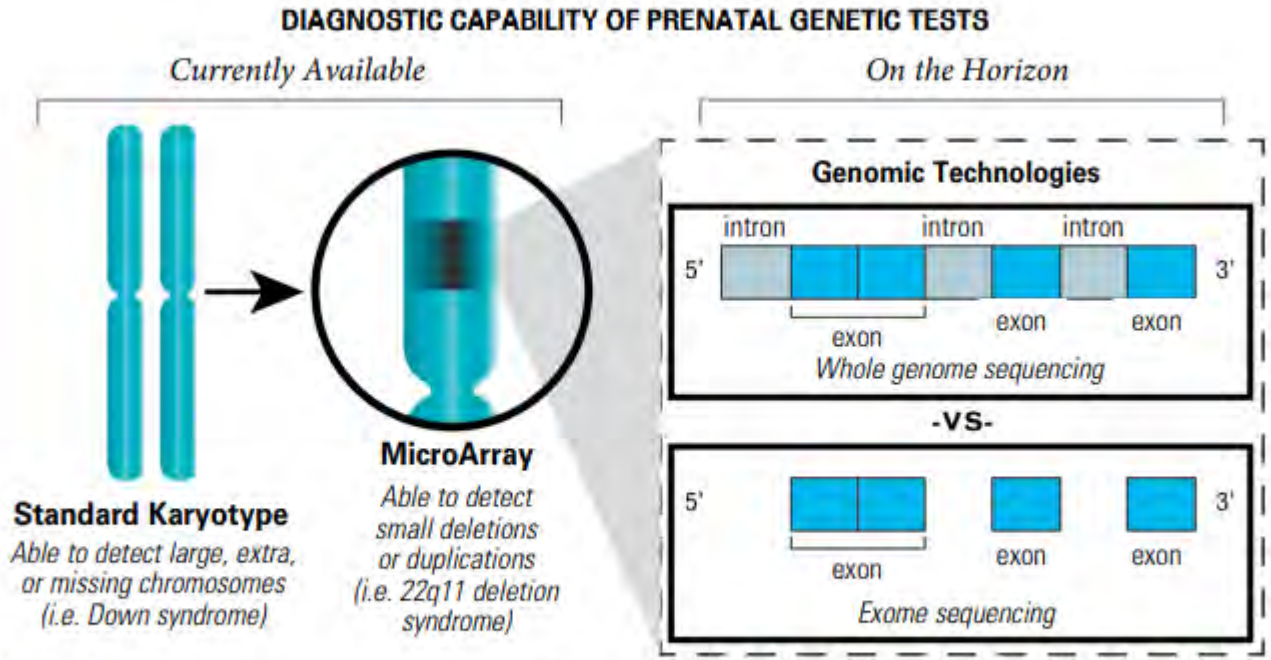


Figure 1. Diagnostic capability of prenatal genetic tests. (Reprinted from Hardisty EE, Vora NL. Advances in genetic prenatal diagnosis and screening. Curr Opin Pediatr 2014;26:634–8.) ⇦

COMMITTEE OPINION Number 682 (Reaffirmed 2020) Committee on Genetics Society for Maternal–Fetal Medicine Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology

Genetics and Pregnancy – Chromosomal Abnormalities

Table 1. Chromosomal Abnormalities in Second-Trimester Pregnancies Based on Maternal Age at Term

	Trisomy 21	Trisomy 18	Trisomy 13	Sex Chromosome Aneuploidy (XXX, XY, XYY, 45, X)	Microarray or Rare Chromosomal Abnormality	All Chromosomal Abnormalities
Age 20	8 per 10,000 1 in 1,250	2 per 10,000 1 in 5,000	1 per 10,000 1 in 10,000	34 per 10,000 1 in 294	37 per 10,000 1 in 270	82 per 10,000 1 in 122
Age 25	10 per 10,000 1 in 1,000	2 per 10,000 1 in 5,000	1 per 10,000 1 in 10,000	34 per 10,000 1 in 294	37 per 10,000 1 in 270	84 per 10,000 1 in 119
Age 30	14 per 10,000 1 in 714	4 per 10,000 1 in 2,500	2 per 10,000 1 in 5,000	34 per 10,000 1 in 294	37 per 10,000 1 in 270	91 per 10,000 1 in 110
Age 35	34 per 10,000 1 in 294	9 per 10,000 1 in 1,111	4 per 10,000 1 in 2,500	35 per 10,000 1 in 285	37 per 10,000 1 in 270	119 per 10,000 1 in 84
Age 40	116 per 10,000 1 in 86	30 per 10,000 1 in 333	14 per 10,000 1 in 714	51 per 10,000 1 in 196	37 per 10,000 1 in 270	248 per 10,000 1 in 40

ACOG Practice Bulleting Screening for Fetal Chromosomal Abnormalities. 2018

Microdeletions, Duplications and other Variants

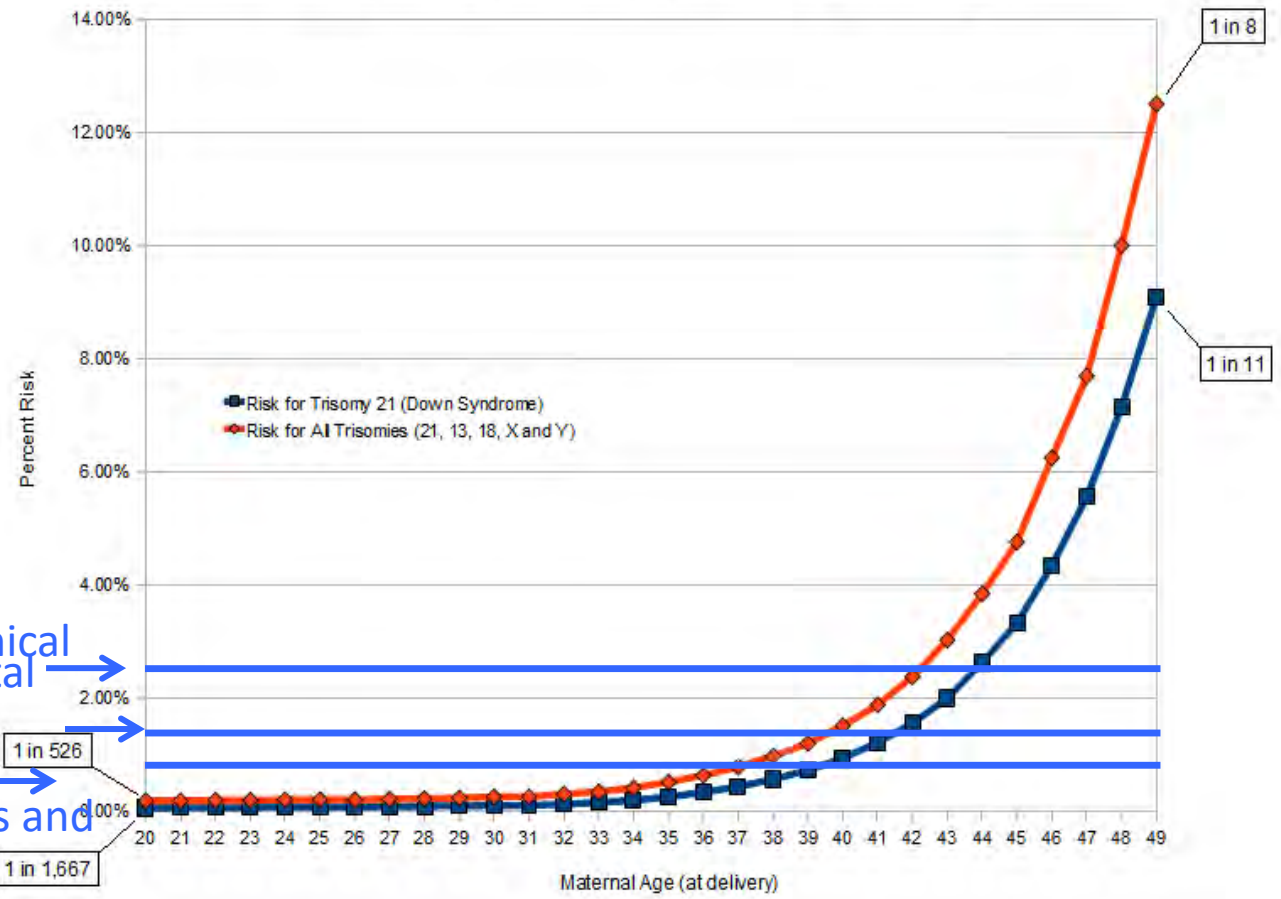
Table 3. Frequency and Clinical Interpretation of Microdeletions and Duplications on Chromosomal Microarray in the 3822 Samples with a Normal Karyotype, According to Indication for Prenatal Testing.

Indication for Prenatal Diagnosis	Normal Karyotype	Common Benign	Pathogenic	Uncertain Clinical Significance (N=130)		Total Known Pathogenic and Potential for Clinical Significance*
				Likely to Be Benign	Potential for Clinical Significance	
	no.		*no. (%)*			*no. (%) [95% CI]†*
Any	3822	1234 (32.3)	35 (0.9)	69 (1.8)‡	61 (1.6)	96 (2.5) [2.1–3.1]
Advanced maternal age	1966	628 (31.9)	9 (0.5)	37 (1.9)	25 (1.3)	34 (1.7) [1.2–2.4]
Positive on Down's syndrome screening	729	247 (33.9)	3 (0.4)	13 (1.8)	9 (1.2)	12 (1.6) [0.9–2.9]
Anomaly on ultrasonography	755	247 (32.7)	21 (2.8)	16 (2.1)	24 (3.2)	45 (6.0) [4.5–7.9]
Other§	372	112 (30.1)	2 (0.5)	3 (0.8)	3 (0.8)	5 (1.3) [0.6–3.1]

* Total includes those predetermined as known to be pathogenic and those classified by the clinical advisory committee as clinically relevant.
† CI denotes confidence interval.
‡ Includes 36 samples determined likely to be benign by the study geneticist and 33 determined by the independent clinical advisory committee on the basis of size, gene content, inheritance, the literature, and ultrasonography findings.
§ Other indications include family history, previous pregnancy with chromosomal abnormalities, and elective decision.

Wapner, et al. December 6, 2012N Engl J Med 2012; 367:2175-2184 DOI: 10.1056/NEJMoa1203382

Risk for pathogenic and potential clinically significant microdeletions and duplications



Variants of clinical significance

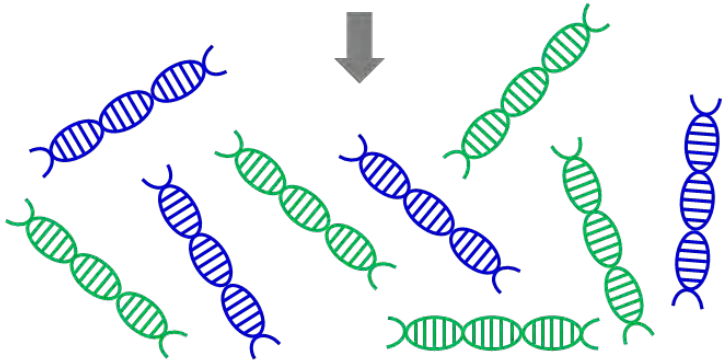
Total

Pathogenic microdeletions and duplications

NIPT

Maternal blood sample

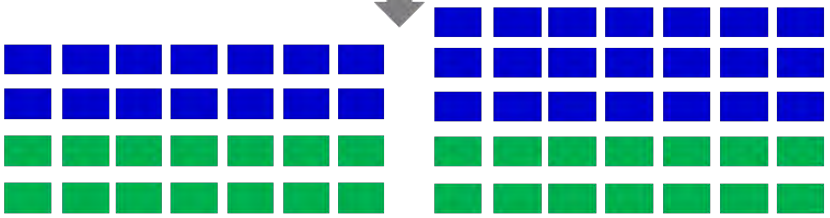
Maternal and fetal cell-free DNA



Cell-free DNA sequenced via massively parallel sequencing (MPS)

CCTAGCTCGAACCTAGCCAAGGTTAACTTAATTCCCCATCATCATATTCC
GGCCTTTAAAATTCCAATCATGTCTCATGGCCATCGTGGAAACTCTAAGGT
CCCATCATCATATTCCATGGCCATCGTGGAAACTCTAAGGTTTGACGTTAA
AGGTCCCTAGCTCGAACCTAGCCAAGGTTAACTTAATTCCCCATCTATTCC

Alignment and counting



Chromosome 21
No Aneuploidy

Chromosome 21
Aneuploidy

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Modified from Drury, et al Cell Free Fetal DNA Testing for Prenatal Diagnosis. Advances in Clinical Chemistry Vol 76, 2016

Pregnancy – NIPT high risk populations

Chromosomal Abnormality	Sensitivity (%)	95% CI (%)	Specificity (%)	95% CI (%)
Trisomy 21	**99.5**	**96.3-99.9**	**100**	**99.87-100**
Trisomy 18	**97.7**	**87.9-99.6**	**99.97**	**99.81-99.99**
Trisomy 13	**100**	**83.2-100**	**99.97**	**99.81- 99.99**

- *High sensitivity and high specificity*
- *Not reportable or no call results – increased risk of chromosomal abnormality – diagnostic testing is recommended*

Geppert, et al Prenatal Diagnosis. 2020;40:454–462.
ACOG Practice Bulleting Screening for Fetal Chromosomal Abnormalities. 2018

Pregnancy – NIPT low risk population

- *Low risk population*
- 13,043 (73.1%) were considered low-risk for aneuploidy < 35
- 3,873 that were ≥35 but had a low-risk result on a blood screening test

Chromosomal abnormality	Sensitivity % (n)	Specificity % (n)	PPV % (n)	NPV % (n)
Trisomy 21	**100 (18/18)**	**99.98 (12,815/12,818)**	**85.71 (18/21)**	**100 (12,815/12,815)**
Trisomy 18	**75 (3/4)**	**99.98 (12,829/12,832)**	**50 (3/6)**	**99.99 (12,829/12,830)**
Trisomy 13	**100 (5/5)**	**99.98 (12,828/12,831)**	**62.50 (5/8)**	**100 (12,828/12,828)**

Dar, et al American Journal of Obstetrics and Gynecology (2022), doi: https://doi.org/10.1016/j.ajog.2022.01.019

Pregnancy – NIPT

Table 3. The Effect of Maternal Age on the Positive Predictive Value of Cell-Free DNA Screening for Trisomy 21, 18, and 13 at 10 Weeks Gestation*

	Maternal Age	Age Related Risk†	Positive Predictive Value‡
Trisomy 21	20	1:804 or 12 per 10,000	38–80%
	35	1:187 or 53 per 10,000	73–95%
	40	1:51 or 196 per 10,000	91–99%
Trisomy 18	20	1:1,993 or 5 per 10,000	11–41%
	35	1:465 or 22 per 10,000	34–75%
	40	1:126 or 79 per 10,000	66–92%
Trisomy 13	20	1:6,347 or 1.6 per 10,000	5–13%
	35	1:1,481 or 7 per 10,000	17–40%
	40	1:401 or 24 per 10,000	43–71%

*Sensitivity and specificity approximately 99%

†Age related risk of aneuploidy per 10,000 pregnancies at 10 weeks gestation based on maternal age at term

‡Percent varies by laboratory

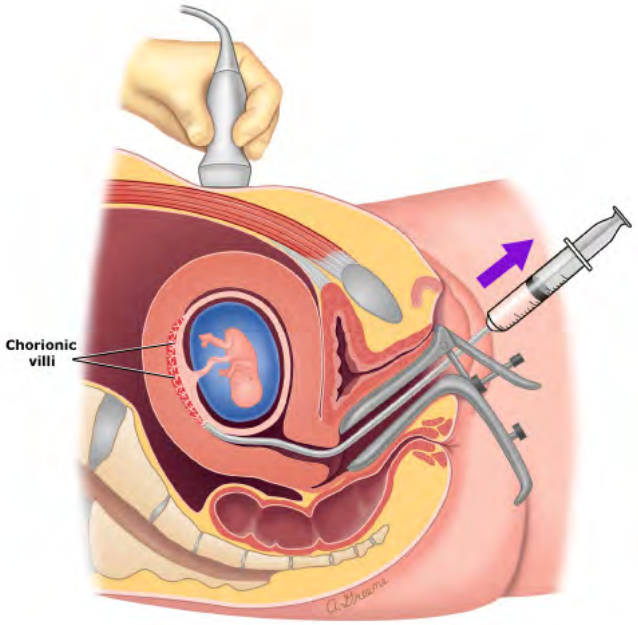
Adapted from University of North Carolina at Chapel Hill. Positive predictive value of cell free DNA calculator. Available at: https://www.med.unc.edu/mfm/nips-calc. Retrieved February 24, 2020.

- *Low positive predictive value means many false positive test results*

ACOG Practice Bulletin Screening for fetal Chromosomal Abnormalities 2018

Pregnancy – Diagnostic Testing

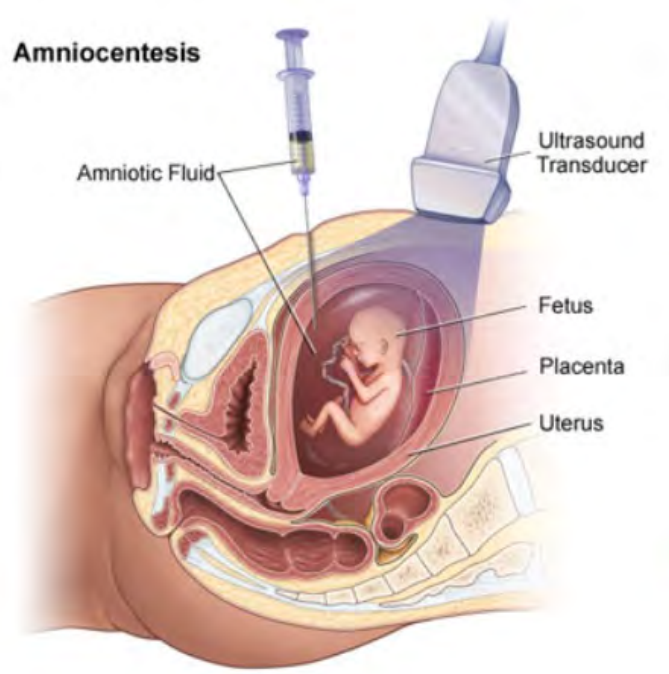
- *Chorionic villus sampling*
- *Karyotype and microarray*
- *Detects 99.8% of trisomies, pathogenic microdeletions/duplications, clinically significant variants, point mutations, chromosomal rearrangements and de novo mutations*
- *Performed between 10-13 weeks*
- *Miscarriage rate overall - 0.5-3.0%*
- *Procedure-related risk of miscarriage 0.22% =1/500*



ACOG Committee Opinion Preimplantation Genetic Testing 2020
Akolekar, et al.Ultrasound Obstet Gynecol 2015; 45: 16–26

Pregnancy – Diagnostic Testing

- *Amniocentesis*
- *Karyotype preferred for balanced translocations and triploidy*
- *Performed between 15-20 weeks*
- *Miscarriage rate overall - 0.5-1.0%*
- *Procedure-related risk of miscarriage 0.11% =1/900*



ACOG Committee Opinion Preimplantation Genetic Testing 2020
Akolekar, et al.Ultrasound Obstet Gynecol 2015; 45: 16–26
Image courtesy -UCLA MFM website

Pregnancy – Prenatal testing

- *Testing for chromosomal abnormalities should be an informed patient choice based on adequate and accurate information*
- *All patients should be offered both screening and diagnostic tests, and all patients have the right to accept or decline testing after counseling*
- *Due to the background rate of pathogenic microdeletions/duplications and clinically significant variants (2.5%) - chromosomal microarray analysis through diagnostic testing should be offered to all women regardless of age*
- *Diagnostic testing/chromosomal microarray is recommended for a fetus with a structural abnormality on ultrasound*
- *Procedure related risk of loss (0.11-0.22%) should be addressed with the patient*
- *At this time, NIPT is a screening test best suited ONLY for identification of aneuploidies (Trisomy 21, 18. and 13?) in high- risk populations*

COMMITTEE OPINION Number 682 Committee on Genetics Society for Maternal–Fetal Medicine Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology 2020

Preimplantation Genetic Testing – Now I am pregnant, what's next?

- *A normal or negative PGT result is not a guarantee of a newborn without genetic abnormalities.*
- *Traditional diagnostic testing or screening for aneuploidy should be offered to all patients who have PGT-A, in accordance to recommendations for all pregnant patients*
- *Confirmation of preimplantation genetic testing – monogenic results with CVS or amniocentesis should be offered*
- *PGT-SR to detect structural chromosomal abnormalities such as translocations - Confirmation of preimplantation genetic testing – and confirmation of unaffected or balanced translocation in offspring via CVS or amniocentesis should be offered,*
- *Limitations of PGT – do not detect microdeletions and microduplications, de novo variants, and imprinting disorders*
- ***PGT and NIPT remain only as screening tests!***

Genetic testing - Beyond

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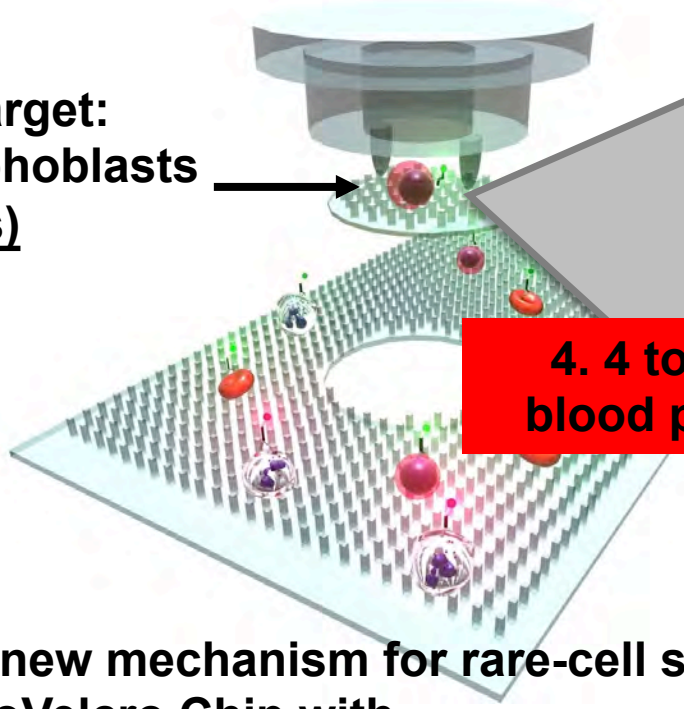
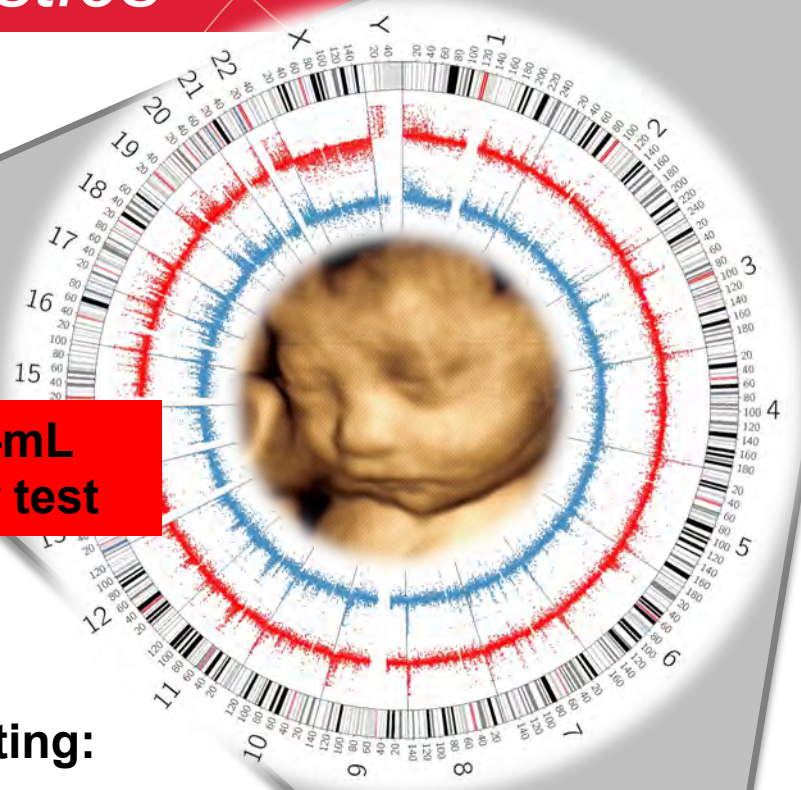
Gavriil P, et al 1993 Pediatr Pathol 13:453-462
Zhang Y, et al 2008 Proteomics 8:4344-4356
Collier AC, et al 2009 J Steroid Biochem Mol Biol 116:21-28
Dolle Piane L, et al 2008 Reproductive Sciences 15:81A-81A

Next-Generation Prenatal Diagnostics

1. Target: Trophoblasts (TBs)



4. 4 to 8-mL blood per test



2. A new mechanism for rare-cell sorting: NanoVelcro Chip with imprinted PLGA nanostructures

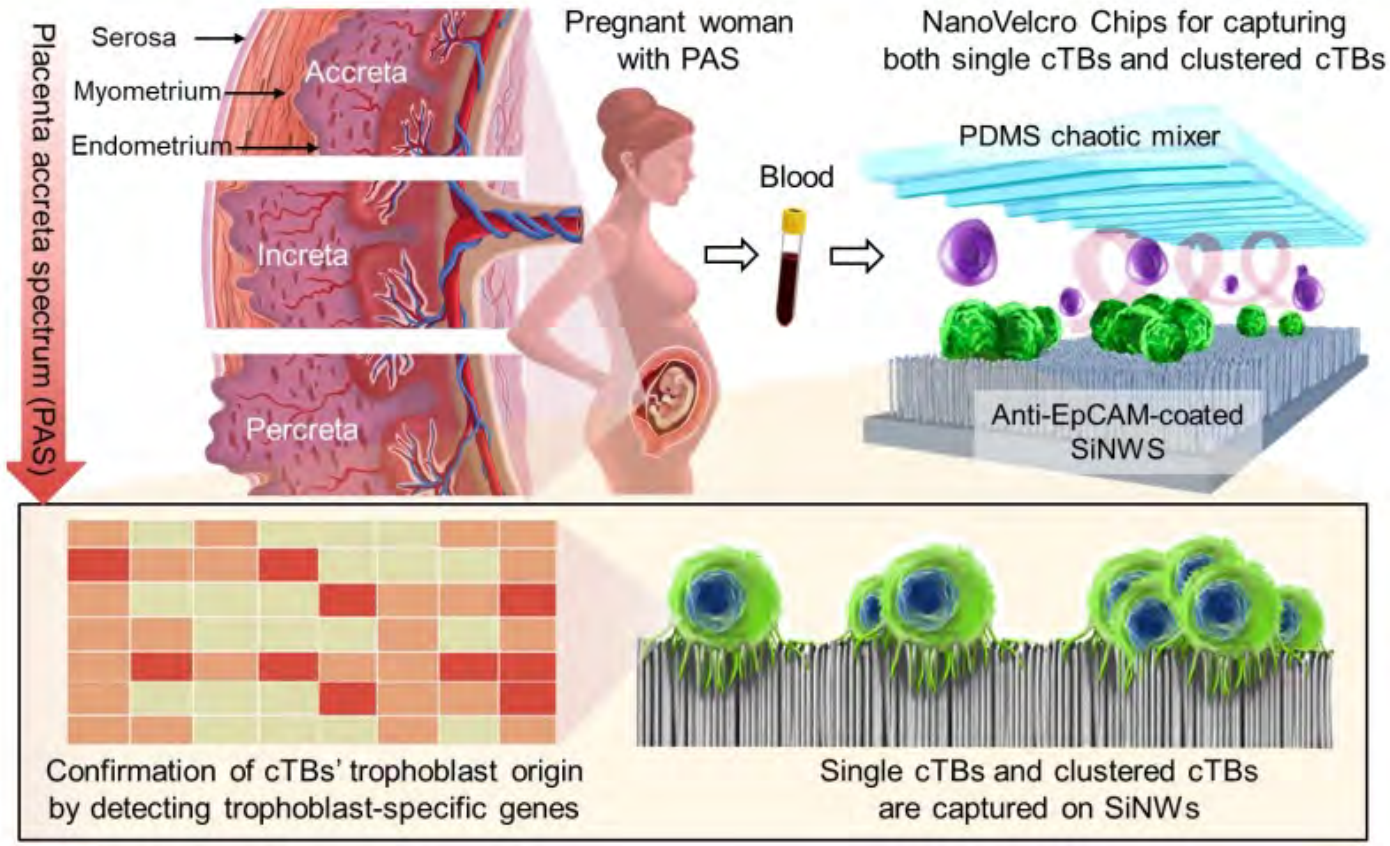
3. Three types of downstream analyses: FISH, microarray, and WGS

Cedars Sinai UCLA Crump Institute for Molecular Imaging

Hou S...Pisarska, Zhu, Tseng. ACS Nano. 2017 Aug 22;11(8)

Circulating Trophoblast Cell Clusters for Early Detection of Placenta Accreta Spectrum Disorder

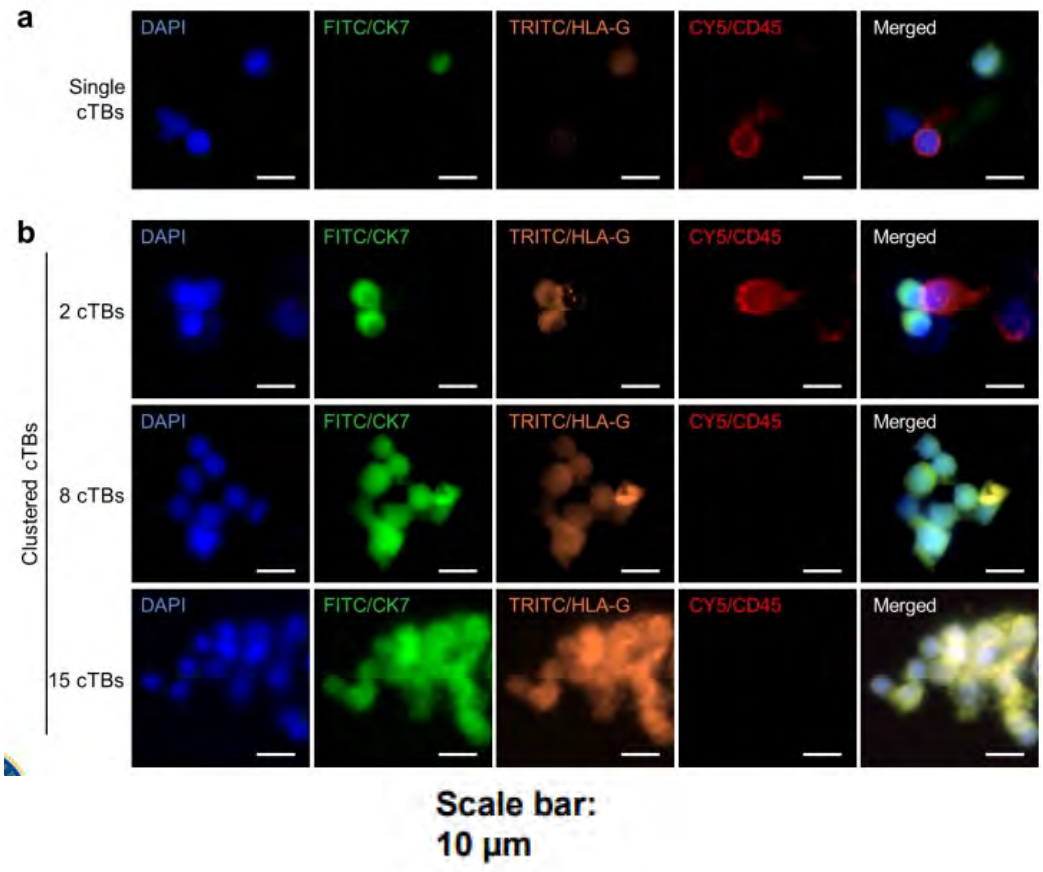
NanoVelcro Chips for Detecting cTBs and cTB clusters

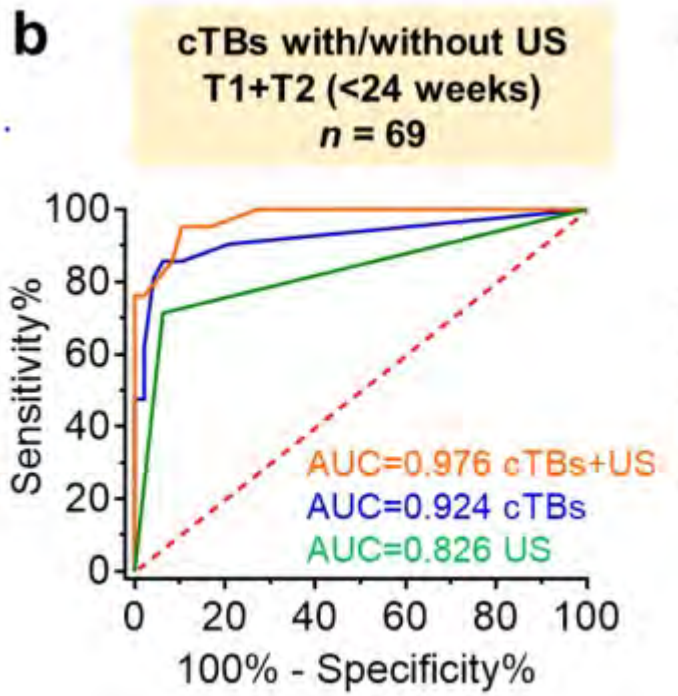


Cedars Sinai UCLA Crump Institute for Molecular Imaging

Afshar, Zhu, Pisarska, Tseng. Nat Commun 2021

Circulating Trophoblast Cell Clusters for Early Detection of Placenta Accreta Spectrum Disorder

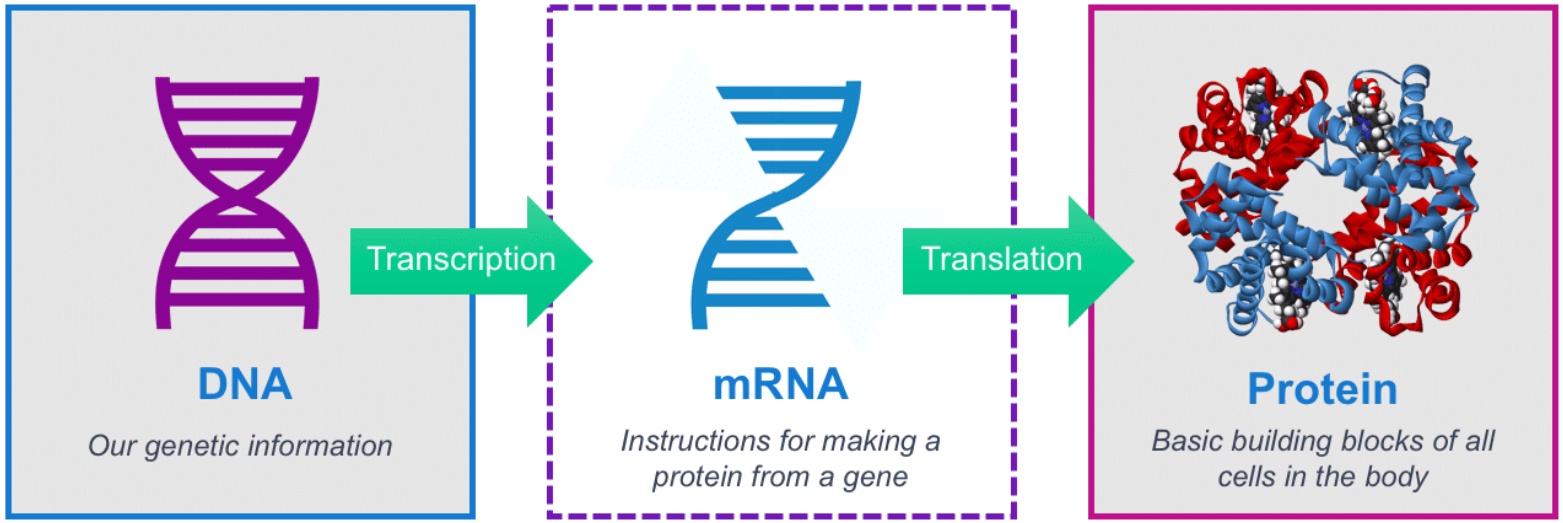




Cedars Sinai UCLA Crump Institute for Molecular Imaging

Afshar, Zhu, Pisarska, Tseng. Nat Commun 2021

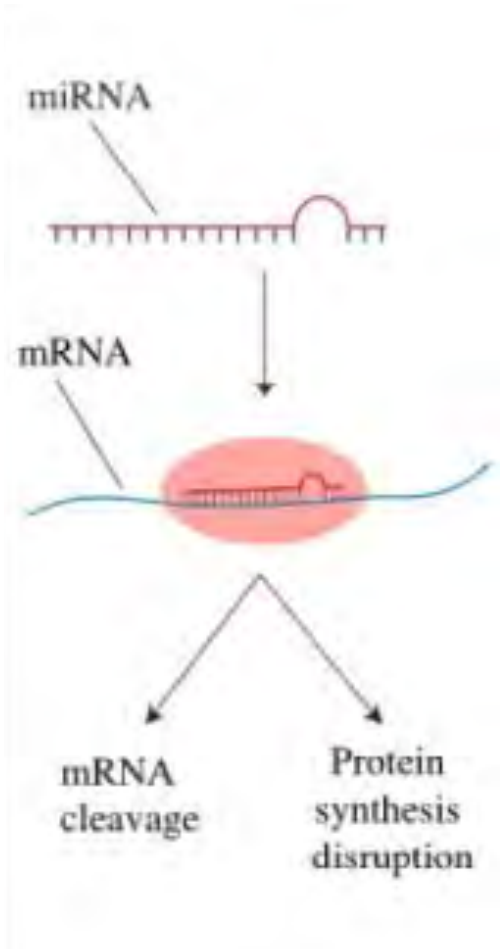
Transcriptome



- *DNA is **transcribed** to RNA which is **translated** to protein*
- *The **transcriptome** is the total messenger RNA expressed in a given tissue*
- *Transcription is regulated by epigenetics: genes can be turned on and off*
- *These epigenetic changes make up the **epigenome***

https://translate.bio/wp-content/uploads/2018/06/Central-Dogma-for-Web-4-2.png

Post-transcriptional regulation



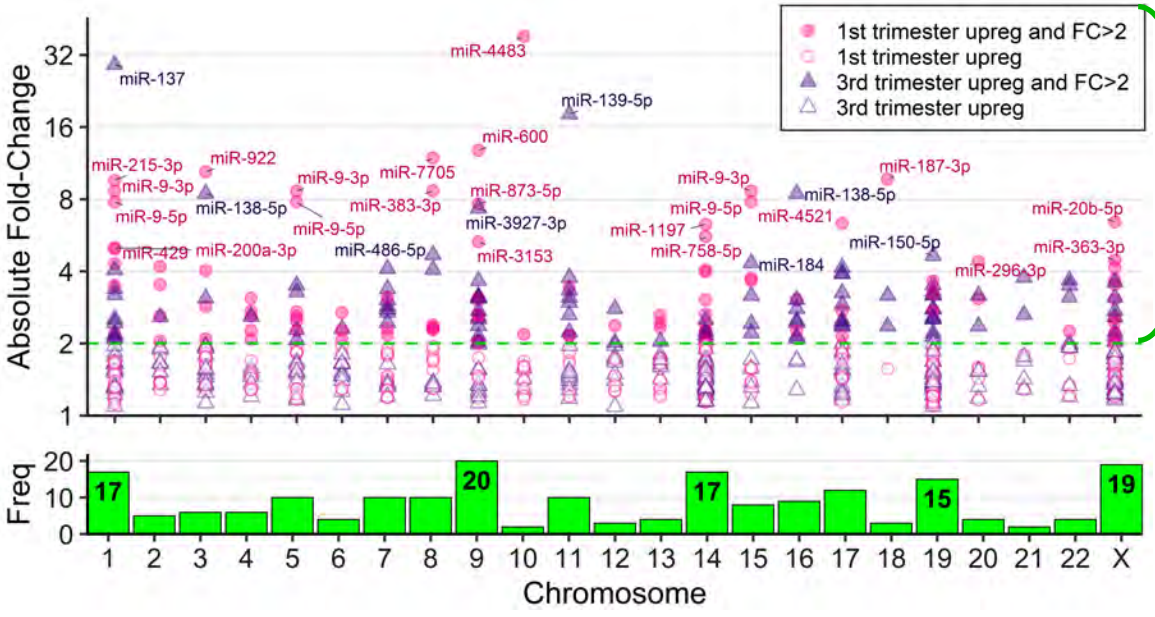
- *miRNAs are short, single-stranded RNA (22 nucleotides)*
- *They bind to RNA transcripts, preventing translation*
- *Stable in the circulation and may be used as markers to predict disease*

Morales-Prieto et al. (2012), *Journal of Reproductive Immunology*
Epigenetics and the human brain, *NLM Openi*

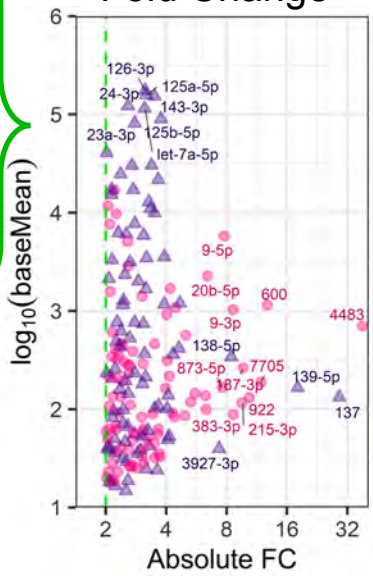
Normative Epigenome

180 differentially expressed miRNAs: FDR<0.05, FC>2, baseMean>10

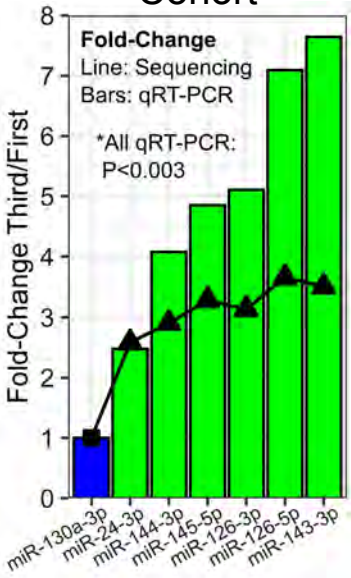
Genome Distribution



Expression vs Fold Change



Validation with qRT-PCR in an Independent Cohort



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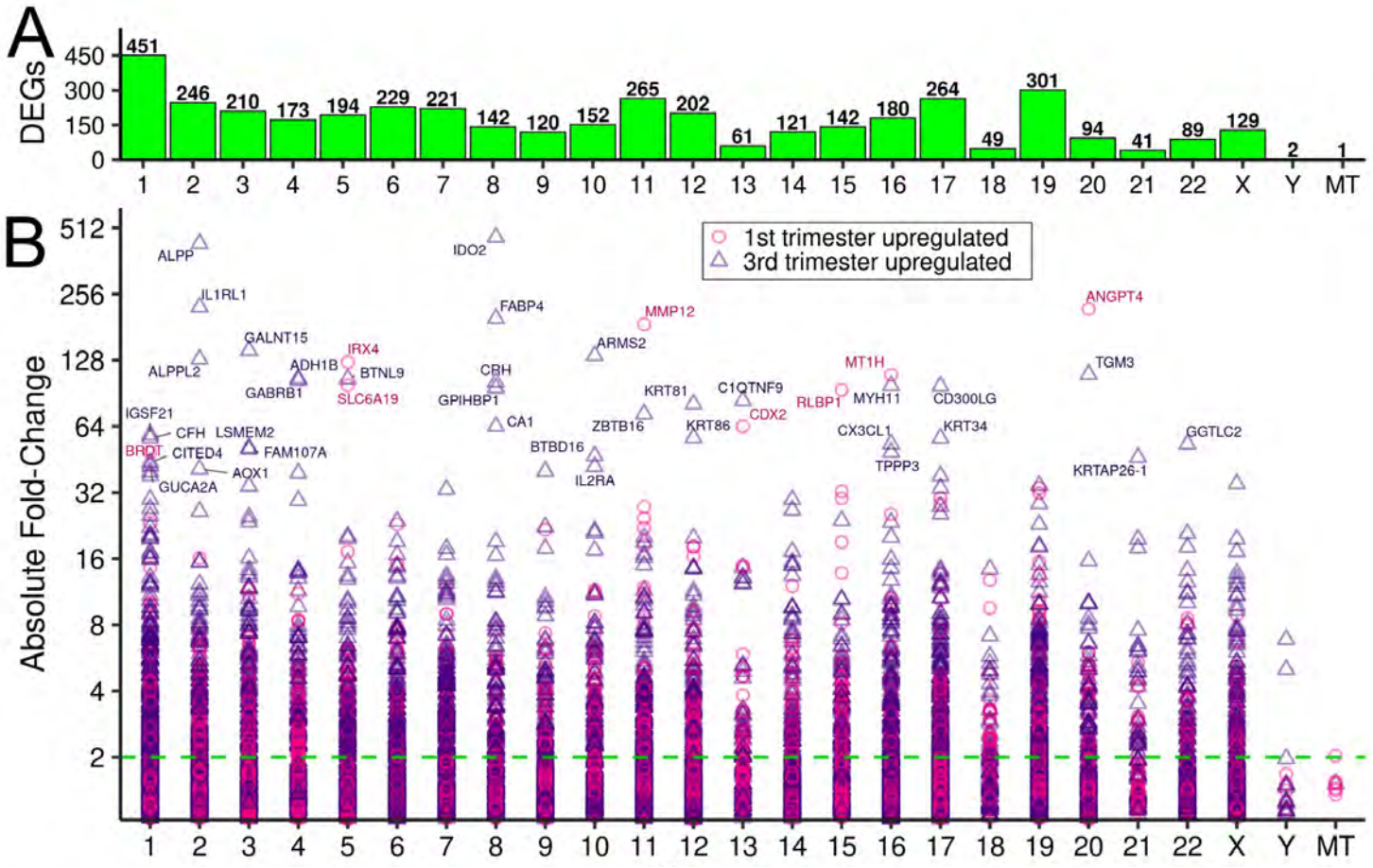
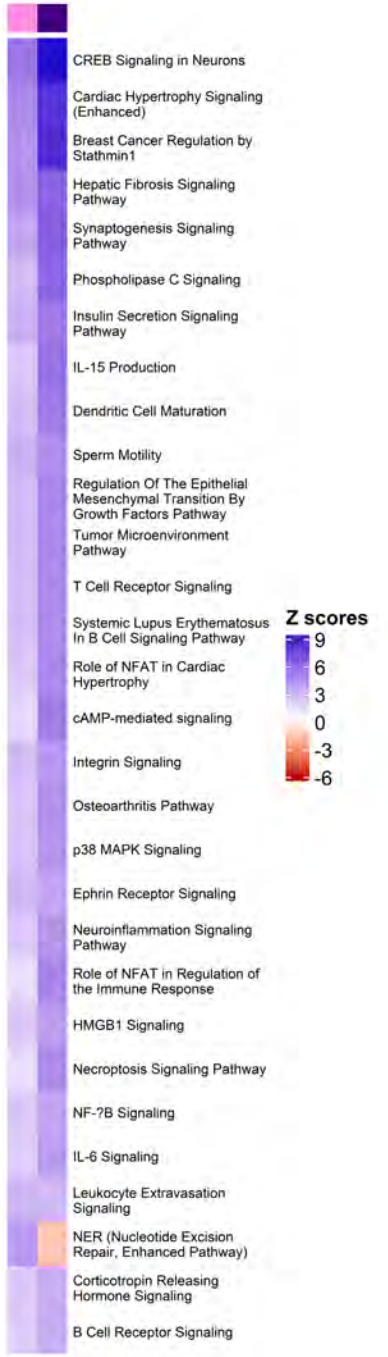
Gonzalez, Pisarska et al. (2021), *Epigenomics*

Normative transcriptome (mRNAs)





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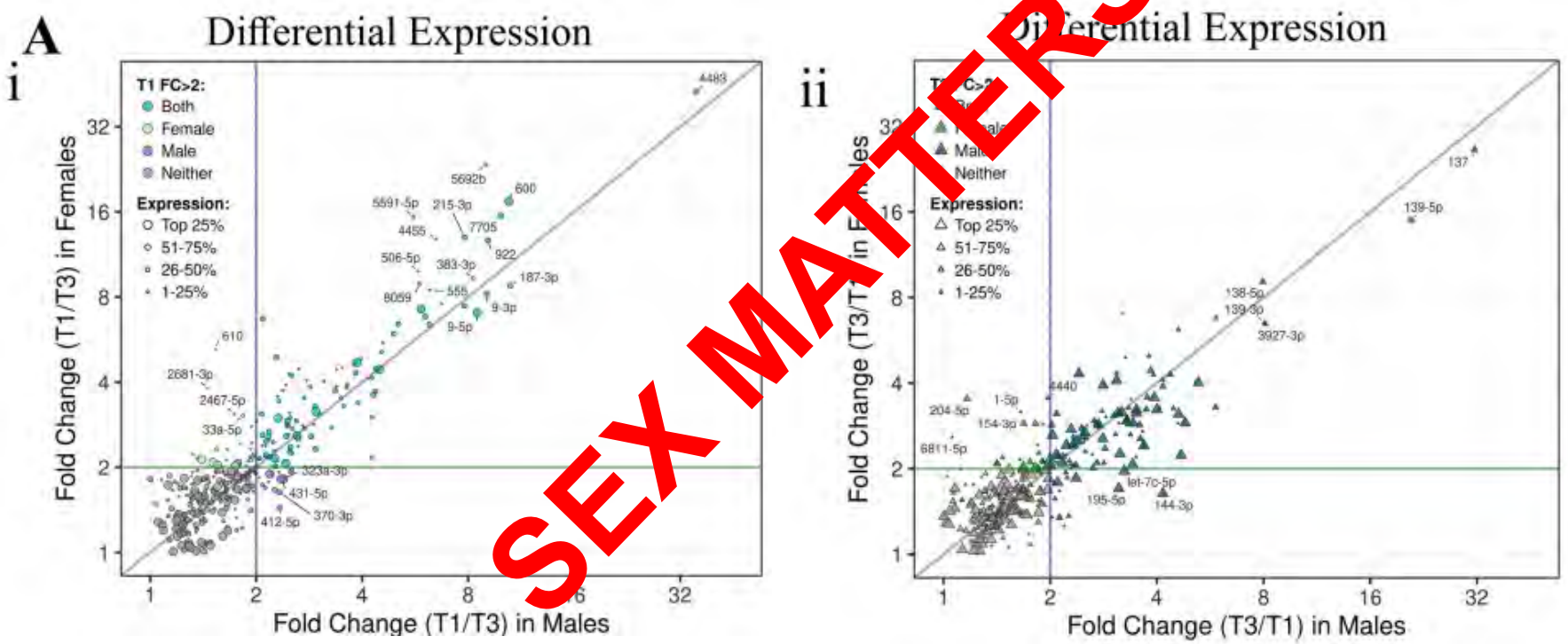
Gonzalez, et al, BOR 2023

Sex differences in miRNAs across gestation



SEX MATTERS

Flowers, et al Biology of Reproduction, 2022, 1–17 https://doi.org/10.1093/biolre/ioab221

Conclusion

- ***Preconception***
  - *Current ACOG recommendations are limited – based on advances in NGS and recent recommendations by ACMG, carrier screening should screen a minimum of 74-112 genetic conditions*
  - *When utilizing commercially available genetic screening – the same panels should be performed for both genetic parents*
- ***Prenatal***
  - *IVF/PGT testing does not replace prenatal genetic counseling with genetic screening and/or diagnostic testing*
  - *NIPT is currently only recommended for high-risk populations for aneuploidy screening (Trisomy 21, 18, and ?13)*
  - *Pathogenic microdeletions/duplications and clinically significant variants affect 2.5% of pregnancies regardless of maternal age*
  - *Diagnostic testing through CVS or amniocentesis should be offered to pregnant patients regardless of age and previous genetic screening*
- ***Future***

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  - Stephen Turner PhD
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Helping Hand of Los Angeles, Inc.

Our patients for participating in our studies to improve outcomes!

Cedars Sinai

Potpourri of

Palliative Care Pearls for

Ob/Gyn Providers

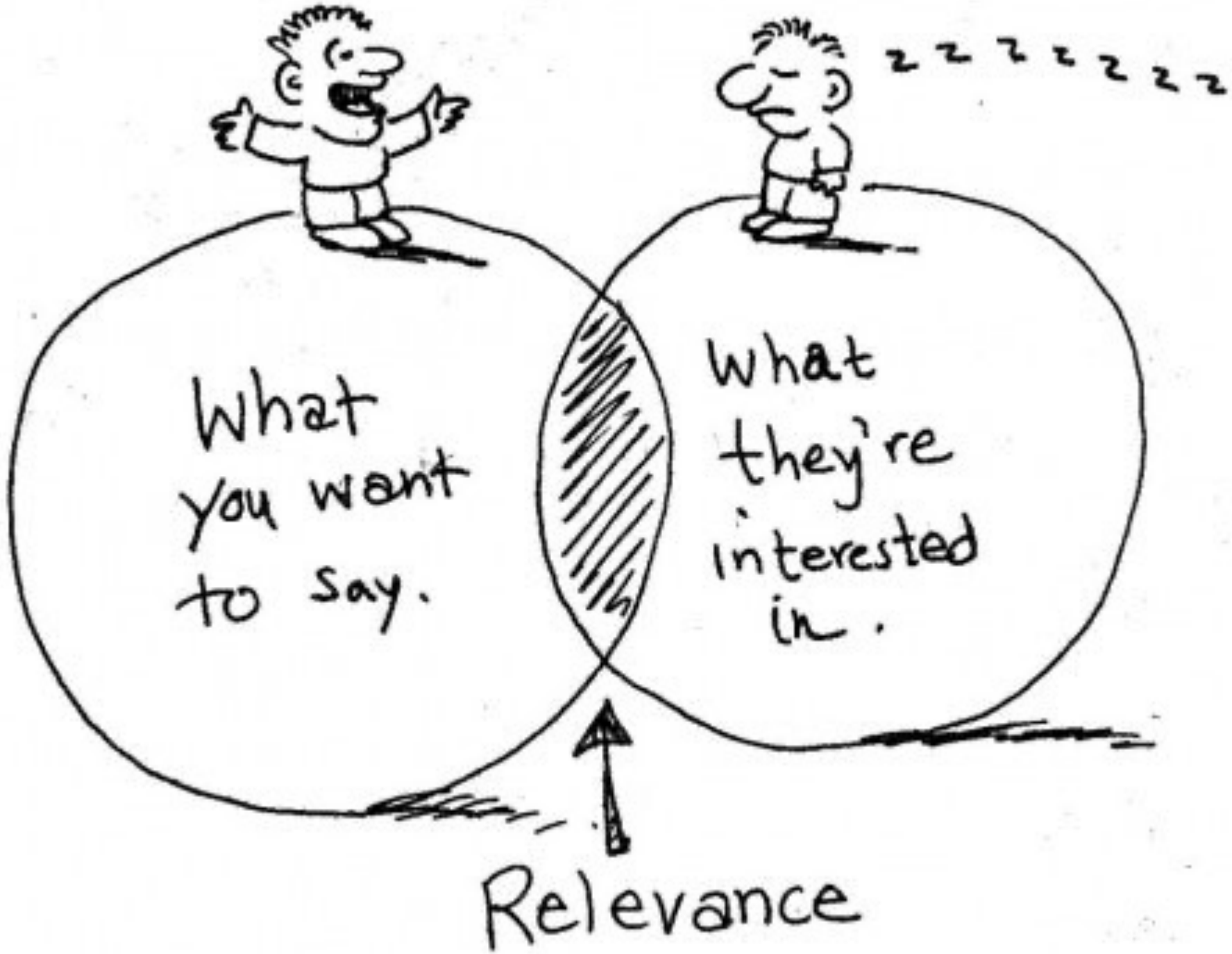
Carolyn Lefkowits MD

University of Colorado
Ob/Gyn Vail Conference

February 20 2024

Disclosures

- Vertex pharmaceuticals ad board


What you want to say.
What they're interested in.
Relevance

Objectives

- Define palliative care and differentiate it from hospice care
- List the requirements for medical decision-making capacity
- Differentiate advance care planning from advance directives
- Utilize best case – worst case – most likely case framework for discussing prognosis
- Incorporate elucidation of patient values into shared decision-making
- Align post-operative opioid prescribing practices with national recommendations

Outline

- What is palliative care?
- Advance care planning
- Complex communication
- Symptom management

Outline

- What is palliative care?
- Advance care planning
- Complex communication
- Symptom management

What is Palliative Care?

Palliative care is specialized medical care for people with serious illnesses. This type of care is focused on providing patients with relief from the symptoms, pain and stress of a serious illness. The goal is to improve quality of life for both the patient and the family.

-Center to Advance Palliative Care (CAPC)

“an extra layer of support”

Palliative Care vs Hospice

- Palliative care is **NOT** synonymous with end of life care or hospice

- Palliative care **CAN** be offered concurrently with curative intent therapy

What services does palliative care provide?

- Assistance with Advance Care Planning
- Communication support - high stakes conversations
- Assessment & treatment of Symptoms
- Psychosocial, spiritual & bereavement support

Primary vs. Specialty Palliative Care

PRIMARY PALLIATIVE CARE

- Basic management pain & other physical symptoms
- Basic management depression & anxiety
- Basic discussions about: prognosis, goals of care, suffering, code status

SPECIALTY PALLIATIVE CARE

- Management refractory pain & other symptoms
- Management complex depression, anxiety, grief, existential distress
- Conflict resolution regarding goals of care
- Addressing cases of near futility

Quill & Abernethy NEJM 2013

"He's our new Palliative Specialist!"

Outline

- What is palliative care?
- Advance care planning
  - Capacity
  - ACP vs Advance directives
  - Code status
- Complex communication
- Symptom management

Medical Decision-Making Capacity

What it is

- Temporal
- Situational
- Requirements
  - Understand relevant information about proposed evaluation/treatment
  - Appreciate their medical situation
  - Use reason to make a decision
  - Communicate a consistent choice

What it isn't

- Agreeing with our recommendation
- Making the same choice we think we'd make for ourselves
- Making what we or patient's friends/family consider a "good" decision

Medical Decision-Making Capacity

Who determines it?

Any licensed physician

Options for next steps if concern for incapacity

- Obtain collateral information
- Consider family/care coordination meeting
- Communicate with PCP
- Consider consult – SW, psychology, palliative care

Advance Care Planning vs Advance Directive

Advance Care Planning (ACP): *process* that supports adults at any age or stage of health in understanding and sharing personal values, life goals and preferences regarding future medical care

Advance Directives (AD): *written statement* of a person's wishes regarding medical treatment

Sudore et al JPSM 2017

3 Types of Advance Directives

1. Medical Power of Attorney: document in which a patient appoints someone to make decisions about her medical care if she cannot make those decisions
   - AKA MD POA, Durable POA for Healthcare (DPAHC), Healthcare Proxy
   - CO is an **all interested parties state**

2. Living Will: document in which a patient's wishes regarding administration of medical treatment are described if patient becomes unable to communicate

3. Physician Orders for Life-Sustaining Treatment (POLST): portable document of provider orders regarding patient preferences for resuscitation and other interventions
   - AKA MOLST, MOST, POST

Code Status

Two flavors of code status discussions

1. Capturing pre-existing preferences (routine)
2. Broader discussion in context of prognosis, goals of care (prn)

Routine Code Status Assessment Language

”I want to ask you something I ask all my patients. We don’t expect this to happen during this hospitalization, but

Normalize the ask

have you ever thought about, if your heart or lungs were to stop working, you were unconscious and not breathing or heart not beating, so you had essentially passed away,

In this circumstance, patient has essentially passed away

Would you want your medical team to perform CPR in an attempt to bring you back or would you prefer to be allowed to pass peacefully”

CPR as an attempt to bring patient back; include alternative to CPR

Critical for patients & families to understand:

in the absence of direction to the contrary,

the **default** in our healthcare system is

to proceed with **all available invasive interventions**

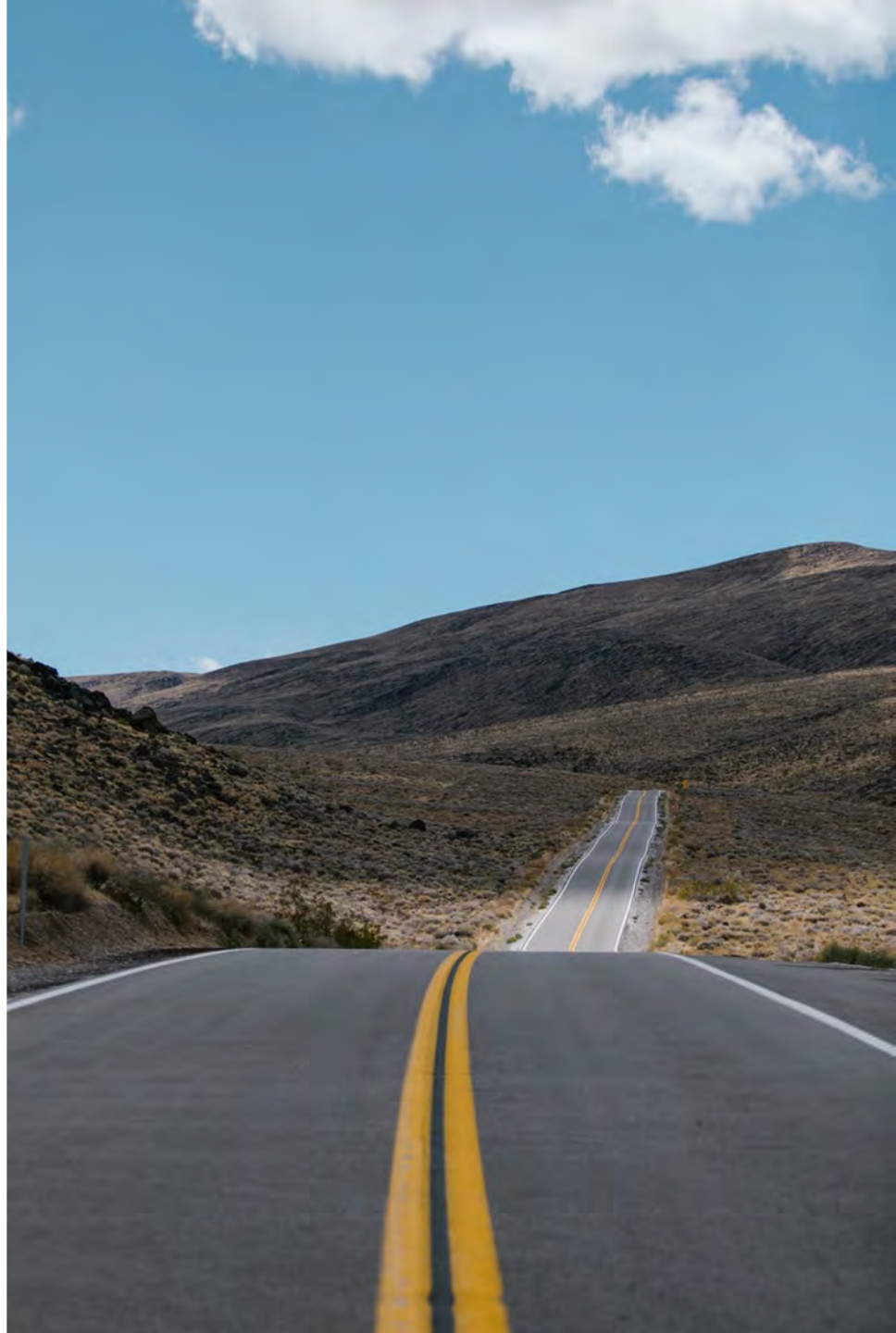
Outline

- What is palliative care?
- Advance care planning
- Complex communication
  - prognosis
  - shared decision-making
- Symptom management

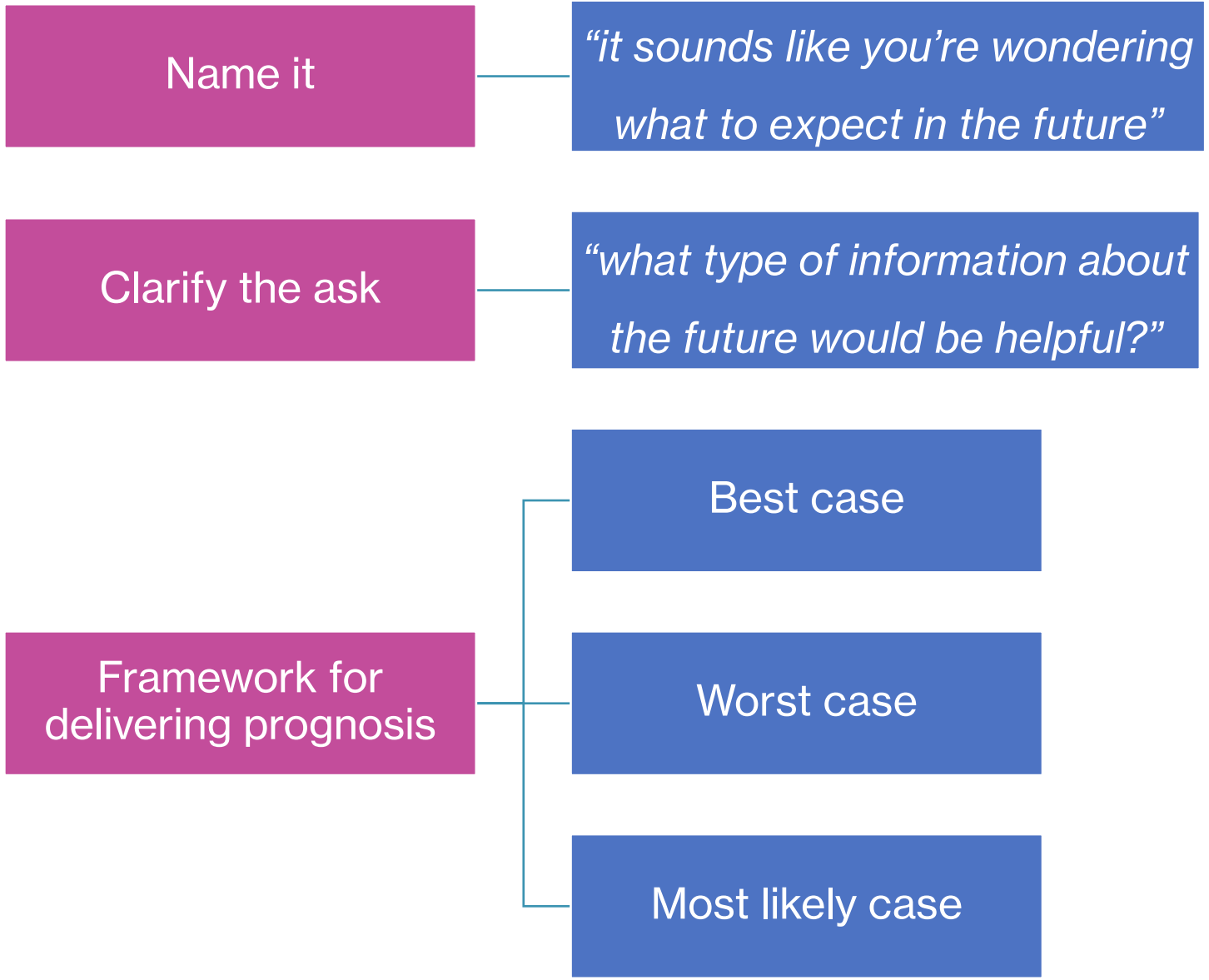
Pro Gnōsis

Prognosis = Future

- How long might I live?
- When can I leave the hospital?
- Will my pelvic pain ever go away?
- Will I always leak urine?
- Will I have another miscarriage?



Structured Approach to Prognosis Discussion



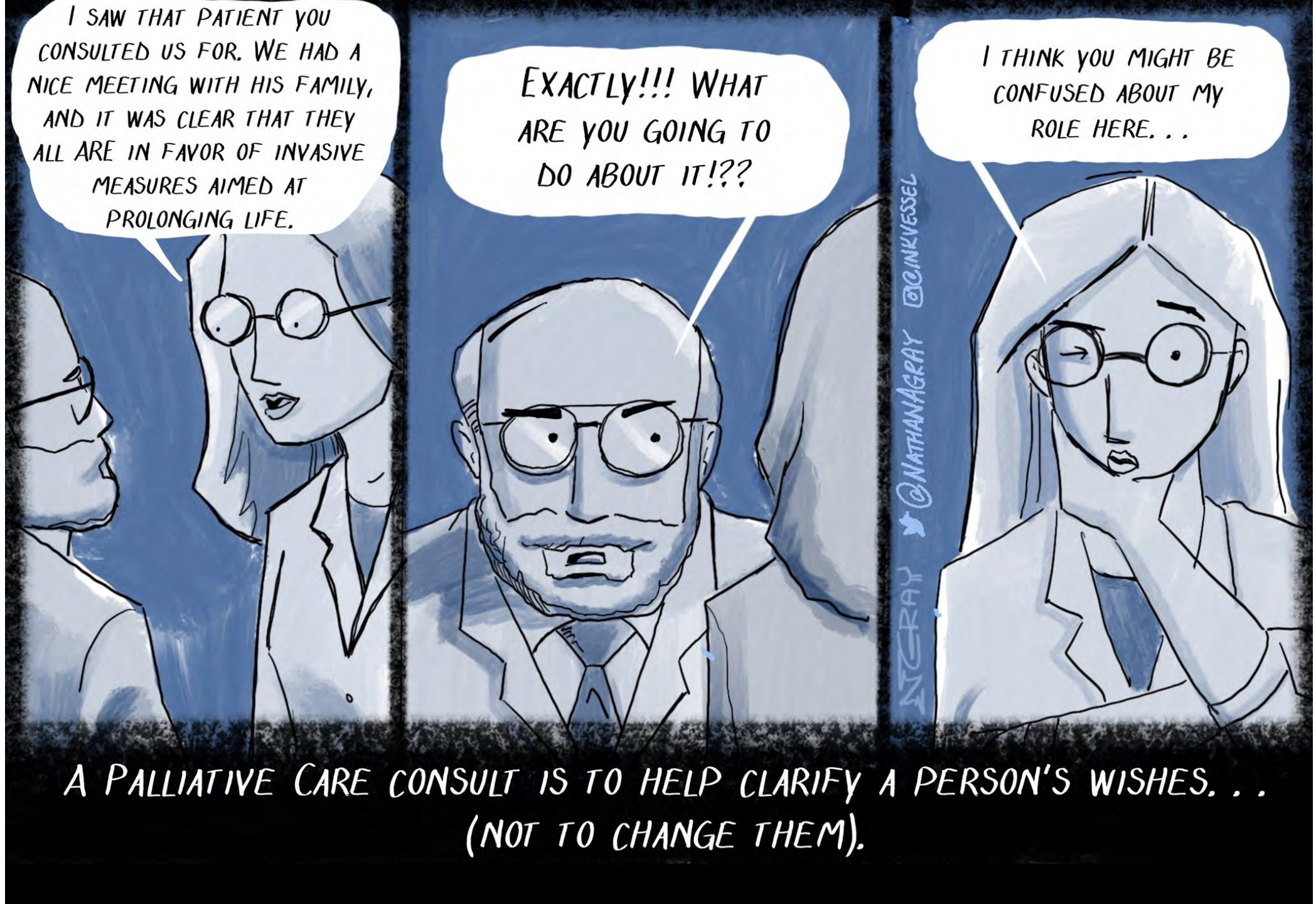
Inability to make perfect predictions is not an excuse to avoid making any predictions

Shared decision-making

"process in which clinicians and patients work together to make decisions ... and care plans based on clinical evidence that balances risks and expected outcomes **with patient preferences and values**"

What it is **NOT**

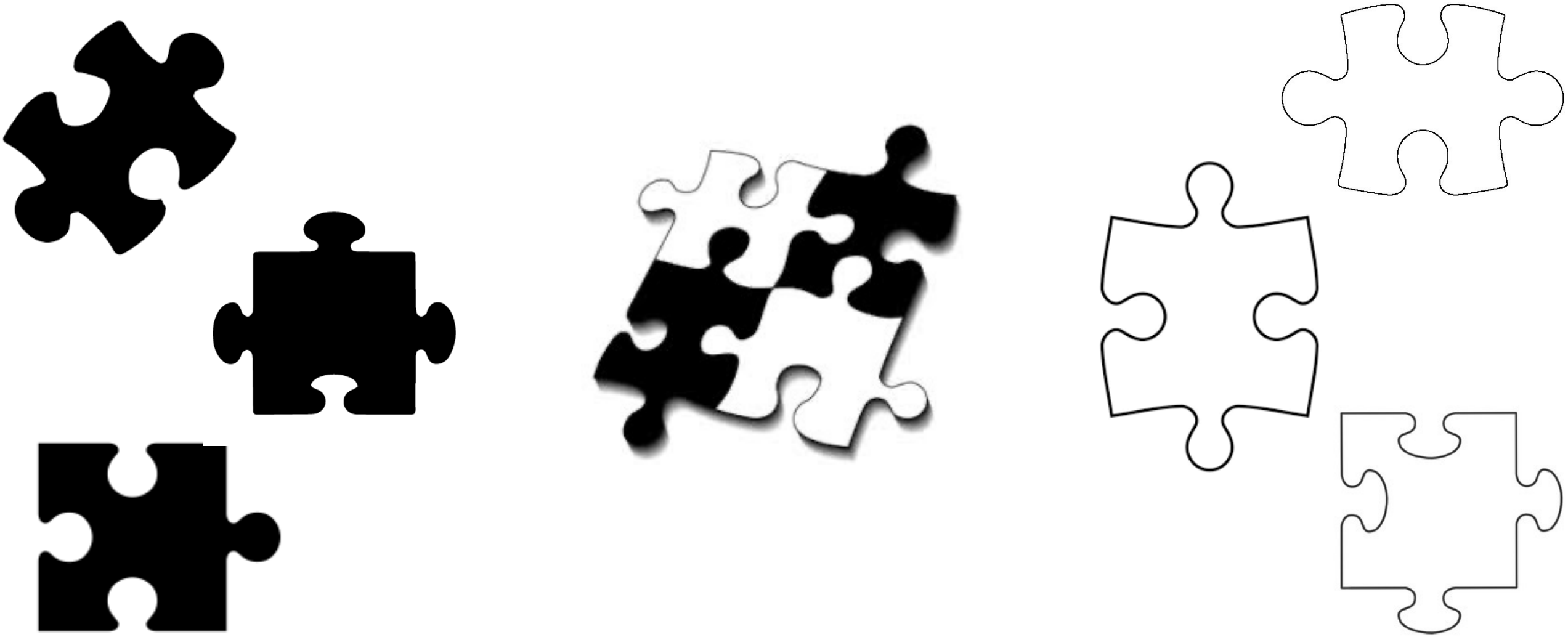
- Giving patients a list of options and asking them to choose
- Shepherding patient toward the "right" option


I SAW THAT PATIENT YOU CONSULTED US FOR. WE HAD A NICE MEETING WITH HIS FAMILY, AND IT WAS CLEAR THAT THEY ALL ARE IN FAVOR OF INVASIVE MEASURES AIMED AT PROLONGING LIFE.
EXACTLY!!! WHAT ARE YOU GOING TO DO ABOUT IT!??
I THINK YOU MIGHT BE CONFUSED ABOUT MY ROLE HERE...
NGRAY @NATHANAGRAY @INKVESSEL
A PALLIATIVE CARE CONSULT IS TO HELP CLARIFY A PERSON'S WISHES... (NOT TO CHANGE THEM).

Shared decision-making: goodness of fit

Patient goals & values

Management options



Exploring patient values/priorities

“Thinking about the future with [your pelvic pain] – what do you hope for most?”

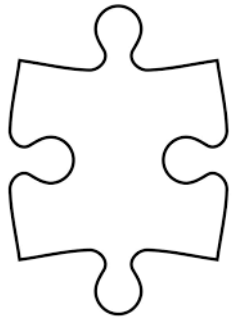
”What bothers you the most about [your hot flashes]?”

“What do you enjoy doing that [your prolapse] interferes with?”

“Are there certain side effects that would be definitely unacceptable to you, where you would feel like the treatment was worse than the problem?”

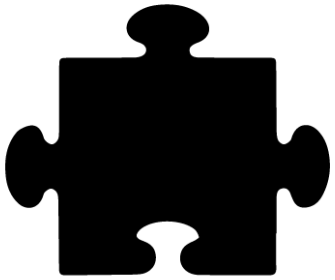
“[Given what I’ve told you so far about our treatment options], what factors might be most important to you in choosing between those options”

Shared decision-making: make a recommendation



"Given what we've discussed about options for management

COMBINED WITH



what you've told me about your values and priorities

I'D RECOMMEND

[whatever management path you recommend]"

Outline

- What is palliative care?
- Advance care planning
- Complex communication
- Symptom management
  - General pearls
  - Opioids

Symptom management pearls

1. Good symptom management starts with good symptom assessment
2. Try to identify etiology of symptom and treat to etiology
3. A constant symptom should be treated with a constant (scheduled) medication
4. Avoid two prn medications for the same indication
5. When assessing efficacy, focus on function

Four Pillars of CO's CURE

1. Limiting opioid usage
2. Using alternatives to opioids (ALTOs) for the treatment of pain
3. Implementing harm reduction strategies
4. Improving treatment and referral of patients with opioid use disorder (OUD)

https://cha.com/wp-content/uploads/2021/05/CURE_ACOG_final.pdf

CO's CURE Best Practices

Work with patients to establish realistic goals and expectations for management of pain

Opioids for Post-operative Pain

Goals for treating acute post-op pain

- Provide adequate pain control: **focus on function!**
- Minimize morbidity
- Return patients safely to opioid independence/baseline use
- Prevent misuse & diversion

“I wish I could tell you we’ll be able to get you pain free. Our goal is to get the pain to a place where it’s tolerable enough that you can do the things you need to go in order to get better, like eat, sleep and walk”

CO's CURE Best Practices

Establish standard prescribing practices and default limits for post-operative opioid prescribing

Case: 45yo P2 pre-op for TAH/BS for 24 week fibroid uterus

- PMH/PSH tobacco use, obesity, no prior surgeries
- SHx married, lawyer
- Current meds: none

How many tabs of 5mg oxycodone would you anticipate prescribing for her at discharge?

1. 0
2. 10
3. 15
4. 20
5. 30

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- SHx married, lawyer
- Current meds: none

How many tabs of 5mg oxycodone would you anticipate prescribing for her at discharge?

1. 0
2. 10
3. 15
4. 20
5. 30

Recommendations for Post-op Opioid Prescribing*

	Overton et al JACS 2018 (Hopkins)	Michigan Opioid Prescribing Engagement Network (OPEN)	Colorado's CURE
MIS or vaginal hysterectomy	0-10	0-15	0-15
Abdominal hysterectomy	0-20	0-20	0-20
Diagnostic laparoscopy			0-10
H/S D&C			0

*number of tabs 5mg oxycodone or equivalent

CO's CURE Best Practices

Order a bowel regimen to prevent Opioid Induced Constipation (OIC)

in pts receiving opioids unless contraindicated

CO's CURE Best Practices

Opioids are NOT recommended as first line analgesia for the following conditions

- Chronic Pelvic Pain
- Endometriosis
- Dysmenorrha
- Dyspareunia
- Ovarian cysts
- Vulvodynia
- 1st trimester miscarriage
- Pain after uncomplicated vaginal delivery

What percentage of Ob/Gyns report prescribing opioids for endometriosis?

1. 5%
2. 10%
3. 25%
4. 50%

What percentage of Ob/Gyns report prescribing opioids for endometriosis?

1. 5%
2. 10%
3. 25%
4. 50%

Opioids for Chronic Non-Malignant Pain

Percent prescribing opioids by indication (n=179 ob/gyns)

- Ovarian cysts 30%
- Endometriosis 24%
- Chronic pelvic pain unknown cause 18%

Madsen et al Green Journal 2018

CO's CURE Best Practices

Tramadol is not a safe opioid. It carries significant side effects and has been associated with significant rates of long-term opioid use

Common Side Effects of Tramadol

Dizziness

Drowsiness

Constipation

Nausea or vomiting

Headache

CO's CURE Best Practices

Avoid or limit if avoidance is not possible prescription or co-adminstration of opioids with barbiturates, benzos, gabapentinoids and other CNS depressants

Opioids
and
Benzodiazepines
The New FDA Black Box Warning

Please identify one thing you learned that you might apply in your clinical practice

Questions?

How Infertility and Treatments Can Affect Human Placenta Function

Margareta D. Pisarska, M.D.

Director, Division of Reproductive Endocrinology and Infertility

Director, Center for Reproductive Medicine

Professor, Cedars-Sinai Medical Center

David Geffen School of Medicine at UCLA

Cedars Sinai

cedars-sinai.org

Disclosures

- *Ferring*
- *Natara*

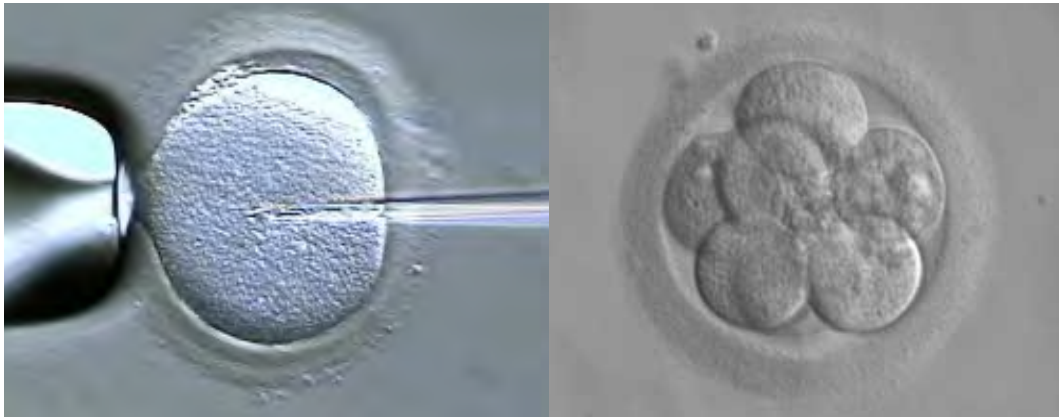
Infertility And Treatment Options

Infertility affects up to 15% of couples

Ovarian Stimulation/IUI

4.6% live births in US

In Vitro Fertilization



1.9% live births in US
8 million babies born worldwide

Cedars Sinai

Pisarska, et al. *J Clin Endocrinol Metab,* 2018
National Health Statistics Reports 2018
CDC, National Center for Health Statistics 2017

Outcomes based on fertility diagnosis

- *Significant difference in maternal age and race*
- *Infertility increases risk for cesarean section*
- *Conceptions from infertile couples deliver earlier*

	Infertile N=277	Fertile N=3016	P-value
Maternal Age, years	37.4±5.3	31.5±5.3	<0.0001
Maternal Race, n(%)			0.023
White	193 (69.9)	2066 (68.8)	
Black- or African-American	16 (15.8)	287 (9.6)	
Asian or Asian-American	49 (17.8)	391 (13.0)	
Other	18 (6.5)	260 (8.7)	
BMI, kg/m^2	23.3±4.6	23.0±4.6	0.3211
Mode of Conception, n(%)			<0.0001
IVF	136 (49.1)	4 (0.13)	
NIFT	73 (26.4)	4 (0.13)	
Presumed Spontaneous	68 (24.5)	3008 (99.7)	
Cesarean Delivery, n(%)	142 (51.8)	1078 (36.1)	<0.001
Gestational age, weeks	38.9±2.3	39.4±1.7	<0.0001
Birth weight, grams[c]	3268±634	3317±510	0.1378

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Wang, et al . J Matern Fetal Neonatal Med 2018

vAMA

- *ART were significantly older*
- *More likely to be white*
- *More likely to be nulliparous*
- *Significantly increased risk for cesarean delivery*
- *Risk of retained placenta was also significantly higher*

TABLE 1

Maternal characteristics and maternal and fetal outcomes in singleton gestations conceived either spontaneously or with assisted reproductive technology (ART).

Variable	Spontaneous (n = 193)	ART (n = 185)	*P* value
Maternal characteristic			
Age (y), mean	45.6 ± 0.1	47.0 ± 2.3	<.05
Race/ethnicity, % white	75.6	88.1	<.002
Parity	1.2 ± 1.8	0.4 ± 0.9	<.001
Maternal outcome			
Postpartum hemorrhage, %	3.1	5.9	NS
Estimated blood loss (mL)			
Vaginal delivery	303 ± 104	324 ± 116	NS
Cesarean delivery	730 ± 284	713 ± 137	NS
Retained placenta, %	0	2.7	<.02
Transfusion, %	2.1	1.1	NS
Hysterectomy, %	0	0.5	NS
Rate of ICU admission, %	0	1.1	NS
Length of stay (d), mean	3.2 ± 2.2	4.2 ± 3.9	<.01
Total CD, %	49.7	75.1	<.001
Primary CD	35.3	71.3	
Repeat CD	22.2	13.5	
Fetal outcome			
Gestational age, wk	38.9 ± 2.4	38.9 ± 2.4	NS
Birth weight, g	3,318 ± 527	3,284 ± 567	NS
NICU admission rate, %	1.5	4.3	NS
Apgar score at 5 min	8.8 ± 1	8.9 ± 0.7	NS

Note: CD = cesarean delivery; ICU = intensive care unit; NICU = neonatal intensive care unit; NS = not significant.

Jackson. Pregnancy in very advanced maternal age. Fertil Steril 2015.

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Jackson, et al Fertil Steril 2015;103:76-80.

Risks associated with infertility and fertility treatments

	spontaneous	NIFT	IVF
gestational diabetes		↑	↑
pregnancy induced hypertension		↑	↑
placenta previa			↑
placental abruption		↑	↑
postpartum hemorrhage			↑
preterm birth			↑
Low birth weight/SGA		↑	↑
perinatal mortality		↑	↑

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Shevell T, 2005 Obstet Gynecol 106:1039-1045
Qin J, 2016 Fertil and Steril 2016
Pisarska M, JCEM 2018

Significant maternal morbidity

Table 2. Rates of Most Commonly Reported and Statistically Significant Severe Maternal Morbidity Indicators and Overall Rate of Any Indicator During Delivery Hospitalizations or Postpartum Readmissions Per 10,000 Deliveries by Assisted Reproductive Technology Status, 2008–2012

	Singleton Pregnancies			Multiple Pregnancies		
Indicator	Non-ART	ART	*P**	Non-ART	ART	*P**
Blood transfusion	36	77	<.001	215	200	.567
Disseminated intravascular coagulation	20	46	<.001	68	98	.042
Mechanical ventilation	18	33	.001	105	143	.034
Adult respiratory distress syndrome	12	21	.009	49	48	1
Eclampsia	11	13	.656	34	41	.488
Heart failure during procedure or surgery	11	23	.001	26	25	1
Hysterectomy	9	27	<.001	38	34	.892
Sepsis	7	15	.004	22	32	.227
Acute renal failure	6	18	<.001	30	32	.881
Puerperal cerebrovascular disorders	6	9	.324	19	18	1
Operations on heart and pericardium	6	12	.041	21	23	.720
Internal injuries of thorax, abdomen, and pelvis	3	14	<.001	10	25	.018
Shock	4	14	<.001	22	16	.585
Overall	126	273	<.001	539	604	.089

ART, assisted reproductive technology.
Data are n unless otherwise specified.
* Holm-Bonferroni corrected $P \leq .001$ denotes statistical significance of Pearson χ^2 and Fisher exact tests.

Martin AS, Obstet Gynecol 2016;127:59-66

Significant Maternal Morbidity (SMM)

- **Using Gold Standard guidelines true SMM cases (Complications)**
  - hemorrhage
  - hypertension/neurologic
  - renal, sepsis
  - pulmonary, cardiac ICU/invasive monitoring
  - surgical, bladder, and bowel
  - Anesthesia
- **Higher rate of women utilizing fertility treatment that has significant maternal morbidity**
-

TABLE 1

Baseline characteristics of the maternal cohort.

Characteristic	SMM (n = 69)	No SMM (n = 6,474)	*P* value
Maternal age (y), n (SD)	34.0 (6.7)	32.9 (5.30)	.18
Maternal race			.001
White	36 (52.2)	4,541 (70.5)	
Black	14 (20.3)	590 (9.2)	
Asian	14 (20.3)	798 (12.4)	
Other	5 (7.3)	512 (8.0)	
Body mass index (kg/m^2)			.50
18.5–24.9	9 (13.6)	1,220 (18.9)	
25–29.9	29 (43.9)	3,021 (46.8)	
≥30	28 (42.4)	2,012 (34.3)	
Multifetal pregnancy	7 (10.1)	159 (2.5)	<.001
Mode of conception			.004
IVF	7 (10.1)	239 (3.7)	
NIFT	3 (4.4)	106 (1.6)	
Spontaneous	59 (85.5)	6,129 (94.7)	
Preterm delivery (<37 wk)	25 (36.8)	470 (7.4)	<.001
Cesarean delivery	55 (79.7)	2,338 (36.1)	<.001
Health insurance			<.001
Government	20 (29)	831 (13)	
Private	49 (71)	5,583 (87)	
Comorbidities			
Coronary heart disease	5 (7)	26 (0.4)	<.001
Diabetes mellitus	10 (15)	455 (7)	0.03
Hypertension	3 (4)	57 (1)	0.03

Note: Data presented as n (%), unless stated otherwise. IVF = in vitro fertilization; NIFT = non-IVF fertility treatment; SMM = severe maternal morbidity.

Wang. Fertility treatment and SMM. Fertil Steril 2016.

Wang et al. Fertil and Steril 2016

Infertility Diagnosis and Maternal Morbidity

- Insurance Claims Database
- *Fertile n=525,695*
- *Infertile n=19,658*
- ***Any severe maternal morbidity including the morbidities noted were associated with the diagnosis of infertility independent of treatment***

TABLE 3
Risk of severe maternal morbidity by fertility group[a]

	AOR (95% CI)			
	Infertile			
	Treatment vs fertile	Diagnosis vs fertile	Testing vs fertile	All infertile vs fertile
Severe maternal morbidity indicator				
Any severe maternal morbidity indicator	1.24 (1.12–1.37)	1.22 (1.13–1.33)	1.09 (0.81–1.45)	1.22 (1.14–1.31)
Acute myocardial infarction	1.68 (0.52–5.46)	0.90 (0.22–3.69)	[b]	1.33 (0.52–3.36)
Acute renal failure	1.03 (0.53–2.02)	0.86 (0.47–1.57)	[b]	0.84 (0.51–1.38)
Acute respiratory distress	1.57 (1.03–2.38)	1.14 (0.76–1.71)	[b]	1.26 (0.93–1.70)
Amniotic fluid embolism	1.61 (0.50–5.18)	1.10 (0.35–3.49)	[b]	1.31 (0.57–3.02)
Aneurysm	[b]	[b]	[b]	[b]
Cardiac arrest or ventricular fibrillation	1.22 (0.29–5.04)	2.68 (1.16–6.20)	[b]	1.94 (0.88–4.31)
Disseminated intravascular coagulation	1.67 (1.33–2.09)	1.34 (1.08–1.66)	1.57 (0.81–3.04)	1.48 (1.26–1.73)
Eclampsia	1.49 (1.02–2.17)	1.30 (0.95–1.79)	0.41 (0.06–2.91)	1.37 (1.05–1.79)
Heart failure during procedure or surgery	1.27 (0.85–1.91)	1.75 (1.3–2.36)	0.89 (0.22–3.57)	1.54 (1.21–1.97)
Internal injuries of the thorax, abdomen, or pelvis	1.61 (0.92–2.84)	1.52 (0.95–2.45)	0.99 (0.14–7.08)	1.77 (1.20–2.61)
Intracranial injuries	1.27 (0.31–5.28)	2.64 (1.14–6.10)	[b]	2.05 (0.97–4.32)
Puerperal cardiovascular disorders	1.05 (0.77–1.43)	1.41 (1.13–1.75)	1.65 (0.81–3.35)	0.94 (0.66–1.33)
Pulmonary edema	1.85 (1.09–3.14)	2.05 (1.36–3.08)	[b]	2.18 (1.54–3.10)
Severe anesthesia complications	0.33 (0.08–1.35)	0.85 (0.42–1.71)	[b]	1.13 (0.49–2.60)
Sepsis	1.04 (0.58–1.85)	0.70 (0.40–1.21)	1.37 (0.34–5.51)	0.90 (0.59–1.36)
Shock	1.76 (1.02–3.05)	1.06 (0.58–1.93)	[b]	1.14 (0.72–1.80)
Sickle cell anemia with crisis	[b]	[b]	[b]	[b]
Thrombotic embolism	1.35 (0.86–2.13)	1.77 (1.27–2.49)	1.21 (0.30–4.88)	1.58 (1.14–2.17)
Blood transfusion	1.69 (1.39–2.07)	1.30 (1.08–1.56)	1.44 (0.79–2.62)	1.50 (1.30–1.72)
Cardiology monitoring	1.01 (0.87–1.18)	1.14 (1.02–1.27)	0.83 (0.53–1.29)	1.09 (0.997–1.20)
Conversion of cardiac rhythm	0.72 (0.10–5.29)	0.95 (0.23–3.88)	[b]	0.83 (0.26–2.68)
Hysterectomy	1.61 (1.03–2.52)	1.10 (0.69–1.77)	1.53 (0.38–6.16)	1.35 (0.97–1.88)
Operations on the heart and pericardium	1.44 (0.86–2.39)	1.09 (0.67–1.77)	2.23 (0.72–6.96)	1.12 (0.77–1.64)
Temporary tracheostomy	[b]	[b]	[b]	[b]
Ventilation	0.95 (0.61–1.47)	1.08 (0.78–1.51)	[b]	0.91 (0.69–1.20)
Intubation	0.92 (0.29–2.92)	0.98 (0.40–2.39)	[b]	0.84 (0.39–1.80)

AOR, adjusted odds ratio; *CI*, confidence interval.

[a] A generalized estimating equation (GEE) model was used to estimate the odds ratios of the diseases between infertile and control groups, adjusted for maternal age, year of delivery, nulliparity, delivery mode, preterm birth, obesity, smoking, hypertension, diabetes, number of prenatal visits, race and ethnicity, and education, accounting for women who had more than 1 delivery of a singleton during the database enrollment period; [b] Calculation of AOR and 95% CI was not possible because of small numbers.

Murugappan et al. Maternal morbidity among infertile women. Am J Obstet Gynecol 2020.

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Murugappan, et al, AJOG 2020

Preterm, late preterm, early term, and term deliveries between infertile and fertile women

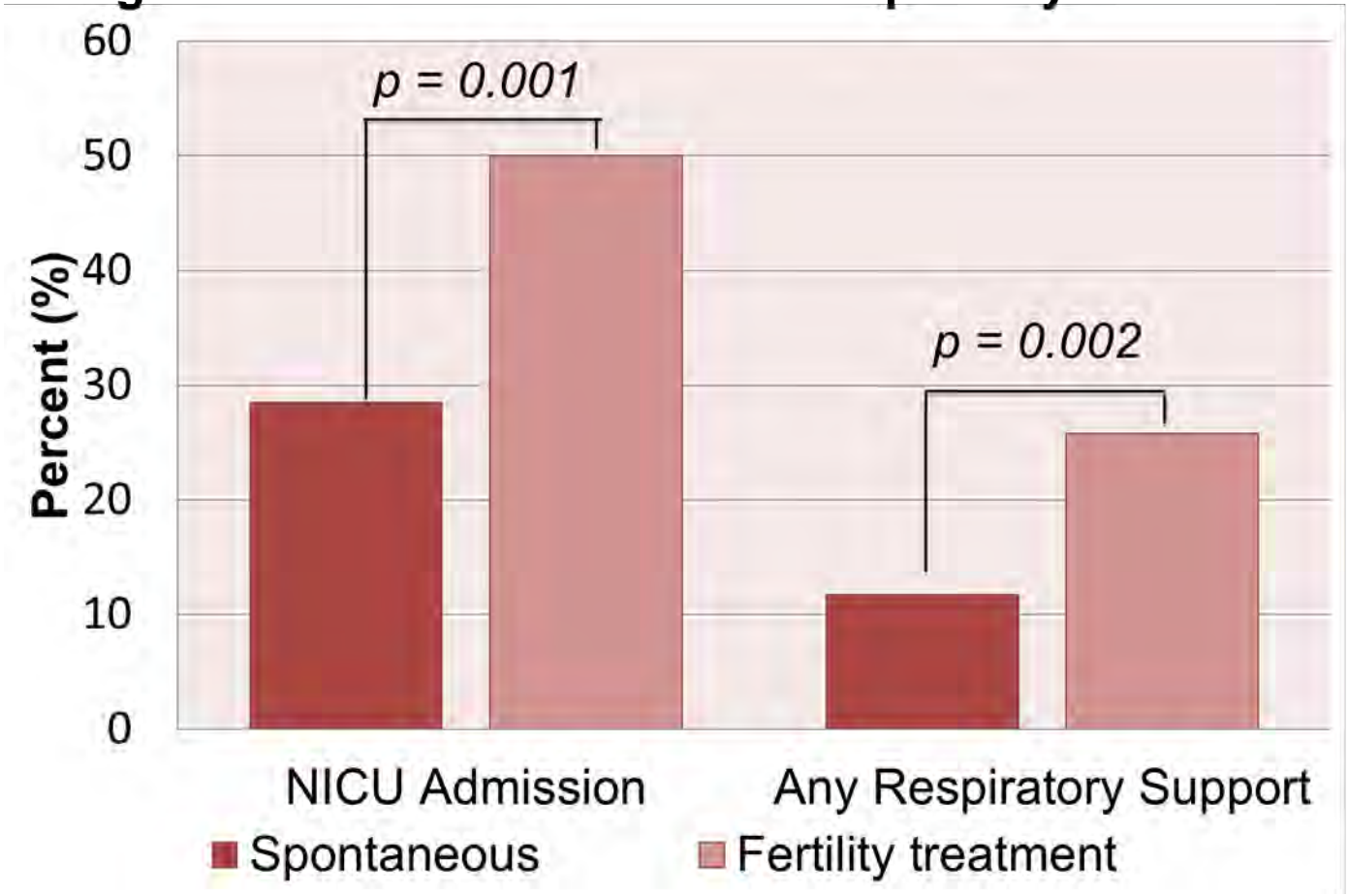
	Infertile N=277	Fertile N=3016	P value
<34 weeks	8 (2.9)	39 (1.3)	0.032[1]
34-36 6/7 weeks	23 (8.3)	130 (4.3)	0.003[2]
37-38 6/7 weeks	58 (20.9)	536 (17.8)	0.19[3]
≥39 weeks	188 (67.9)	2311(76.6)	0.001[4]

Adjusted for maternal age and race

Wang, et al . J Matern Fetal Neonatal Med 2018

Late preterm infants (34 0/7 to 36 6/7 weeks)

Figure 1: NICU Admission and Respiratory Outcomes



continuous positive airway pressure [CPAP] intermittent mechanical ventilation [IMV])

Table 4. Odds Ratio for Any Birth Defects According to Type of Assisted Conception and Multiplicity.*

Type of Assisted Conception	Singleton Births		
	Defect	Unadjusted Odds Ratio	Adjusted Odds Ratio†
	no. of births with defect/ total no. of births		
Any	361/4333	1.45 (1.30–1.63)	1.28 (1.14–1.43)
IVF			
Fresh- or frozen-embryo cycles	105/1484	1.25 (1.02–1.52)	1.06 (0.87–1.30)
Fresh-embryo cycles	71/1005	1.25 (0.98–1.59)	1.05 (0.82–1.35)
Frozen-embryo cycles	34/479	1.24 (0.88–1.76)	1.08 (0.76–1.53)
ICSI			
Fresh- or frozen-embryo cycles	91/939	1.72 (1.38–2.15)	1.55 (1.24–1.94)
Fresh-embryo cycles	76/713	1.95 (1.53–2.48)	1.73 (1.35–2.21)
Frozen-embryo cycles	15/226	1.17 (0.70–1.97)	1.10 (0.65–1.85)
GIFT	34/319	1.98 (1.40–2.80)	1.73 (1.21–2.47)
Intrauterine insemination	54/580	1.67 (1.25–2.23)	1.46 (1.09–1.95)
Donor insemination	36/428	1.51 (1.08–2.11)	1.37 (0.98–1.92)
Ovulation induction	19/306	1.08 (0.68–1.74)	0.99 (0.62–1.59)
Clomiphene citrate at home	7/36	3.87 (1.58–9.51)	3.19 (1.32–7.69)
Other§	15/241	1.07 (0.63–1.82)	0.96 (0.56–1.63)
Spontaneous conception after previous birth from assisted reproductive technology	96/1306	1.27 (1.02–1.59)	1.26 (1.01–1.57)
Infertile but no history of treatment with assisted reproductive technology	52/600	1.54 (1.15–2.05)	1.37 (1.02–1.83)
No use of assisted reproductive technology and fertile	16,841/293,314	1.00	1.00

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Davies, et al, NEJM 2012; 366:1803-13

Risks of Birth Defects

Table III Risk of birth defects among singletons by maternal characteristics and mode of conception.*

		Major birth defect**		Blastogenesis		Cardiovascular		Musculoskeletal		Genitourinary-male		Chromosomal		Any birth defect	
		AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI
Group***	Naturally conceived	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	OI/IUI conceived	1.16	0.97, 1.38	1.11	0.66, 1.85	0.96	0.74, 1.24	1.29	0.86, 1.94	1.25	0.90, 1.73	1.00	0.60, 1.68	1.12	0.99, 1.26
	ART siblings	1.08	0.98, 1.19	1.19	0.90, 1.58	1.10	0.96, 1.26	**1.32**	**1.04, 1.67**	0.96	0.78, 1.19	0.94	0.69, 1.27	**1.15**	**1.08, 1.23**
	ART-auto-fresh, no ICSI	**1.18**	**1.05, 1.32**	0.99	0.69, 1.42	**1.20**	**1.03, 1.40**	1.19	0.89, 1.57	1.11	0.88, 1.41	0.65	0.44, 0.95	**1.18**	**1.09, 1.27**
	ART-auto-fresh, yes ICSI-no MF	**1.30**	**1.16, 1.45**	**1.49**	**1.08, 2.05**	**1.28**	**1.10, 1.48**	**1.34**	**1.01, 1.78**	1.09	0.85, 1.39	0.89	0.63, 1.26	**1.22**	**1.13, 1.32**
	ART-auto-fresh, yes ICSI-yes MF	**1.42**	**1.28, 1.57**	**1.56**	**1.17, 2.08**	**1.45**	**1.27, 1.66**	1.25	0.96, 1.64	**1.33**	**1.08, 1.65**	0.93	0.66, 1.33	**1.38**	**1.29, 1.48**
Maternal	18–29	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Age (years)	30–34	**1.09**	**1.05, 1.12**	0.92	0.83, 1.02	**1.17**	**1.11, 1.23**	0.97	0.89, 1.06	1.08	1.00, 1.17	**1.76**	**1.52, 2.03**	**1.07**	**1.05, 1.10**
	35–37	**1.11**	**1.06, 1.16**	0.83	0.72, 0.96	**1.34**	**1.26, 1.43**	0.91	0.81, 1.04	1.11	1.00, 1.23	**3.46**	**2.95, 4.05**	**1.13**	**1.10, 1.17**
	38–40	**1.10**	**1.03, 1.17**	0.96	0.80, 1.14	**1.52**	**1.40, 1.64**	0.97	0.83, 1.14	1.03	0.90, 1.18	**6.79**	**5.800, 7.96**	**1.23**	**1.18, 1.28**
	41–43	**1.13**	**1.03, 1.24**	1.10	0.85, 1.43	**1.77**	**1.59, 1.97**	1.12	0.89, 1.42	1.19	0.98, 1.45	**15.4**	**12.99, 18.25**	**1.42**	**1.34, 1.51**
	≥44	**1.30**	**1.07, 1.59**	**1.80**	**1.12, 2.88**	**2.58**	**2.11, 3.16**	1.42	0.89, 2.26	1.32	0.87, 2.00	**28.7**	**22.47, 36.67**	**1.68**	**1.49, 1.90**
BMI (kg/m^2)	12–24	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	25–29	1.01	0.97, 1.06	1.00	0.88, 1.14	1.03	0.96, 1.09	1.04	0.93, 1.17	0.99	0.89, 1.09	1.10	0.94, 1.30	1.00	0.97, 1.04
	30–59	**1.18**	**1.12, 1.24**	1.10	0.96, 1.26	**1.23**	**1.16, 1.31**	**1.25**	**1.11, 1.41**	0.96	0.86, 1.08	1.09	0.92, 1.29	**1.13**	**1.10, 1.17**
Diabetes	None	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	Pre- or gestational	**1.34**	**1.27, 1.41**	**1.46**	**1.25, 1.69**	**1.47**	**1.37, 1.57**	1.05	0.90, 1.22	**1.14**	**1.01, 1.30**	1.11	0.93, 1.32	**1.26**	**1.21, 1.30**
Hypertension	None	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	Pre- or gestational	**1.43**	**1.36, 1.51**	1.13	0.96, 1.33	**1.49**	**1.40, 1.60**	1.04	0.90, 1.21	**1.71**	**1.54, 1.91**	1.00	0.83, 1.21	**1.34**	**1.29, 1.39**
Infant sex	Female	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	–	–	1.00	Reference	1.00	Reference
	Male	**1.53**	**1.49, 1.58**	**1.17**	**1.08, 1.27**	0.96	0.92, 1.00	**1.44**	**1.34, 1.54**	–	–	1.01	0.92, 1.11	**1.55**	**1.52, 1.58**

*Models adjusted for all factors listed above, as well as maternal race and ethnicity, education, parity, and State and year of birth. ART births limited to autologous-fresh with partner ejaculated sperm. Bolded values are significantly increased.
**Major defects are limited to nonchromosomal only.
***Group (n, children): naturally conceived (1 066 652); OI/IUI conceived (6899); non-ART siblings (22 821); ART-auto-fresh, no ICSI (all infertility diagnoses, no ICSI: 16 433); ART-auto-fresh, yes ICSI-no MF (yes ICSI, no male factor diagnosis: 14 071); ART-auto-fresh, yes ICSI-yes MF (yes ICSI, yes male factor diagnosis: 16 629). AOR, adjusted odds ratio.
Major birth defects as defined by the National Birth Defects Prevention Network (NBDPN) (see Supplementary Table SI).
Any birth defect is any ICD-9 code with the first 3 digits 740–759, and any ICD-10 code inclusive of Q00.0–07.9, 10–18.9, 20–28.9, 30–45.9, 50–56.4, 60–87.89 and 89–99.9.

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Luke B, Brown ML, Wantman E… Hum Reprod 2021

Risk Assessment

- *Despite increased risk of adverse outcomes, the overall incidence and relative risk of these outcomes is low.*

Table 1. Risks Associated With In Vitro Fertilization–Conceived Pregnancies Compared With Naturally Conceived Counterparts—Singleton, Twin, and Nonstratified Gestations

Risk	Absolute Risk
Among singleton pregnancies	
Preterm delivery[50]	Half day earlier IVF–ICSI vs SC 9.7% IVF–ICSI vs 7.9% SC
Low birth weight delivery[50]	33 g less IVF–ICSI vs SC 6.8% IVF–ICSI vs 4.9% SC
Severe maternal morbidity (blood transfusion most common)[63]	273/10,000 IVF–ICSI vs 126/10,000 SC
Among twin pregnancies	
Monozygotic twins[31,32]	1.2–2.5% IVF–ICSI vs 0.4% SC
Preterm delivery[26–28]	Comparable
Low birth weight delivery[26–28]	Comparable
Not stratified	
DNA methylation[71,72]	Comparable
Imprinting disorder[71,72]	0.15% IVF–ICSI vs 0.02% SC
Any cardiac defect including ASD, VSD[70]	1.30% IVF–ICSI vs 0.68% SC

IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; SC, spontaneous conception; ASD, atrial septal defect; VSD, ventricular septal defect.

Kawwass, et al Obstet Gynecol 2018;132:763–72

Infertility is the contributor to outcomes associated with placentation

- *Maternal morbidity is associated with diagnosis of infertility regardless of treatment*
- *Adverse outcomes are associated with both IVF and NIFT*
- *Congenital anomalies are associated with underlying infertility*
- *Time to pregnancy increases risk of congenital malformations*

- ***Models to study the effect of IVF need to include an infertile cohort***

- *Outcomes are related to placentation defects*
  - *Mother - diabetes, hypertension, preeclampsia, placenta previa and accreta, retained placenta and abruption as well as SMM*
  - *Child- prematurity, growth restriction, and birth defects*

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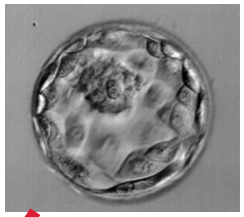
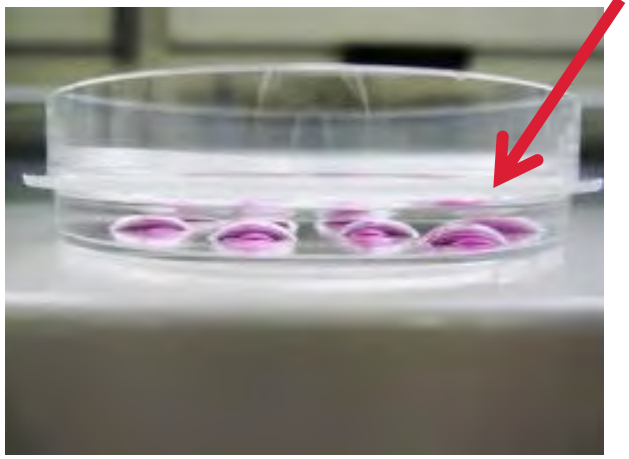
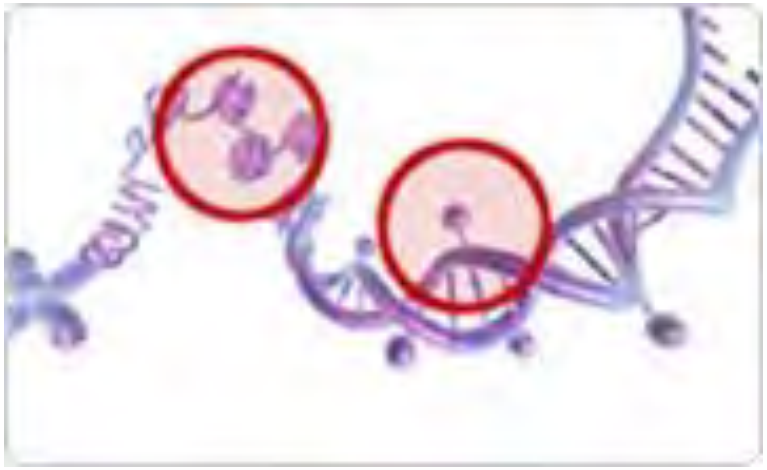
Murugappan AJOG 2020; Shevell T 2005 Obstet Gynecol ; Davies NEJM 2012; Zhu JL Br Med J 2006; Qin J Fertil and Steril 2016; Jackson Fertil Steril 2015; Wang Fertil and Steril 2016; Pisarska M, JCEM 2018

Are the adverse outcomes associated with ART due to the in vitro fertilization process, the treatments or the inherent infertility we are trying to overcome?





?



Prevalence of ART in patients with BWS

TABLE 3

Prevalence of ART in patients with BWS.

Reference no.	Type of study	No. of BWS cases	Prevalence of ART in BWS cohort (cases)	Prevalence of ART in reference population	Type of ART	Association between BWS and ART
62[a]	Case series	65[b]	4.6% (3[b])	0.8%	IVF/ICSI	Suggestive
63	Case series	149	4% (6[c])	1.2%	3 IVF/3 ICSI	Suggestive
64	Case series	149	4% (6[c])	1.3%	4 IVF/2 ICSI	Suggestive
65	Case-control	37	10.81%[d] (4)	0.67%[d]	3 IVF/1 ICSI	Suggestive
66[a]	Case-series	341	5.6%(19)	NA	5 IVF/5 ICSI[e]	NA
67	Survey	209	2.9% (6[c])	0.8%	1 IVF/5 ICSI	Suggestive
71	Survey	71	5.6% (4)	0.92%	IVF/ICSI	Suggestive

[a] Data from the same BWS registry (NCI BWS registry and Washington University BWS registry).
[b] Only BWS cohorts beginning in 2001 were used to calculate prevalence.
[c] The frequency of children born after ART in BWS cohort was significantly higher than the expected ART cases based on the ART prevalence in the general population.
[d] Fisher's exact test, two-sided, $P=0.006$.
[e] Data on type of ART obtained from 12 patients (two patients had only ovarian stimulation with intrauterine insemination).

Manipalviratn. Imprinting disorders and ART. Fertil Steril 2009.

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Manipalvirtan, et al, Fertil Steril 2009;91:305-15

Cohort studies of children

TABLE 4

Number of cases of BWS in a cohort study of children conceived naturally and after ART.

Reference no.	No. of cases of BWS in children born after ART	Number of children born after ART	No. of cases BWS in children conceived naturally	Number of children conceived naturally
68	0	6,052	0	442,349
69	0	16,280	NA	2,039,943
70	1	1,524	NA	NA

NA = Not available.

Manipalviratn. Imprinting disorders and ART. Fertil Steril 2009.

Adverse pregnancy outcomes: methylation

Differences in DNA methylation and gene expression in term placenta from children conceived in vitro versus in vivo

Term placenta and cord blood and may not reflect the early changes that occur as a direct result of the IVF conditions in ART.

Term placenta may reflect changes in the intrauterine environment, which has been associated with an altered fetal epigenome leading to altered gene expression.

Placental Weight, Fetal Weight and Fetal Weight to Placenta Weight Ratio

Figure 1: Placental and Birth Weight Parameters

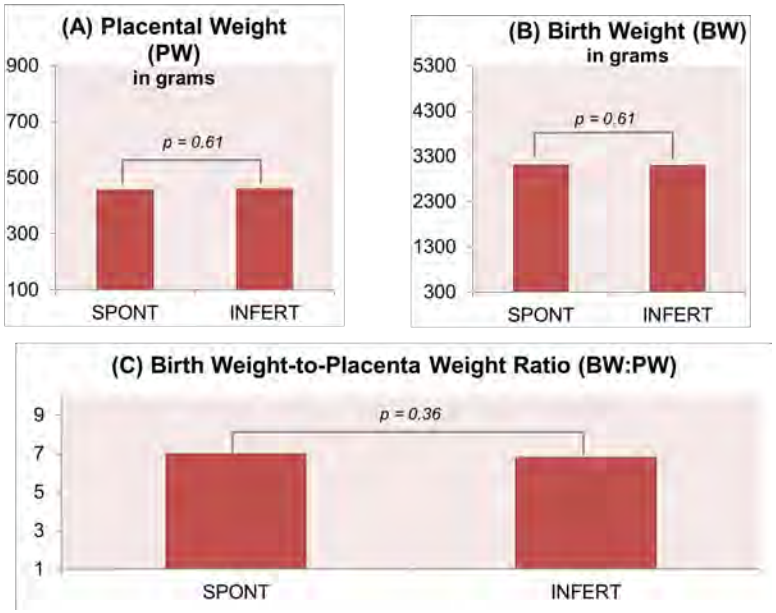

Figure 2: Placental Characteristics

	SPONT N=1333	INFERT (NIFT+IVF) N=110	p-value
Preeclampsia findings, n (%)	111 (8.3%)	9 (8.2%)	0.96
Chorioamnionitis, n (%)	392 (29.4%)	35 (31.8%)	0.59
Accreta, n (%)	16 (1.2%)	4 (3.6%)	0.036
Placental Shape, n (%)			0.23
Discoid	737 (55.3%)	58 (52.7%)	
Ellipsoid	202 (15.2%)	15 (13.6%)	
Ovoid	200 (15%)	14 (12.7%)	
Circular/Round	63 (4.7%)	5 (4.5%)	
Other	50 (3.8%)	9 (8.2%)	

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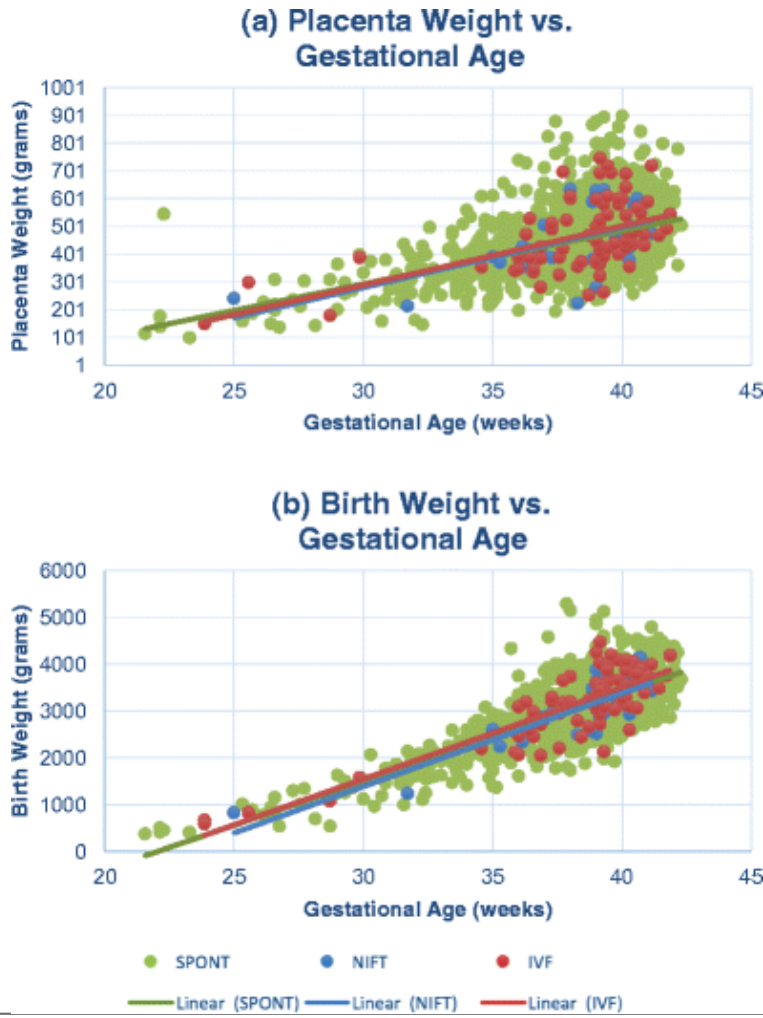
Sundheimer, et al. J Assist Reprod Genet. 2018

Placental Weight, Fetal Size and Fetal Size to Placenta Weight Ratio

- *Linear regression demonstrates that regardless of gestational age, the placenta weight, fetal weight and fetal size to placenta weight do not vary by mode of conception.*



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Sundheimer, et al. J Assist Reprod Genet. 2018

Placentation

Abnormal placentation is associated with adverse pregnancy outcomes - preeclampsia, PIH, gestational diabetes, previa, abruption, placental retention

Pregnancies conceived with infertility and treatments are at risk of:

abnormal placentation

abnormal placental morphology and cord insertion

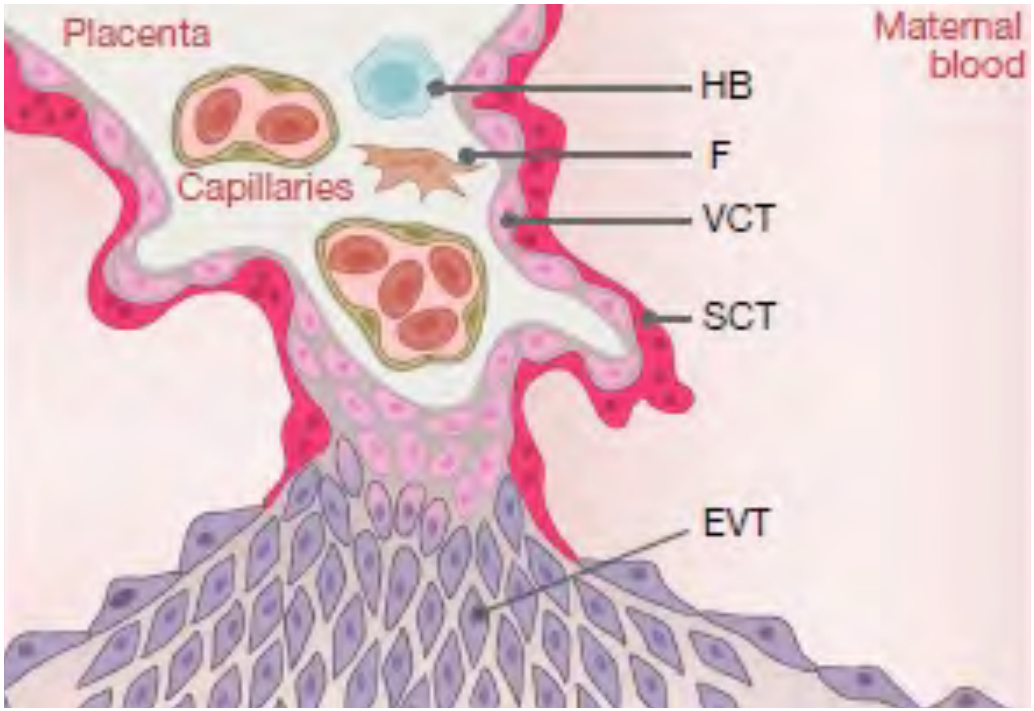
abnormal protein profiles

increased metabolism and clearance of steroids by the placenta

Small for gestational age babies

Gavriil P, et al 1993 Pediatr Pathol 13:453-462
Zhang Y, et al 2008 Proteomics 8:4344-4356
Collier AC, et al 2009 J Steroid Biochem Mol Biol 116:21-28
Delle Piane L,et al 2008 Reproductive Sciences 15:81A-81A

Placentation



The placenta is made up of important cell types

Villous cytotrophoblasts (VCT): undifferentiated precursor cells

Extravillous trophoblasts (EVT): Invade decidua and maternal blood vessels

Syncitiotrophoblasts (SCT): Facilitate nutrient exchange and produce hormones

Endothelial cells: Line fetal blood vessels

Immune cells: stromal fibroblasts (F), dendritic cells, macrophages or Hofbauer cells (HB)

Vento-Tormo et al (2019), *Nature*

Model of Placentation

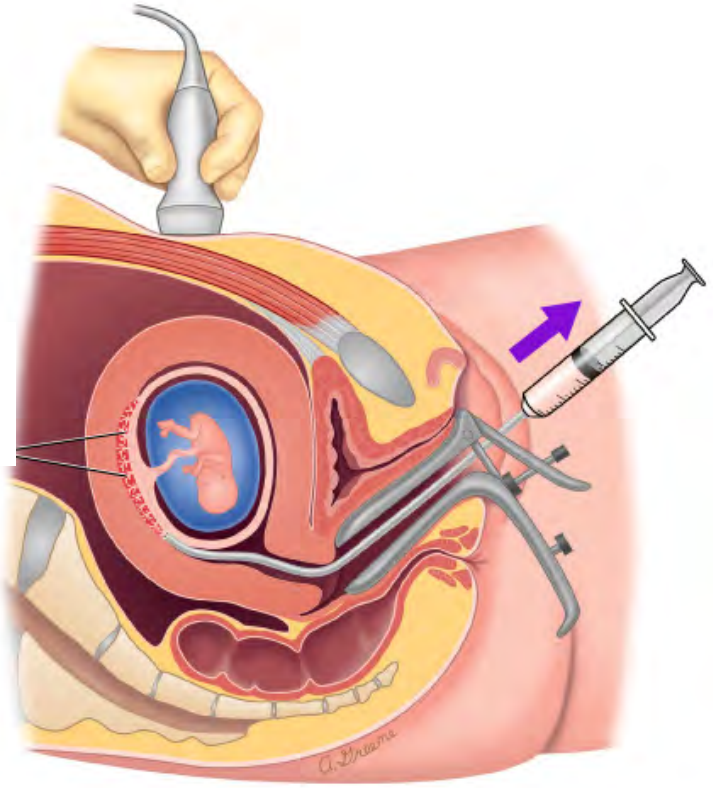
- **1st trimester placenta tissue**

Chorionic villus sampling

Prenatal diagnostic test at 11-13 weeks

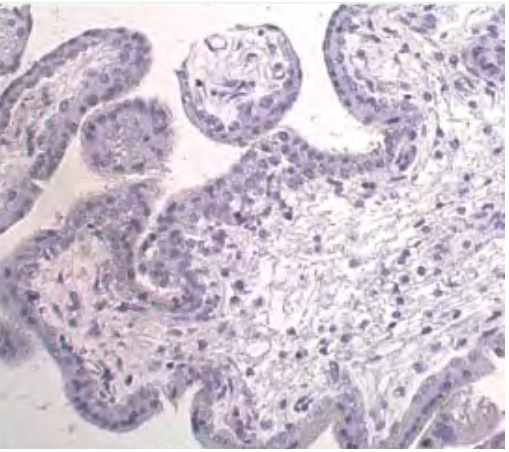
Ongoing pregnancies that deliver at term

Chorionic villi

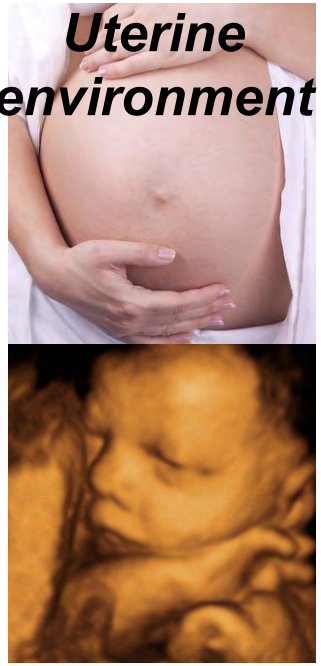


Are the outcomes associated with ART due to the in vitro fertilization process, the treatments or the inherent infertility we are trying to overcome?

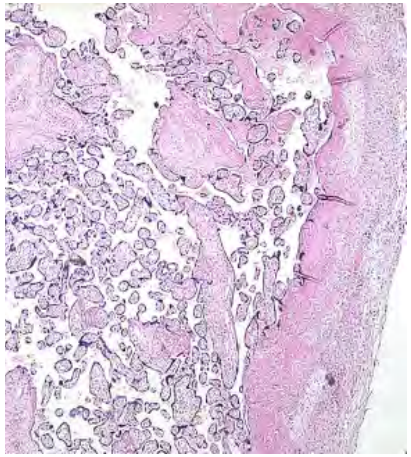
Cells from early placentation



Earliest time point in ongoing pregnancy



Uterine environment



Cells from delivery

Outcomes

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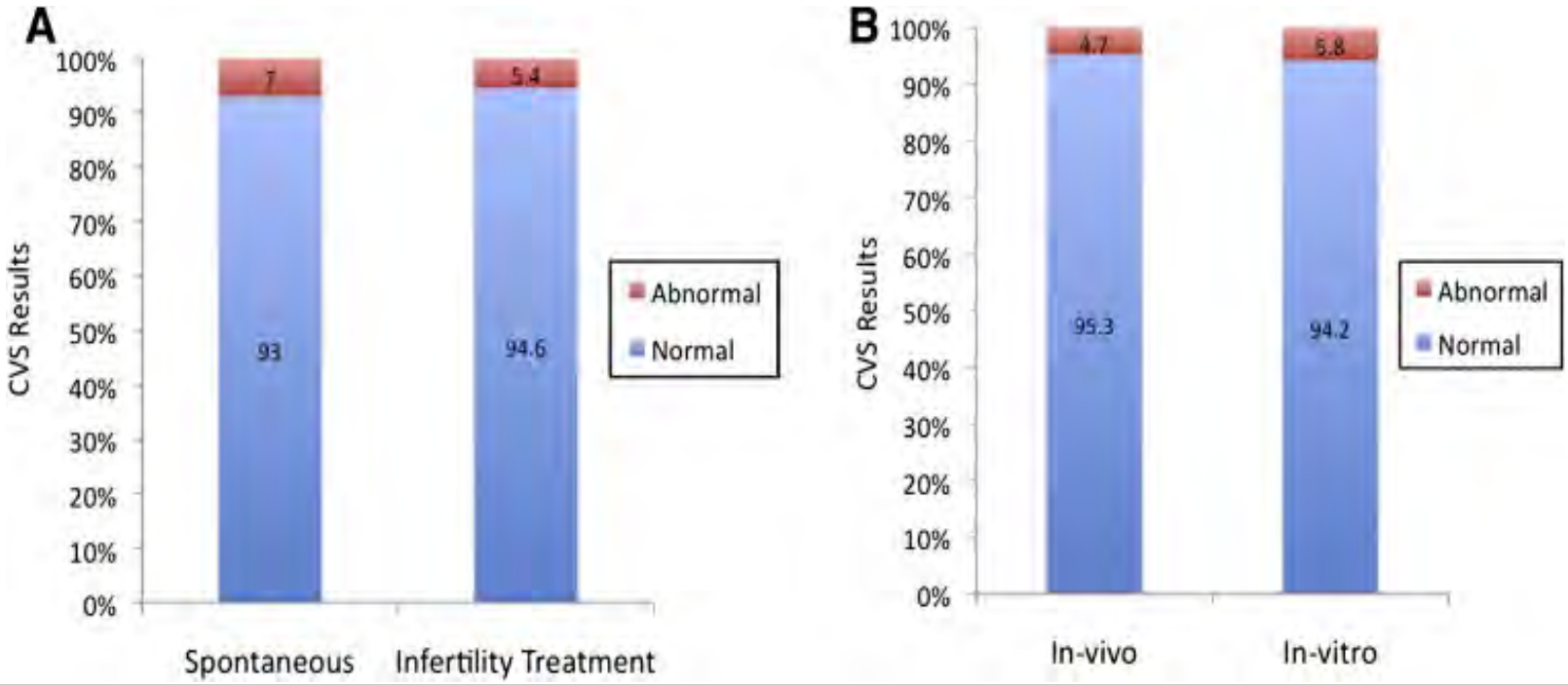
Cytogenetic Abnormalities assessed by CVS in Spontaneous vs. Infertile Patients

- 1,606 women conceived spontaneously
- 559 women conceived through infertility treatment
  - 233 conceived in vivo
  - 326 conceived in vitro



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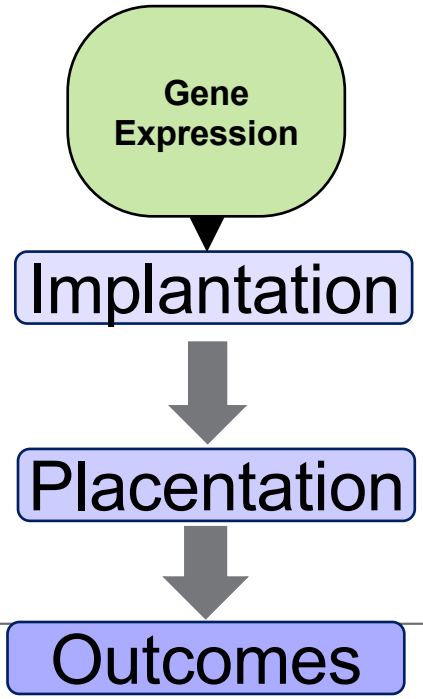
Conway Fertil Steril 2011 Feb;95(2):503-6

Spontaneous/ Medical Assisted/ART (SMAART) Cohort

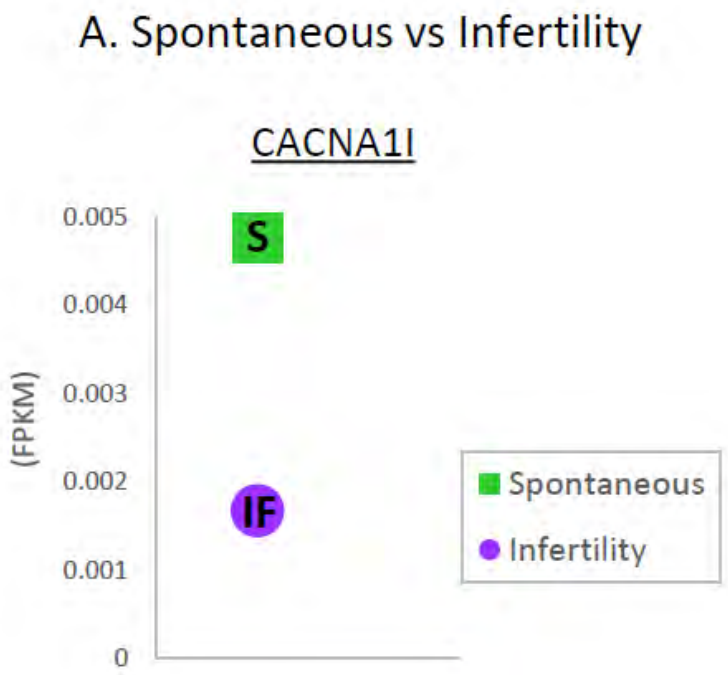
- **a cohort of pregnancies conceived either spontaneously or in couples with infertility conceived either through non-IVF fertility treatment (NIFT) or IVF, that are enrolled in the late first trimester of pregnancy at the time of Chorionic Villus Sampling (CVS) and followed until delivery**
  - 208 spontaneous conceptions
  - 201 pregnancies conceived with a history of Infertility
    - 90 conceived with NIFT
    - 111 conceived with IVF

Sun, et al. JCEM. 2018

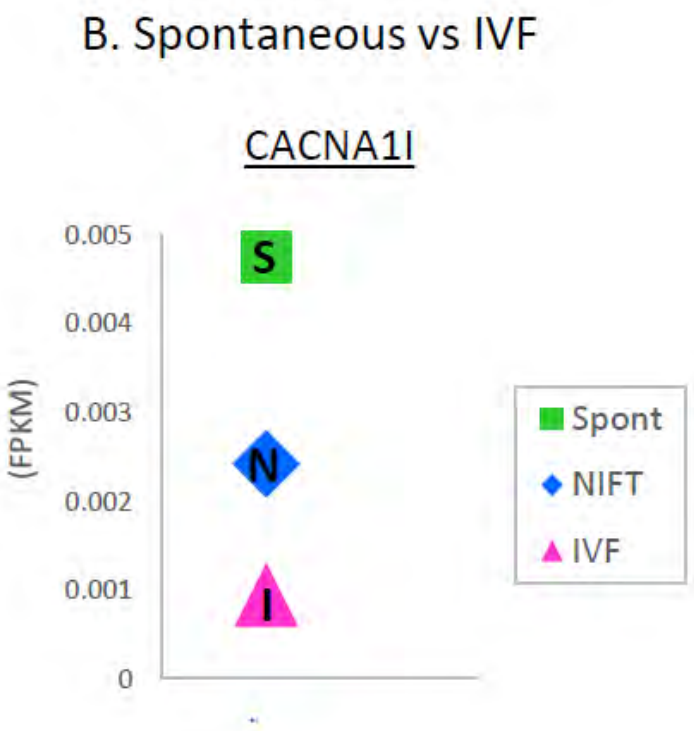
SMAART Cohort



SMAART Transcriptome cohort



Calcium voltage-gated channel subunit alpha1



Calcium voltage-gated channel subunit alpha1

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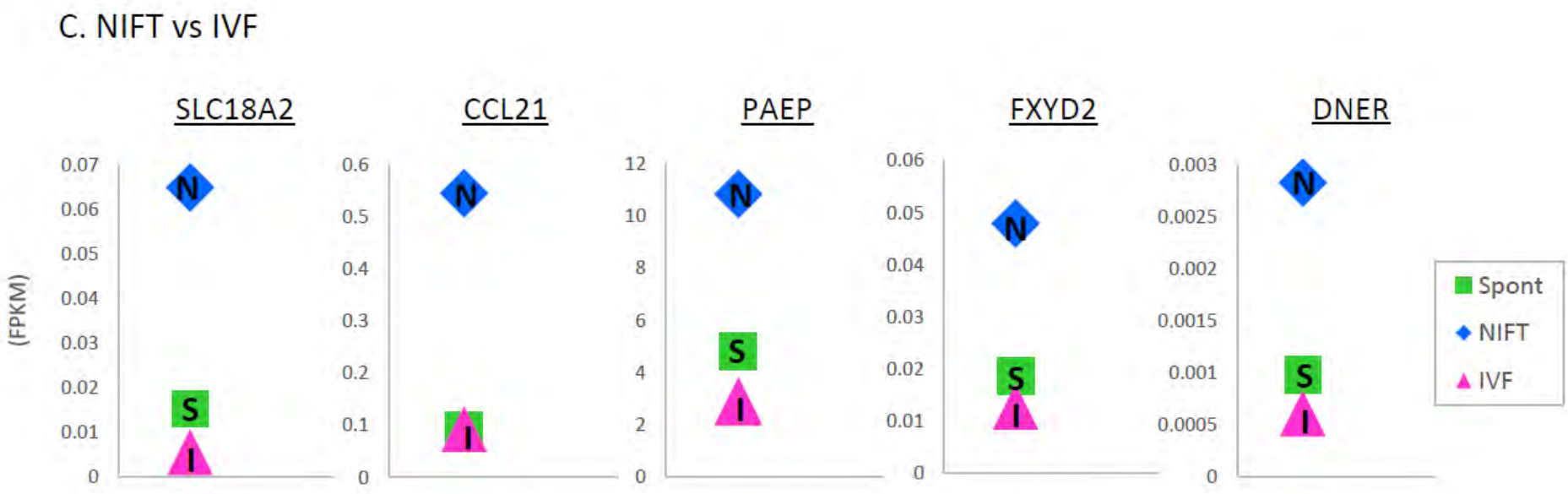
Lee et al, Fertil and Steril 2018

SMAART Transcriptome cohort



Solute carrier family 18 member A2

C-C motif chemokine ligand 21

Progestagen associated endometrial protein

FXYD domain containing ion transport regulator 2

Delta/notch like EGF repeat containing

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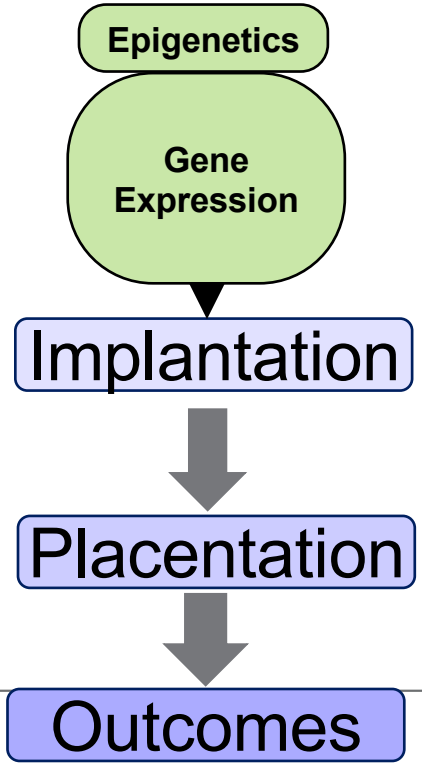
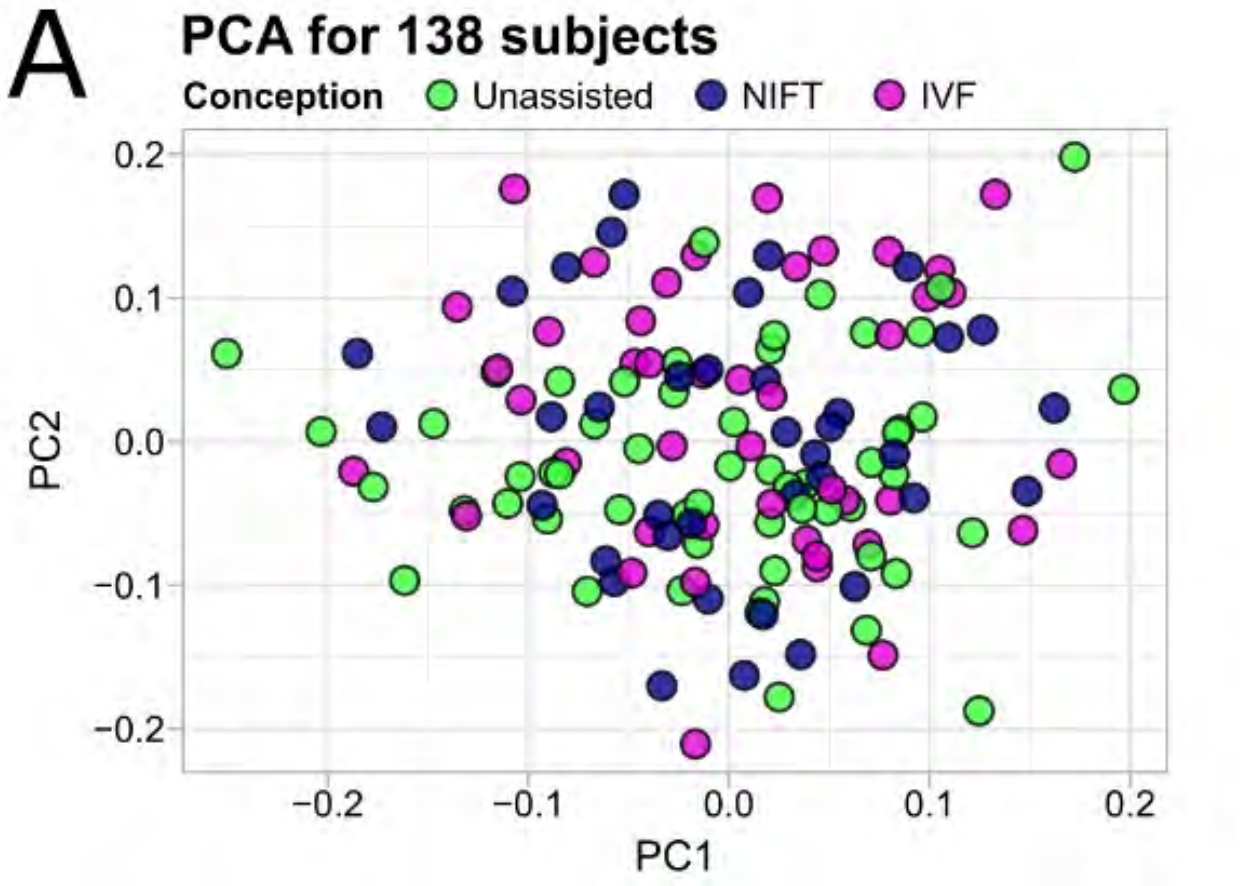
Lee et al, Fertil and Steril 2018

SMAART Cohort



Global methylation alterations due to infertility and treatments

- *Principle Component analysis does not demonstrate clustering*



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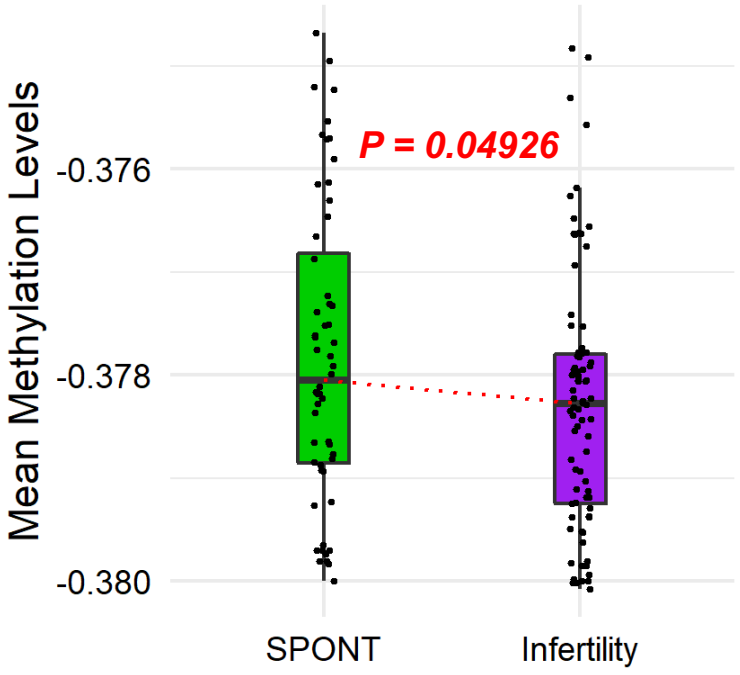
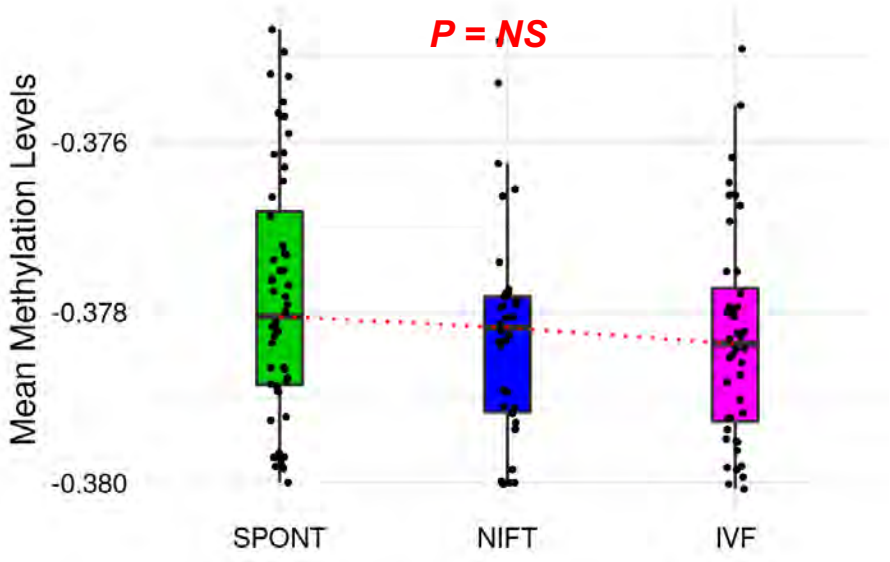
Gonzalez, et al. Fertil Steril 2023
Xu et al, Repro Sciences 2016

Global methylation alterations due to infertility and treatments

- *Median β values were significantly lower in the infertility cohort compared to the spontaneous cohort.*
- *Median β values were lower in the NIFT and IVF cohort compared to spontaneous cohort, but overall there was no significant difference among the groups.*
- *Infertility may be associated with global hypomethylation and not the specific treatment.*





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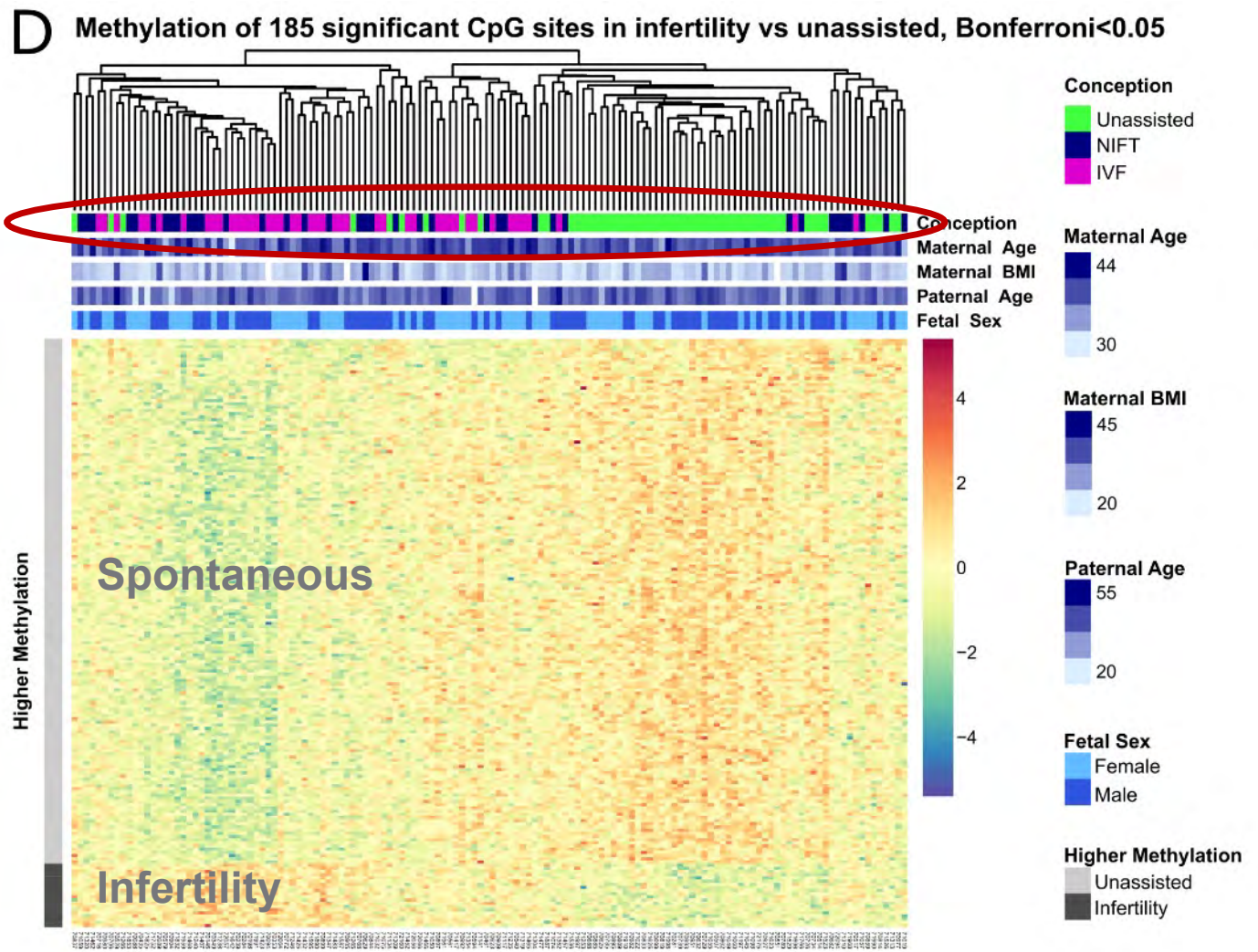
Gonzalez, et al. Fertil Steril 2023
Xu et al, Repro Sciences 2016

Global Differential Methylation due to infertility and treatments

- *Clustering is identified between the infertility and spontaneous cohort.*
- *Within the infertility cohort, there is no clustering of NIFT or IVF cohorts, suggesting diversity among the infertility group, independent of treatment utilized.*



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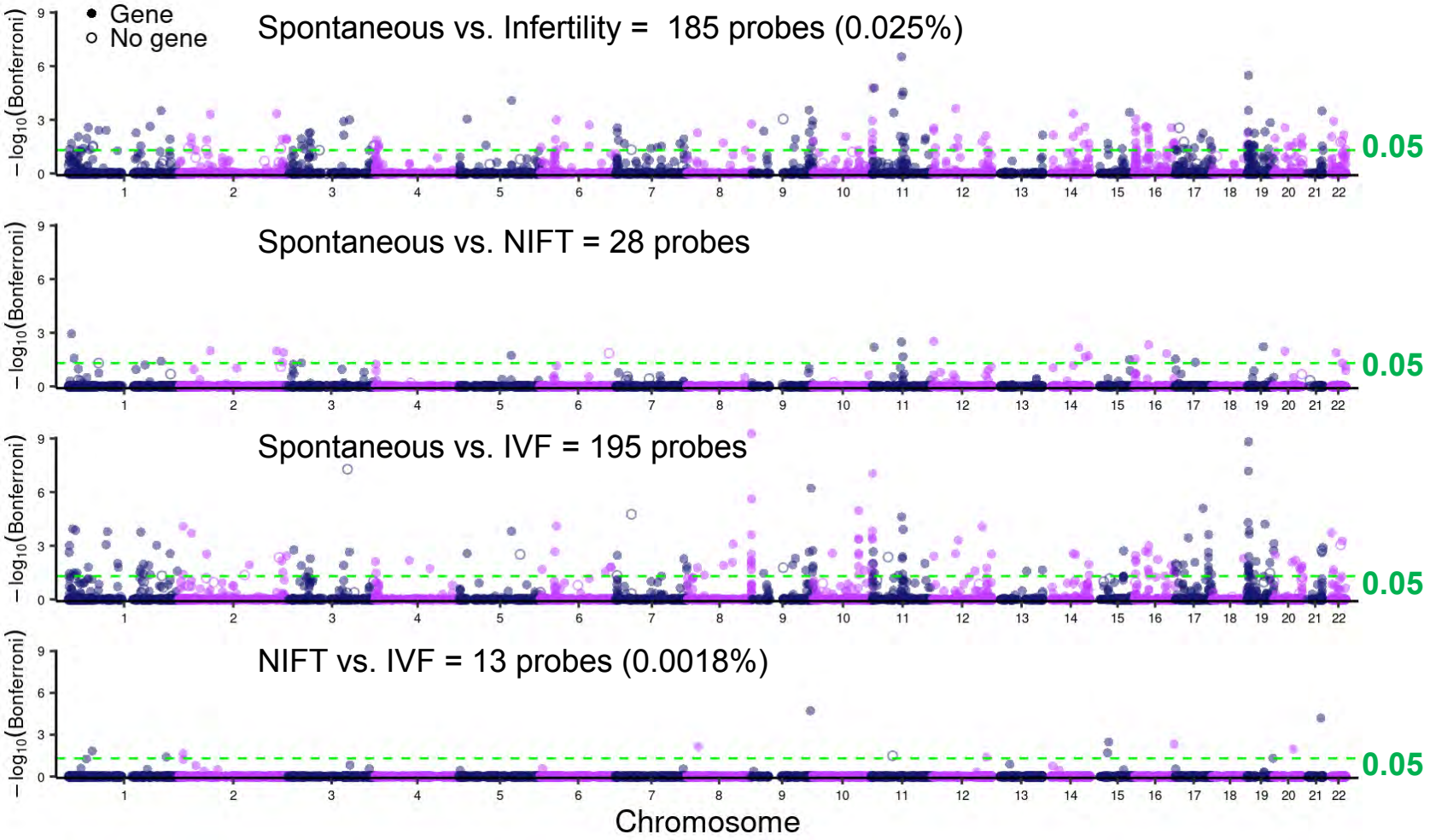
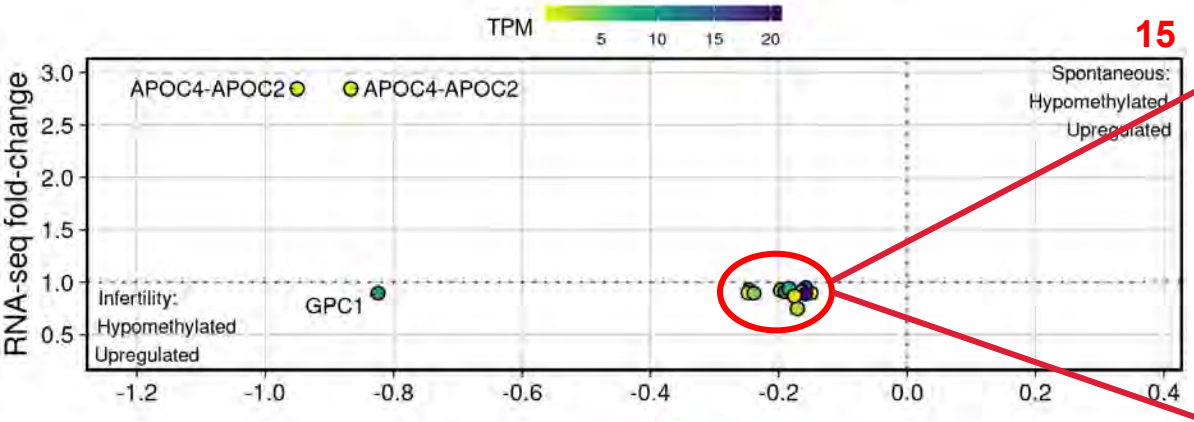
Gonzalez, et al. Fertil Steril 2023

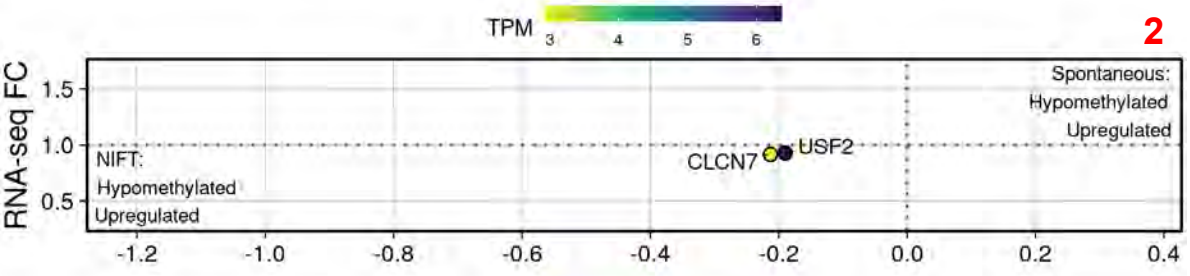
Chromosomal Distribution of Differentially Methylated Probes due to infertility and treatments

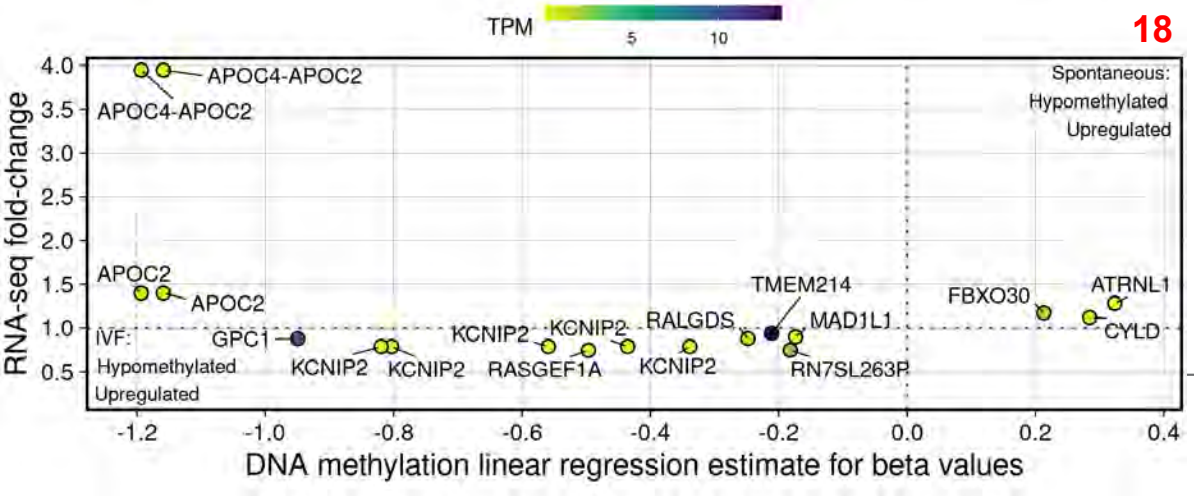


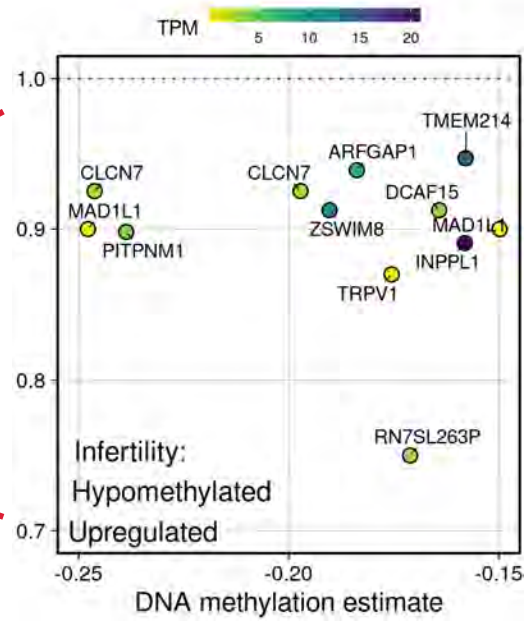
Gonzalez, et al Fertil Steril 2023

Differential methylation and gene expression in infertility and treatments









Differentially methylated probes and associated DEGs:

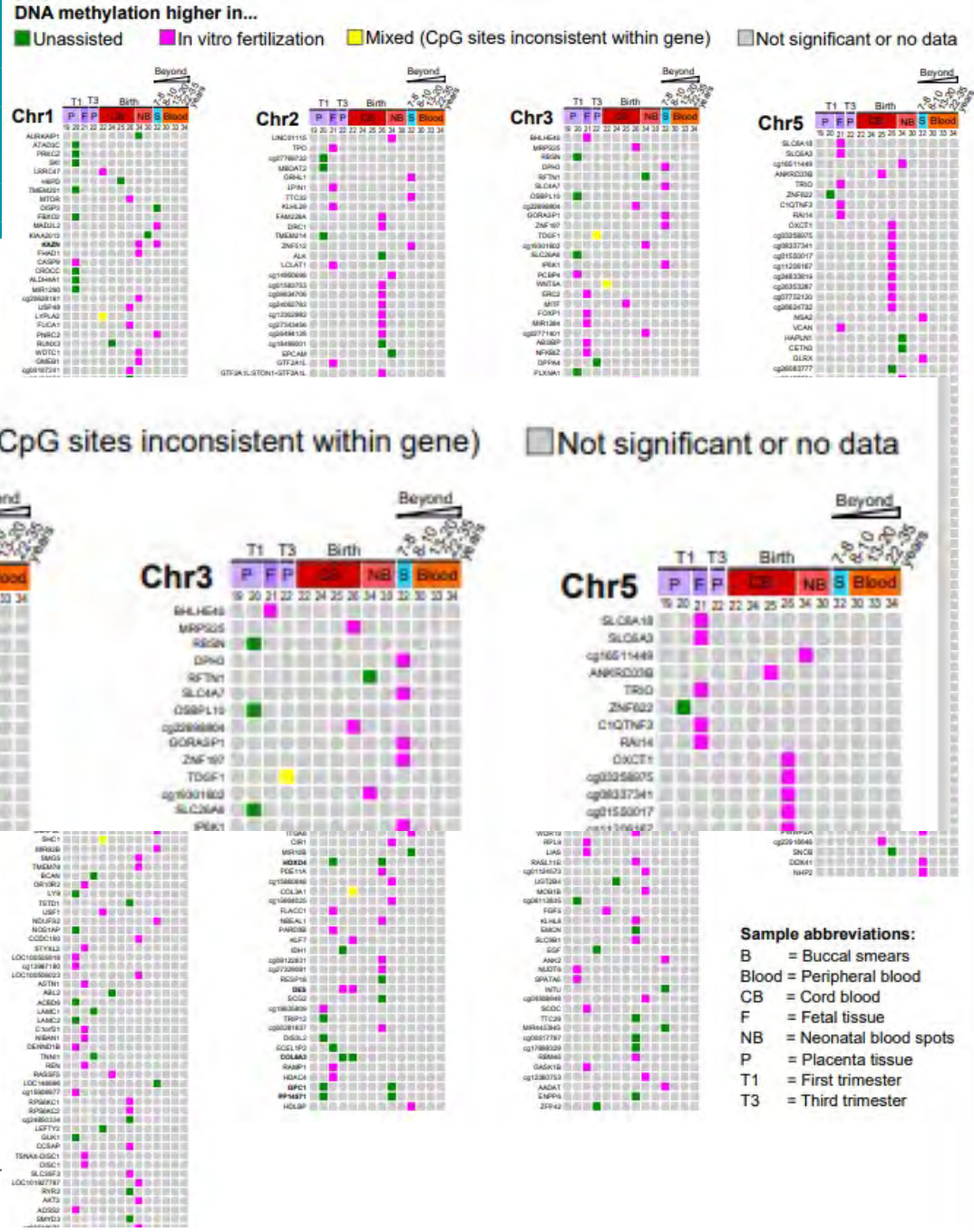
- **Spontaneous vs. Infertility =15**
- **NIFT vs. Spontaneous = 2**
- **IVF vs. Spontaneous = 18**
- **NIFT vs. IVF = 0**

Methylation Changes Across the Lifespan
A Systematic Review

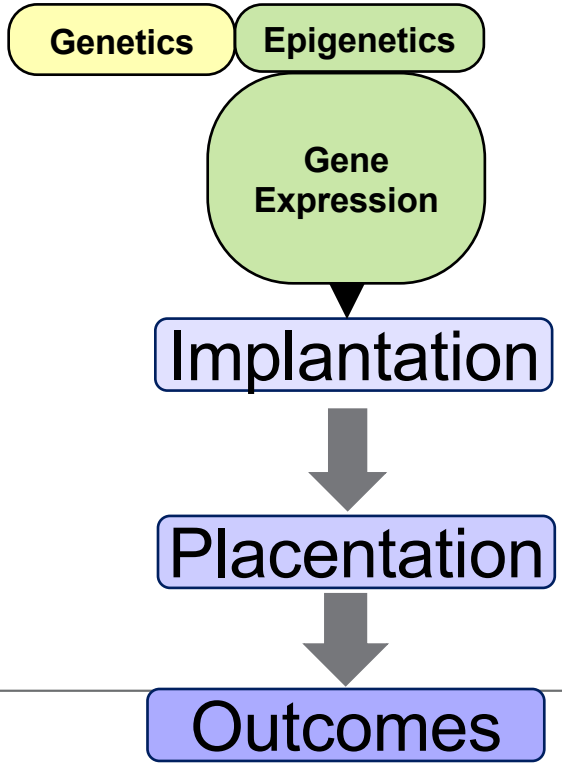
	Trophectoderm	Pregnancy			Newborn		Childhood		Adult
		1st Trimester Placenta	Fetal Tissue	Term Placenta	Cord Blood	Newborn Dried Blood Spot	Buccal Smears	Peripheral Blood	Peripheral Blood
Infertile vs Fertile	Denomme (2021)								
IVF (+/- ICSI) vs Unassisted		Xu (2017) Gonzalez (2022)	Liu (2021)	Katari (2009)	Katari (2009) Melamed (2015) Tobi (2020) Haberg (2022)	Novakovic (2019) ** Yeung (2021)	Ducreux (2021)	Yeung (2021)	Novakovic (2019)** Penova-Veselinovic (2021)
ICSI Only vs Unassisted					El Hajj (2017) Gentilini (2018)	Estill (2016) Yeung (2021)			
NIFT vs Unassisted		Xu (2017) Gonzalez (2022)				Estill (2016) Yeung (2021)		Yeung (2021)	
IVF vs NIFT		Xu (2017) Gonzalez (2022)		Choufani (2019) *		Estill (2016)			
Infertility (NIFT + IVF +/- unassisted with h/o infertility) vs Fertile		Gonzalez (2022)		Choufani (2019)	Caramaschi (2021)	Estill (2016) Yeung (2021)		Yeung (2021)	

*NIFT cohort contained those with history of infertility conceiving unassisted
** IVF cohort Also contained GIFT

Interpreting Data in a Larger Context: Systematic Review

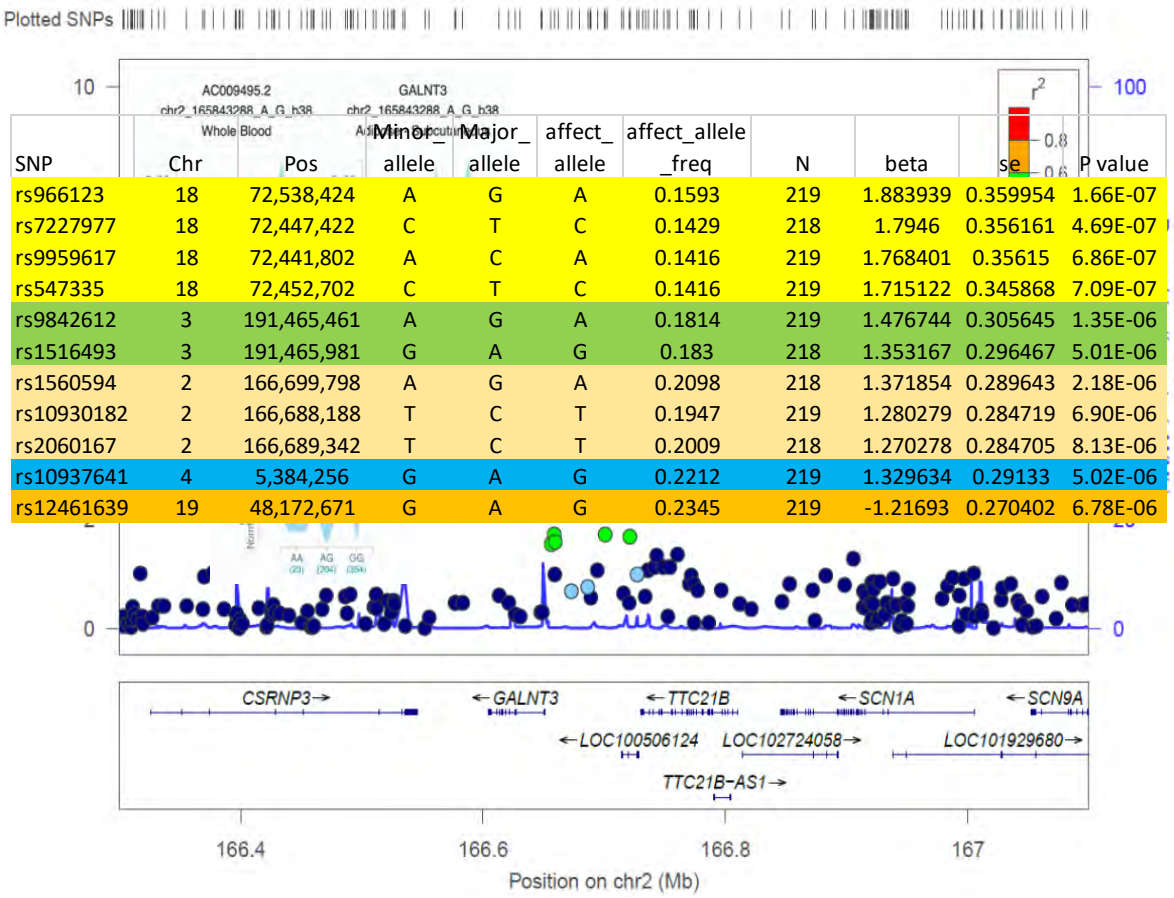


SMAART Cohort



Single nucleotide variants (SNVs) that associate with infertility – Family associated GWAS

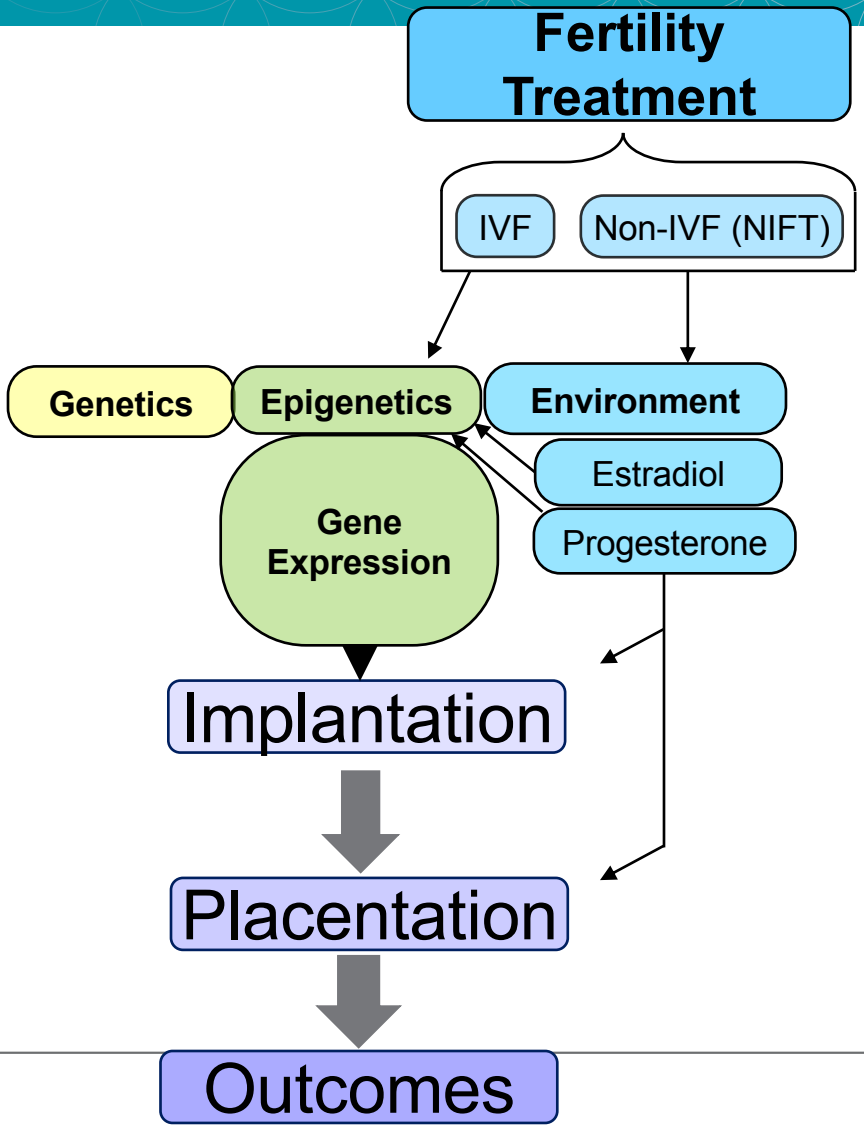
- None of the SNVs met the genome-wide significance threshold of $5x10^{-8}$
- Of the 637,072 SNVs that passed quality control measures – 11 SNVs were identified with sub-genome-wide significance ($p \leq 1x10^{-5}$) representing 5 loci



SNP	Chr	Pos	Minor_ allele	Major_ allele	affect_ allele	affect_allele _freq	N	beta	se	P value
rs966123	18	72,538,424	A	G	A	0.1593	219	1.883939	0.359954	1.66E-07
rs7227977	18	72,447,422	C	T	C	0.1429	218	1.7946	0.356161	4.69E-07
rs9959617	18	72,441,802	A	C	A	0.1416	219	1.768401	0.35615	6.86E-07
rs547335	18	72,452,702	C	T	C	0.1416	219	1.715122	0.345868	7.09E-07
rs9842612	3	191,465,461	A	G	A	0.1814	219	1.476744	0.305645	1.35E-06
rs1516493	3	191,465,981	G	A	G	0.183	218	1.353167	0.296467	5.01E-06
rs1560594	2	166,699,798	A	G	A	0.2098	218	1.371854	0.289643	2.18E-06
rs10930182	2	166,688,188	T	C	T	0.1947	219	1.280279	0.284719	6.90E-06
rs2060167	2	166,689,342	T	C	T	0.2009	218	1.270278	0.284705	8.13E-06
rs10937641	4	5,384,256	G	A	G	0.2212	219	1.329634	0.29133	5.02E-06
rs12461639	19	48,172,671	G	A	G	0.2345	219	-1.21693	0.270402	6.78E-06

- Allele of the SNV2, risk SNV rs1560594, p=2.18 x 10^{-6}, eQTL plots demonstrate associations for the noncoding transcript AC009495.2, GALNT3 and TTC21B in whole blood and adipose.

SMAART Cohort



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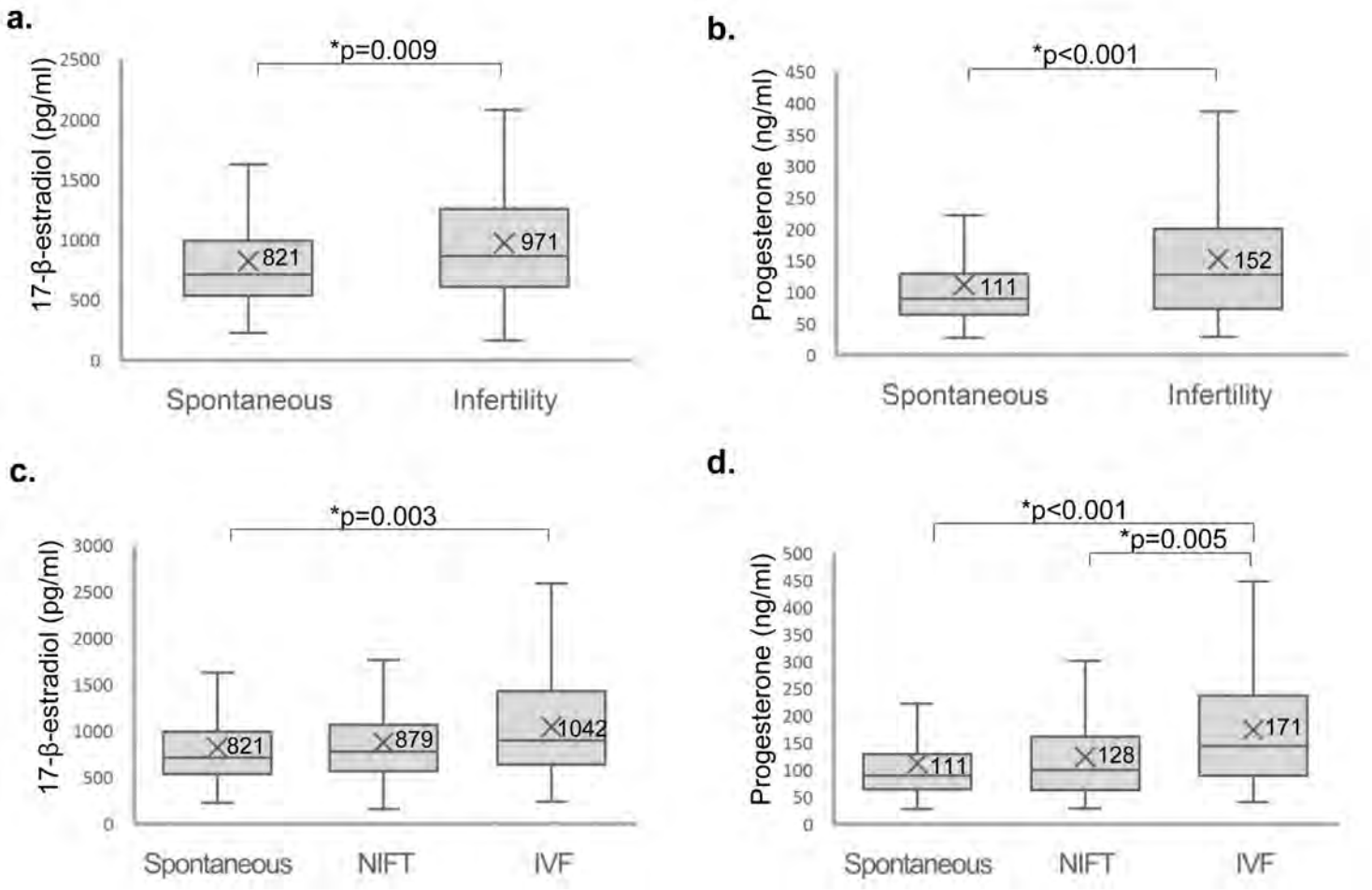
Supraphysiologic Hormones

- *Supraphysiologic hormone levels have been implicated in increased rates of low birth weight and small for gestational age babies.*
- *Since pregnancies conceived through fertility treatments are exposed to elevated estradiol and progesterone levels, either endogenously through treatments or exogenously to supplement the pregnancy, we wanted to determine whether previous treatments impact the hormonal milieu of an ongoing pregnancy.*

The Supraphysiologic Hormonal Milieu



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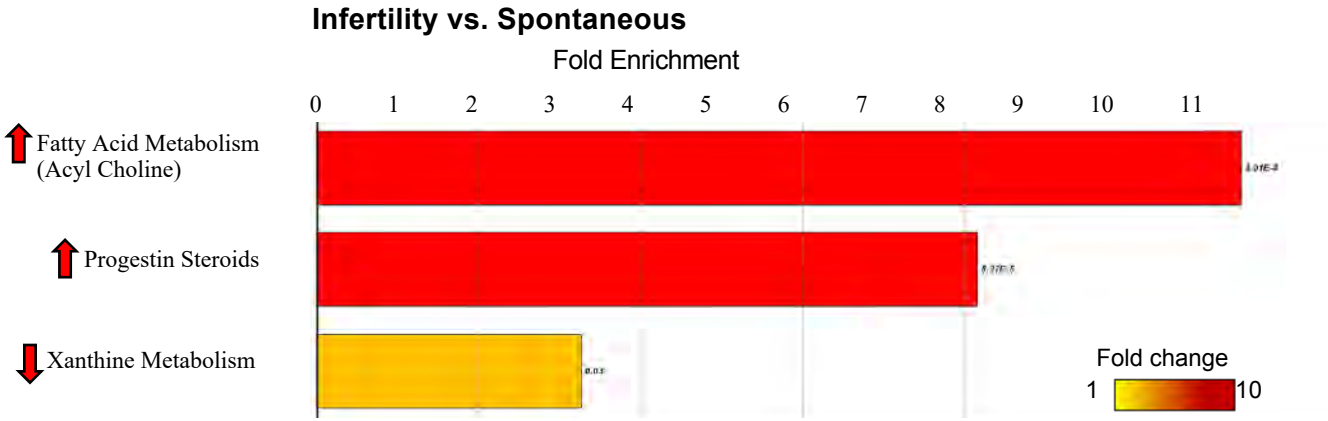
Sun, et al. JCEM. 2018

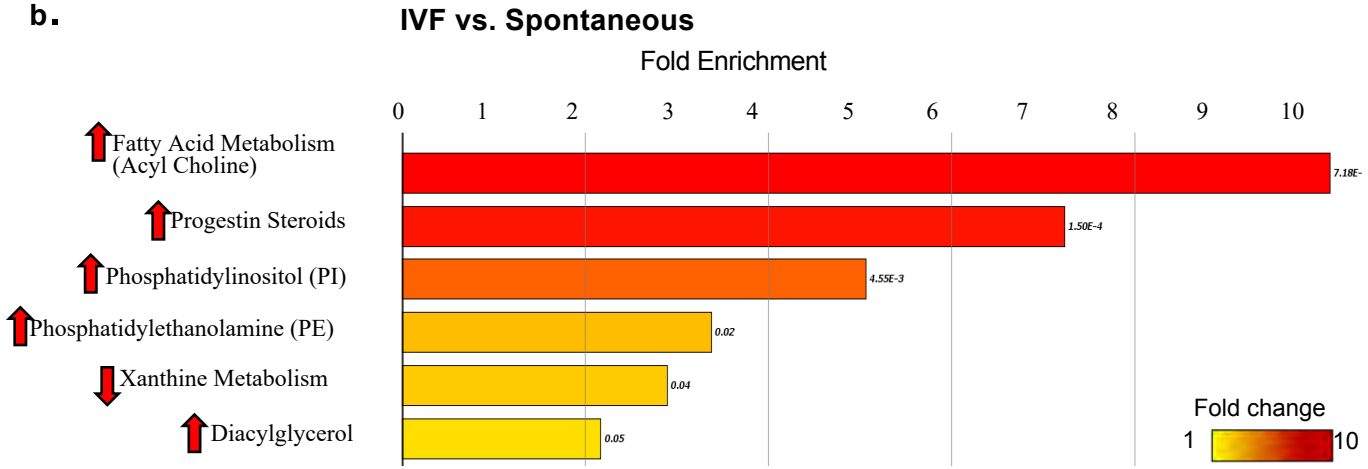
Differences in metabolomic profiles in late first trimester

Pathway enrichment analysis

a.



b.



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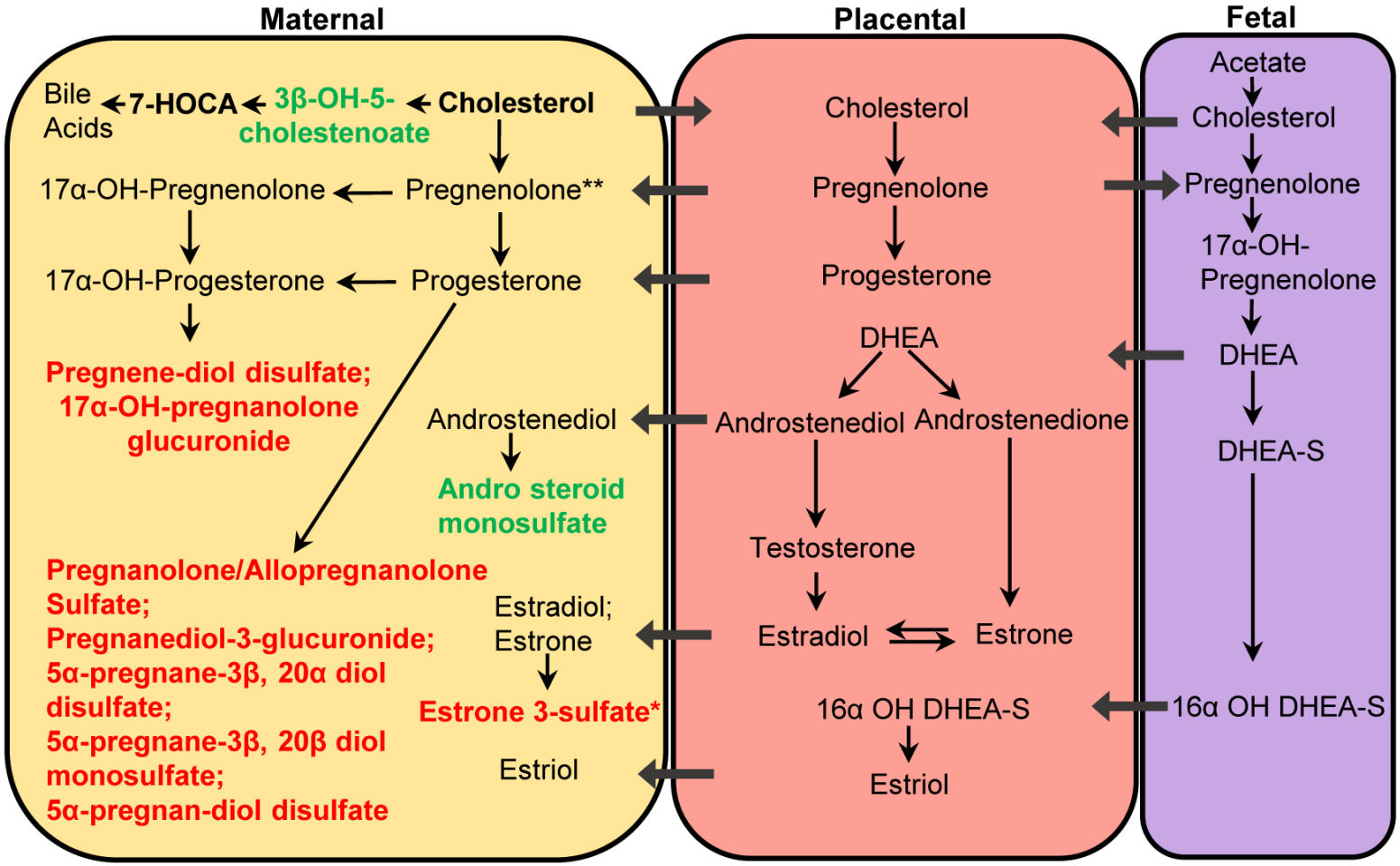
Sun, et al. JCEM. 2018

Model of steroid hormones and metabolites within the maternal-placental-fetal unit



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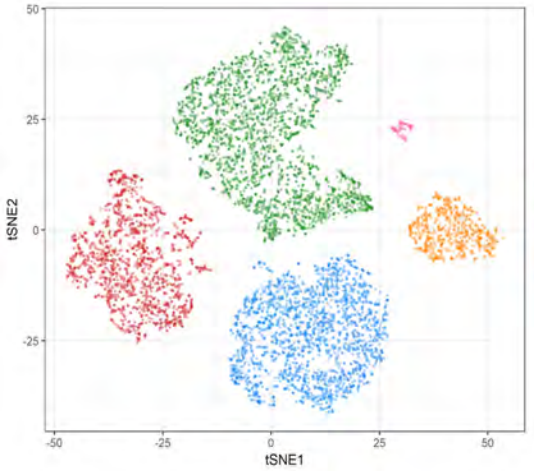
Sun, et al. JCEM. 2018

First Trimester Chorionic Villi- Single Cell Sequencing



P1 Trophoblast Cells
P2 Stromal Cells
P3 Macrophages
P4 Dendritic Cells
P5 Endothelial Cells

P1 (Trophoblast)	Molecule Type	p-value	Targets
BMP4	Growth factor	3.9E-21	26
beta-estradiol	Chemical – endogenous	9.34E-15	60
PGR	Ligand-dependent nuclear receptor	2.35E-13	22
ERBB2	Kinase	3.81E-12	33
ESR1	Ligand-dependent nuclear receptor	5.54E-12	44
TGFB1	Growth factor	9.98E-10	48
HRAS	Enzyme	1.98E-09	26
PTEN	Phosphatase	5.12E-09	22
TP53	Transcription regulator	9.39E-09	43
TNF	Cytokine	2.39E-08	45
P2 (Stromal)	**Molecule Type**	**p-value**	**Targets**
TGFB1	Growth factor	3.26E-29	98
beta-estradiol	Chemical – endogenous	5.06E-27	99
FGF2	Growth factor	8.5E-24	42
CTNNB1	Transcription regulator	1.52E-23	58
WNT3A	Cytokine	1.53E-21	34
AHR	Ligand-dependent nuclear receptor	5.98E-20	37
TGFB2	Growth factor	9.85E-19	22
TGFB3	Growth factor	2.83E-18	22
TWIST1	Transcription regulator	2.97E-18	25
HRAS	Enzyme	8.9E-18	45

P3 (macrophages)	Molecule Type	p-value	Targets
CSF2	Cytokine	5.32E-20	35
TNF	Cytokine	6.32E-20	66
leukotriene D4	Chemical - endogenous	3.48E-19	16
IL13	Cytokine	1.59E-15	28
IFNG	Cytokine	6.54E-15	50
beta-estradiol	Chemical – endogenous	2.19E-14	60
IL1B	Cytokine	5.7E-14	39
CSF1	Cytokine	3.34E-12	18
IL4	Cytokine	3.63E-12	36
IL2	Cytokine	8.48E-11	27
P4 (Dendritic-like)	**Molecule Type**	**p-value**	**Targets**
IFNG	Cytokine	4.82E-27	48
TGFB1	Growth factor	4.45E-20	46
TNF	Cytokine	1.91E-18	44
IL13	Cytokine	1.61E-17	23
IL27	Cytokine	6.75E-17	16
IL4	Cytokine	4.2E-16	30
CIITA	Transcription regulator	5.3E-15	10
IL1B	Cytokine	5.48E-15	29
CSF3	Cytokine	3.81E-14	15
beta-estradiol	Chemical - endogenous	5.37E-14	40
P5 (Endothelial)	**Molecule Type**	**p-value**	**Targets**
KLF2	Transcription regulator	4.38E-10	10
TNF	Cytokine	8.04E-09	25
TGFB1	Growth factor	8.61E-09	25
CAV1	Transmembrane receptor	7.25E-08	8
ENG	Transmembrane receptor	4.63E-07	5
ESR1	Ligand-dependent nuclear receptor	2.27E-06	18
SRC	Kinase	5.46E-06	6
TCF7L2	Transcription regulator	5.68E-06	9
ERBB2	Kinase	6.54E-06	13
miR-199a-5p	Mature microRNA	7.77E-06	5

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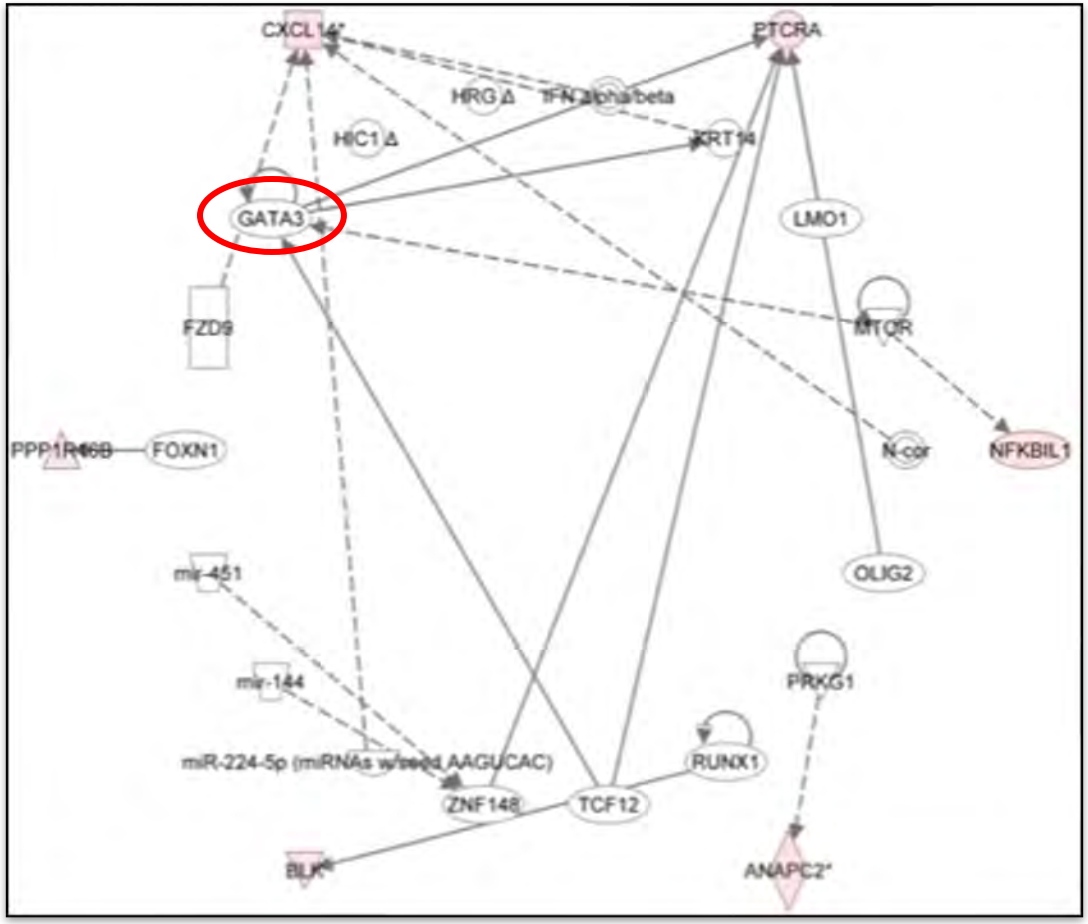
Sun, Gonzalez, Deng, Pisarska et al.
https://www.biorxiv.org/content/10.1101/641118v1

Upstream Analysis of Differentially Methylated Genes



- Directs trophectoderm differentiation in the blastocyst
- *R*egulates trophoblast function important for:
- Placental vascularization
- Syncytiotrophoblast formation
- Reduced *GATA3* expression in mice shows decreased embryo hatching and implantation

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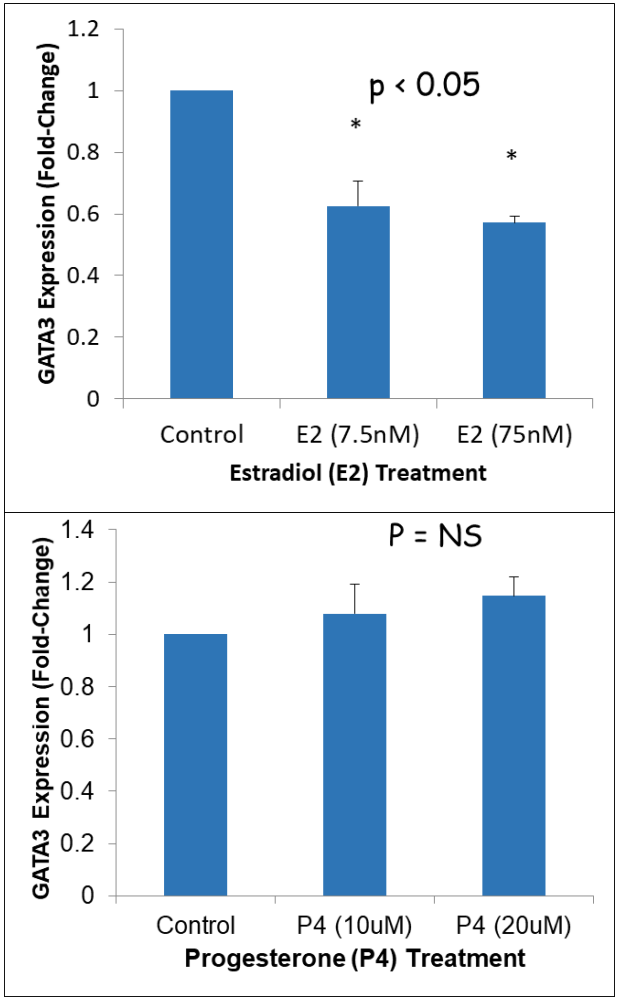
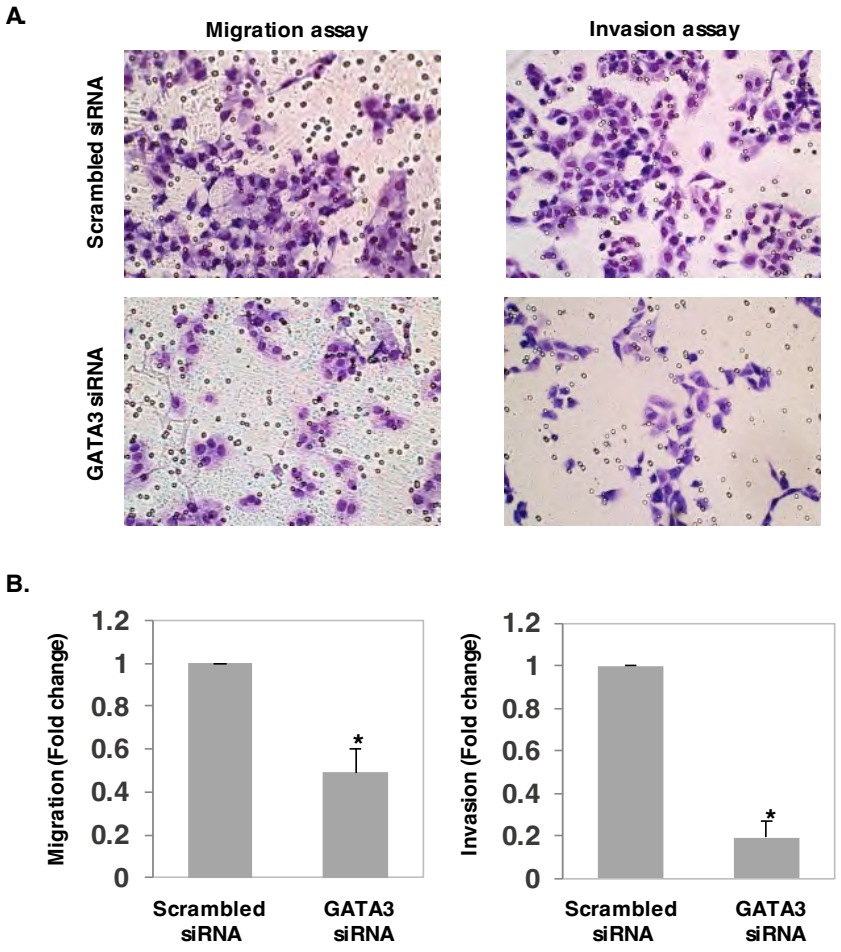
Lee B. and Kroener L, et al. BOR 2016

Estradiol downregulates GATA3 and downregulation of GATA3 inhibits migration and invasion





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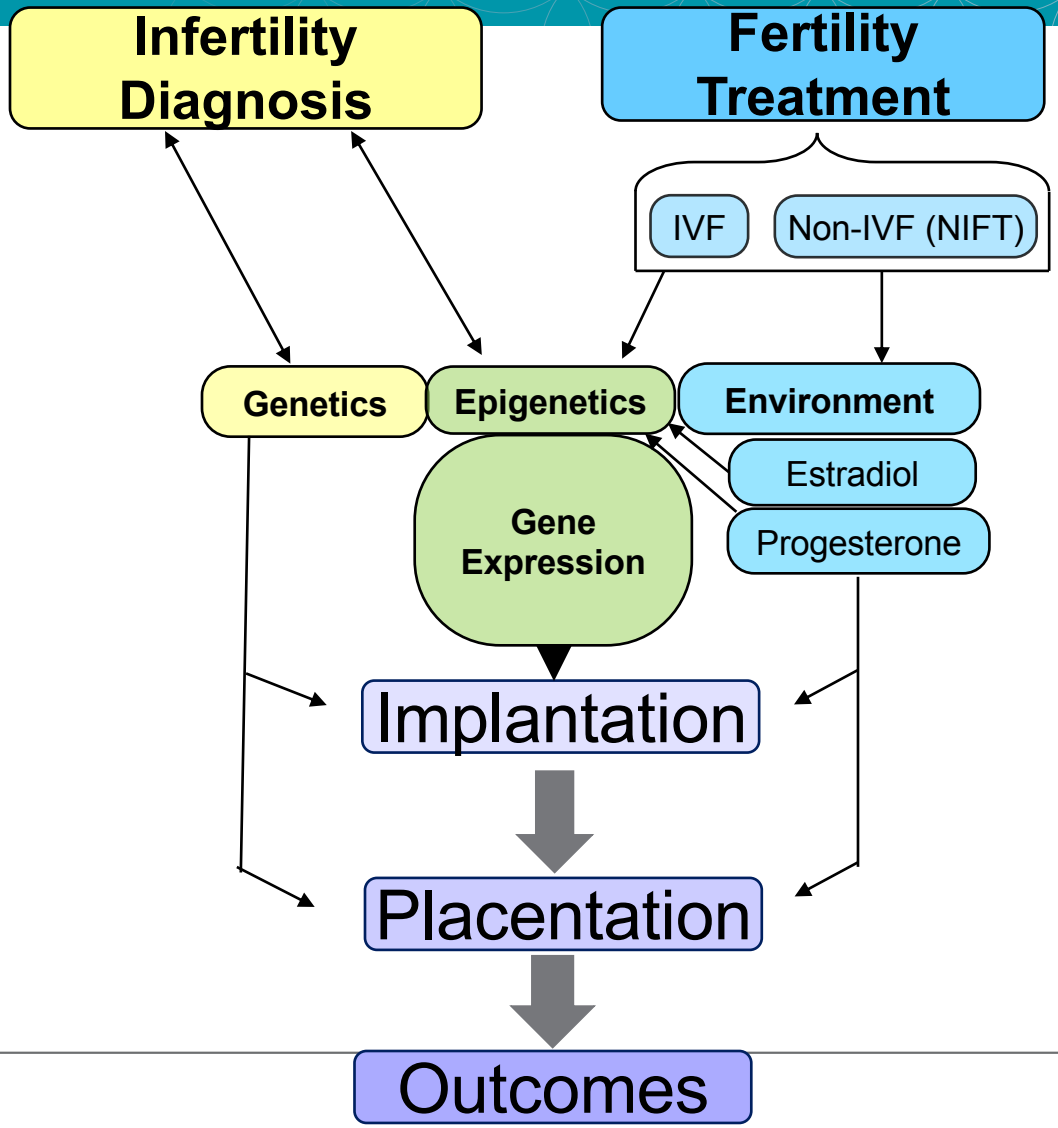
Lee B. and Kroener L, et al. BOR 2016

SMAART Cohort



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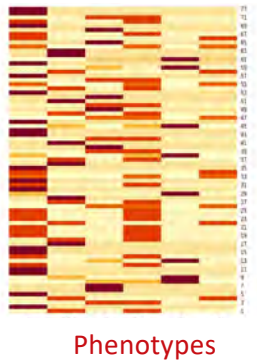
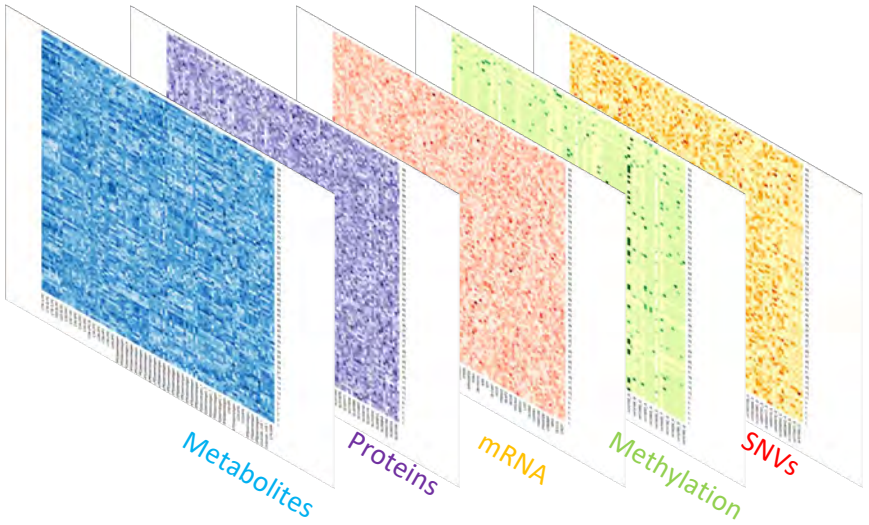
Impact of infertility on placentation through a multi-omics analysis

Regularized Canonical Correlation Analysis - Provides correlation across a large data landscape using small sample sizes





Data	Features
Phenotypes	7 traits
Genomics - OmniExpressExome Chip	688,534 SNVs
Methylomics - methylation EPIC Array (Illumina)	865,855 sites
Transcriptomics -Total RNA sequencing	61,801 genes
Metabolomics of mother's serum (Metabolon)	704 metabolites

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Genetic/epigenetic impact of infertility on placentation through a multi-omics analysis

Correlation Component	Spont	Infertility	Sex	Mat Age	Race	CVS age
1	0.048				0.99	0.05
2				-0.11		
3	0.99		-0.11			
4			0.11	0.99		
5	0.11		0.99			
6	-0.034	0.002	-0.99			0.06

- *Component 3 contains the association of infertility with the rest of the data landscape*
- *Effect of sex, maternal age, race, and CVS age are separated from the effect of infertility*

- ***296 Features Identified in Component 3***

- *Genomics: 40 Features (SNVs)*
- *Methylomics: 40 Features (methylated regions)*
- *Metabolomics: 8 Features (metabolites)*
- *Transcriptomics: 209 Features (transcripts)*

- ***Central Theme – Mitochondrial Regulation***

- ***Mitochondrial Regulatory Genes***
  - *ARAF*
  - *MYOF*
  - *PRKCZ*
  - *DNAJC1*
  - *MTFR1*
- ***Mitochondrial small RNAs***
- *Nuclear encoded*
- *Regulators of mitochondrial transcription*
  - *MTATP6P9,23,31*
  - *MTCO2P7; MTCYBP42*
  - *MTND1P2,20,28,31*
  - *MTND2P15,20*
  - *MTND4P1,4,8*

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Conclusions

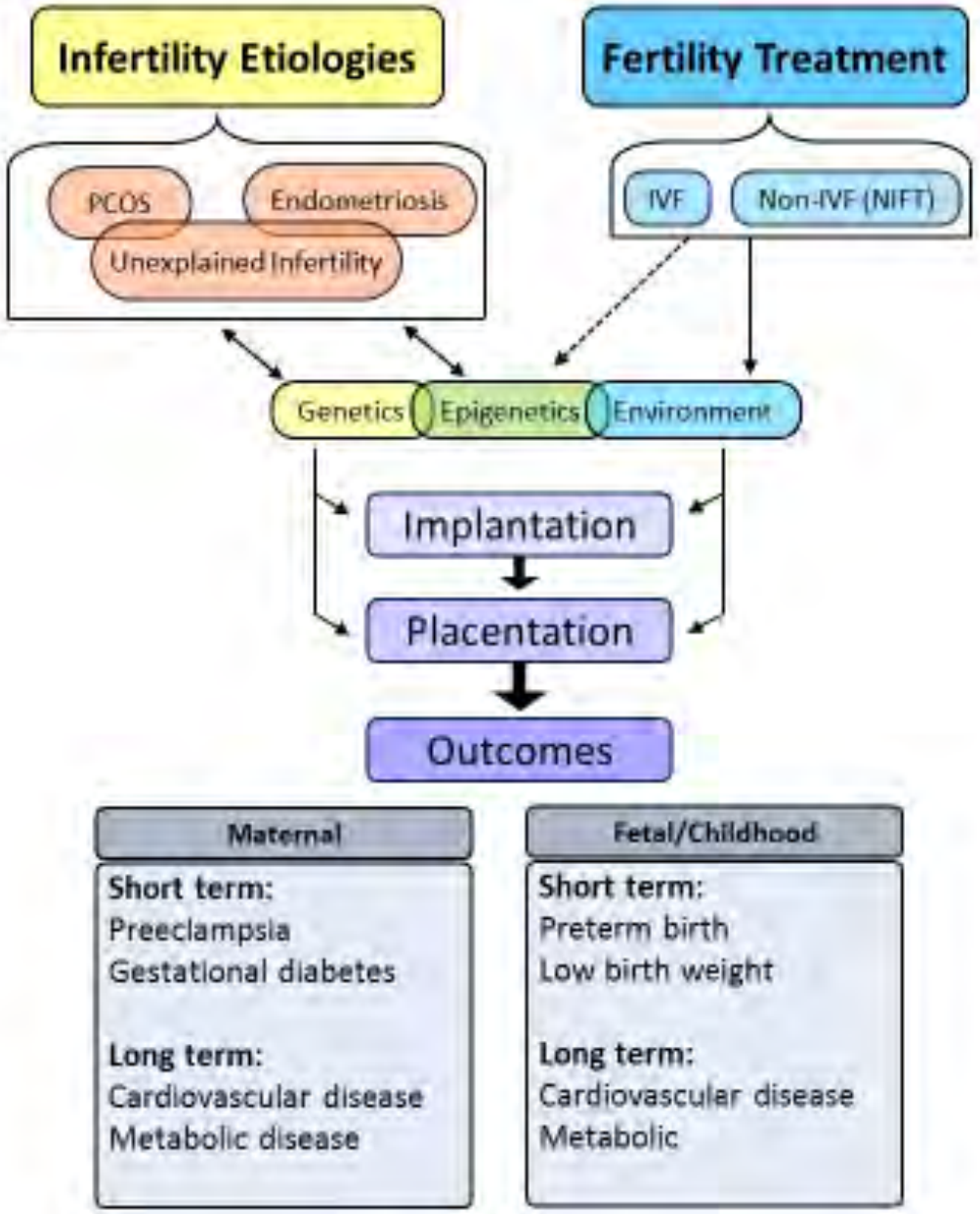
- *Infertility and/or the treatments are associated with some increased risks of adverse outcomes to mother and child including:*
  - *Mother -diabetes, pregnancy induced hypertension, placenta previa and abruption as well as SMM*
  - *Child- prematurity, growth restriction, and birth defects*

- *RISKS ARE SMALL*
- *Risks are independent of treatment utilized*
- *Outcomes are related to placentation*

Conclusions

- *Genetics of infertility appears to be a major contributor that may alter methylation and gene expression*
- *Supraphysiologic hormonal states may be a contributor*
  - *Altered methylation*
  - *Reprogramming the placenta to maintain a high hormonal state*
  - *Impacting trophoblast invasion and migration*
- *Multi-omics suggest genetics/epigenetics are impacting mitochondrial genes in the first trimester placenta*

Future Directions- Infertility Etiology



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Pisarska et al JCEM 2019

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  - *Amy Flowers, PhD*
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- Pediatrics
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- University of Virginia
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  - Stephen Turner PhD
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U01EB02642 (NIBIB/NICHD)

Our patients for participating in our studies to improve outcomes!

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WEDNESDAY

University of Colorado **Anschutz Medical Campus**

My Achy Breaky Heart: Heart Failure and Pregnancy

49th Annual Vail OB-GYN Conference

February 21, 2024

Josephine C. Chou, MD, MS, FACC
Director, Cardio-Obstetrics Program
Assistant Professor, Cardiovascular Medicine
University of Colorado, Aurora, CO

Disclosures

- none

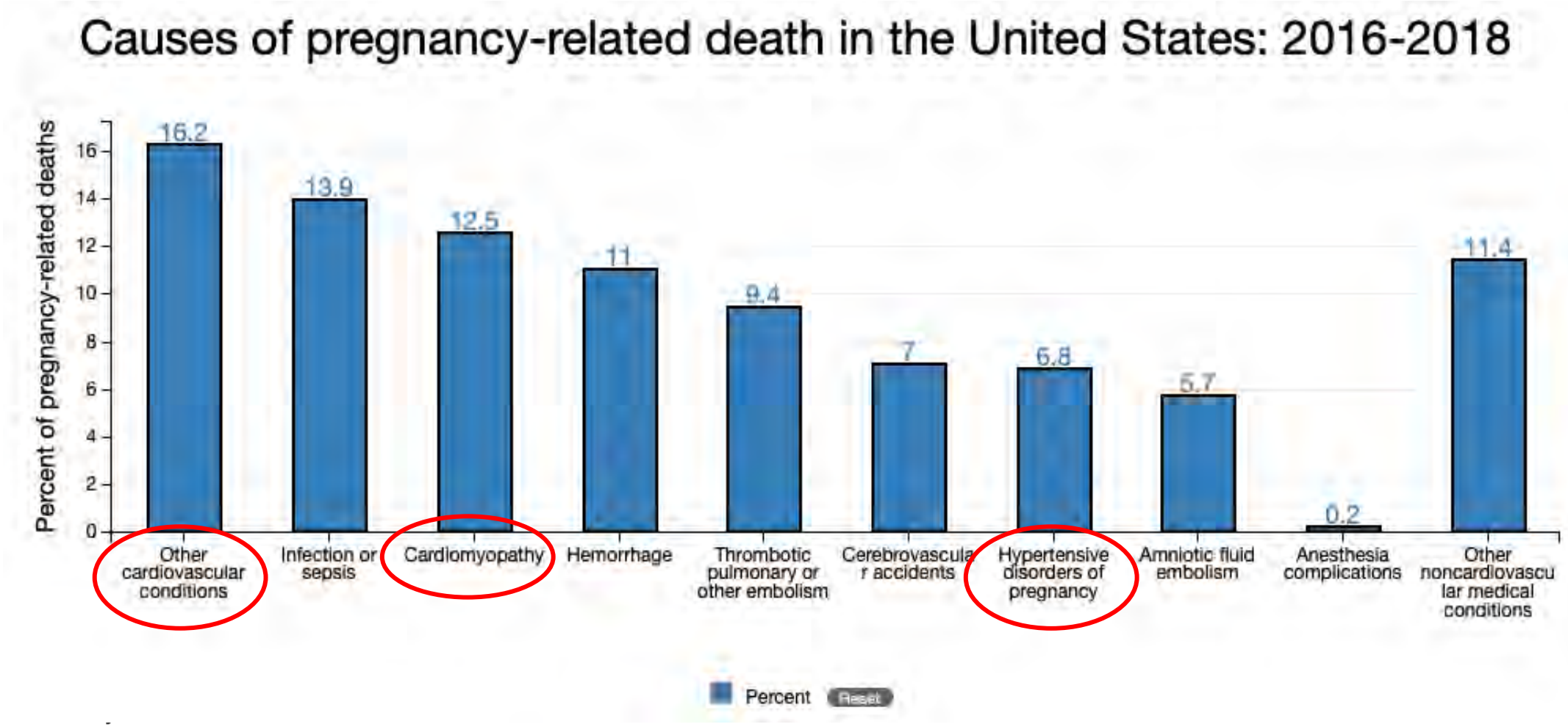
Objectives

- Review the causes of heart failure in pregnancy
- Understand the evaluation and treatment cardiomyopathy in pregnancy
- Know the role of a multi-disciplinary team in the management of pregnant patients with cardiomyopathy

Outline

- Why is heart failure (HF) in pregnancy important?
- Diagnosis: when to suspect HF in pregnancy
- Etiologies of HF in pregnancy
- Management of HF in pregnancy
  - Delivery considerations
  - Medical management
- Postpartum considerations: Subsequent pregnancies
- Special focus on peripartum/postpartum cardiomyopathy (PPCMP) – unique risk factors, management, and prognosis

Cardiovascular disease is the leading cause of pregnancy-related death in the US



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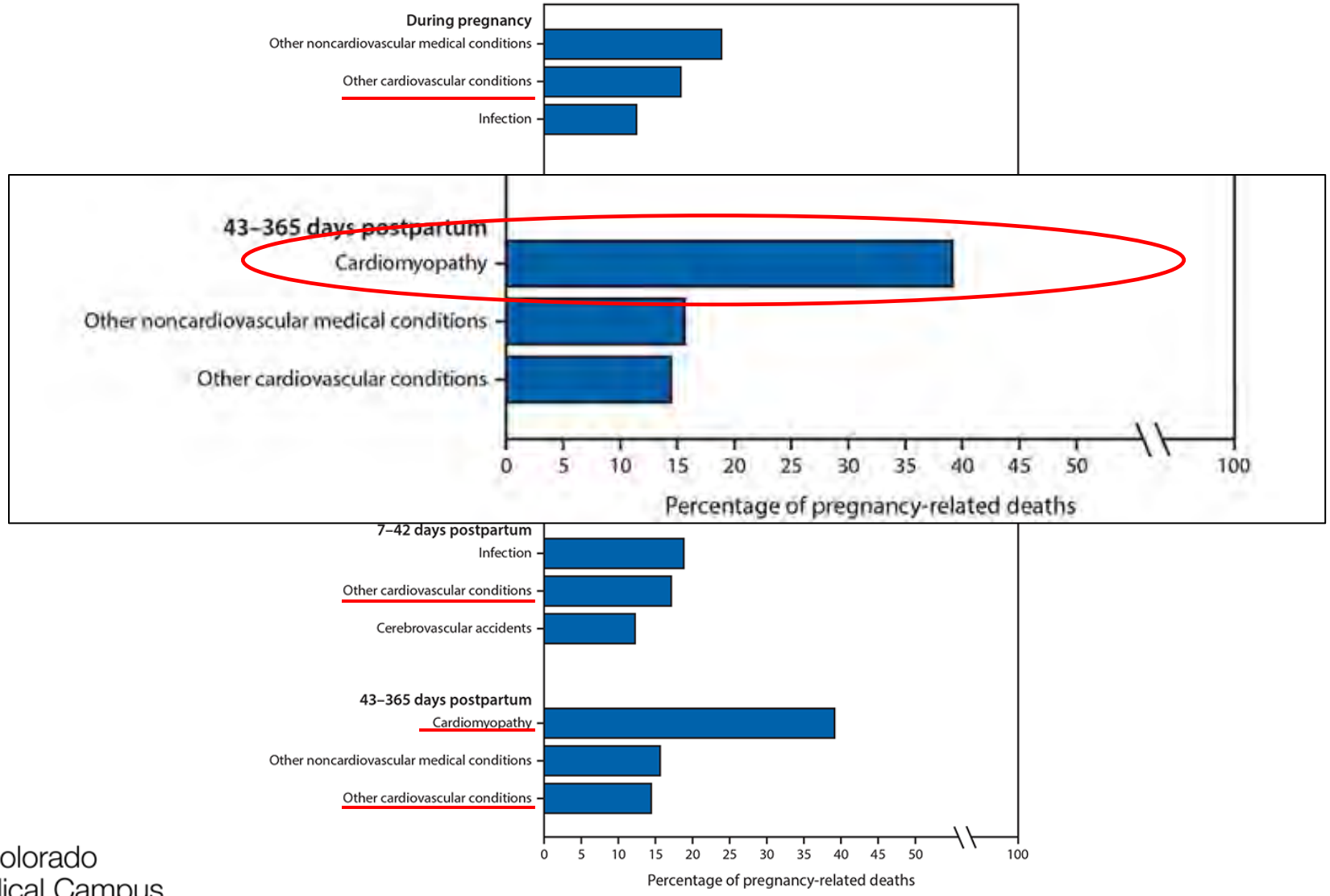
https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html

Timing of pregnancy-related mortality



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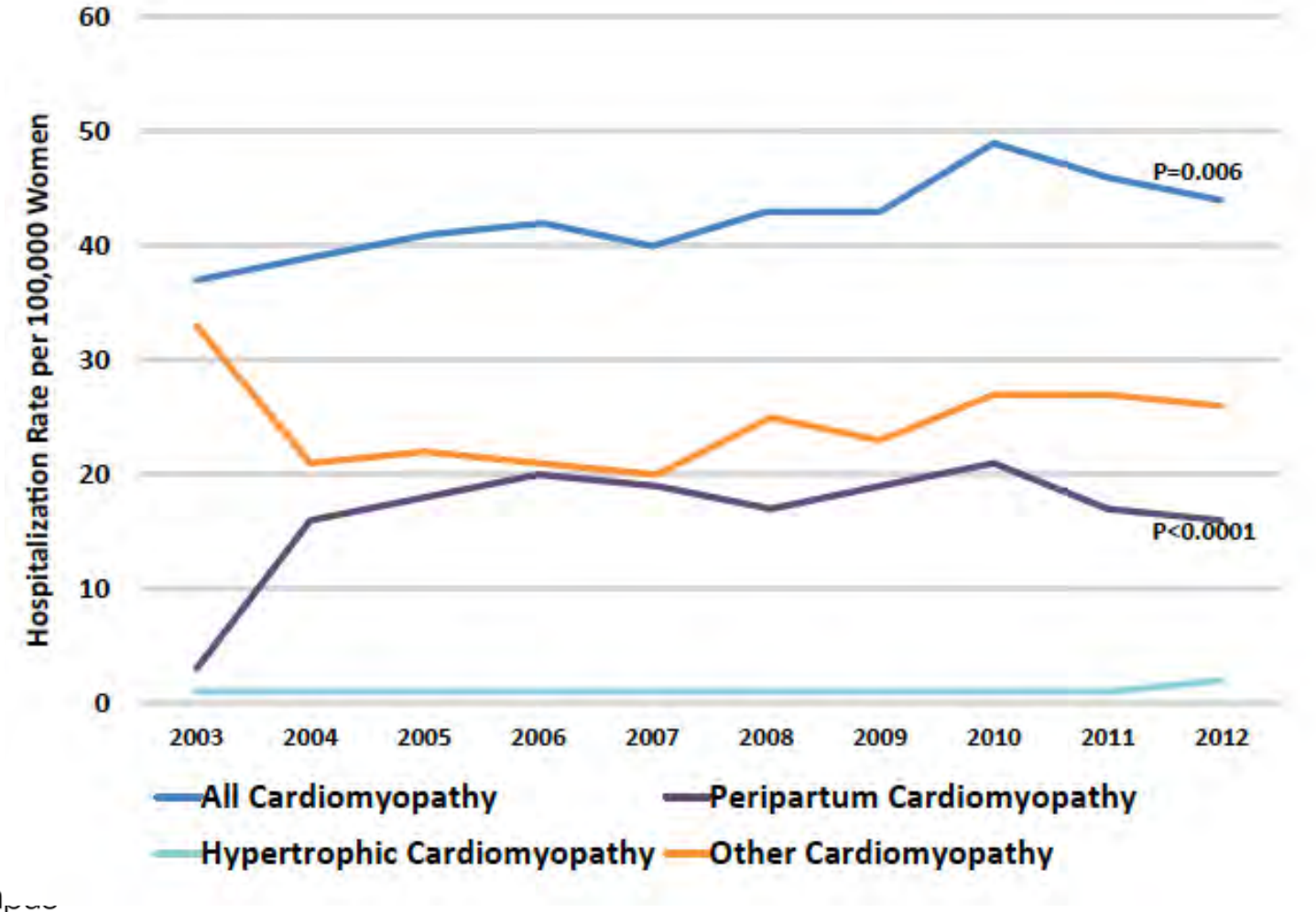
https://www.cdc.gov/mmwr/volumes/68/wr/mm6818e1.htm

Cardiomyopathy in pregnancy is increasing in frequency



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Am J Cardiol 2017;119:1694e1700

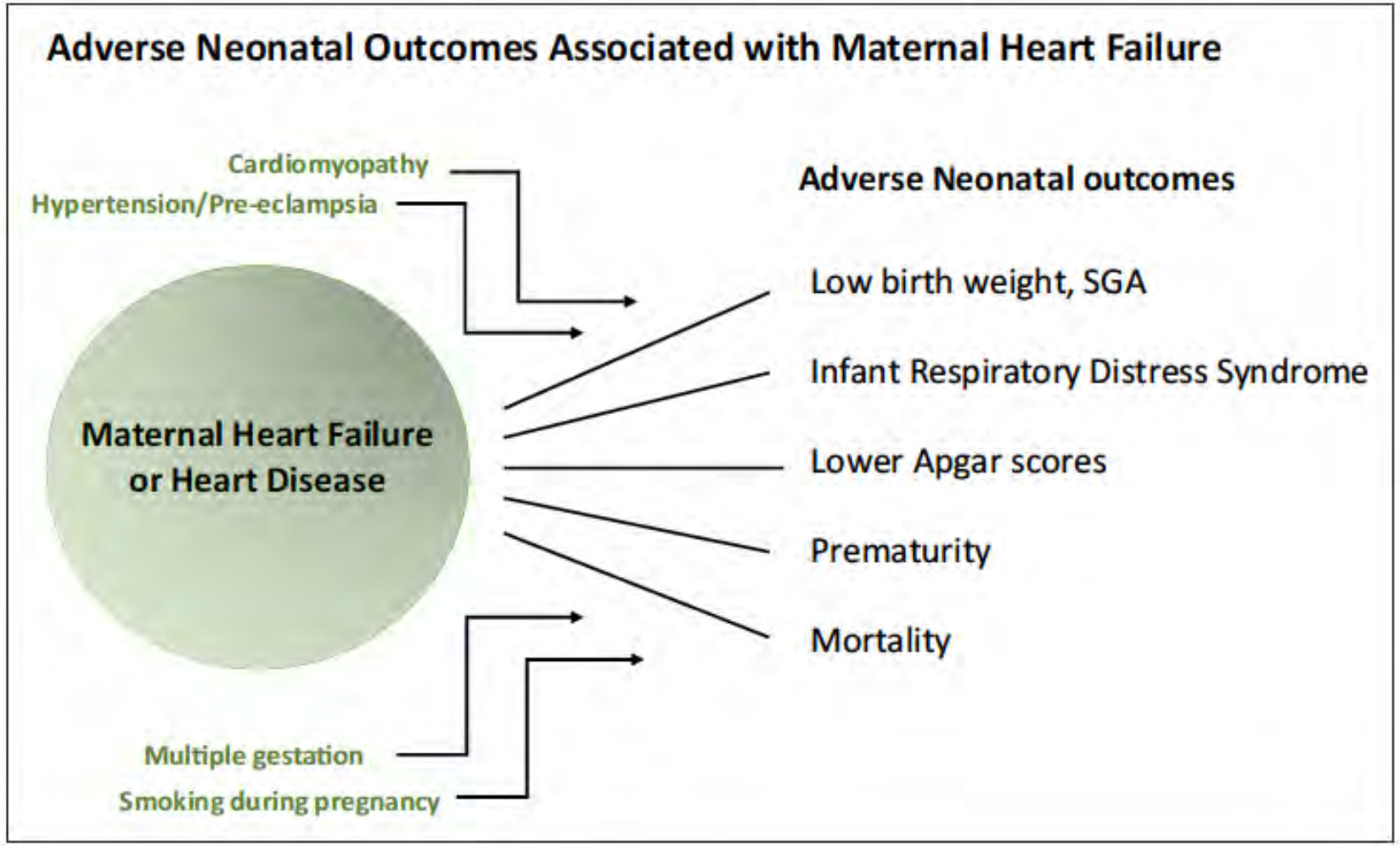
Cardiomyopathy is associated with maternal morbidity

TABLE 2 Outcomes of Women With or Without Cardiomyopathy at Delivery and by Cardiomyopathy Subtype

Outcome	CDM (n = 2,078)	No CDM (n = 4,438,439)	p Value
Major adverse cardiac events*	874 (42.1%)	16,344 (0.4%)	<0.001
Mortality (maternal)	17 (0.82%)	291 (0.01%)	<0.001
Heart failure	686 (33.01%)	1,002 (0.02%)	<0.001
Cardiac arrhythmias	248 (11.93%)	13,788 (0.31%)	<0.001
Cerebrovascular events	3 (0.14%)	396 (0.01%)	<0.001
Acute myocardial infarction	26 (1.25%)	115 (0.002%)	<0.001

(J Am Coll Cardiol HF 2015;3:257–66

Maternal cardiomyopathy affects neonatal outcomes



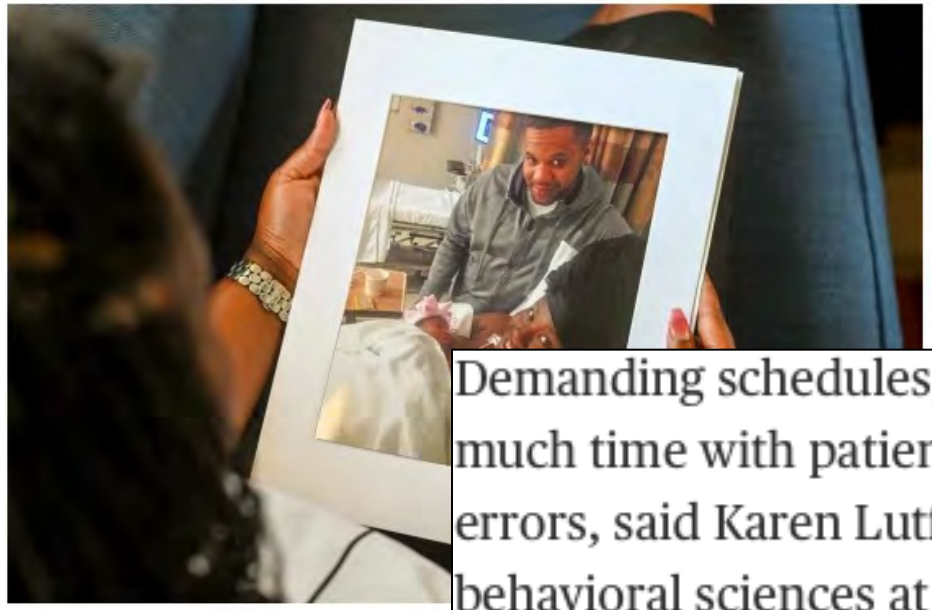
J Am Heart Assoc. 2021;10:e021019

Medical mistakes are more likely in women and minorities

NBC NEWS

Jan. 15, 2024, 3:30 AM MST

By Liz Szabo | KFF Health News



Charity Watkins holds her daught

Charity Watkins sensed something was deeply wrong when she experienced exhaustion after her daughter was born.

At times, Watkins, then 30, had to stop on the stairway to catch her breath. Her obstetrician said postpartum depression likely caused the weakness and fatigue. When Watkins, who is Black, complained of a cough, her doctor blamed the flu.

When a physician finally examined Watkins three days later, he

wollen, a sign that

he doctor

on in which the

gen-rich blood to

eeks in intensive

ost you."

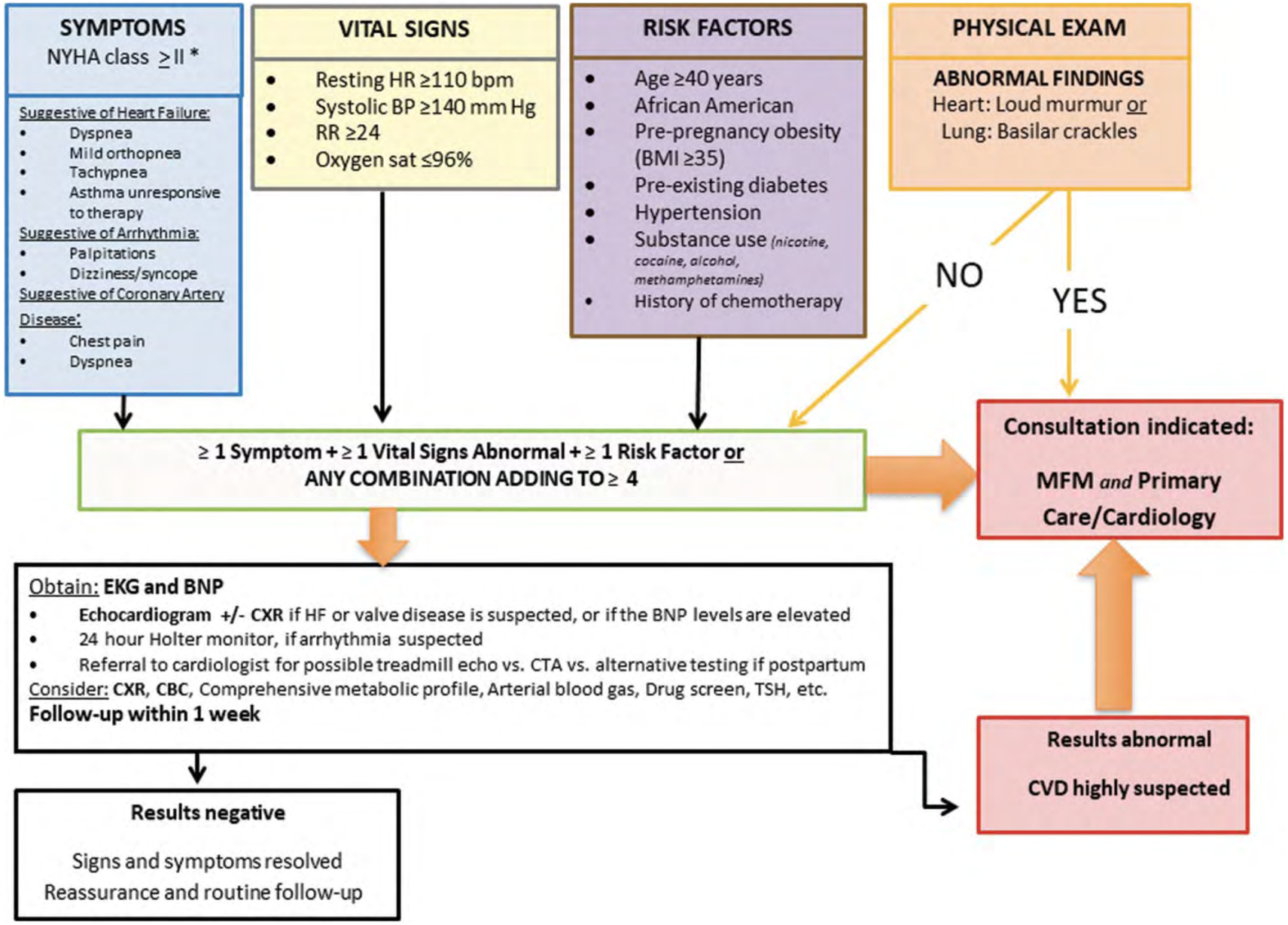
Demanding schedules, which prevent doctors from spending as much time with patients as they'd like, can contribute to diagnostic errors, said Karen Lutfey Spencer, a professor of health and behavioral sciences at the University of Colorado-Denver.

"If they were less certain, they were less likely to take action, such as ordering tests," Spencer said. "If they were less certain, they might just wait to prescribe treatment."

Diagnosis – when to suspect HF?

How to tell from normal pregnancy?

- Symptoms
- Vitals/exam
- Risk factors



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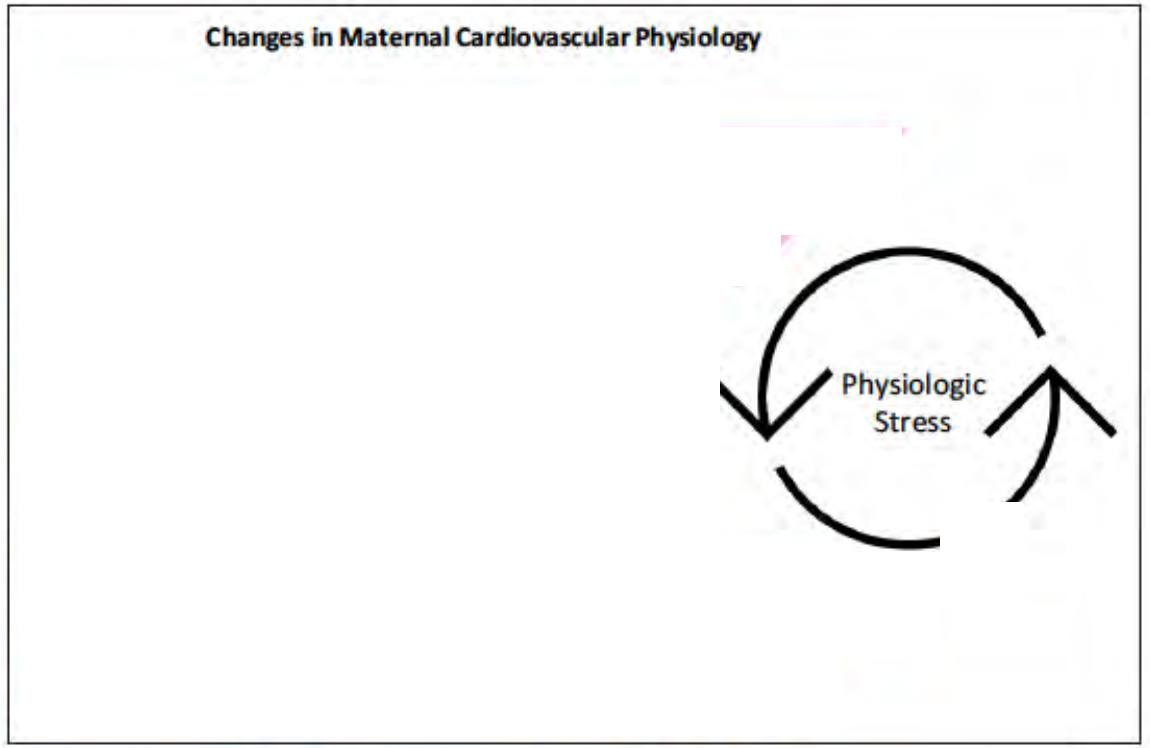
ACOG Practice Bulletin No. 212: Pregnancy and Heart Disease. Obstet Gynecol. 2019 May;133(5):e320-e356

Normal cardiovascular changes with pregnancy

- CV hemodynamic changes in pregnancy
  - Systemic vascular resistance decreases by 20%
  - Heart rate increases by 15-30%
  - Plasma volume increases by 30%
  - Cardiac output increases by 30-50%
- Shifts occur early in second trimester and plateau in 3rd trimester
- During labor and delivery: augmentation of stroke volume, heart rate, and cardiac output (up to 30%)



- Rapid normalization postpartum – most changes within 1st 10 days (especially CO and SVR), normalization by 24 weeks
- Biomarkers (ie: BNP, troponin) remain within normal limits throughout pregnancy, labor/delivery, and postpartum

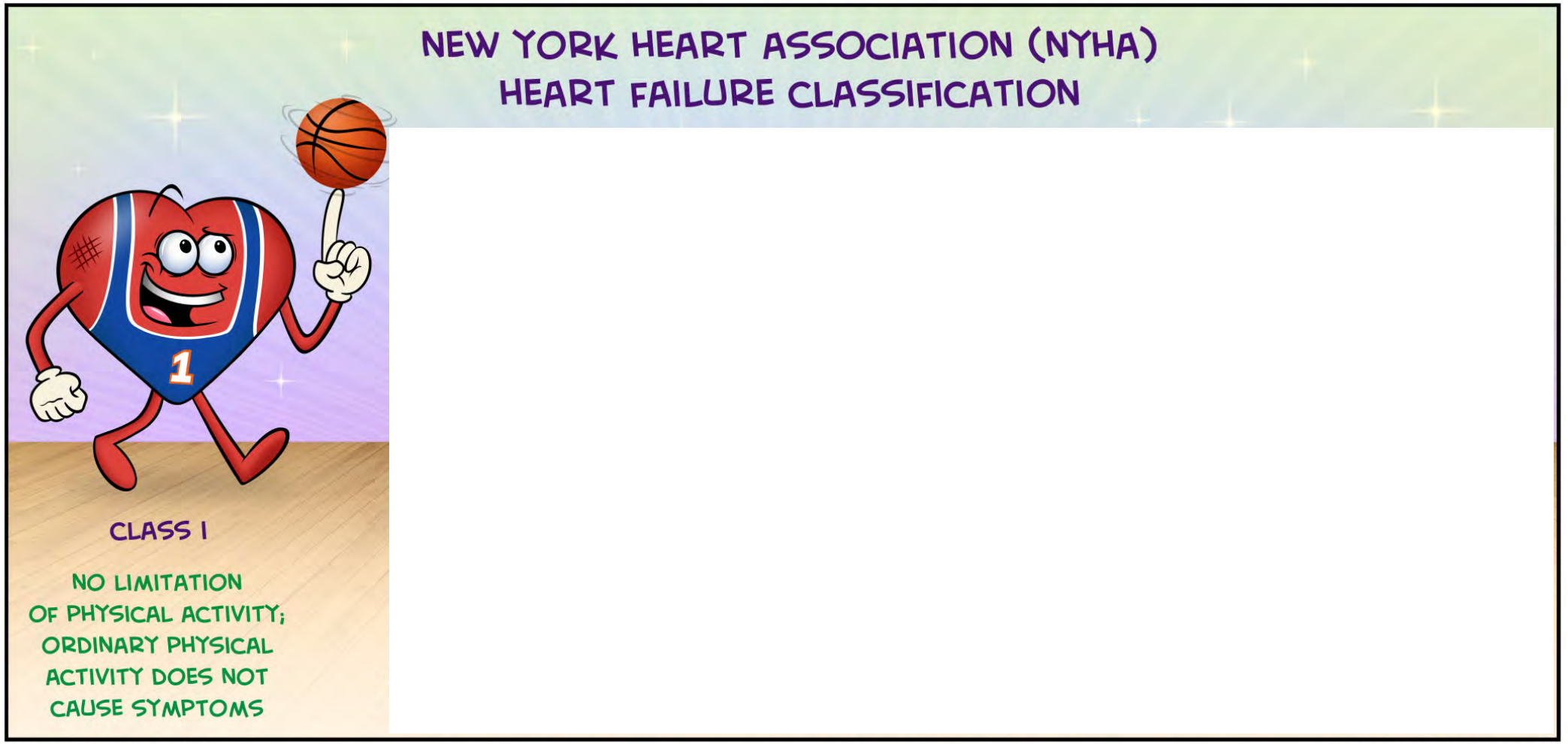
Yucel et al. Curr Treat Options Cardio Med 2017;19:73
J Am Heart Assoc. 2021;10:e021019

Common cardiac symptoms in pregnancy

- Palpitations: “rapid heart beat”, “fluttering”, or “pounding heart”
  - Increased visceral awareness plus hemodynamic and hormonal changes
  - Most common arrhythmias are isolated PACs and PVCs
- Mild lower extremity edema
  - Usually limited to pedal or ankle area and is dependent/positional
- Dyspnea
  - Mild hyperventilation (due to progesterone)
  - Mild in severity, plateaus or diminishes closer to term
  - Does not significantly alter exercise capacity
- Easy fatigability
  - Does not significantly alter exercise capacity

Zeldis. Clin Chest Med 1992;13:567-85

Functional assessment: NYHA class



https://twitter.com/medcomic/status/1488901185062985729/photo/1

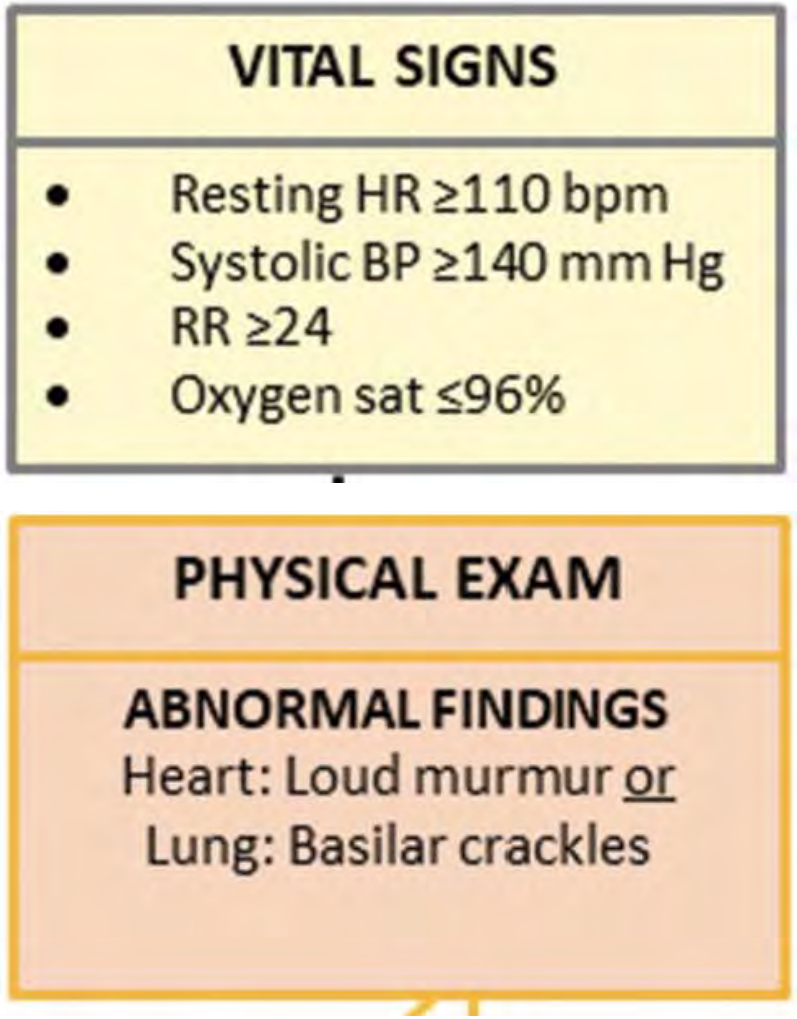
Less common symptoms in normal pregnancy

- Orthopnea
  - Due to upward pressure of uterus on diaphragm
  - Typically worst during later stages of pregnancy and resolve postpartum
- Lightheadedness, syncope
  - Related to uterine venous occlusion or peripheral vasodilatation
- Chest pain
  - Uterine pressure on diaphragm

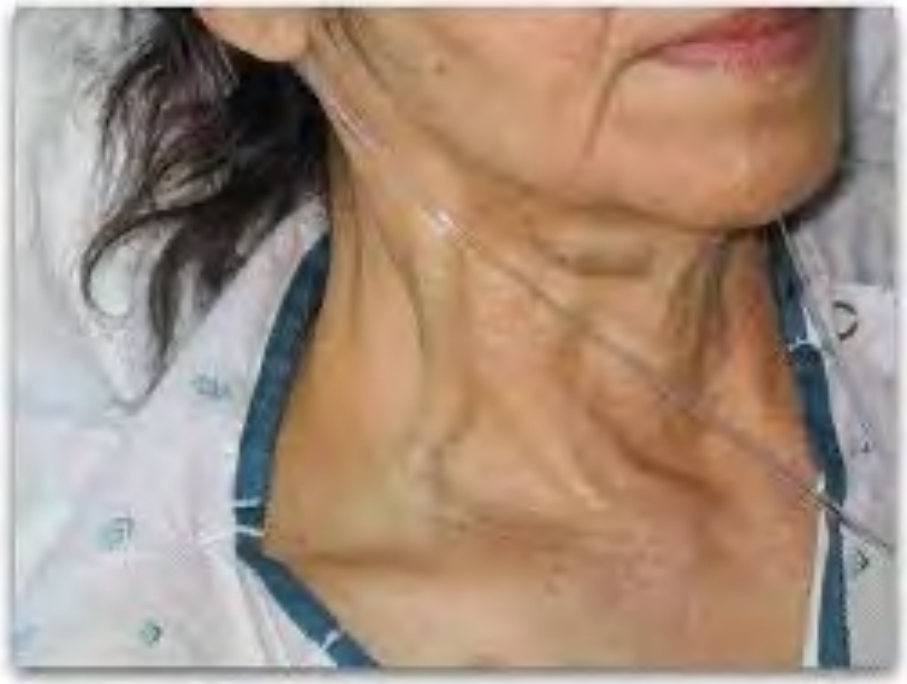
Zeldis. Clin Chest Med 1992;13:567-85
Obstet Gynecol. 2019 May;133(5):e320-e356

Cardiovascular exam in pregnancy

- Brisk arterial pulse
- JVP more conspicuous but normal pressure
- Soft systolic ejection murmur or venous hum
- Louder heart sounds
- Wider physiologic splitting
- Physiologic S3 common
- Larger PMI and shifted to the left
- Mild pedal or ankle edema



Jugular Venous Pressure



Jugular Vein	Carotid Artery

"Red flag" signs and symptoms

Vitals and labs
- Resting HR >120 bpm
- BP >= 160 mmHg
- Hypoxia
- Elevated BNP
- Elevated troponin

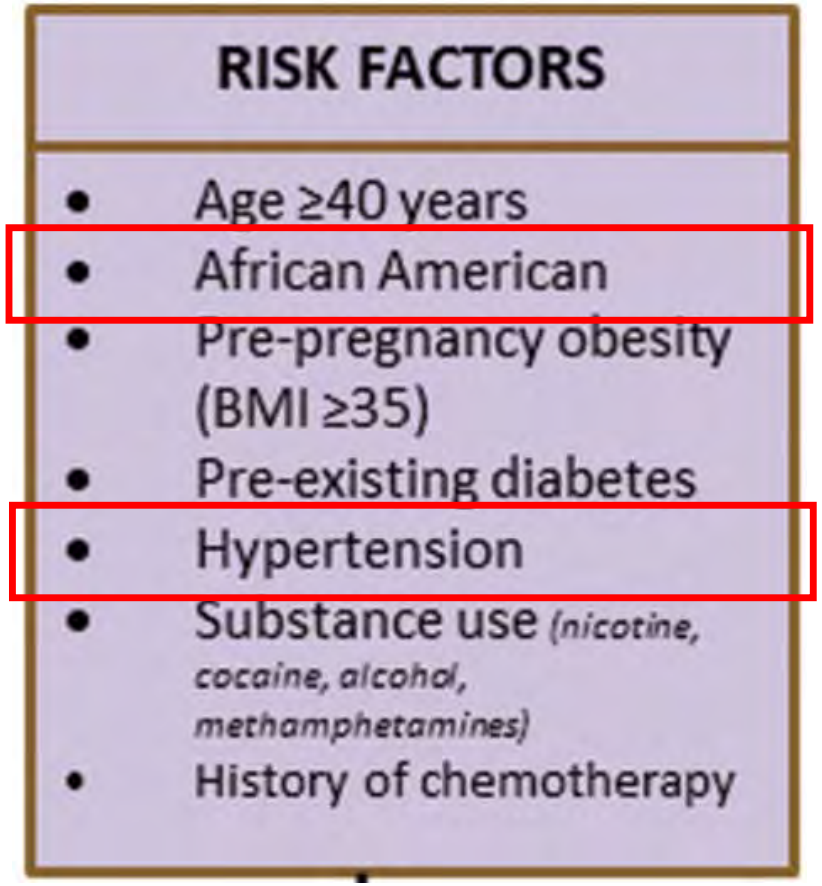
Exam
- Elevated JVP
- S4 gallop
- Loud murmurs
- Lung crackles
- Marked edema (up to or past the knees)

Symptoms
- Severe dyspnea (esp at rest)
- Chest pain (exertional)
- Syncope

- **Persistence or worsening of pregnancy signs or symptoms in the post partum period**

ACOG Practice Bulletin No. 212: Pregnancy and Heart Disease. Obstet Gynecol. 2019 May;133(5):e320-e356

Risk factors for CVD



- Black race [1,2]
  - Higher rates of mortality (OR 1.45), MI (OR 1.23), PPCMP (OR 1.71)
  - PPCMP: more severe LV dysfunction at presentation and lower rates of LV recovery
- HTN, incl HDP [3]
  - Subclinical CVD even in otherwise normal pregnancies
  - Pre-existing CVD: 30% of patients develop HF with HDP
  - PPCMP patients are 4X more likely to have preeclampsia as compared to general population

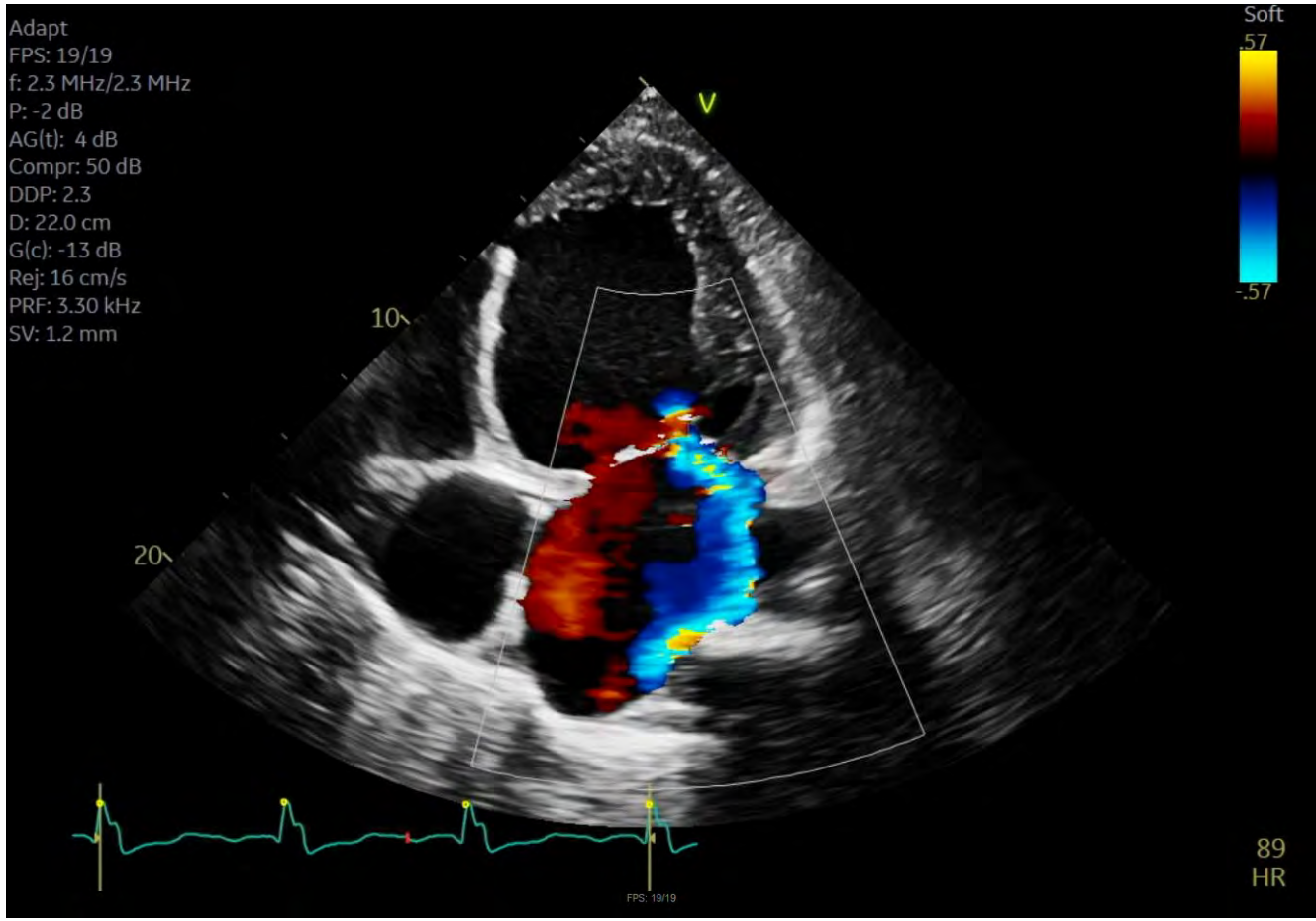
(1) *J Am Heart Assoc. 2021;10:e017832*
(2) *J Am Coll Cardiol 2015;66:905–14*
(3) *Heart 2014;100:231–238*

Initial diagnostic evaluation

- EKG
- Echocardiogram
- Labs: BNP (can consider CMP, drug screen, troponin)
- Cardiology or CardioOB and MFM referral

Example patient

- 32yo female G5P4004 currently at 36 weeks gestation, presenting with dyspnea
- Vitals: comfortable, afebrile, BP 100/70, HR 110, PaO2 99% RA
- Exam: JVP 15cm, tachy/regular with soft S4 gallop, systolic murmur at apex, lungs clear, gravid abdomen, 2+ LE edema to the thighs
- Echo: LVEF 25%, LVEDD 6.5 cm, normal RV, severe central MR, PASP 50-55 Hg
- Now what?



Management of Acute Heart Failure during Pregnancy

Acute heart failure during pregnancy

- **Cardiovascular challenges during delivery**
  - Positional hypotension
  - Increased cardiac output
  - Blood loss
  - Volume administration
- **Multidisciplinary team recommended**
  - Cardiology: CardioOB, Heart Failure, Interventional,
  - CT surgery
  - MFM (or High-risk Obstetrics)
  - Anesthesia: Cardiac and Obstetric
  - Critical care
  - Neonatology

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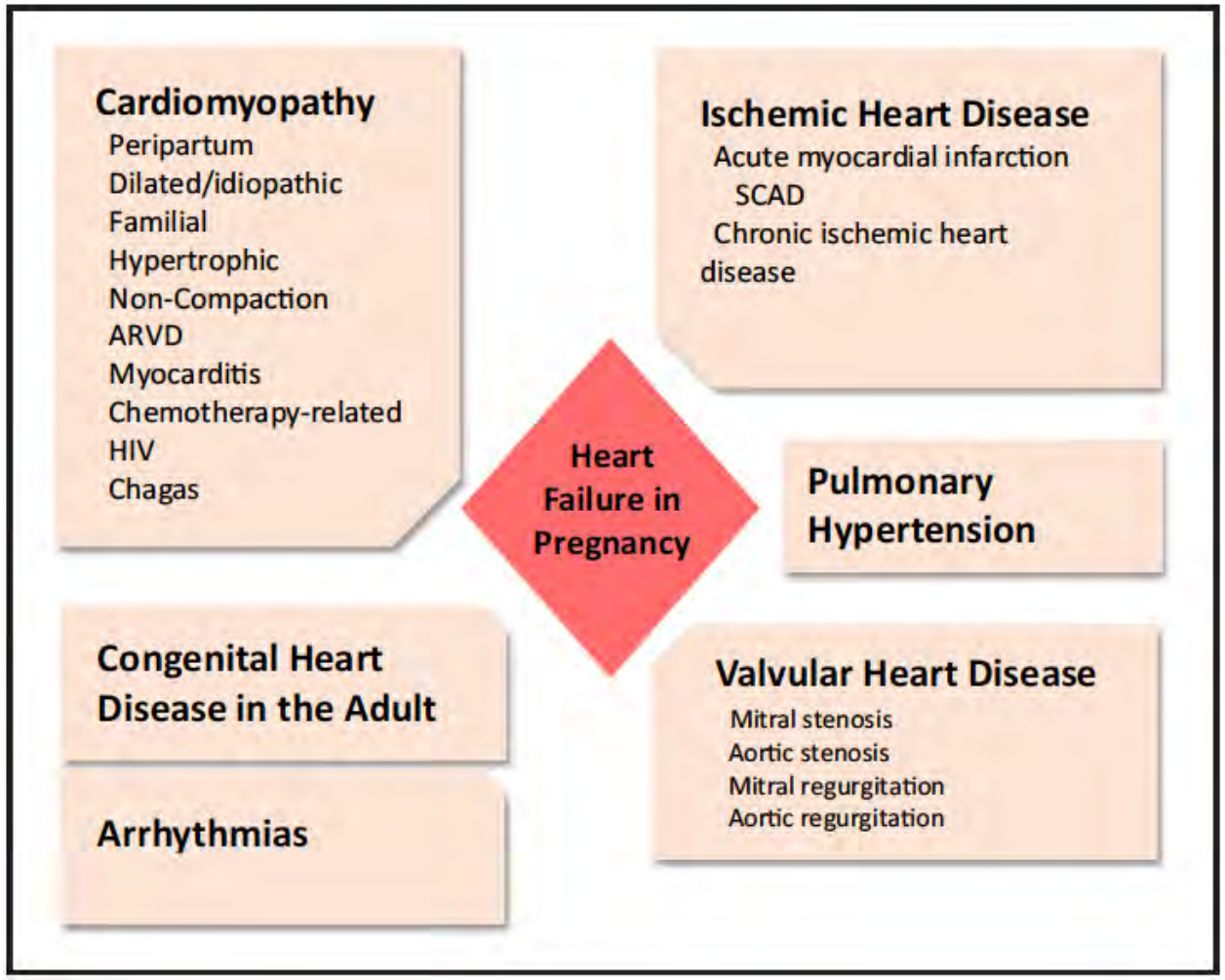
Broad DDx for Heart Failure Symptoms in Pregnancy



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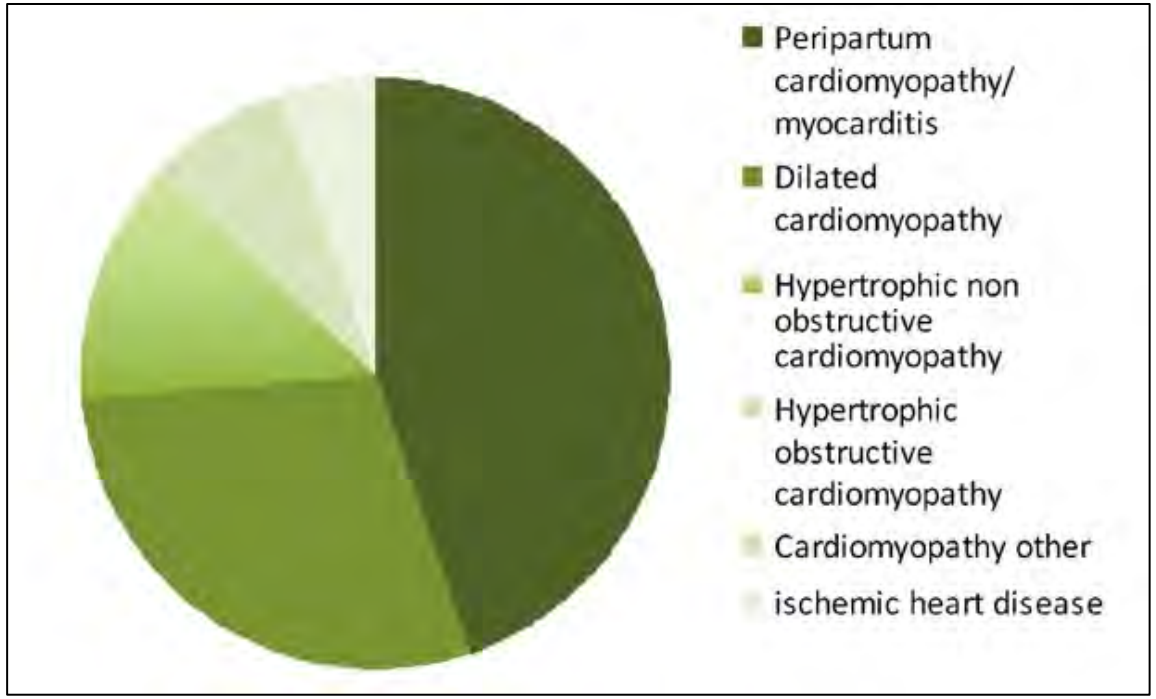
J Am Heart Assoc. 2021;10:e021019

Causes of cardiomyopathy in pregnancy

PPCMP: Idiopathic LV dysfunction (LVEF <45%) with or without LV dilatation presenting in the last month of pregnancy or in the months following delivery

- Most common CMP in pregnancy, but is a diagnosis of exclusion

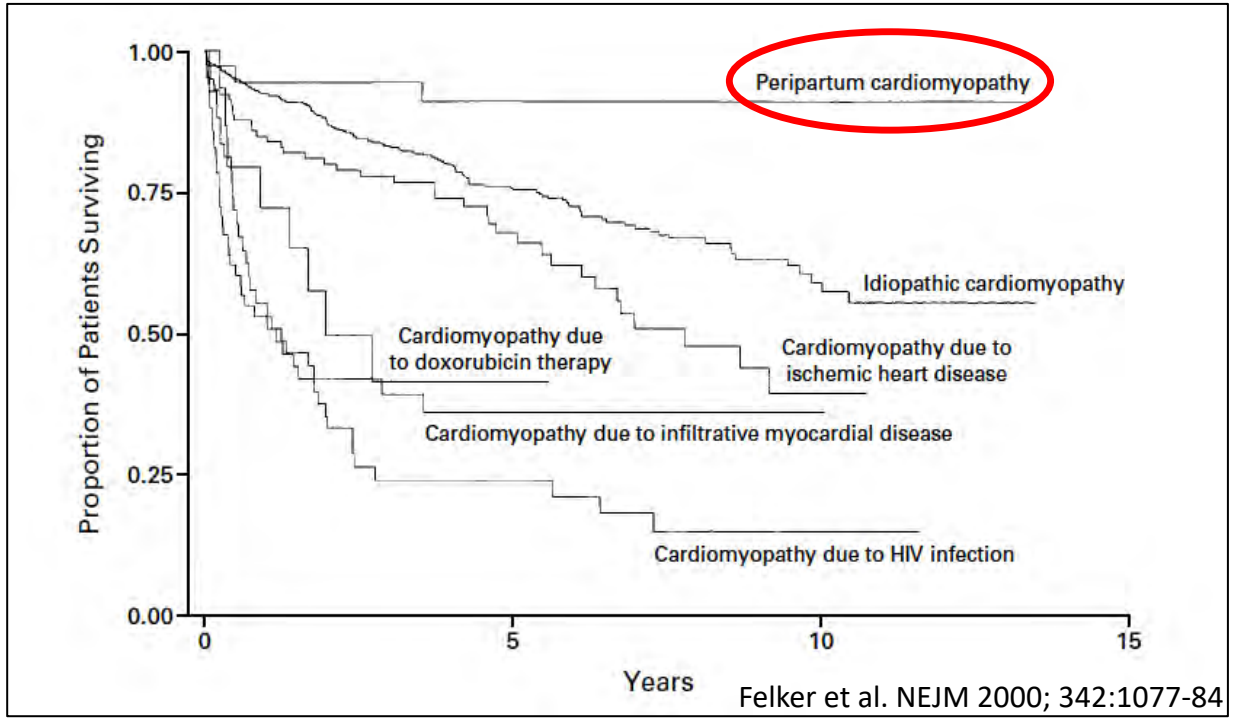
- Differential diagnosis:
  - Hypertensive heart disease: preeclampsia, gestational HTN
  - Ischemic heart disease: SCAD, ASCVD
  - Pre-existing cardiomyopathy: genetic/familial, idiopathic, congenital
  - Acute myocarditis
  - Stress-induced cardiomyopathy
  - Heritable systemic disease: metabolic (mitochondrial disease), muscular dystrophy carrier (dystrophinopathy, myotonic dystrophy)



Heart 2014;100:231–238.

PPCMP is unique

- PPCMP with highest rates of survival compared to other forms of HF (1)
- Most recovery within 3-6 months (2)
- Delayed recovery can occur even up to 2 years – by then 83% recover (3)



Felker et al. NEJM 2000; 342:1077-84

<u>Adverse predictors for recovery:</u> (4)

- Severe LV dysfunction (LVEF <30%)
- Black or African descent

Breastfeeding has <u>not</u> been proven to be detrimental to recovery (2)

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(1) Cooper. J Cardiac Fail 2012;18:28-33
(2) McNamara. J Am Coll Cardiol 2015;905-14
(3) Pillarisetti. J Am Coll Cardiol 2014;63:2831–9
(4) Davis. J Am Coll Cardiol 2020;75:207–21

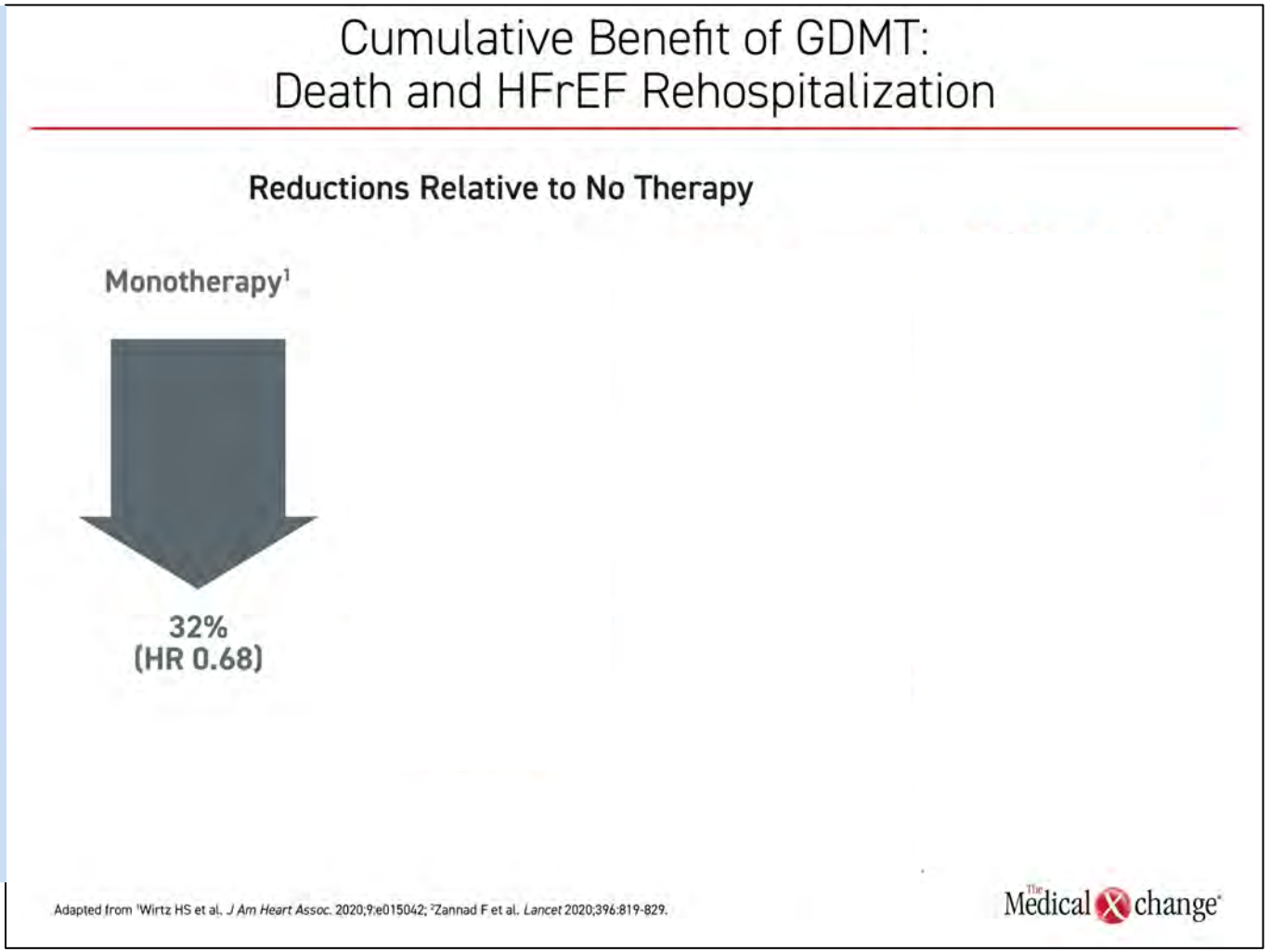
Guideline Directed Medical Therapy (GDMT) for Cardiomyopathy: “Quad therapy”

”HF beta-blocker”
Coreg
Toprol (metoprolol succinate)
Bisoprolol

Mineralocorticoid receptor antagonist (spironolactone, eplerenone)

ACEi
ARB
ARB+neprilysn inhibitor (ARNI; Entresto)

Sodium glucose co-transporter inhibitor-2 (SGLT2-i)



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J Am Coll Cardiol. 2022 Feb, 79 (5) 504–510

Can you still use GDMT in pregnancy or lacatation?

Medication[1]	**During Pregnancy**	**During lactation**
Beta-blocker - metoprolol succinate, carvedilol	Yes	Yes
ACEi/ARB	Avoid	Enalapril, captopril
ARNI (Entresto)	Avoid	No human data
Mineralocorticoid receptor antagonist	Spironolactone (not preferred)	Spironolactone
SGLT2i	No human data	No human data
Hydralazine/nitrates	Yes	Yes
Loop diuretics	Yes	Yes
Digoxin	Yes	Yes

Anticoagulation

- Treat for LVEF <40% **AND** systemic thromboembolism (LV thrombus, DVT, PE, CVA) or another indication for anticoagulation (ie: afib)
- May consider for LVEF <40% during pregnancy and up to 8 weeks postpartum
- Heparins safe in pregnancy and lactation. Coumadin safe in lactation.

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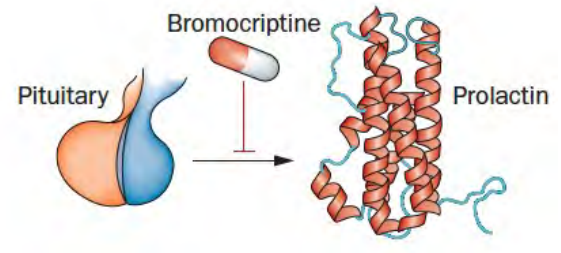
(1) Davis. J Am Coll Cardiol 2020;75:207–21
(2) Regitz-Zagrosek. Eur Heart J (2018) 39, 3165–3241

Bromocriptine: Targeted treatment for PPCMP?



- Bromocriptine: ergot derivative that inhibits prolactin secretion
- Prolactin levels are elevated in late pregnancy to promote lactation
  - May be myotoxic and contribute to cardiomyopathy
- 2018 ESC Guidelines CVD during Pregnancy[(2)]: Consider bromocriptine for severe PPCMP treatment (Level IIB, Evidence B)
  - Pilot/registry data and small RCT suggestive of benefit in LV recovery in PPCMP
  - Considerations: Effect of background HF GDMT; no placebo control; different population (Black participants – 1-2% in bromocriptine studies)
- Other bromocriptine risks: thromboembolic risk, lactation-suppressant
- Bromocriptine is considered experimental for PPMCP in US/Canada
- **REBIRTH** (**R**andomized **E**valuation of **B**romocriptine **I**n Myocardial **R**ecovery **TH**erapy)
  - Inclusion criteria: new or recurrent PPCMP with EF =<40% (remote visits feasible)
  - Bromocriptine vs placebo with prophylactic anticoagulation and HF GDMT
  - Observational breastfeeding cohort

CV risk for subsequent pregnancy

WHO 2-3 depending on individual

Mild left ventricular impairment
Hypertrophic cardiomyopathy
Native or tissue valvular heart disease not considered WHO 4
Marfan syndrome without aortic dilatation
Heart transplantation

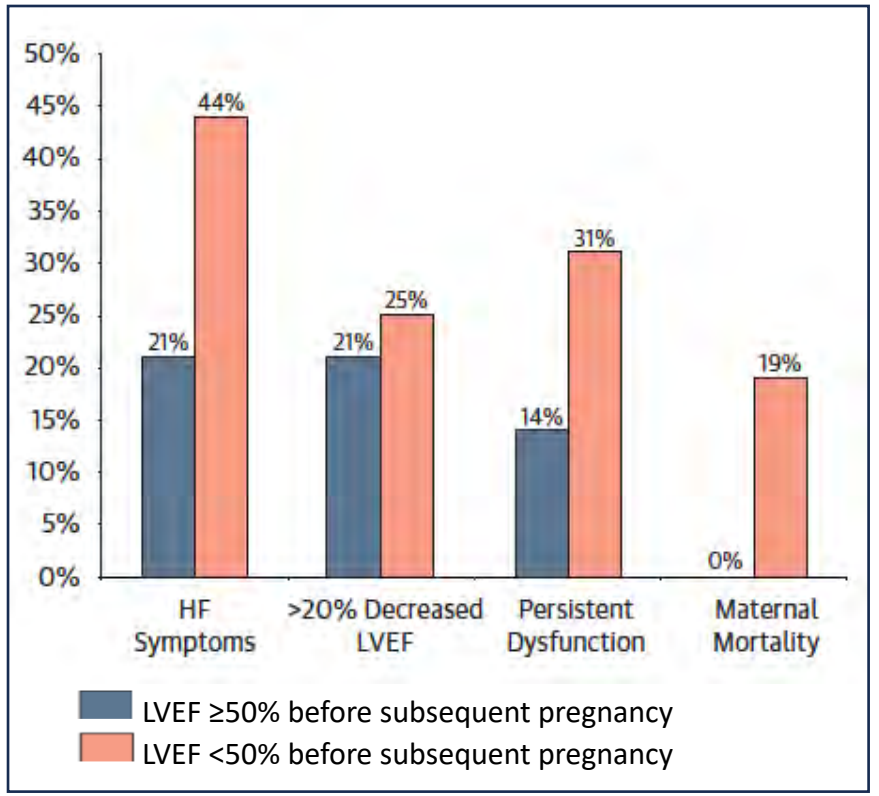
Table 4 Conditions in which pregnancy risk is WHO 4

- Pulmonary arterial hypertension of any cause
- Severe systemic ventricular dysfunction
  - NYHA III–IV or LVEF <30%
- Previous peripartum cardiomyopathy with any residual impairment of left ventricular function
- Severe left heart obstruction
- Marfan syndrome with aorta dilated >40 mm

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Subsequent pregnancy after PPCMP

- Pre-pregnancy LVEF is the best predictor of relapse with subsequent pregnancy
- Patients with persistent LV dysfunction (EF <50%) [1]
  - 1) Higher risk of further decline in LVEF
  - 2) Lower likelihood of recovery
  - 3) Higher rates of maternal mortality
- Normalization of LV function does **not guarantee** an uncomplicated subsequent pregnancy [2]
  - Limited HF GDMT use in pregnancy
- Long term mortality and risk of adverse cardiac outcomes high after subsequent pregnancy, regardless of LV recovery [3]
- If considering another pregnancy after PPCMP:
  - Preconception counseling with cardioOB and MFM



(1) JACC 2014;64(15):1629-36
(2) J Heart Lung Transplant 2023;42:e1−e42
(3) J Am Coll Cardiol 2023;82:16–26

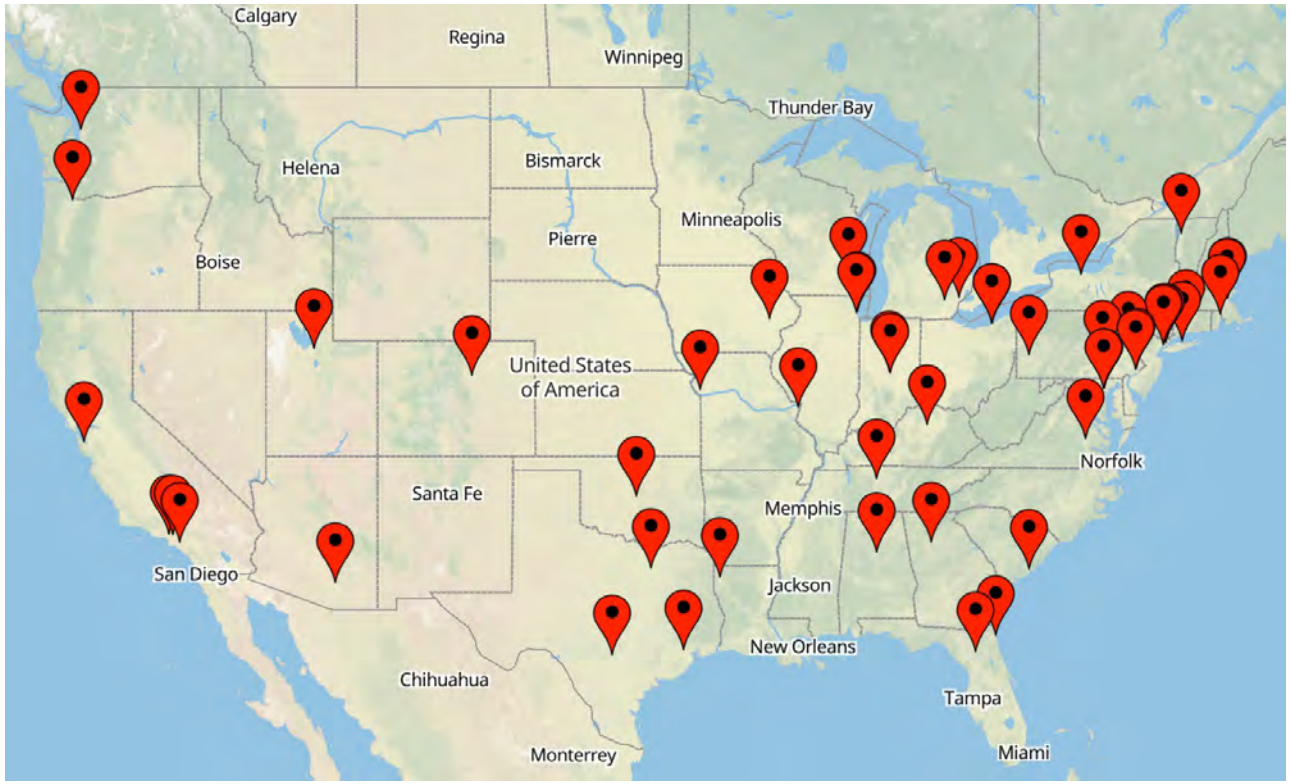
The Rise of Cardio-Obstetrics

- CU CardioOB: Multidisciplinary subspecialty dedicated to the pregnancy-related care of patients with CVD
- Clinical care: Multidisciplinary cardiac care team
  - Cardiology
    - Amber Khanna, MD: Adult Congenital Heart Disease
    - Alexis Tumolo, MD: Electrophysiology
    - Josephine Chou: General cardiology and heart failure
  - Maternal Fetal Medicine
    - Shannon Son, MD
    - Allison Faucett, MD
  - OB Anesthesia
    - Cristina Wood, MD
  - Cardiology and MFM nursing (Renee Julien, Lindsey French-Stewart)
- Education
- Research

REBIRTH

- New PPCMP with EF <40%
- CU coordinator: Emanual.gebreab@cuanschutz.edu
- CU Site PI: Josephine.chou@cuanschutz.edu

National REBIRTH sites



https://peripartumcmnetwork.pitt.edu

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Conclusions

- Heart failure is a leading cause of pregnancy-related morbidity and mortality
- PPCMP is the most common form of cardiomyopathy diagnosed pregnancy
- Recognition of heart failure symptoms in pregnancy and postpartum is critical to early diagnosis and treatment
- Acute heart failure in pregnancy management is complex, and a multi-disciplinary team approach to care including Cardio-Obstetrics is highly recommended
- Ongoing education and research can hopefully help optimize treatments for pregnant patients HF and CVD

THANK YOU

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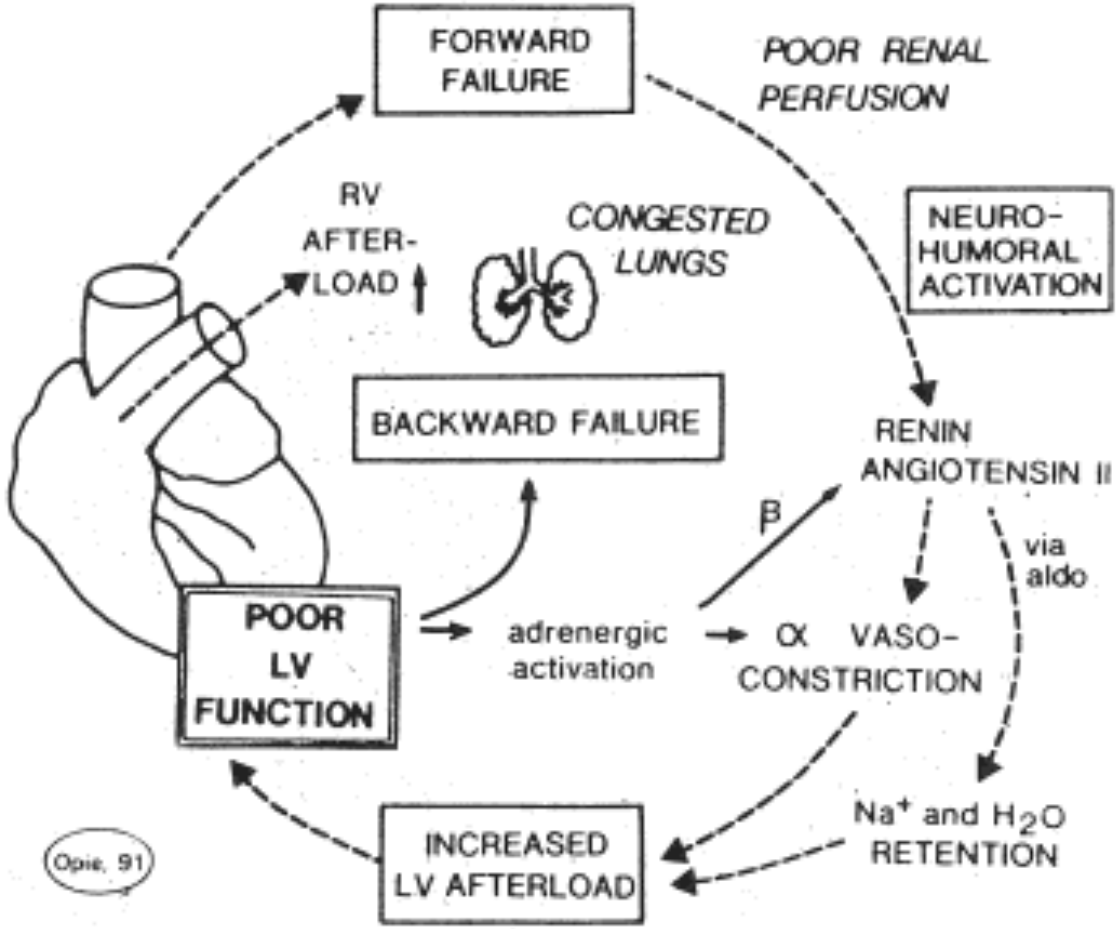
Case 2 - JM

- 42yo Caucasian female presenting with chest pain, progressive LE edema to the upper thighs, PND, orthopnea, and dyspnea (now SOB at rest)
- PMHx: G1P0 – currently 39 weeks GA
- Vitals: afebrile, HR 110s, RR 20, BP 110/60, PaO2 97% on 2L NC
- PE: NAD, tachy but regular with loud S3 gallop, bibasilar crackles, gravid/firm, 4+ pitting edema to upper thighs
- Labs: Cr 0.8, NT-pro BNP 3,245, troponin <0.01, UA no protein
- CXR: pulmonary edema with pleural effusion
- EKG: sinus tachycardia without ST changes
- Echo: EF 30% with global hypokinesis, non-dilated LV, normal RV size/function, no valvular abnormalities, no pericardial effusion

Case 2 - JM

- Gentle diuresis peripartum
- Underwent induction of labor with epidural, successful vacuum assisted vaginal delivery
- Transferred to CCU postpartum – continued diuresis, started on heart failure medications and bromocriptine with coumadin
- Coronary angiogram and cardiac MRI unremarkable
- Discharged on hospital day 7
- Regular heart failure cardiology follow up postpartum - last EF 48% with preserved RV function

Pathophysiology of heart failure and GDMT



HF Guideline Directed Medical Therapy (GDMT) or "Quad Therapy"

- Beta-blockade
  - Carvedilol (Coreg)
  - Metoprolol succinate (Toprol-XL)
  - Bisoprolol
- Renin-angiotensin system inhibition
  - ACE-inhibitors (ACEi)
  - Angiotensin-receptor blocker (ARB)
  - ARB + neprilysin inhibitor (ARNI) - Entresto
- Aldosterone antagonism
  - Spironolactone or Eplerenone
- SGLT2i (sodium glucose transport inhibition)
  - Empagliflozin or Dapagliflozin

HF GDMT in PPCMP: Registry data

	IMP % ($n = 82$)	NIMP % ($n = 14$)	Full recovery % ($n = 45$)
Beta-blockers	95 ($n = 78$)	50 ($n = 7$)	93 ($n = 42$)
ACE Inhib or ARB	93 ($n = 76$)	71 ($n = 10$)	91 ($n = 41$)
ACE Inhib	84 ($n = 69$)	64 ($n = 9$)	80 ($n = 36$)
ARB	11 ($n = 9$)	8 ($n = 1$)	14 ($n = 6$)
MRA	65 ($n = 53$)	57 ($n = 8$)	56 ($n = 25$)
Diuretics	76 ($n = 62$)	86 ($n = 12$)	65 ($n = 29$)
Digitalis	5 ($n = 4$)	21 ($n = 3$)	4 ($n = 2$)

Haghikia et al. Basic Res Cardiol 2013;108:366

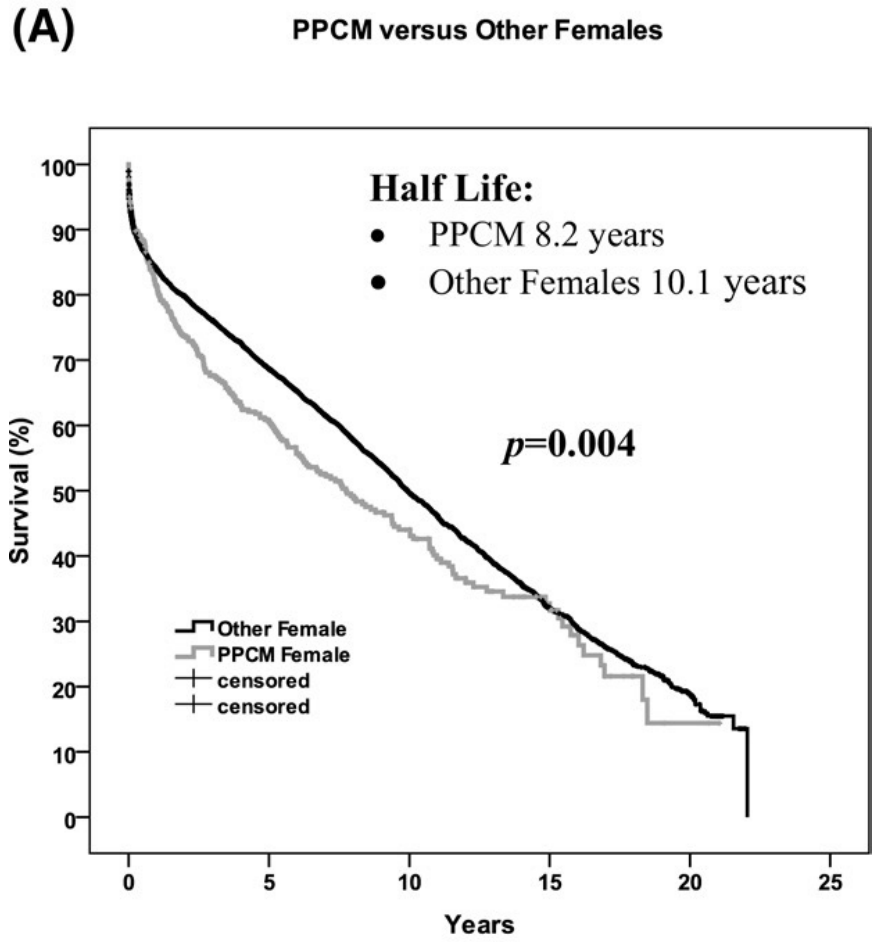
Patient TB

- 32yo female with history of cardiomyopathy, currently at 36 weeks gestation, presenting with dyspnea
- PMHx: 4 prior term pregnancies
  - G1 and G2: term vaginal delivery, uncomplicated
  - G3: Term SVD uncomplicated. Admitted with SOB 3 days postpartum, LVEF 45% -> recovered spontaneously without meds by 1 mo PP. Diagnosed with recovered PPCMP.
  - G4: Limited prenatal and cardiology care. LVEF 60% at 30wk GA. Term SVD (declined f/u echo). Readmitted 1 week PP with SOB, LVEF 35%. Coronary CTA and CMRI unrevealing. Started on Toprol and enalapril with recovery of LVEF to 50% by 6 mo PP. Declined birth control. Lost to follow up.
  - G5: No prenatal or cardiology care. Off all GDMT.
- Social Hx: Intermittent tobacco and EtOH use. Intermittently homeless. Domestic violence victim. All children in foster care.

Advanced HF therapies in PPCMP

- Durable MCS in PPCMP (INTERMACS) (1)
  - Overall "good" survival: 85% at 1 year, 68% at 3 years
  - Low recovery rates (~6%)
  - 48% transplanted by 3 years
- Heart transplant after PPCMP (2)
  - Lower graft survival with PPCMP as indication for transplant

<u>All options for recovery should be exhausted in PPCMP before undertaking advanced therapies</u>



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Circ Heart Fail 2014;7:300-9
JHLT 2012;31:180-6

Patient TB follow up

- Hospital course
  - Diuresed with IV Lasix with symptomatic improvement
  - Restarted Toprol
  - Deemed not a candidate for advanced HF therapies due to social factors
- Subsequent pregnancy care
  - Underwent induction of labor with early epidural with successful unassisted vaginal delivery of baby boy (immediate child protective custody)
  - Initially agreed to tubal ligation -> declined at last minute -> Nexplanon placed
  - Started Entresto; declined bromocriptine/anticoagulation
- 3mo PP: LVEF 30% with LVEDD 6.0 cm. Declined ICD.

PPCMP basics

- Definition: Idiopathic cardiomyopathy with LV dysfunction (LVEF <45%) with or without LV dilatation presenting in the last month of pregnancy or in the months following delivery
- Incidence in the US 1:3000 (African Americans – 1:1500)
- Risk factors: multi-fetal gestation, hypertension, African or African-American race
- Etiology: multifactorial – placental and hormonal anti-angiogenic factors, pregnancy-related inflammation, and genetic factors

Alloimmune Disorders in Pregnancy

(RBC & Thrombocytopenia in the Fetus)

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University of Colorado School of Medicine

Henry L. Galan, MD

Discloses no relevant financial relationships with commercial interests.

Colorado Fetal Care Center

Colorado Fetal Care Center

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childrenscolorado.org/fetal-care

Objectives

Following this lecture, the participant will be able to:

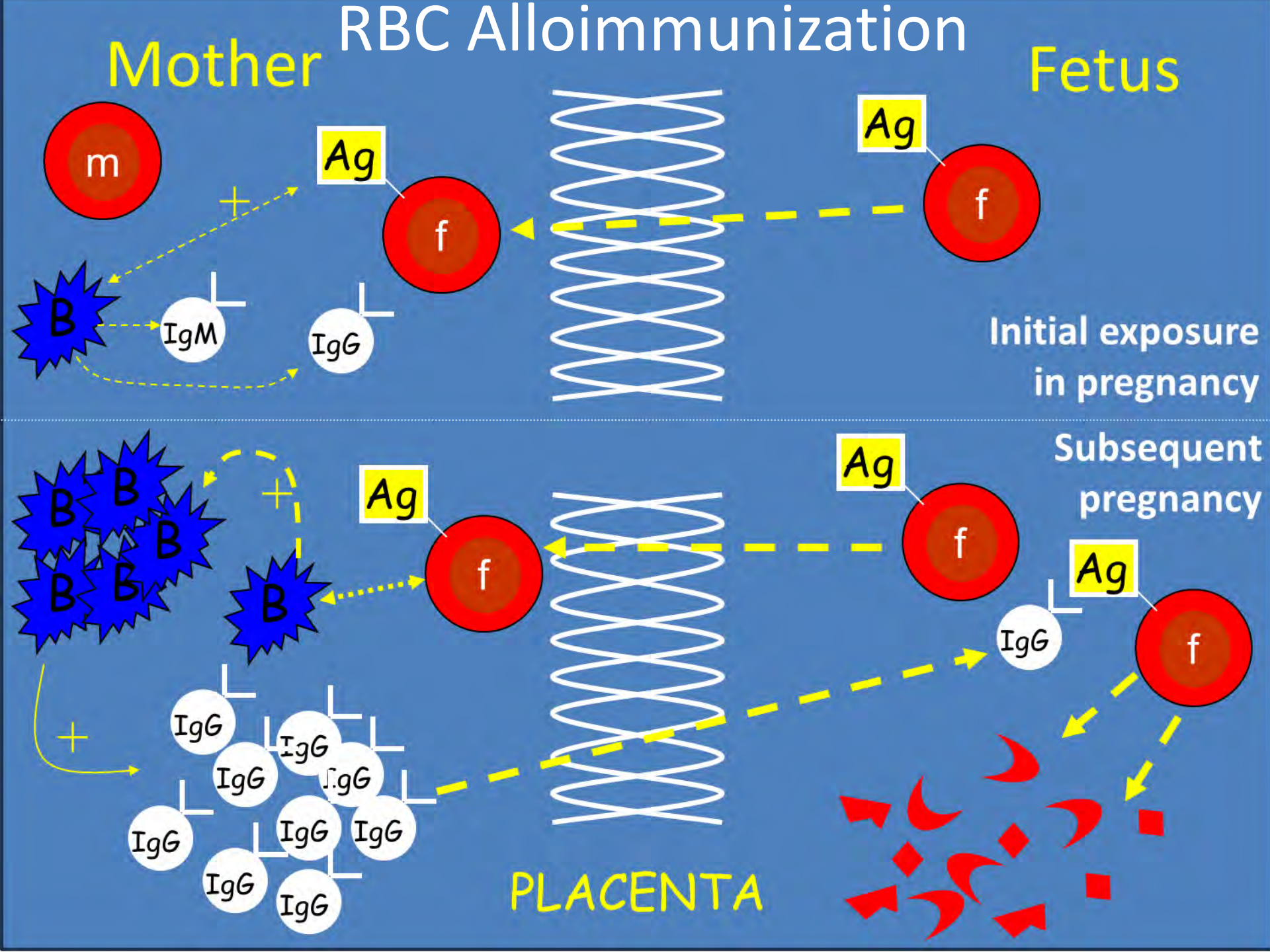
1. Identify which patients are at risk for RBC and platelet alloimmunization through screening processes
2. Discuss and use prevention strategies for Rh disease
3. Recognize when workup for NAIT should be performed.
4. Discuss referral and management (including delivery timing) approaches for RBC and platelet alloimmunization.
5. Discuss the implications for future pregnancies.

Alloimmune Diseases in Pregnancy

- Similar to graft-vs-host reaction

  "Mother develops an Ab directed against a fetal Ag that crosses the placental barrier to cause fetal disease."

- Alloimmune conditions in pregnancy:
  - RBC: Hemolytic disease of the Fetus and Newborn (HDFN)
    - In U.S.: 1-2% pregnancies (10-15% women are Rh-)
  - Plt: Fetal Neonatal Alloimmune thrombocytopenia (FNAIT)
    - 0.1-0.3% incidence in pregnancy
  - Liver: Gestational Alloimmune Liver Disease (GALD)
    - 4/10,000 live births


RBC Alloimmunization
Mother
Fetus
m
Ag
f
Ag
f
B
IgM
IgG
Initial exposure
in pregnancy
Subsequent
pregnancy
B
B
B
B
B
B
Ag
f
Ag
f
Ag
IgG
f
IgG
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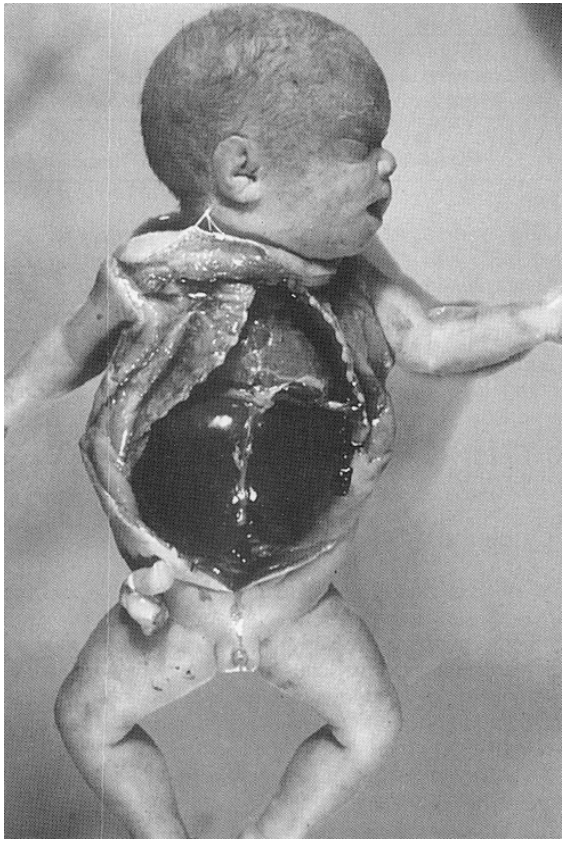
IgG
PLACENTA

Extramedullary Hematopoesis

Hydrops Fetalis & Death



Hepatosplenomegaly

Red Cell Alloimmunization

- >400 red cell antigens
- Mother Lacks Ag $\rightarrow$ Produce Ab
- Maybe harmful to the fetus or patient given a blood tx
- Isoimmunization uncommon. Why?
  - variable antigenicity
  - maternal immune response to Ag is variable
  - insufficient transplacental passage of Ag or Ab
  - protection by ABO incompatibility

ABO Incompatibility

- Most common cause of HDN
- 20% of all infants
  - 5% are clinically affected
  - Mild disease
    - Neonatal Jaundice or anemia
    - No erythroblastosis fetalis
  - Affects future offspring – “not progressive”

ABO Incompatibility

Why no concern antenatally?

- Milder than D-isoimmunization
- IgM isoantibodies- don't cross the placenta
- Fewer A and B Ag sites on fetal RBCs
- Offers some protection against D isoimm.
  - Fetal RBCs that cross - rapidly destroyed

Bottomline....

- Pediatric concern – not an OB concern

Rh Alloimmunization in Pregnancy

How common is it?

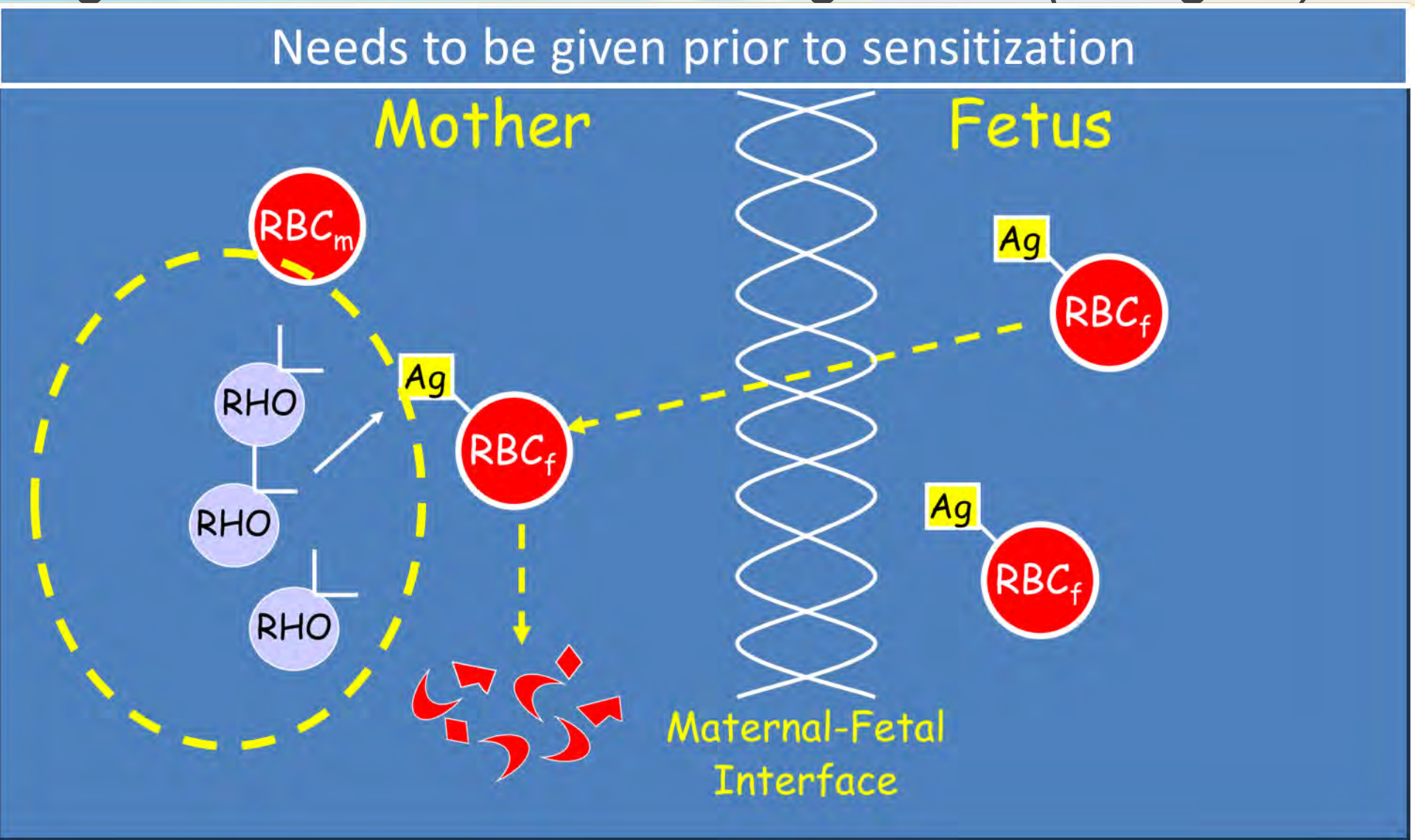
- In U.S.: 15% incidence of Rh- status; varies by race & ethnicity:
- Rh negative status:
  - Whites 15%
  - African Americans 5-8%
  - Asians & Native American 1-2%

- Basques – 30 to 35 percent
- White North Americans or Europeans – 15 percent
- Black or African Americans – 8 percent
- Africans – 4 to 6 percent
- Indians – 5 percent
- Native Americans and Inuit people – 1 to 2 percent
- Japanese – 0.5 percent
- Thais – 0.3 percent
- Chinese – 0.3 percent

Zipursky & Paul, Global burden of Rh Dz, 2011

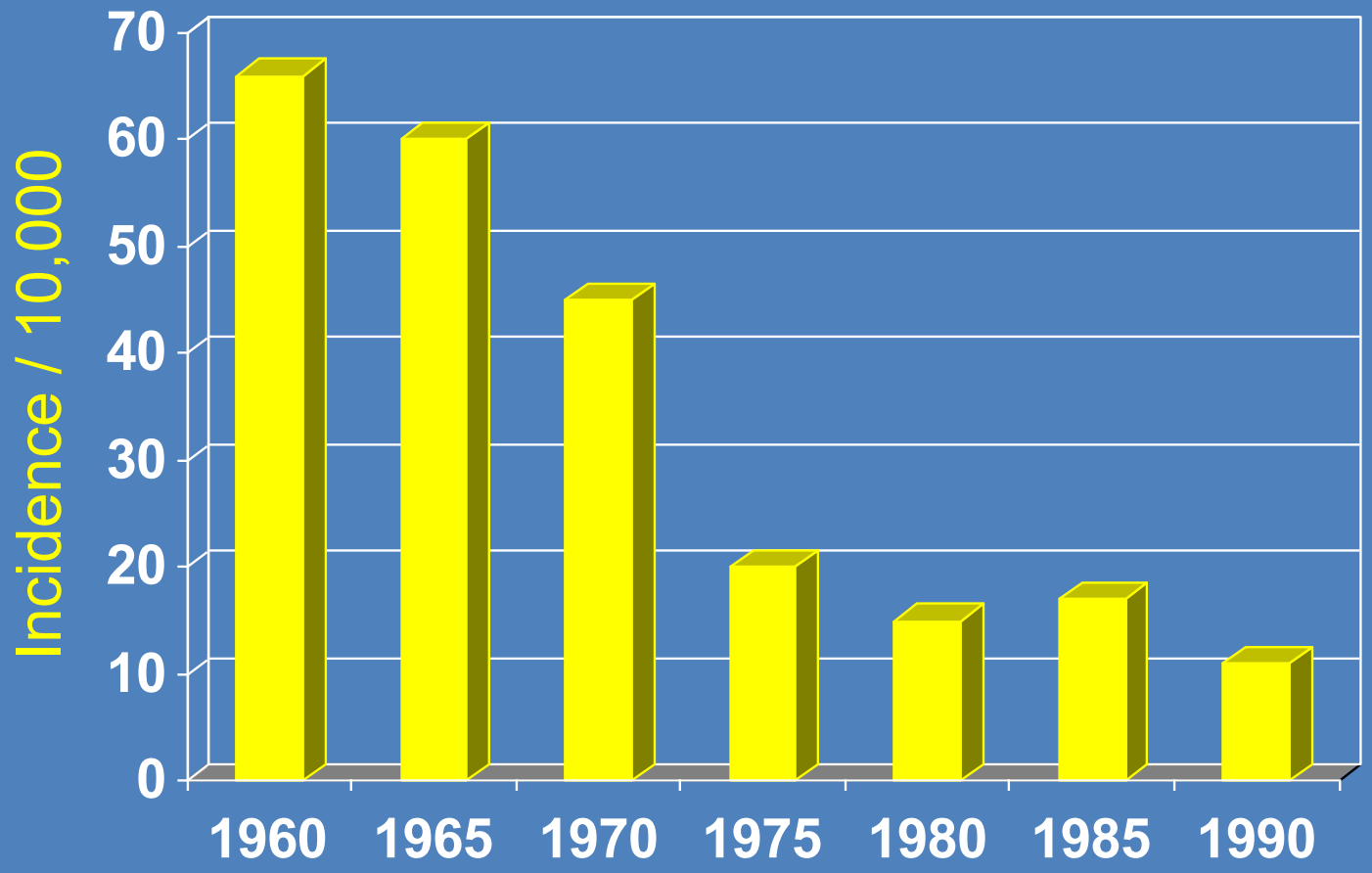
- Among whites:
  - Rh- woman has an 85% chance of reproducing with a Rh + male
  - 60% are heterozygous and 40% are homozygous at the D locus

The immune globulin used specifically to bind the Rh D antigen is referred to as Rh D immune globulin or anti-D immune globulin (Rhogam).



Incidence of RH HDN in USA

1960-1990

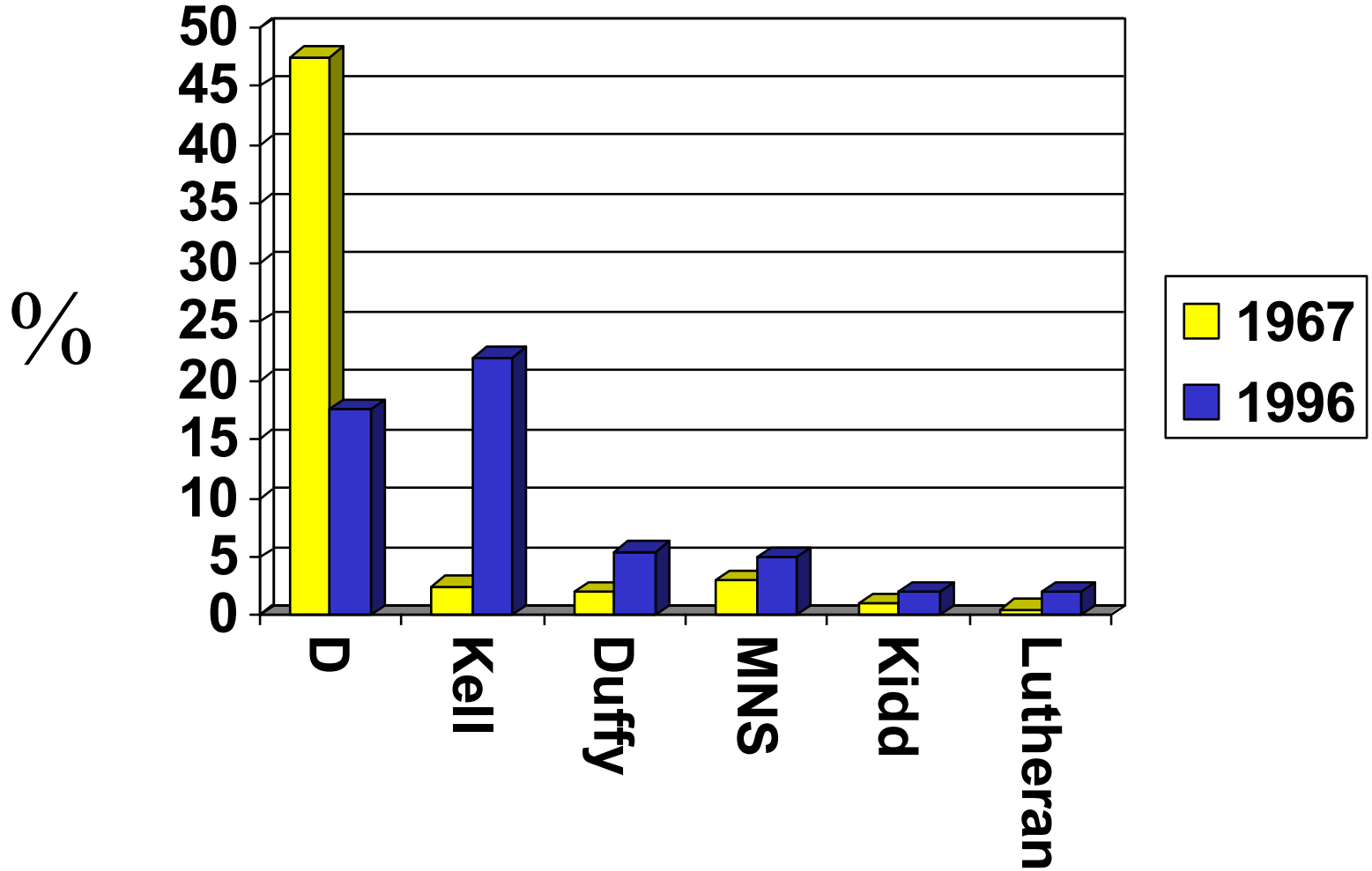


- **Alloimmunization from “irregular or atypical” (e.g. non-Rh) antigens *cannot* be prevented by prophylactic administration of immune globulin**

Leads to isoimmunization by other multiple antibodies

Frequency of Fetal Isoimmunization in USA

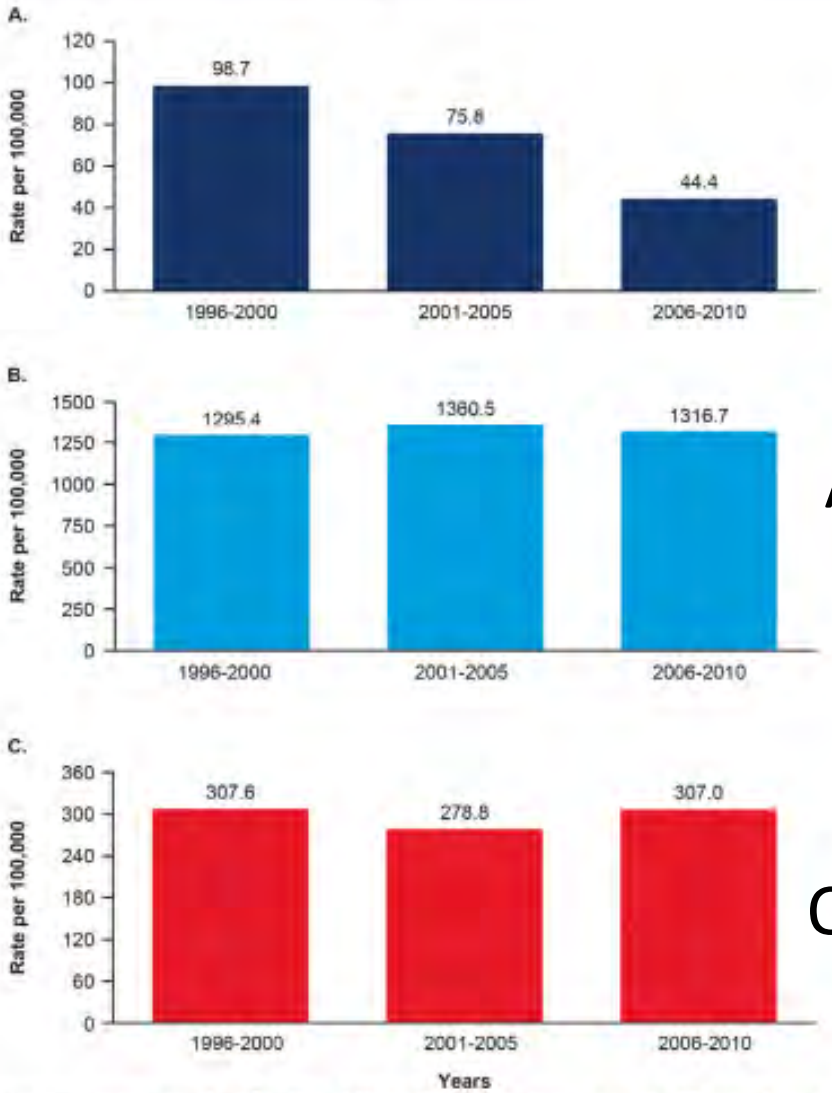
1967 vs 1996



Queenan et al. Ob-Gyn, 1969; Geifman-Holtzman et al. Ob-Gyn 1997

Rate of HDFN Alloimmunization by Year in US 1996-2010

- National Hospital Discharge Survey
  - 1996-2010
  - 480,245 livebirths (1700 annual cases)
  - HDFN by ICD-9 diagnosis
- Prevalence of HDFN:
  - 1695 cases / 100,000 LB (about 1-2% LB)
  - Among newborns with HDFN, 0.6% of cases were severe.



Yu. Live birth prevalence HDFN in US 1996-2010. Am J Glob Rep 2023;3:100203

“Irregular” red blood cell antigens

Table 1. Atypical Antibodies and Their Relationship to Fetal Hemolytic Disease

Blood Group System	Antigens Related to Hemolytic Disease	Hemolytic Disease Severity	Proposed Management
Lewis	*		
I	*		
Kell	K	Mild to severe†	Fetal assessment
	k	Mild	Routine obstetric care
	Ko	Mild	Routine obstetric care
	Kp^a	Mild	Routine obstetric care
	Kp^b	Mild	Routine obstetric care
	Js^a	Mild	Routine obstetric care
	Js^b	Mild	Routine obstetric care
Rh (non-D)	E	Mild to severe†	Fetal assessment
	C	Mild to severe†	Fetal assessment
	c	Mild to severe†	Fetal assessment
Duffy	Fy^a	Mild to severe†	Fetal assessment
	Fy^b	‡	Routine obstetric care
	By^3	Mild	Routine obstetric care
Kidd	Jk^a	Mild to severe	Fetal assessment
	Jk^b	Mild	Routine obstetric care
	Jk^3	Mild	Routine obstetric care
MNSs	M	Mild to severe	Fetal assessment
	N	Mild	Routine obstetric care
	S	Mild to severe	Fetal assessment
	s	Mild to severe	Fetal assessment
	U	Mild to severe	Fetal assessment
	M^g	Moderate	Fetal assessment
MSSs	Mt^a	Moderate	Fetal assessment
	Vw	Mild	Routine obstetric care
	Mur	Mild	Routine obstetric care
	Hil	Mild	Routine obstetric care
	Hut	Mild	Routine obstetric care
Lutheran	Lu^a	Mild	Routine obstetric care
	Lu^b	Mild	Routine obstetric care
Diego	Di^a	Mild to severe	Fetal assessment
	Di^b	Mild to severe	Fetal assessment
Xg	Xg^a	Mild	Routine obstetric care
P	$PP_{1}P^k$ (Tj^a)	Mild to severe	Fetal assessment
Public antigens	Yt^a	Moderate to severe	Fetal assessment
	Yt^b	Mild	Routine obstetric care
	Lan	Mild	Routine obstetric care
	En^a	Moderate	Fetal assessment
	Ge	Mild	Routine obstetric care
	Jr^a	Mild	Routine obstetric care
	Co^a	Severe	Fetal assessment
	Co^{1-3}	Mild	Routine obstetric care
Private antigens	Batty	Mild	Routine obstetric care
	Becker	Mild	Routine obstetric care
	Berrens	Mild	Routine obstetric care

Table 1. Atypical Antibodies and Their Relationship to Fetal Hemolytic Disease *(continued)*

Blood Group System	Antigens Related to Hemolytic Disease	Hemolytic Disease Severity	Proposed Management
Private antigens	Bles	Moderate	Fetal assessment
	Evans	Mild	Routine obstetric care
	Gonzales	Mild	Routine obstetric care
	Good	Severe	Fetal assessment
	Heibel	Moderate	Fetal assessment
	Hunt	Mild	Routine obstetric care
	Jobbins	Mild	Routine obstetric care
	Radin	Moderate	Fetal assessment
	Rm	Mild	Routine obstetric care
	Ven	Mild	Routine obstetric care
	Wright[a]	Severe	Fetal assessment
	Wright[b]	Mild	Routine obstetric care
	Zd	Moderate	Fetal assessment

*Not a proven cause of hemolytic disease of the newborn

†With hydrops fetalis

‡Not a cause of hemolytic disease of the newborn

Modified from Weinstein L. Irregular antibodies causing hemolytic disease of the newborn: a continuing problem. Clin Obstet Gynecol 1982;25:321.

ACOG Practice Bulletin, 2018

Antigen system	Specific antigen	Antigen system	Specific antigen	Antigen system	Specific antigen
Frequently associated with severe disease					
Kell	-K (K1)				
Rhesus	-c				
Infrequently associated with severe disease					
Colton	-Coa	MNS	-Mta	Rhesus	-HOFM
	-Co3		-MUT		-LOCR
Diego	-ELO		-Mur		-Riv
	-Dia		-Mv		-Rh29
	-Dib		-s		-Rh32
	-Wra		-sD		-Rh42
	-Wrb		-S		-Rh46
Duffy	-Fya		-U		-STEM
Kell	-Jsa		-Vw		-Tar
	-Jsb	Rhesus	-Bea	Other antigens	-HJK
	-k (K2)		-C		-JFV
	-Kpa		-Ce		-JONES
	-Kpb		-Cw		-Kg
	-K11		-Cx		-MAM
	-K22		-ce		-REIT
	-Ku		-Dw		-Rd
	-Ula		-E		
Kidd	-Jka		-Ew		
MNS	-Ena		-Evans		
	-Far		-e		
	-Hil		-G		
	-Hut		-Goa7		
	-M		-Hr		
	-Mia		-Hro		
	-Mit		-JAL		
Associated with mild disease					
Dombrock	-Doa	Gerbich	-Ge2	Scianna	-Sc2
	-Gya		-Ge3	Other	-Vel
	-Hy		-Ge4		-Lan
	-Joa		-Lsa		-Ata
Duffy	-Fyb	Kidd	-Jkb		-Jra
	-Fy3		-Jk3		

Non-Rhesus-D antibodies associated with hemolytic disease of the fetus and newborn

Moise K. Semin Fetal Neonatal Med. 2008 Aug;13(4):207-14

Screening for RBC Alloimmunzation

ACOG & Am Assoc of Blood Banks

All pregnant women, at first prenatal visit of each pregnancy should be tested for…

ABO blood group, RH-D type & RBC Ab screen (ABS)

- Repeat ABS before Rhogam administration:

  28 weeks

  Postpartum

  At time of any event…

ACOG PB 192, 2018

Volume of M-F hemorrhage leading to Rh D alloimmunization can be as small as 0.1ml

Box 1. Potential Sensitizing Events in Rh D-Negative Women in Pregnancy	**M-F Hemorrhage Risk**
Chorionic villus sampling, amniocentesis, cordocentesis	CVS: 14%; Amnio:2-6%
Threatened miscarriage or miscarriage	1st trimester: 3-11%
Ectopic pregnancy	ruptured: 24%
Evacuation of molar pregnancy	
Therapeutic termination of pregnancy	< 8 wks: 3-11%
Antepartum hemorrhage	
Abdominal trauma	up to 40%
Intrauterine fetal death	
External cephalic version	2-6%
Delivery	3rd trimester: 45%

ACOG PB 181, 2017

Management of Alloimmunization

Colorado Fetal Care Center

Once RBC Alloimmunization is established (positive maternal ABS)….

Determine if fetus is at risk

- FOR Non-RH+ ABS…Determine FOC Ag status / NIPT
- FOR RH+ ABS…Determine FOC Rh status (Ag status)
  - FOC Rh Negative → done—no further testing (Paternity?)
  - FOC Rh Positive → Zygosity Testing
    - homozygous (40%) → No further FOC testing (all fetuses Rh+)
    - heterozygous (60%) → ***fetal*** genotyping (cf fDNA over amnio)

If FOC Rh homozygous *OR* carries the non-Rh RBC Ag *OR* if unknown paternal status, *OR* Ag+ fetus by cf fDNA or amnio

Serial antibody titers

Serial Ab Screens

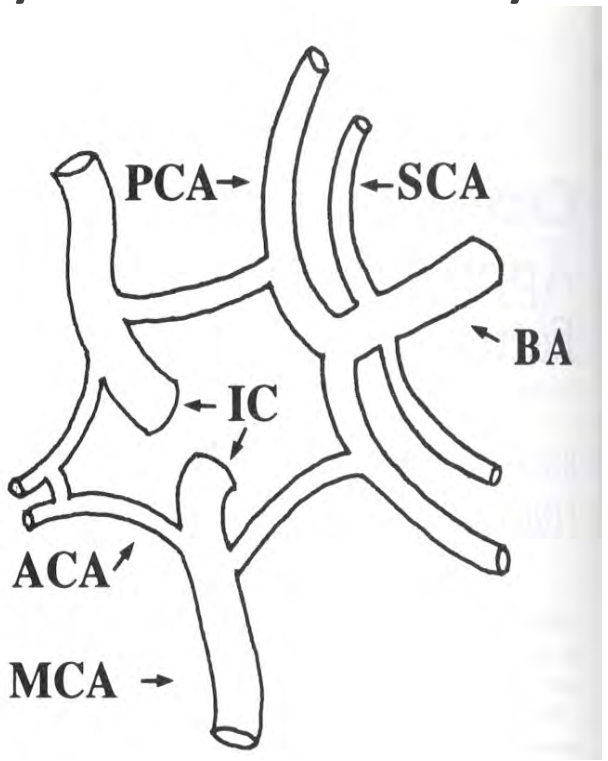
- Serial Ab titers until a “Critical Threshold Titer” is reached (monthly, q 2 wks if rising).
  - Critical titer varies by hospital
    - Typically: 1:16 or 1:32 (most are 1:16)
    - Check with your hospital blood bank
  - Exception is anti-Kell Ab which is 1:8

Critical Threshold Ab Screens

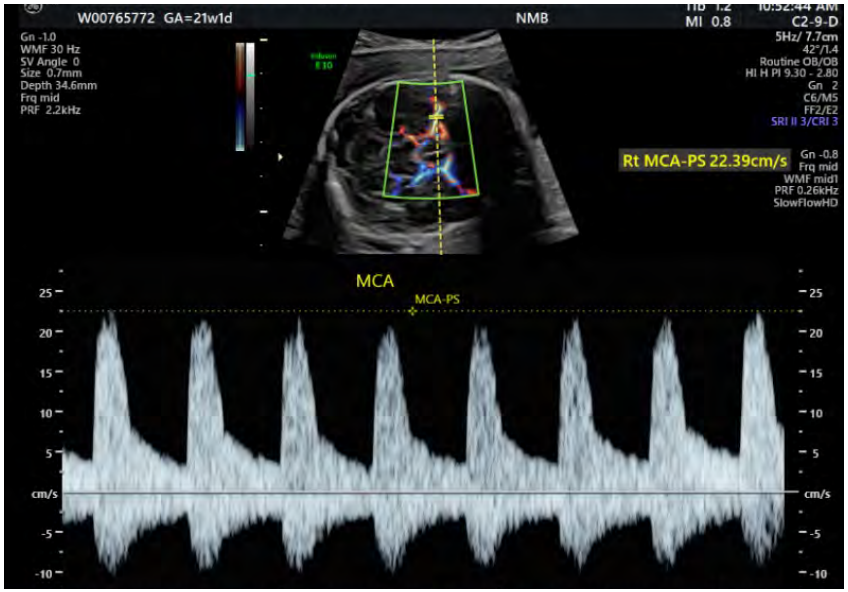
- Once met → Evaluate for fetal anemia.
- MCA PSV Doppler replaced ΔOD450
- Fetal anemia ↓s blood viscosity → ↑s velocity

PW Doppler of MCA

Circle of Willis



MCA Doppler Predicts Fetal Anemia



- >1.50 MoM MCA peak velocity for the detection of moderate/severe anemia
  - Sensitivity: 100%
  - False positive: 12%
  - Positive predictive rate: 65%
  - Negative predictive rate: 100%

Mari et al. NEJM 2000;342:9-14

Fetal Blood Sampling & Transfusion

RBC Alloimmunization

Delivery Timing

- Controversial
- Sensitized but critical titer not reached: 39w
- Mild disease (critical titer reached; normal MCA): 38-39w
- Moderate-Severe disease (e.g. IUTs):
  - 32-34w (historically)
  - If last transfusion 35-36w, delivery 37-38w
  - Phenobarbitol 30mg/d 1 week prior to delivery (?)

RBC Alloimmunization

Next Pregnancy

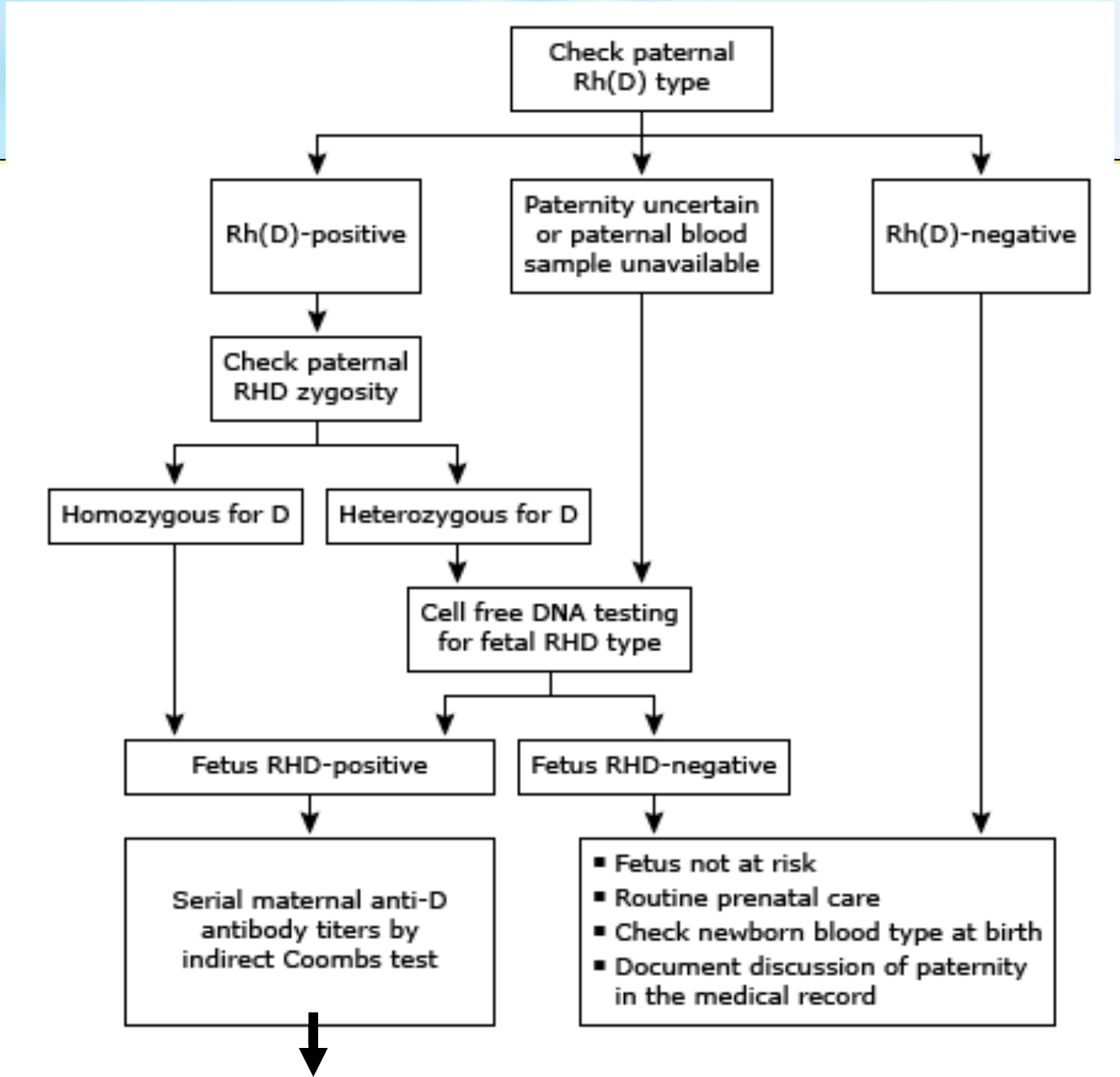
- Prior IUT, hydrops, HDFN PTB or NN exchange tx can expect development of severe fetal anemia if next fetus is Ag+ for offending Ab (e.g. FOC status: repeat zygosity testing. Same FOC?)
- Determine fetal Ag status early & begin MCA PSV at 16-18 weeks.
- Increasingly severe HDFN
- *Coming Soon*: mAb against IgG

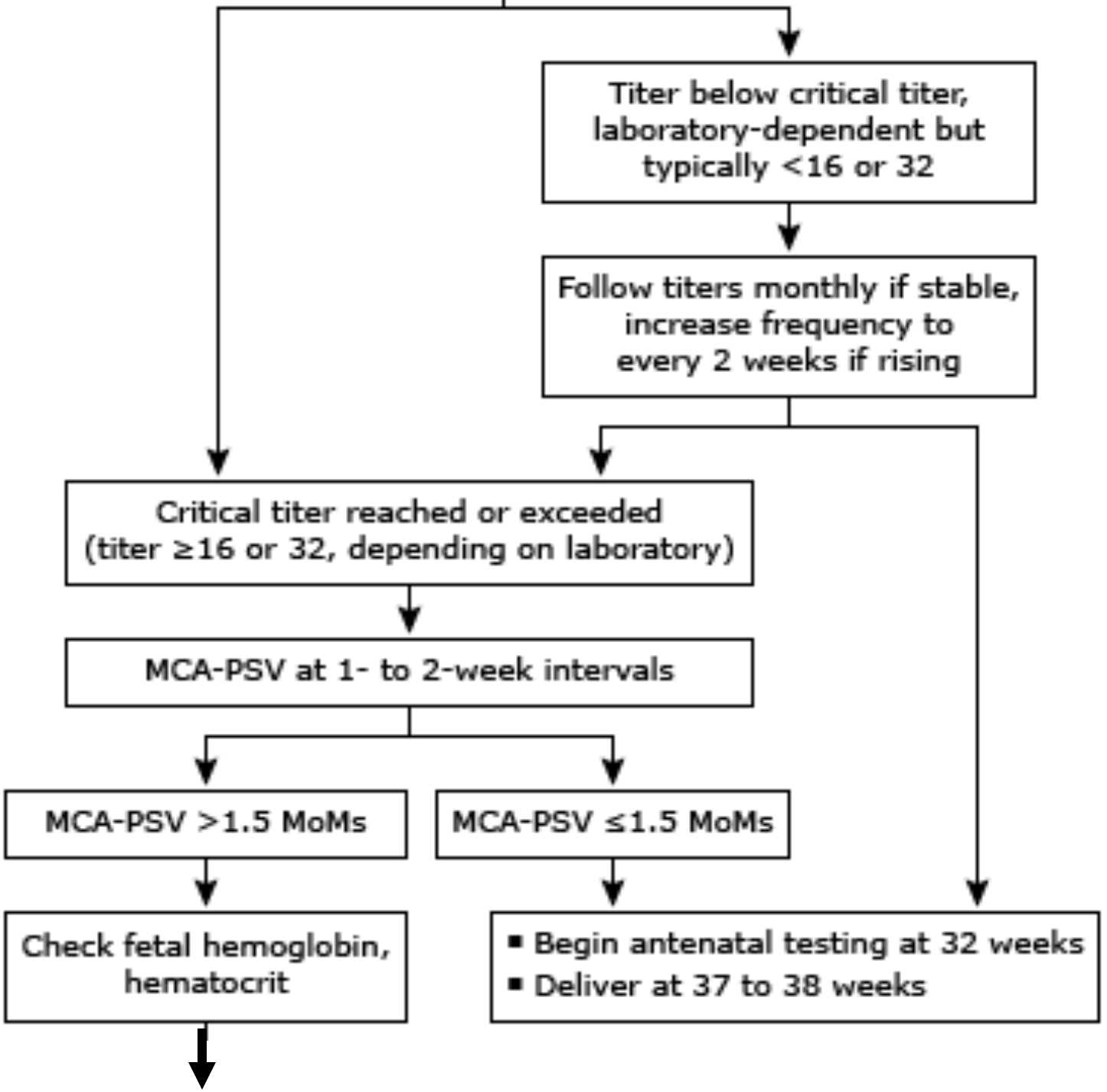
RBC Alloimmunization

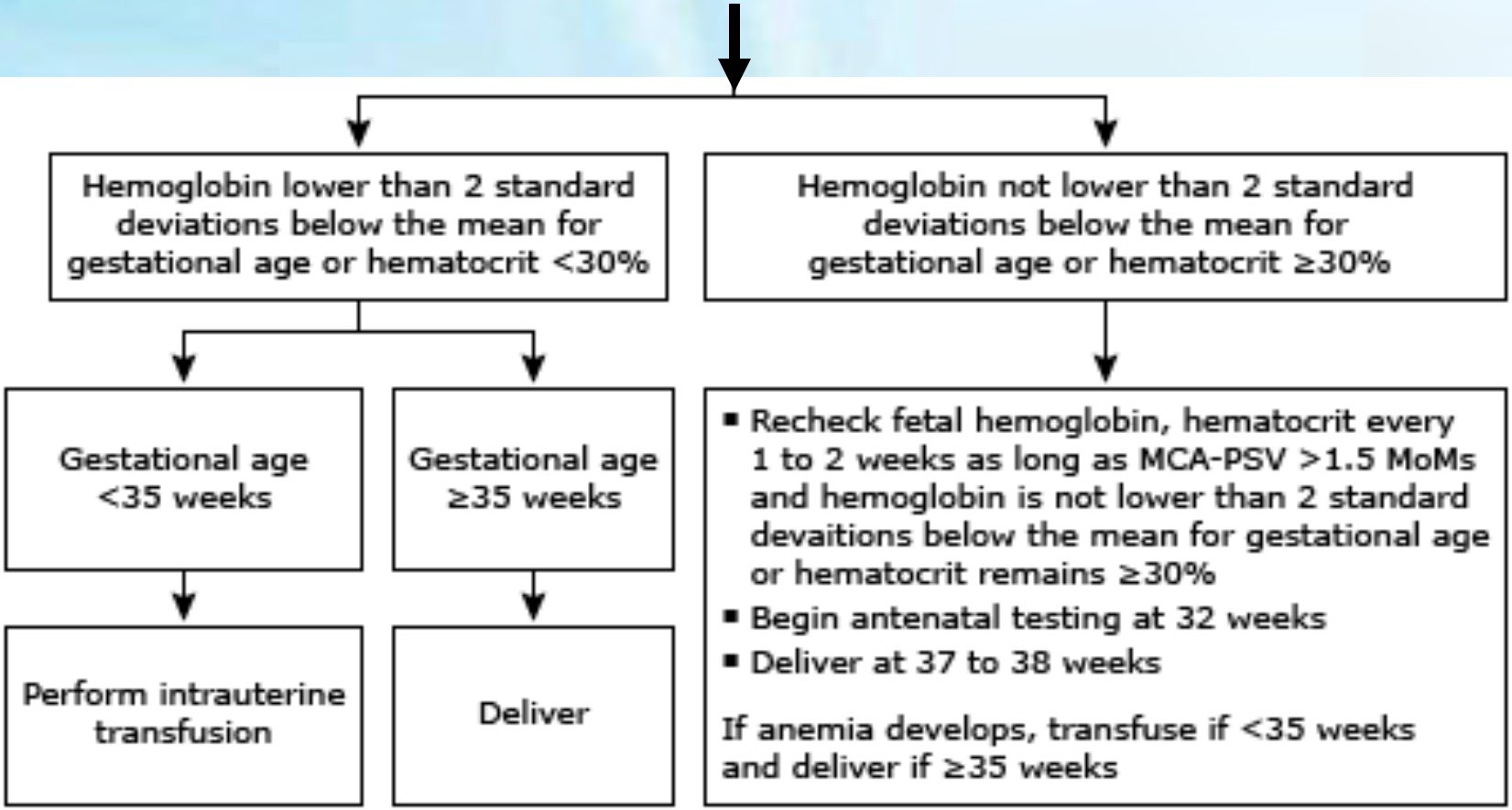
Next Pregnancy

- Nipocalamib treatment for severe HDFN
  - mAb blocks placental transfer of IgG and lowers maternal titers (FcRn receptor blockade)
- Phase II trial completed
  - 50% pts w prior early onset severe HDFN did not receive IUTs until after 32w.
- Phase III / RCT starting. Entry criteria:
  - Alloimmunization to D, c, E, Kell, Jka
  - Critical titer & positive cf fDNA for Ag at screening
  - 1 or more previous transfusions in prior pregnancy
  - <15w in current pregnancy
- Several U.S. fetal treatment centers participating
  - Study visits, travel & infusions covered.

Many Algorithms Published for RBC Alloimmunization




Titer below critical titer, laboratory-dependent but typically <16 or 32
Follow titers monthly if stable, increase frequency to every 2 weeks if rising
Critical titer reached or exceeded (titer ≥16 or 32, depending on laboratory)
MCA-PSV at 1- to 2-week intervals
MCA-PSV >1.5 MoMs
MCA-PSV ≤1.5 MoMs
Check fetal hemoglobin, hematocrit
Begin antenatal testing at 32 weeks
Deliver at 37 to 38 weeks


Hemoglobin lower than 2 standard deviations below the mean for gestational age or hematocrit <30%
Hemoglobin not lower than 2 standard deviations below the mean for gestational age or hematocrit ≥30%
Gestational age <35 weeks
Gestational age ≥35 weeks
Perform intrauterine transfusion
Deliver
Recheck fetal hemoglobin, hematocrit every 1 to 2 weeks as long as MCA-PSV >1.5 MoMs and hemoglobin is not lower than 2 standard devaitions below the mean for gestational age or hematocrit remains ≥30%
Begin antenatal testing at 32 weeks
Deliver at 37 to 38 weeks
If anemia develops, transfuse if <35 weeks and deliver if ≥35 weeks

Fetal & Neonatal Alloimmune Thrombocytopenia (FNAIT)

Colorado Fetal Care Center

FNAIT

- Fetal-Neonatal alloimmune thrombocytopenia (TCP) is the *platelet equivalent* of hemolytic disease of the fetus and newborn.
- Develops as a result of maternal alloimmunization to fetal platelet antigens with transplacental transfer of platelet specific antibody and subsequent platelet destruction.
- 15 plt specific antigens described. Most severe cases due to sensitization to HPA 1a
- Affects 1 in 1000-3000 live births

ACOG PB 207, 2019

Williamson et al. Blood, 1998

FNAIT: Management & Outcome of a Large International Retrospective Cohort (2017)

HPA type	Cases, n (%)	Mean PC $\times 10^9$/l	ICH, n
HPA-1a	544 (88)	105	19
HPA-5b	23 (3.6)	136	2
HPA-3a	7 (1.1)	147	
HPA-5a	4 (0.6)	184	
HPA-15a	5 (0.8)	200	
HPA-1a + -5b	18 (3)	94	2
HPA-1a + other	5 (0.8)		
Negative	2 (0.03)		
Unknown	7 (1.1)		
Total	615		

PC = Platelet count.

Kamphuis MM, Tiller H et al. Fetal Diagn Ther 2017;41(4):251

Causes of Maternal TCP in Pregnancy

Maternal TCP & Fetal TCP Risk

Box 1. Causes of Thrombocytopenia in Pregnancy

- Gestational thrombocytopenia
- Hypertension in pregnancy
  - Preeclampsia
  - HELLP syndrome
- Primary immune thrombocytopenia
- Secondary immune thrombocytopenia
  - Antiphospholipid syndrome
  - Systemic lupus erythematosus
  - Infectious (such as HIV, hepatitis C virus, cytomegalovirus, *Helicobacter pylori*)
  - Drug-induced thrombocytopenia (use of drugs such as heparins, antimicrobials, anticonvulsants, analgesic agents)
- Association with systemic conditions
  - Disseminated intravascular coagulation
  - Thrombotic thrombocytopenia/hemolytic uremic syndrome
  - Splenic sequestration
  - Bone marrow disorders
  - Nutritional deficiencies
- Congenital thrombocytopenia

Abbreviations: HELLP, hemolysis, elevated liver enzymes, and low platelet count; HIV, human immunodeficiency virus.

ACOG PB 207, 2019

Neonatal Thrombocytopenia Risk

Gestational thrombocytopenia → Low:0.1-2.3%

Preeclampsia → Low: 0.0-1.8%

Primary immune thrombocytopenia →

- ITP
  - plt <150k, 25% risk (not severe)
  - No correlation b/w maternal & fetal plt counts
  - Although 8-15% newborns will be treated for TCP, severe complications are rare (<<1%)

- Thus, these conditions of maternal TCP are low risk for fetal complications and more of a neonatal concern

FNAIT

General Features

- Uncomplicated pregnancy & maternal plt cts are normal
- 25% FNAIT occur in the first pregnancy
- Leading cause of severe TCP in fetus & neonate
- Majority of NAIT mild (petechiae, bruising or TCP on CBC)
- Leading cause of *intracranial hemorrhage* (ICH) in term NN
- 15% of infants with plt cts <50 x 10^9/L have an ICH
- ICH: 80% occur antenatally and ½ can be seen prenatally
- High recurrence risk (upwards of 100%) if subsequent sibling carries the offending plt antigen

ACOG PB 207, 2019; Peterson et al.Br J Haematol 2013;161:3
Kovanlikaya et al. Pediatr Blood Cancer, 2017

FNAIT

Screening & Diagnosis

- Screening
  - No blood screening test
  - History of an affected child
    - Unexpected thrombocytopenia
    - History of ICH
  - Direct relation to such a woman
  - Incidentally found to lack HPA-1a

Thus, reliant on the screening history at OB intake.

- Diagnosis: laboratory workup
  - Experienced reference laboratory
  - Flow cytometry: rapid method of detecting plt reactive Abs
  - Screen for Class I HLA Ab and for the specific glycoprotein the maternal Ab is targeting.

FNAIT

Antenatal Imaging

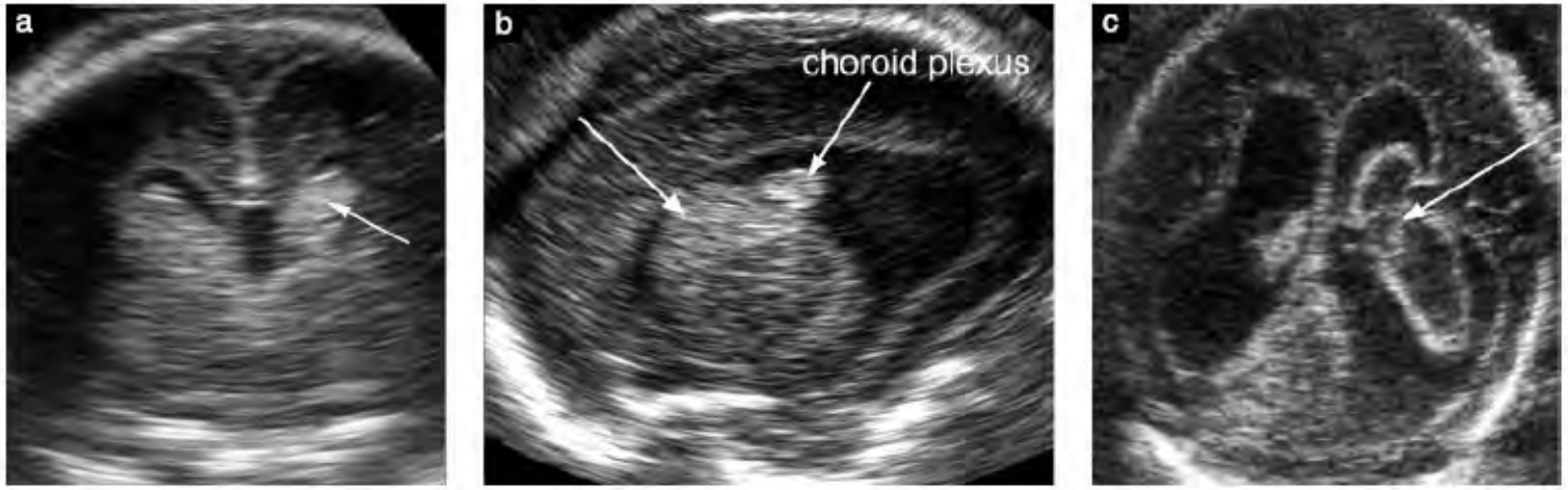
Prenatal Ultrasound

- ICH (acute vs chronic)
- Ventriculomegaly
- Porencephalic cysts
- ICH documented as early as 14 weeks

MRI

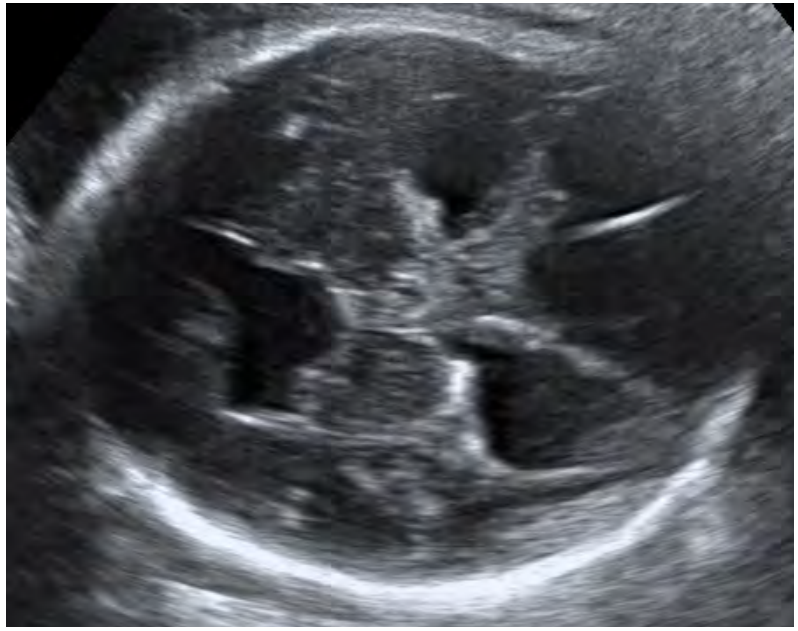
- T1 weighted images to identify blood
- May detect hemorrhage not seen on US
- Maybe useful in identifying old vs new hemorrhage

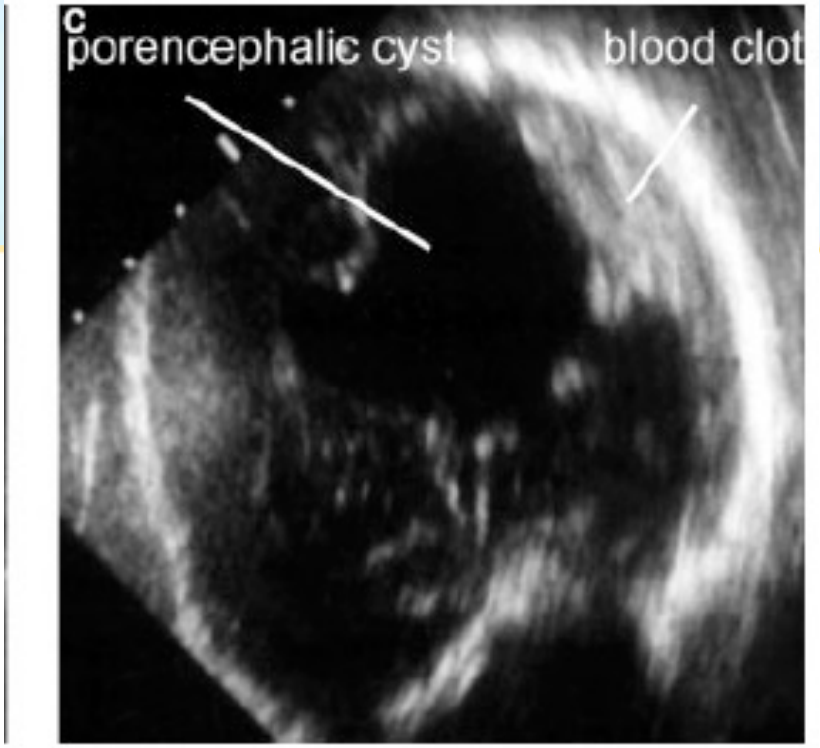
Recent Bleed



Older Bleeds

Porencephaly
& ventriculomegaly





Newborn Findings

generalized bruising, suffusions, petechiae

FNAIT

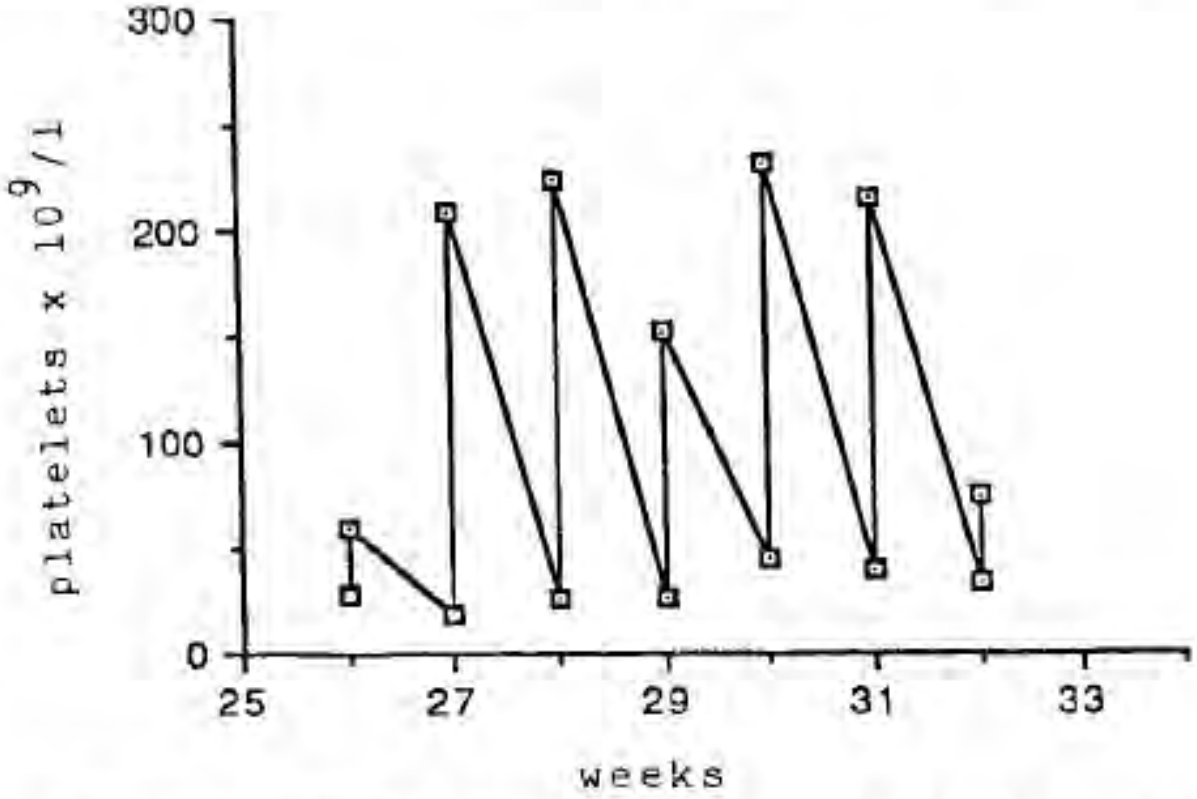
Management

Primary goal in OB mgmt of FNAIT: ICH prevention

Optimal treatment remains uncertain.

- Patients stratified based on + or – ICH and GA at manifestation of ICH in sibling(< or >28 weeks)…1996 RCT & 2017 MA
  - Several therapies & dosing strategies
    - Maternal IVIG at 12wks: 1mg/kg for ICH <28w; 2mg/kg if ICH >28w
      - At 20 wks dosing doubled; Prednisone added
    - No plt sampling for therapy monitoring (11% exsanguination risk).
  - None of these were effective in all cases in the RCT
    - IVIG generally improved fetal plt ct by 68K by delivery
    - 0/55 ICH w IVIgG (10 in sibs)
    - Platelet transfusions increase plt ct, but short ½-life & high IUFD complication rate in other studies (11%)

Weekly Platelet Transfusions for AIT



Platelet count (× 10^9/l) before and after weekly platelet transfusions between 26 and 32 weeks' gestation in fetus with alloimmune thrombocytopenia.

Nicolini et al. Lancet 1988;2:506

FNAIT

Management

- Historically, FBS included in FNAIT management to assess effectiveness of therapy
  - Prospective therapeutic studies – FBS not needed.
- IVIG w or w/o corticosteroids equally effective vs IUT platelet transfusion in raising plts w/o exsang risk.
- Consensus guidelines:
  - early empiric initiation of IVIG +/-steroids based on risk stratification.
  - FBS reserved for >32 wks to assess tx effect IF, SVD desired
  - CS at 37 weeks recommended.

Bussel et al. AJOG 2010;203:135.14; Berkowitz et al. Obstet Gynecol 2007;110:249
Winkelhorst et al. Blood 2017;129:1538–47. (Systematic Review)
Pacheco et al. Obstet Gynecol 2011;118:1157–63

Comparison of Anti-D HDFN & FNAIT

Factors that Differ	FNAIT caused by anti HPA-1a	HDFN caused by anti-D
At-Risk Pregnancies	~2% of women HPA-1a-negative; <1% also DRRB3*0101 positive	Approximately 10% of women (D-)
Occurrence of disease	First pregnancy, commonly	2nd & subsequent pregnancies (commonly anti-D)
Ab response after incompatible transfusion	Anti-HPA-1a is rarely formed	Anti-D is most frequent
Effect of alloantibodies	Thrombocytopenia	Anemia, hemolysis
Causes of fetal death	Intracranial hemorrhage	Heart failure, hydrops
Causes of neonatal death	Intracranial hemorrhage	Kernicterus/bilirub encephalopathy
HLA association with Ab response	>90% HLA DRB3*0101; >90% HLA DOB1*0201	Weak or no association
Routine screening	None	First prenatal visit; D phenotype
Antibody detection	Postnatally; usually after birth of baby with thrombocytopenia	1st & 3rd trimester by screening
Ab concentration in preg	Some correlation w TCP severity	Good correlation w anemia severity
Postnatal antibody	Remains for years	Declines after months
Noninvasive fetal dx	None	Doppler of MCA for fetal anemia
Tx to pregnant woman	IVIG ± steroids; dose/duration based on prior history	None; IVIG now for early disease
Tx of babies in severe cases	Fetal IUT & Neonatal transfusion	Fetal IUT, NN exchange Tx, phototx
Immunization prevention	None	Ante & post-natal RhIG

Key Points & Clinical Pearls

HDFN

Clinical Pearls

1. The major cause of HDF is D and kell sensitization, not ABO incompatibility.
2. Ab titers remains the mainstay for screening & detection of sensitized mothers.
3. Know the critical titer at your hospital (1:16 or 1:32).
4. Kell does not act like other RBC antigens and requires a lower threshold for FBS (1:8).
5. Ultrasound is useful for establishing dates, evaluating for hydrops, HSM, MCA PSV and for transfusions.
6. MCA peak systolic velocity has replaced amnio and serial ΔOD 450 testing for fetal anemia.

FNAIT
Clinical Pearls

- Screening **focus**: OB history & Newborn outcomes at initial PNV
- Suspect FNAIT: Unexplained fetal/NN TCP, hemorrhage or ICH
- What tests should be ordered?
  - HPA type & zygosity of both parents; confirm incompatible
  - Use an experienced regional reference laboratory
  - Plt typing helpful when FOC is heterozygous; can be done from amnio or from cf fDNA testing.
- Primary goal in OB management of FNAIT: ICH prevention
- Early detailed anatomic survey by ultrasound & serial ultrasound evaluations
- Early referral to MFM for IgG ± steroid therapy

Thank you!

METABOLIC BARIATRIC SURGERY IN WOMEN'S HEALTH

Akshay Chauhan, MD
Associate Professor of Surgery
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Department of Surgery
UNIVERSITY OF COLORADO **ANSCHUTZ MEDICAL CAMPUS**

DISCLOSURES

Intuitive Foundation Inc fellowship grant 2019-2023

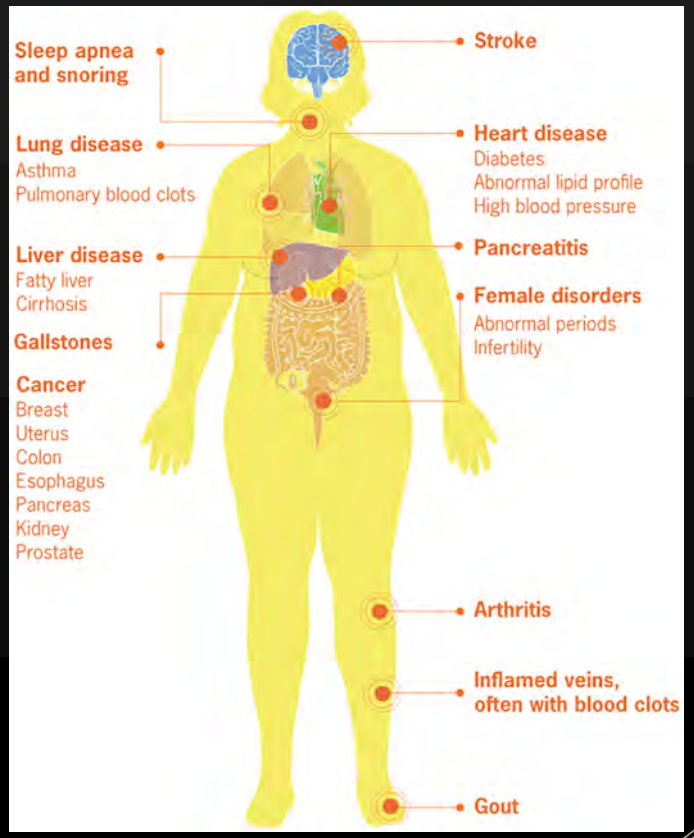
Consultant for Intuitive proctoring services

OBJECTIVES

- Discuss the rising incidence of obesity
- Why discussing obesity is relevant in women and how to overcome barriers in our current environment
- Describe surgical advancement of metabolic surgery
- Describe evidence-based positive outcomes of metabolic surgery on women and fetal health

What is obesity and why does it matter to women's health?

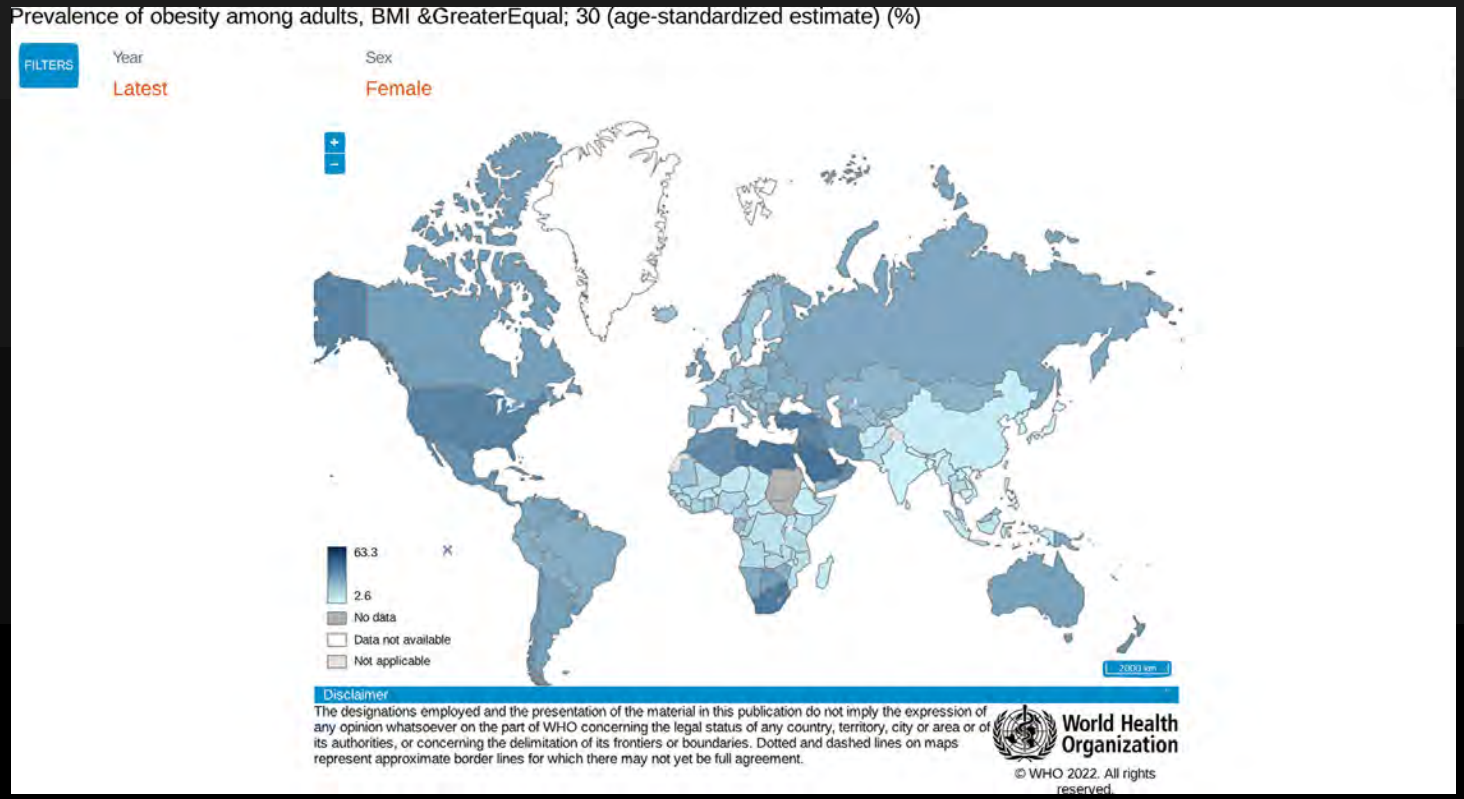
Obesity is defined by the World Health Organization (WHO) as abnormal or excessive adipose accumulation that puts health at risk



Intl J Gynecology & Obste, Volume: 160, Issue: S1, Pages: 35-49, First published: 12 January 2023, DOI: (10.1002/ijgo.14549)

Global rise of obesity in women

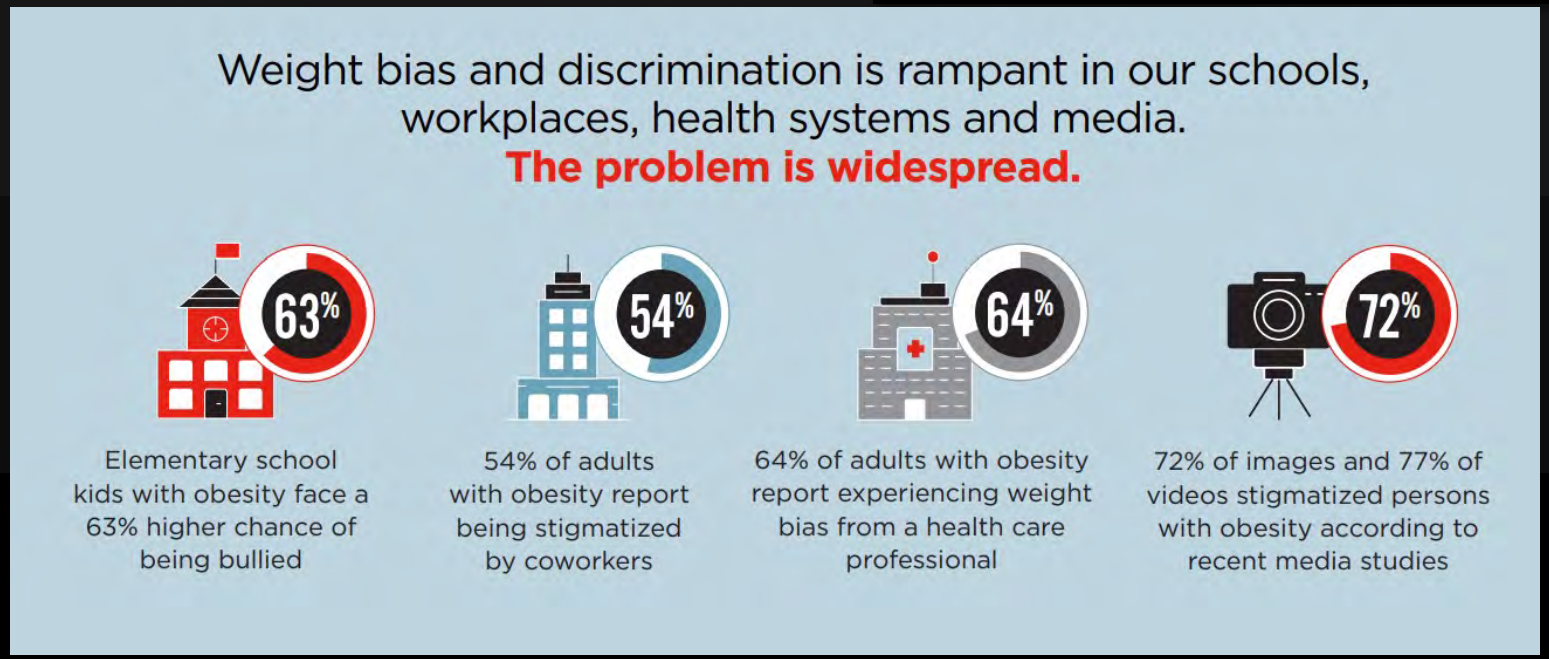
The prevalence of obesity in women of reproductive age (20 to 39) in the US is 39.7%. Prevalence is found to be lowest among non-Hispanic Asian women (17.2%) and higher in non-Hispanic White (39.8%).



Social and cultural barriers to obesity care

- Weight bias, stigma, discrimination
- Weight-inclusive language and images
- Cultural considerations and sensitives

Category	Definition
Weight bias	Negative attitudes toward people with obesity
Weight stigma	Stereotypes and labels used for people with obesity
Weight discrimination	Negative actions taken against people with obesity causing social disadvantage



Before we talk to women about obesity let's make a pledge

WHY BARIATRIC SURGERY: SWEDISH OBESE SUBJECTS STUDY

- Followed around 4,000 obese subjects for ten years,

50 % had surgery; and 50% did not

- The surgery group lost 14-25% body weight over ten years, the other maintained +/- 2%.

- Also resulted in improved lifestyle factors such as being more physically active and lower risk factors for hypertriglyceridemia, DM, and hyperuricemia.

Sjöström L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjöström CD, Sullivan M, Wedel H., Swedish Obese Subjects Study Scientific Group Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. New Engl J Med. 2004;351:2683–2693. doi: 10.1056/NEJMoa035622.[.

Bariatric surgery eligibility and utilization

The prevalence of obesity is similar among adult male and female patients (35.5% and 35.8%, respectively).

Significantly higher proportion of eligible women received bariatric surgery compared to eligible men

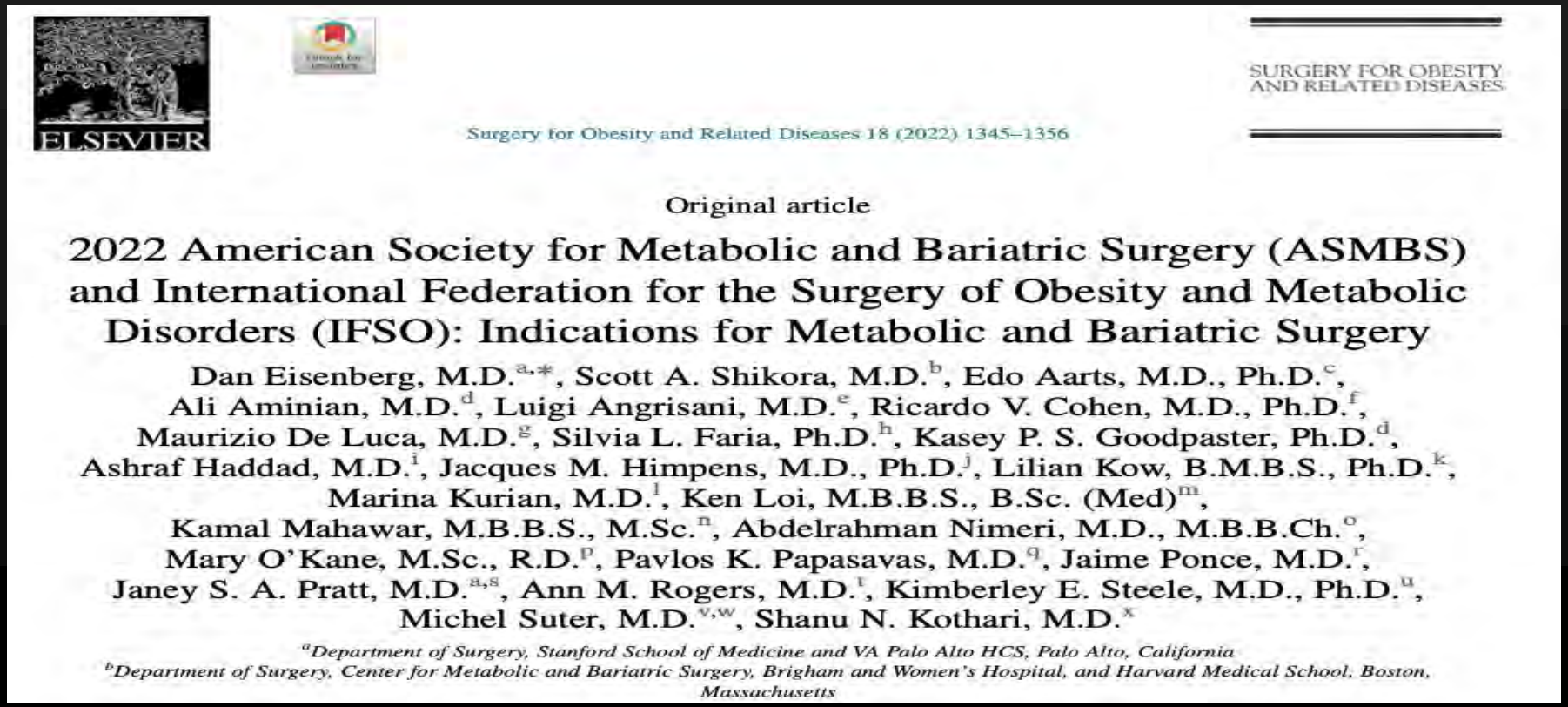
A higher proportion of female bariatric surgery patients are younger (less than 45 years old)

Knowledge gap, provider referral, and patient selection patterns

Knowledge gap and increased perceived risk on behalf of providers and patients pose significant barriers between morbidly obese patients and surgical treatments.

Perceptions of weight loss surgery as carrying increased risk further hinder access across genders

ASMBS /IFMSO 2022 UPDATED INDICATIONS



SURGERY FOR OBESITY AND RELATED DISEASES

Surgery for Obesity and Related Diseases 18 (2022) 1345–1356

Original article

2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): Indications for Metabolic and Bariatric Surgery

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MAJOR UPDATES TO 1991 NIH GUIDELINES FOR BARIATRIC SURGERY

- Metabolic and bariatric surgery(MBS)is recommended for individuals with a body mass index(BMI) **35kg/m2**,regardless of presence, absence, or severity of co-morbidities.
- MBS should be considered for individuals with metabolic disease and BMI of **30-34.9 kg/m2.**
- BMI thresholds should be adjusted in the Asian population such that a BMI 25 kg/m2 suggests clinical obesity, and individuals with BMI !27.5 kg/m2 should be offered MBS.
- Long-term results of MBS consistently demonstrate safety and efficacy.
- Appropriately selected children and adolescents should be considered for MBS.

SURGERY: CLASSIFIED BY FUNCTION

Restrictive:

- Laparoscopic Sleeve Gastrectomy (LSG)
- Laparoscopic Gastric Banding

Restrictive and Malabsorptive:

- Roux en Y gastric bypass
- BPD-DS Biliopancreatic Diversion with Duodenal Switch
- SADI (Single Anastomosis Duodenal ileal bypass)

SLEEVE GASTRECTOMY

Approximately 70% of the stomach is removed and a staple line is created leaving a much smaller space and reducing ghrelin production.

- Pros:

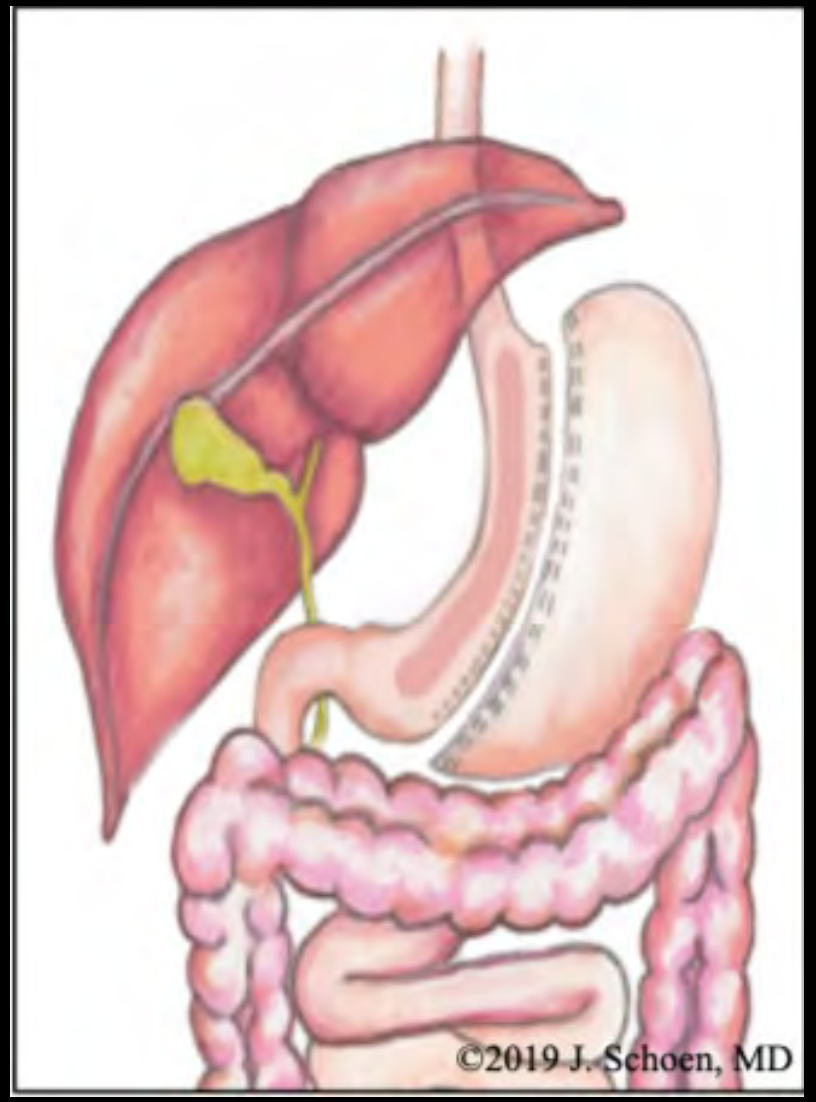
1. Less post operative complications

(Marginal Ulcers, internal hernia and GJ stricture)

2. Shorter operation time
3. Success in same day surgery

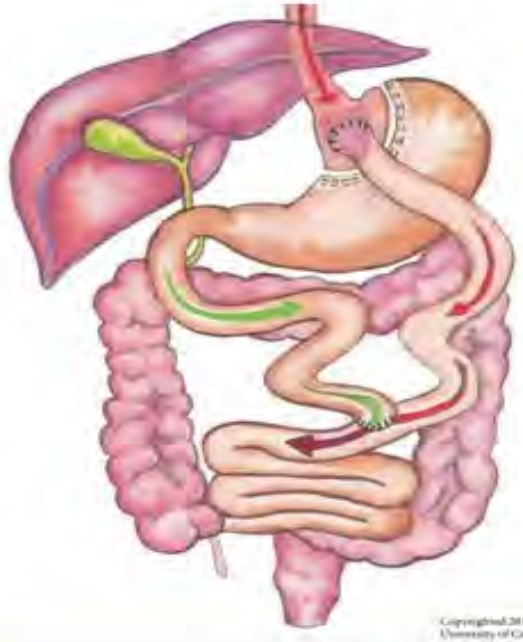
- Cons:

1. Increased post-op Nausea and vomiting
2. Concern for Barret's esophagus



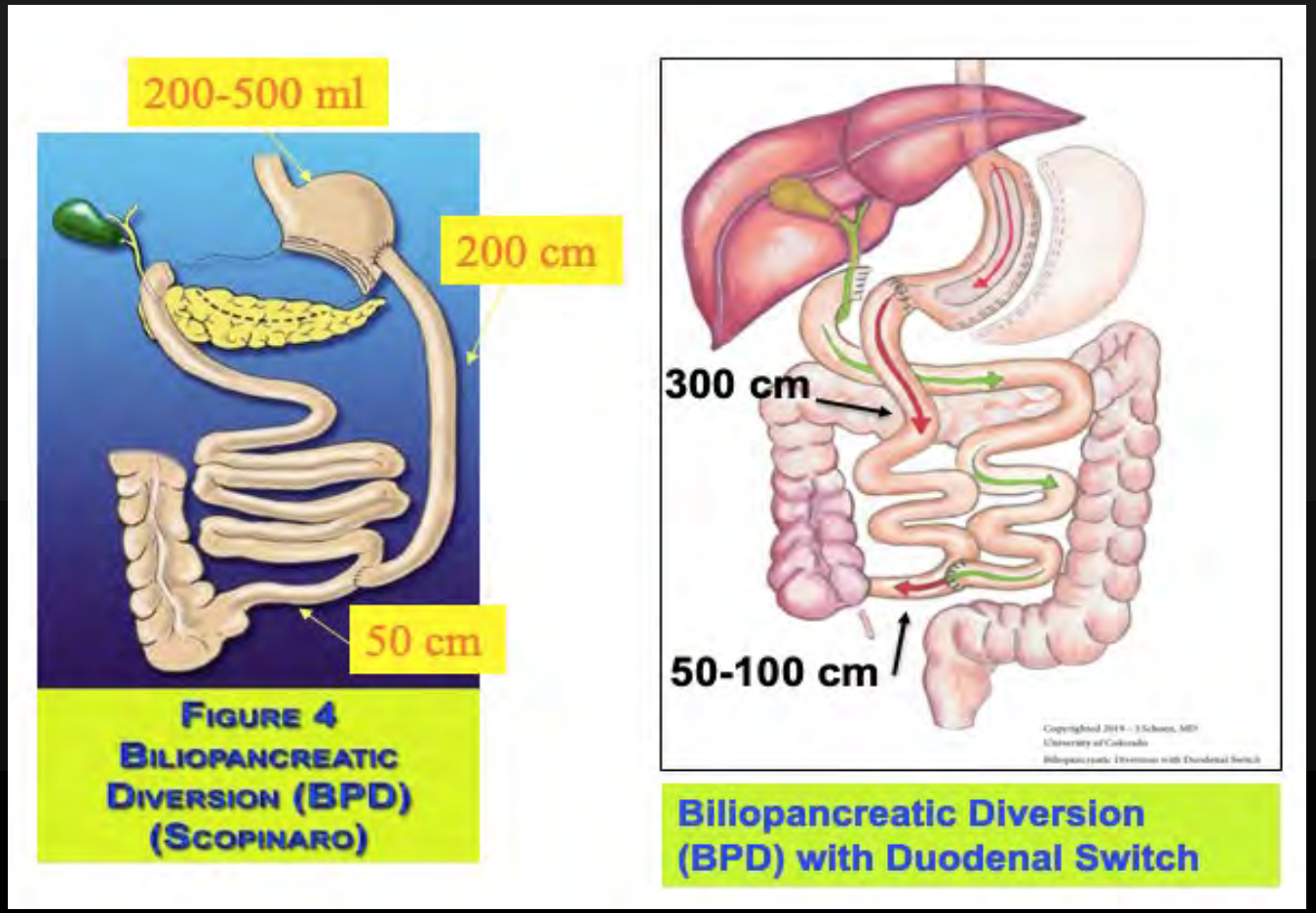
LAPAROSCOPIC ROUX EN Y GASTRIC BYPASS

- lesser curve 15 cc pouch
- complete gastric division
- antecolic or retrocolic Roux limb: 60-150 cm
- 0.8 cm – 2.0 cm gastrojejunostomy



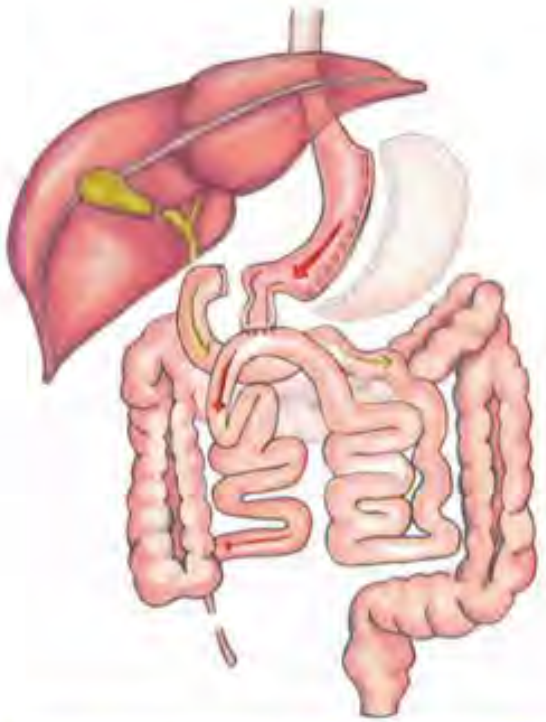
Laparoscopic Roux-en-Y Bypass

BPD-DS BILIOPANCREATIC DIVERSION WITH DUODENAL SWITCH



SADI (SINGLE ANASTOMOSIS DUODENAL ILEAL BYPASS)

- Simplified version of the BPD-DS
- Revisional option for patients who have failed previous bariatric sleeve surgeries



Single Anastomosis Duodenal-ileal Bypass with sleeve gastrectomy (SADI-S)

SADI-S

Pros

- Excellent weight loss results and long-term success
- Ideal for poorly controlled Diabetes or dyslipidemia (high cholesterol). SADI and BPD are the most effective treatments for patients with Type II DM on insulin
- No Dumping Syndrome
- Low risk of marginal ulcers (which can occur with Gastric Bypass)

Cons

- Moderate risk of long-term nutritional deficiencies; patients will need special vitamin and nutritional supplements
- Frequent blood tests the first 1-2 years
- Can have loose and/or more frequent bowel movements, particularly after rich or oily food.

Weight Loss Comparison

	Adjustable Gastric Band	Sleeve Gastrectomy	Gastric Bypass	Biliopancreatic Diversion (BPD), SADI-S
Time course (time to goal)	2-3 years	1 year	1-2 years	1-2 years
Success Rate	50%	70-80%	80-90%	>90%
Excess Weight Loss	40%	60-70%	70-80%	80-90%

Does Bariatric Surgery Improve Pregnancy Outcomes?

BACKGROUND AND PURPOSE:

- Bariatric surgery for obesity usually results in long-term weight control and improved health outcomes
  - Data on pregnancy outcomes after bariatric surgery are limited
- Getahun et al. (AJOG, 2021) examined the association between bariatric surgery and adverse perinatal outcomes in pregnant women

METHODS:

- Retrospective cohort study
- Population
  - Women eligible for bariatric surgery: (1) BMI ≥40 kg/m2 with no comorbidities or (2) a BMI between 35 and 40 kg/m2 in the presence of certain obesity-related comorbidities (eg, diabetes mellitus and severe sleep apnea)
  - Delivered ≥20 weeks
- Exposures
  - Bariatric surgery
    - All surgeries included
- Primary outcomes
  - Perinatal outcomes

Getahun etal; Perinatal outcomes after Bariatric Surgery. Am J Obstet Gynecol 2022;226:121.e1-16.

RESULTS:

- 20,213 women eligible for surgery
  - Received bariatric surgery: 9.3%
  - Most common surgeries were Roux-en-Y gastric bypass and vertical sleeve gastrectomy
- Bariatric surgery was associated with a reduction in the risks for
  - Gestational diabetes (aOR 0.60; 95% CI, 0.53–0.69); P<.001)
  - Preeclampsia (aOR 0.53 (95% CI, 0.46 to 0.61); P<0.001)
  - Chorioamnionitis (aOR 0.45 (95% CI, 0.32 to 0.63); P<0.001)
  - Cesarean delivery (aOR 0.65 (95% CI, 0.59 to 0.72); P<0.001)
  - Large for gestational age neonate (aOR 0.23 (95% CI, 0.19 to 0.29); P<0.001)
  - Macrosomia (aOR 0.24 (95% CI, 0.19 to 0.30); P<0.001)
  - Neonatal intensive care unit admission (aOR 0.70 (95% CI, 0.61 to 0.81); P<0.001)
- Bariatric surgery was also associated with a significantly increased risk for
  - Small for gestational age (SGA) neonates (aOR 2.46 (95% CI, 2.16 to 2.79); P<0.001
  - Postpartum hemorrhage (PPH): aOR, 1.79 (95% CI, 1.30 to 2.46); P<.001

CONCLUSION:

- Bariatric surgery was associated with improved pregnancy outcomes such as reduced risk of preeclampsia or cesarean delivery, but risk was increased for SGA neonates

Getahun etal; Perinatal outcomes after Bariatric Surgery. Am J Obstet Gynecol 2022;226:121.e1-16.

Does Bariatric Surgery Decrease Cancer Risk?

BACKGROUND AND PURPOSE:

- In the US, over a third of adults meet the threshold for obesity (BMI ≥ 30 kg/m^2)
- Obesity is related to a higher risk for multiple cancers
  - Esophageal adenocarcinoma, postmenopausal (≥ 55 years) breast cancer, cancers of the kidney, colon, rectum, gastric cardia, liver, gallbladder, pancreas, ovary, uterus, thyroid, multiple myeloma and meningioma
- Schauer et al. (Annals of Surgery, 2017) sought to determine whether bariatric surgery is correlated with a lower risk of cancer

METHODS:

- Multisite retrospective observational cohort study of patients undergoing bariatric surgery (2004 – 2014)
- Subjects undergoing surgery were compared to nonsurgical (control) patients that matched by age, sex, study site, body mass index
- Models were used to assess cancer risk up to 10 years post-bariatric surgery

RESULTS:

- 22,198 surgery subjects and 66,427 no surgery subjects participated in the study
- After an average 3.5 year follow-up, 2543 incident cancer were detected
- Patients who underwent bariatric surgery had 33% lower hazard for cancer development (hazard ratio [HR] 0.67; 95% CI 0.60-0.74, P<0.001)

Bariatric Surgery and the Risk of Cancer in a Large Multisite Cohort
Ann Surg 2019 Jan;269(1):95-101

- In women who had bariatric surgery, there were fewer
  - Incident cancers (HR 0.64; 95% CI 0.57 – 0.72, P < 0.001)
  - Obesity-associated cancers (HR 0.58; 95% CI 0.49 – 0.67, P < 0.001)
  - Not Obesity-associate cancers (HR 0.74; 95% CI 0.62 – 0.89, P = 0.001)
- Bariatric patients had a lower risk for the following obesity-associated cancers
  - Postmenopausal breast cancer (HR 0.58; 95% CI 0.44 – 0.77, P < 0.001)
  - Colon cancer (HR 0.59; 95% CI 0.36 – 0.97, P = 0.04)
  - Endometrial cancer (HR 0.50; 95% CI 0.37 – 0.67, P < 0.001)
  - Pancreatic cancer (HR 0.46; 95% CI 0.22 – 0.97, P = 0.04)

CONCLUSION:

- Bariatric surgery was associated with a lower risk of cancer, especially obesity-related cancers

Bariatric Surgery and the Risk of Cancer in a Large Multisite Cohort
Ann Surg 2019 Jan;269(1):95-101

Is Bariatric Surgery Associated with a Decreased Risk for Breast Cancer?

BACKGROUND AND PURPOSE:

- Obesity is associated with an increased risk of breast cancer
- Feigelson et al. (Annals of Surgery, 2019) assessed whether bariatric surgery in pre- and postmenopausal women is associated with reduced risk of breast cancer

METHODS:

- Retrospective cohort study
- Participants
  - Obese female patients enrolled in an integrated health care delivery system
  - Ages 18-79 years
  - Obesity: Defined as BMI greater than or equal to 35 kg/m^2
- Exposure: Bariatric surgery
  - Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding, and sleeve gastrectomy)
- Matching to adjust for biases when comparing exposed to unexposed patients, including
  - BMI, age, study site, and comorbidities
- Analysis
  - Statistical models used to examine breast cancer incidence up to 10 years after bariatric surgery

Bariatric Surgery is Associated With Reduced Risk of Breast Cancer in Both Premenopausal and Postmenopausal Women.
Feigelson, Heather Spencer PhD et al
Annals of Surgery. 272(6):1053-1059, December 2020

RESULTS:

- 17,998 women with bariatric surgery | 53,889 without bariatric surgery
  - 301 premenopausal breast cancer cases
  - 399 postmenopausal breast cancer cases
- Bariatric surgery was associated with a lower risk of breast cancer overall ($P < 0.001$)
  - Hazard ratio (HR) 0.63 (95% CI, 0.52–0.76)
- Bariatric surgery was associated with a reduced risk of both premenopausal and postmenopausal breast cancer
  - Premenopausal: Hazard ratio (HR) 0.72 (95% CI, 0.54–0.94)
  - Postmenopausal: HR 0.55 (95% CI, 0.42–0.72)
- In premenopausal women, the effect of surgery was more pronounced among ER-negative cases
  - HR 0.36 (95% CI, 0.16–0.79)
- In postmenopausal women, the effect of surgery was more pronounced among ER-positive cases
  - HR 0.52 (95% CI, 0.39–0.70)

CONCLUSION:

- Bariatric surgery was associated with an 37% lower risk of breast cancer overall compared to severely obese women
- This effect was significant in both pre and postmenopausal women

Bariatric Surgery is Associated With Reduced Risk of Breast Cancer in Both Premenopausal and Postmenopausal Women.
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Maternal Overweight, Obesity and Congenital Malformations – How Strong is the Link?

BACKGROUND AND PURPOSE:

- Previous studies have established an association between maternal obesity and congenital anomalies
- Limited data on the relationship with the overweight category and if there is a relationship between the increasing severity of obesity and birth defects
- Persson *et al.* (BMJ, 2017) sought to estimate the associations between early pregnancy BMI, including overweight and obese, and congenital anomalies

METHODS:

- Population based cohort study of 1,243,957 live born singleton infants
  - Study used the Swedish birth register which includes information on almost 100% of deliveries
  - Prenatal care is publicly funded and standardized
  - Live singleton births (from 22 completed weeks gestation)
  - Excluded infants with chromosomal aberrations, genetic syndromes, malformation syndromes with known causes, and related viral infections
- Primary outcome measure
  - Offspring with any major congenital malformation
- Additional outcomes
  - Analysis of congenital malformation subgroups with a prevalence of ≥ 1/1000

Persson et al. Risk of major congenital malformations in relation to maternal overweight and obesity severity: cohort study of 1.2 million singletons
BMJ 2017; 357 :j2563 doi:10.1136/bmj.j2563

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RESULTS:

•Offspring of obese mothers had a higher risk ratio for congenital malformations with increasing weight
- Overweight: risk ratio 1.05 (95% CI 1.02 to 1.07)
- Obesity class I: risk ratio 1.12 (95% CI 1.08 to 1.15)
- Obesity class II: risk ratio 1.23 (95% CI 1.17 to 1.30)
- Obesity class III: ratio 1.37 (95% CI 1.26 to 1.49)

•The most common malformation was cardiac, but malformations of the nervous system were especially sensitive to increasing weight with the highest risk ratios
- Compared to normal weight women, obesity class III women had almost double the risk of a major nervous system anomaly

•Genital and digestive system malformations were increased in offspring of obese mothers

CONCLUSION:

•Risks of any major congenital malformation and several subgroups of organ specific malformations progressively increased with maternal overweight and increasing severity of obesity

•Unclear as to mechanism, as even when excluding diabetes, risk remains
- Adipose tissue is an active endocrine organ and there may be related inflammation/vascular dysfunction and dysregulation of placental metabolism
- Folic acid deficiency is common in obesity

Persson et al. Risk of major congenital malformations in relation to maternal overweight and obesity severity: cohort study of 1.2 million singletons
BMJ 2017; 357 :j2563 doi:10.1136/bmj.j2563

Is Bariatric Surgery Associated with Decreased Risks for Severe Birth Defects?

BACKGROUND AND PURPOSE:

•BMI and hyperglycemia are associated with poor perinatal outcomes including birth defects
•Neovius et al. (JAMA, 2019) sought to determine if gastric bypass surgery is associated with reduced risk for major birth defects

METHODS:

•Nationwide matched cohort study
•Participant groups
- Live-born singleton infants born to women who underwent
  - Roux-en-Y gastric bypass surgery **vs**
  - Women who did not undergo bariatric surgery

RESULTS:

•2,998 infants born post-bariatric surgery | 97.4% were matched with 30,573 controls
•Major birth defects were less frequent in women who had bariatric surgery
- Bariatric surgery group: 3.4%
- Controls: 4.9%
- Risk ratio 0.67 (95% CI, 0.52 to 0.87)
- Risk difference, −1.6% (95% CI, −2.7% to −0.6%)

•NTDs
- Bariatric surgery group: 0 cases
- Controls: 20 cases

Association of Maternal Gastric Bypass Surgery With Offspring Birth Defects
Martin Neovius, PhD[1]; Björn Pasternak, MD, PhD[1]; et al
JAMA. 2019;322(15):1515-1517. doi:10.1001/jama.2019.12925

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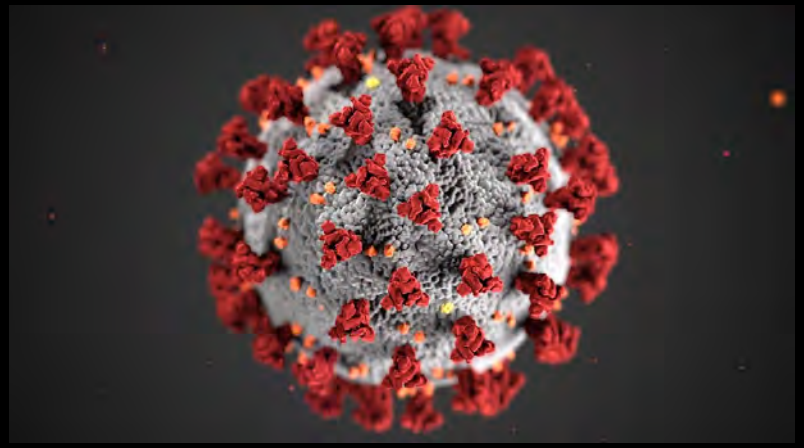
Summary and Conclusions

- Increasing Obesity in North America especially in women
- Women are subject to obesity related bias and discrimination which has significant effect on their ability to seek medical or surgical treatment
- Women fare much better in surgical outcomes
- Tremendous benefit from metabolic surgery towards resolution of several obesity related conditions and increasing longevity
- Establishing a dialogue between Primary care/GI/OBGYN about pros and cons will help bridge the gap which currently exists in access to Metabolic Surgery

THANK YOU FOR YOUR TIME AND QUESTIONS

Are We Post-Pandemic? What's Next in COVID Management and Prevention



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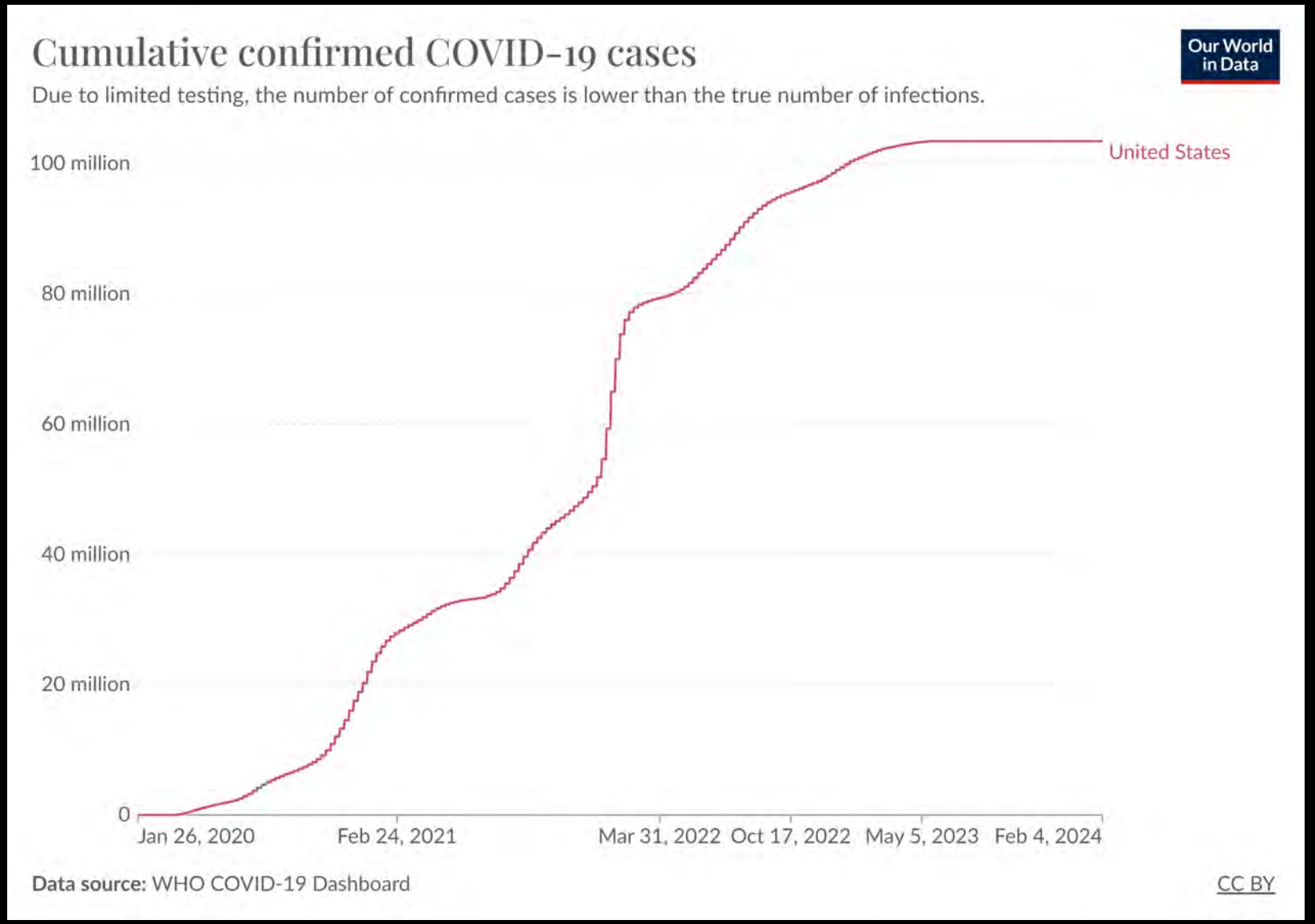
Disclosures

- Participated in Medical Advisory Board for Pfizer COVID-19 vaccination in pregnancy trial
- Site PI for a Pfizer COVID-19 vaccination in pregnancy Phase 2/3 trial
- Site PI for a Pfizer RSV vaccination in pregnancy trial
- Site PI for a Pfizer pharmacokinetics of Paxlovid in pregnancy study

Learning Objectives

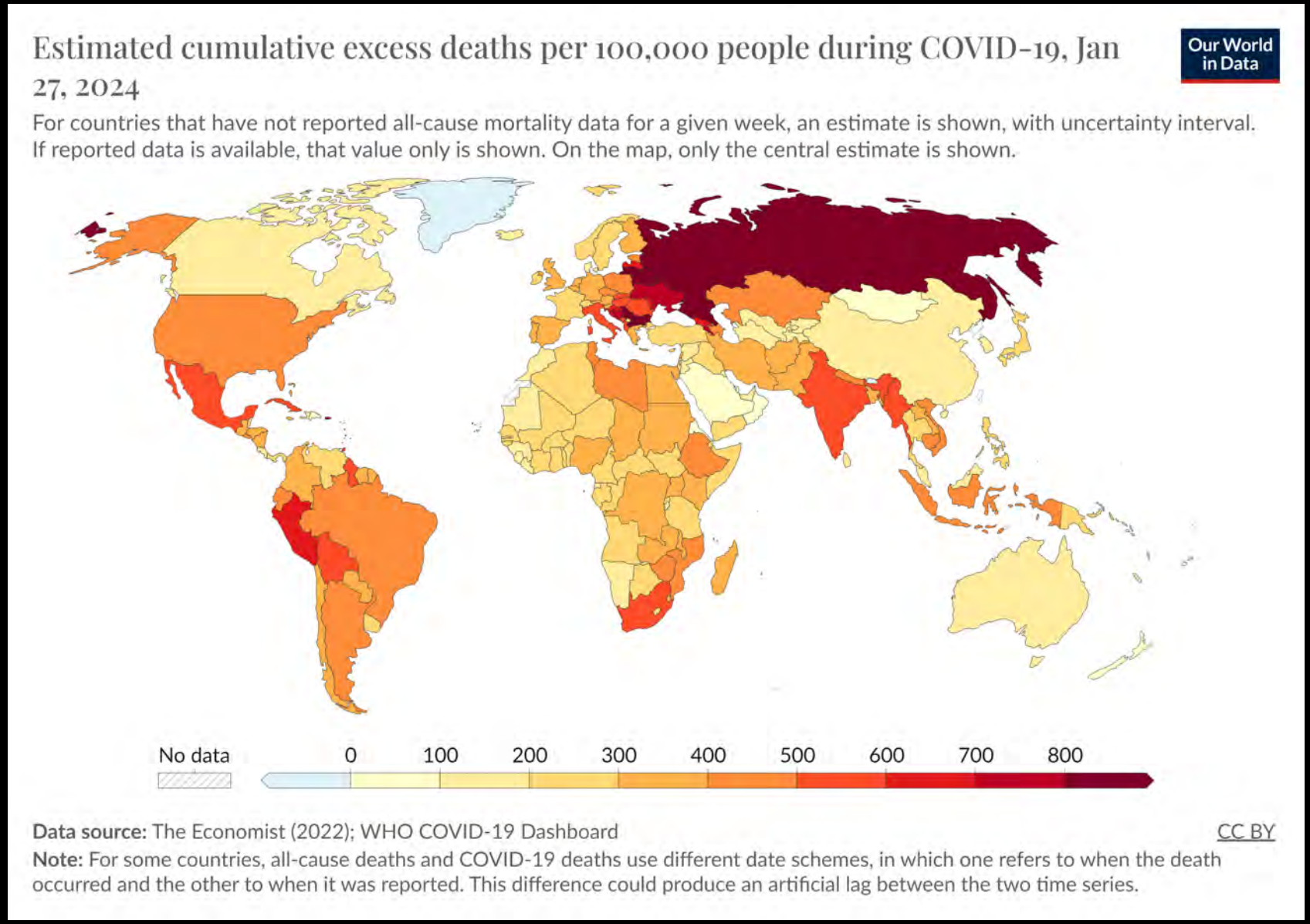
- Describe anticipated outcomes for individuals with SARS-CoV-2 during pregnancy or postpartum
- Describe efficacy and outcomes associated with SARS-CoV-2 vaccination in pregnancy
- Describe current treatments for COVID in pregnancy
- Discuss long COVID or Post Acute Sequelae of SARS-CoV-2

The COVID-19 Pandemic

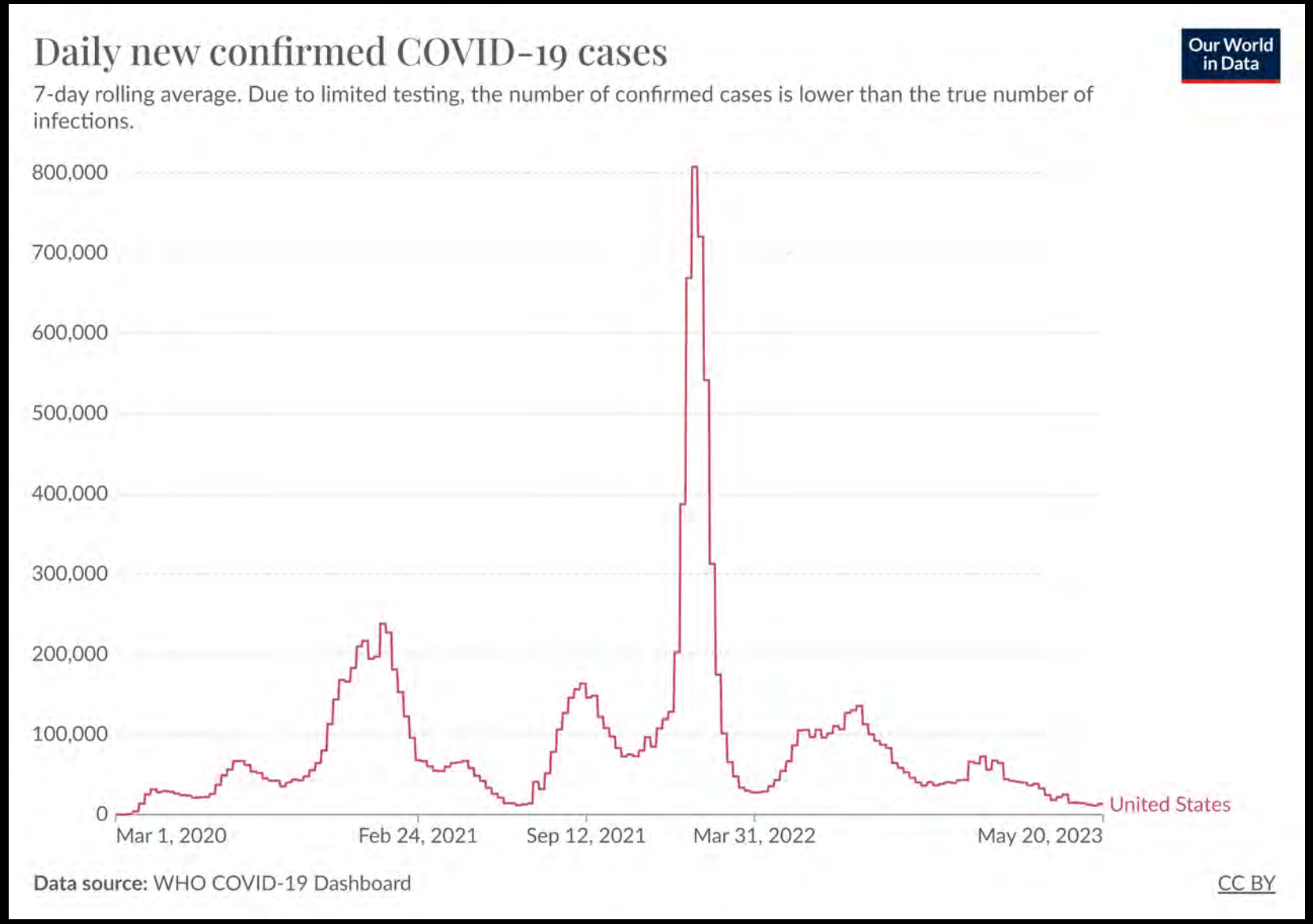


https://ourworldindata.org/covid-cases?country=~USA#select-countries-to-show-in-all-charts

Excess Deaths During Pandemic



Is the pandemic over?



Pregnant Compared with Non-Pregnant

- MMWR report of cases submitted to the CDC from Jan 22 to October 3, 2020
  - **N= 1,300,938 females of reproductive age** who tested positive for SARS-CoV-2
  - Data on pregnancy status available for 35.5% of these individuals (461,825)
    - 88.7% were symptomatic
  - Among symptomatic people, 5.7% (23,434) were pregnant

MMWR Weekly Report (Nov 2, 2020)

Pregnant Compared with Non-Pregnant

- **After adjustment for age, comorbidities and race/ethnicity, pregnant individuals were at increased risk of**
  - **ICU admission: 10.5 vs 3.9 per 1,000 cases**(aRR 3.0, 95% CI=2.6-3.4)
  - **Mechanical ventilation: 0.5% vs 0.3%** (aRR 1.7, 95% CI 1.2-2.4)
  - **Risk of death: 1.5 vs 1.2 per 1,000 cases** (aRR 1.7, 95% CI 1.2-2.4)
- **Disparities were prevalent**
  - Individuals who identified as Black represent 14% of cohort, but 37% of deaths overall and 27% of deaths among pregnant people

MMWR Weekly Report (Nov 2, 2020)

SARS-CoV-2 in Pregnancy

- Retrospective cohort of all deliveries from April-Nov
  - All-payer database encompassing 20% of U.S. population
  - Identified participants with billing codes
- N=406,446 patients hospitalized for childbirth
  - 6,380 (1.6%) COVID-19 diagnostic code

Jering KS et al, JAMA Int Med

Outcome	No COVID N=400,066	With COVID N=6,380	Unadjusted OR	Adjusted OR
Cesarean	27.5%	28.9%	1.08 (1.02-1.14)	**1.07 (1.02-1.13)**
PTL	4.0%	5.2%	1.31 (1.17-1.46)	**1.19 (1.06-1.33)**
PTB	5.8%	7.2%	1.26 (1.14-1.38)	**1.17 (1.06-1.29)**
Stillbirth	0.3%	0.5%	1.66 (1.18-2.33)	1.23 (0.87-1.75)
PreE	6.8%	8.8%	1.36 (1.22-1.46)	**1.21 (1.11-1.33)**
Eclampsia	0.1%	0.1%	1.74 (0.86-3.52)	1.56 (0.77-3.16)
HELLP	0.2%	0.5%	2.10 (1.48-2.97)	**1.96 (1.36-2.81)**
VTE	0.1%	0.2%	3.52 (2.09-5.92)	**3.43 (2.01-5.82)**
ICU	0.4%	3.3%	7.84 (6.78-9.06)	**6.47 (5.55-7.55)**
Vent	0.1%	1.3%	25.77 (20.03-33.15)	**23.70 (17.95-31.29)**

Jering KS et al, JAMA Int Med

NICHD MFMU GRAVID

NICHD MFMU GRAVID Study

- Retrospective cohort study 17 U.S. hospitals participating in the NICHD Maternal-Fetal Medicine Units Network
- 14,104 pregnant or postpartum patients
- Delivered March-Dec 2020

Metz et al JAMA 2022

NICHD MFMU GRAVID

- 2,352 patients had SARS-CoV-2 infection
- Compared with those without SARS-CoV-2 who delivered on randomly selected dates (n=11,752)
- Primary Outcome
  - Maternal death or serious morbidity from common pregnancy complications including hypertensive disorders of pregnancy, postpartum hemorrhage, and infections other than SARS-CoV-2

Metz et al JAMA 2022

Serious Maternal Morbidity

Outcome	SARS-CoV-2 N=2352	No SARS-CoV-2 n=11,752	Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)
Composite death or serious morbidity	13.4%	9.2%	1.45 (1.29-1.64)	1.41 (1.23-1.61)
Death	0.2%	0%	-	-
Hypertensive disorders of pregnancy	10.1%	6.5%	1.56 (1.35-1.79)	1.53 (1.31-1.79)
Postpartum hemorrhage	2.6%	2.4%	1.06 (0.81-1.40)	1.13 (0.83-1.53)
Infection other than SARS-CoV-2	2.3%	0.9%	2.61 (1.88-3.63)	2.08 (1.41-3.05)

Stratified by Infection Severity

- Adverse outcomes among those with moderate or higher disease severity (except HDP)
  - Need to prevent progression to higher disease severity
  - Vaccines and treatments for COVID-19

Metz et al JAMA 2022

Vaccine Efficacy

- Population-based data from Scotland (Dec 2020-Oct 2021)
- Vaccine coverage lower for pregnant (32.3%) compared with non-pregnant females (77.4%)
- Compared SARS-CoV-2 infection outcomes vaccinated vs unvaccinated pregnant people

Stock et al Nature Medicine 2022

Vaccine Efficacy

- 77.4% of SARS-CoV-2 infections were in unvaccinated individuals
  - 11.5% partially vaccinated
  - 11.1% fully vaccinated
- 91% of SARS-CoV-2 infections associated with hospitalization
- 98% of SARS-CoV-2 infections associated with critical care admissions were in unvaccinated individuals

Stock et al Nature Medicine 2022

Vaccine Efficacy

- Of 2,364 total births, 11 stillbirths and 8 livebirths resulted in neonatal deaths
- All perinatal deaths occurred in unvaccinated individuals

Stock et al Nature Medicine 2022

Vaccine Efficacy

- Retrospective cohort 15,865 pregnant patients
- Vaccinated (at least 2 doses of mRNA vaccine) compared with unvaccinated
  - n=2,069 vaccinated group and 13,796 unvaccinated
- Lower rates of adverse perinatal outcomes with vaccination
  - Perinatal death (0.5% vs 0.8%, aOR 0.20, 95% CI 0.05-0.88)
  - Preterm delivery (aOR 0.63, 95% CI 0.48-0.82)
  - Very low birth weight (aOR 0.35, 95% CI 0.15-0.84)
  - NICU admission (aOR 0.66, 95% CI 0.52-0.85)

Morgan JA et al, Obstet Gynecol 2023

Vaccine Efficacy

- Systematic review and meta of 23 studies including 117,552 COVID-19 vaccinated pregnant people
- Effectiveness 89.5% (95% CI 69.0-96.4%) against SARS-CoV-2 infection 7 days after 2nd dose
- Risk of stillbirth lower in vaccinated (pOR 0.85, 0.73-0.99)
- No evidence of higher risk of miscarriage, earlier gestational age at delivery, abruption, pulmonary embolism, PPH, maternal death, ICU admission, lower birthweight, NICU

Prasad et al Nat Commun 2022

Vaccine Efficacy Against Neonatal Disease

- Case-control study
- 537 case infants hospitalized for COVID under 6 months of age (181 Delta, 356 Omicron)
- 16% case infants and 29% control infants born to unvaccinated mothers
- Effectiveness of maternal vaccination against neonatal hospitalization for COVID was 52% overall
  - 69% efficacy when administered after 20 weeks' gestation

Halasa NB et al New Eng J Med 2022

Vaccine Boosters

- Prospective cohort
- 31 pregnant, 12 lactating, 20 nonpregnant age-matched controls
- 15 dyads with cord blood
- Increased IgG levels against Omicron spike with booster
- Levels in pregnant and lactating similar to nonpregnant controls
- Spike-specific IgG levels in cord increased with time since vaccination

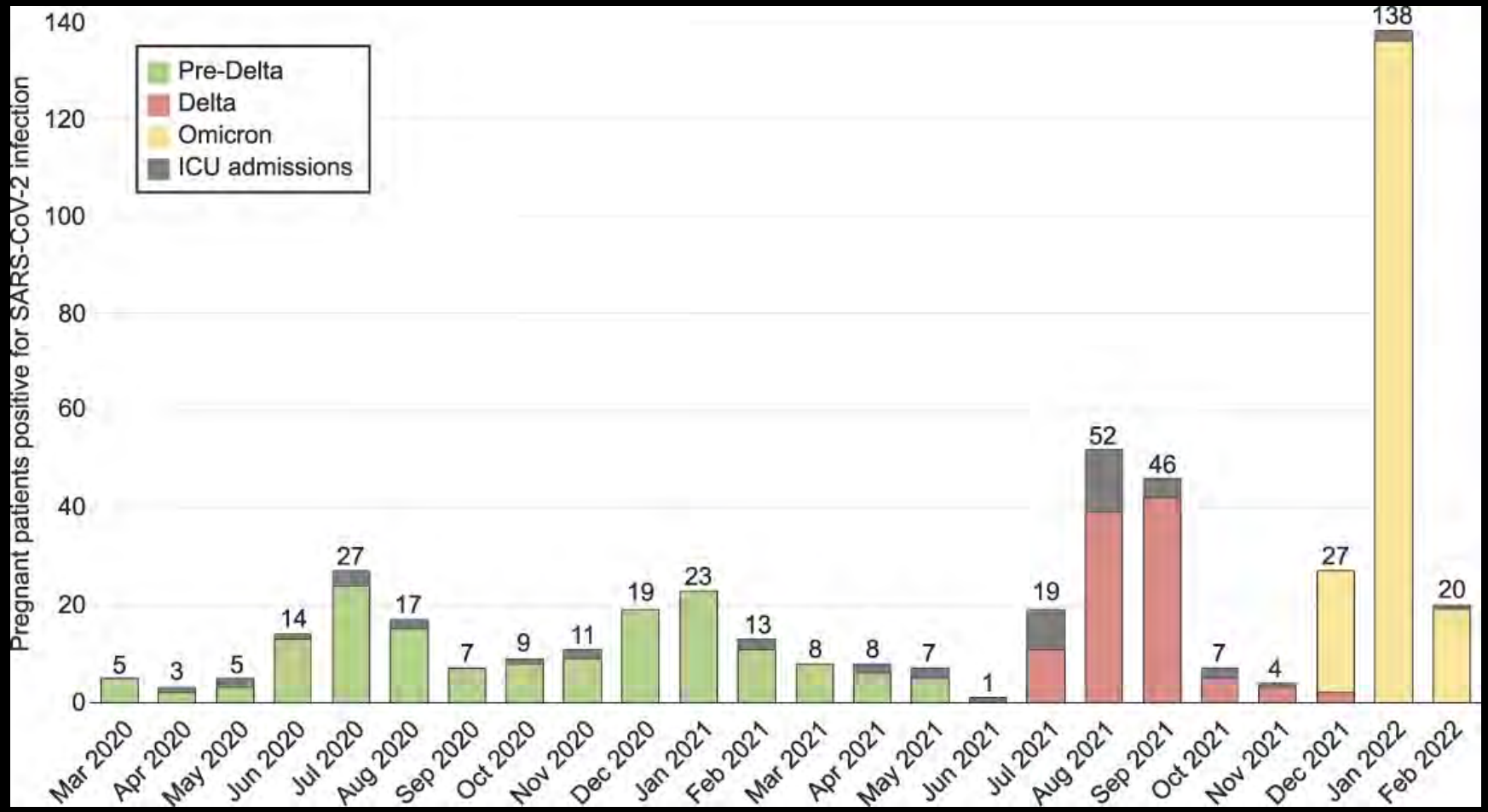
Atyeo et al Am J Obstet Gynecol 2022

Vaccine Boosters

- Annual booster along with flu vaccination
- Primarily for maternal benefit (similar to flu)
- In contrast to seasonal RSV vaccination aimed solely to produce antibodies for neonatal transfer

Variant Matters

- Severe-critical disease: 1.8% Omicron, 13.3% pre-Delta, 24.1% Delta



Seasely et al Obstet Gynecol 2022

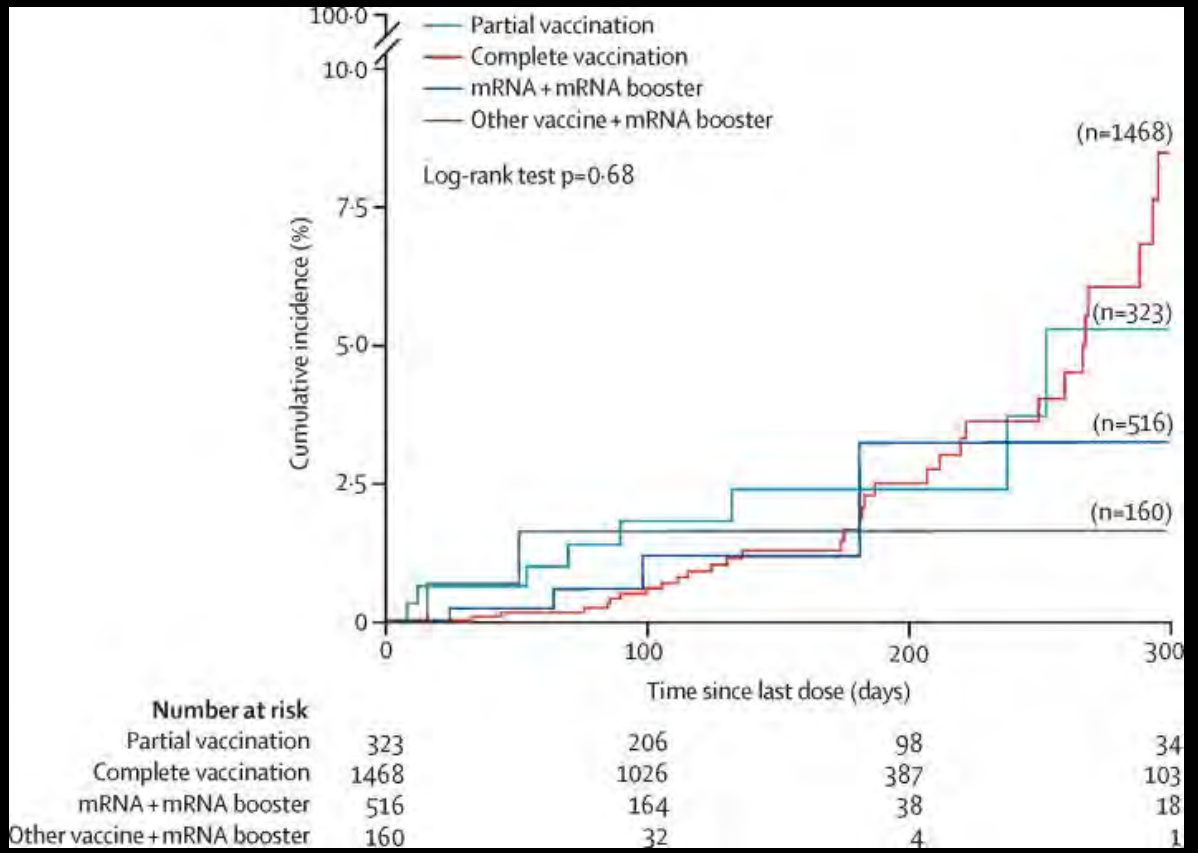
SARS-CoV-2 Variant

- CDC MMWR
  - Increased risk of stillbirth with SARS-CoV-2 infection
    - March 2020-Sept 2021, aRR 1.90 (95% CI 1.69-2.15)
    - During period with Delta variant, aRR 4.04 (95% CI 3.28-4.97)

CDC MMWR 2021

Omicron Variant INTERCOVID Data

- 4618 pregnant people with SARS-CoV-2 during Omicron dominance
  - n=1545 with COVID
- Those with COVID higher rates of maternal morbidity and mortality
- Unvaccinated experienced higher rates of maternal morbidity
- Booster protective



Villar et al Lancet 2023

Omicron Variant INTERCOVID Data

- For pregnant people with COVID-19, vaccine highly effective in preventing severe disease
- Vaccine effectiveness for those with complete regimen 76%
- Vaccine effectiveness for those with a booster 91%

Villar et al Lancet 2023

Omicron Variant CDC Data

- Premier Healthcare Database
- Evaluated pre-Delta, Delta, Omicron
- Exposure to COVID-19 identified by diagnostic code for COVID-19 during delivery hospitalization
- During Omicron period, COVID-19 remained associated with sepsis, ARDS, shock, renal failure, ICU, mechanical ventilation, death

Carlson J et al Obstet Gynecol 2024

Antenatal Surveillance

- During early and Delta variant predominance performed growth ultrasounds
- Non-stress tests for abnormal growth
- Fetal deaths from massive perivillous fibrin deposition and placental insufficiency
- No longer conducting antenatal surveillance for SARS-CoV-2 infection alone

COVID-19 Treatment in Pregnancy

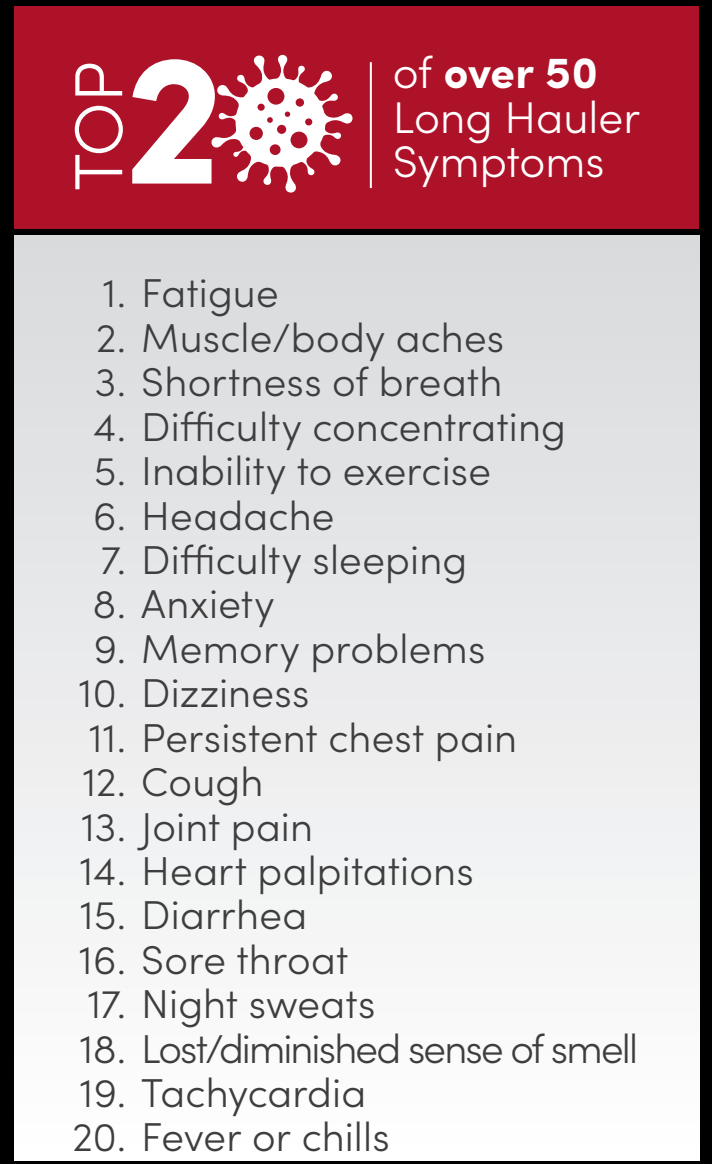
- Treatment in pregnant individuals similar to non-pregnant high risk populations
- Paxlovid for mild to moderate COVID (outpatient) to prevent progression to severe disease
- Dexamethasone and remdesivir if requiring oxygen
- Molnupiravir should be avoided
- Insufficient evidence for or against UFH/LMWH

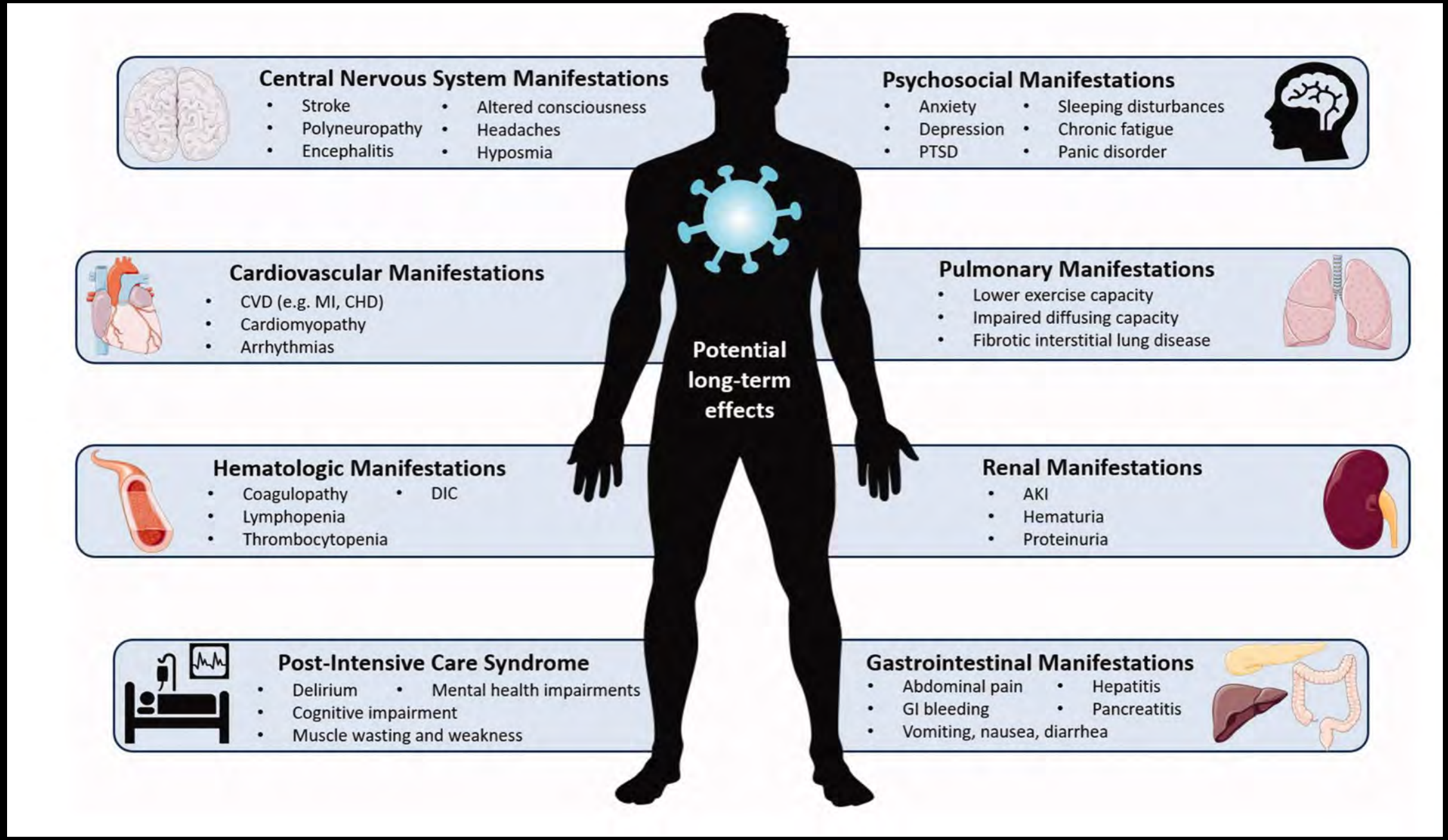
https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf

What’s Next?

Long COVID or PASC

- Long COVID or Post-Acute Sequelae of COVID (PASC)
- Occurs in 10-25% of people who acquire SARS-CoV-2
- Possibly resulting from inflammatory response, viral reservoirs
- Public health crisis





Victoria Higgins, Dorsa Sohaei, Eleftherios P. Diamandis & Ioannis Prassas (2021) COVID-19: from an acute to chronic disease? Potential long-term health consequences, Critical Reviews in Clinical Laboratory Sciences, 58:5,297-310, DOI: 10.1080/10408363.2020.1860895

NIH RECOVER-Pregnancy Cohort

- Remains unclear how pregnancy affects PASC
- NIH RECOVER Cohort designed to understand prevalence and pathophysiology of PASC
- Established RECOVER-Pregnancy Cohort to follow people with SARS-CoV-2 during pregnancy
  - May observe differential prevalence or risk factors

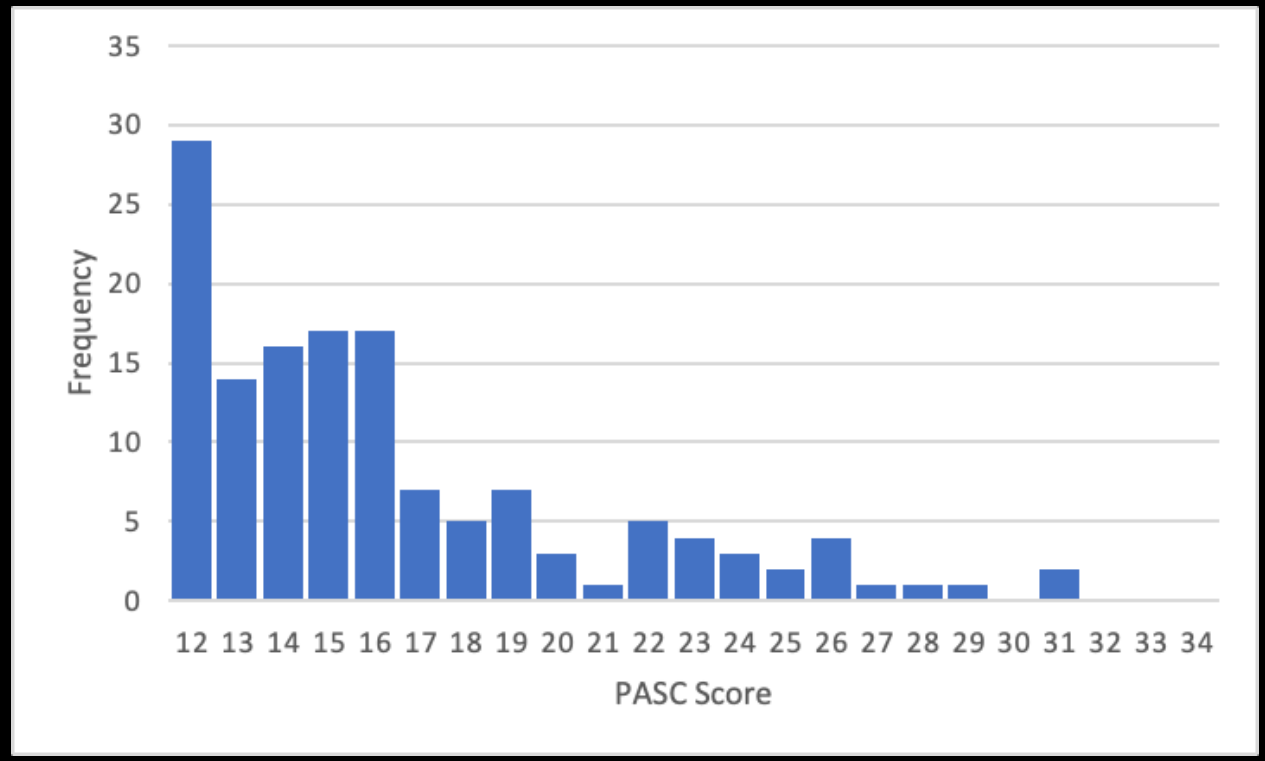
NIH RECOVER Initiative

RECOVER
Researching COVID to Enhance Recovery

- To estimate the prevalence of Post-Acute Sequelae of SARS-CoV-2 infection (PASC or long COVID) after infection with SARS-CoV-2 during pregnancy in the RECOVER- Pregnancy Cohort and characterize associated risk factors

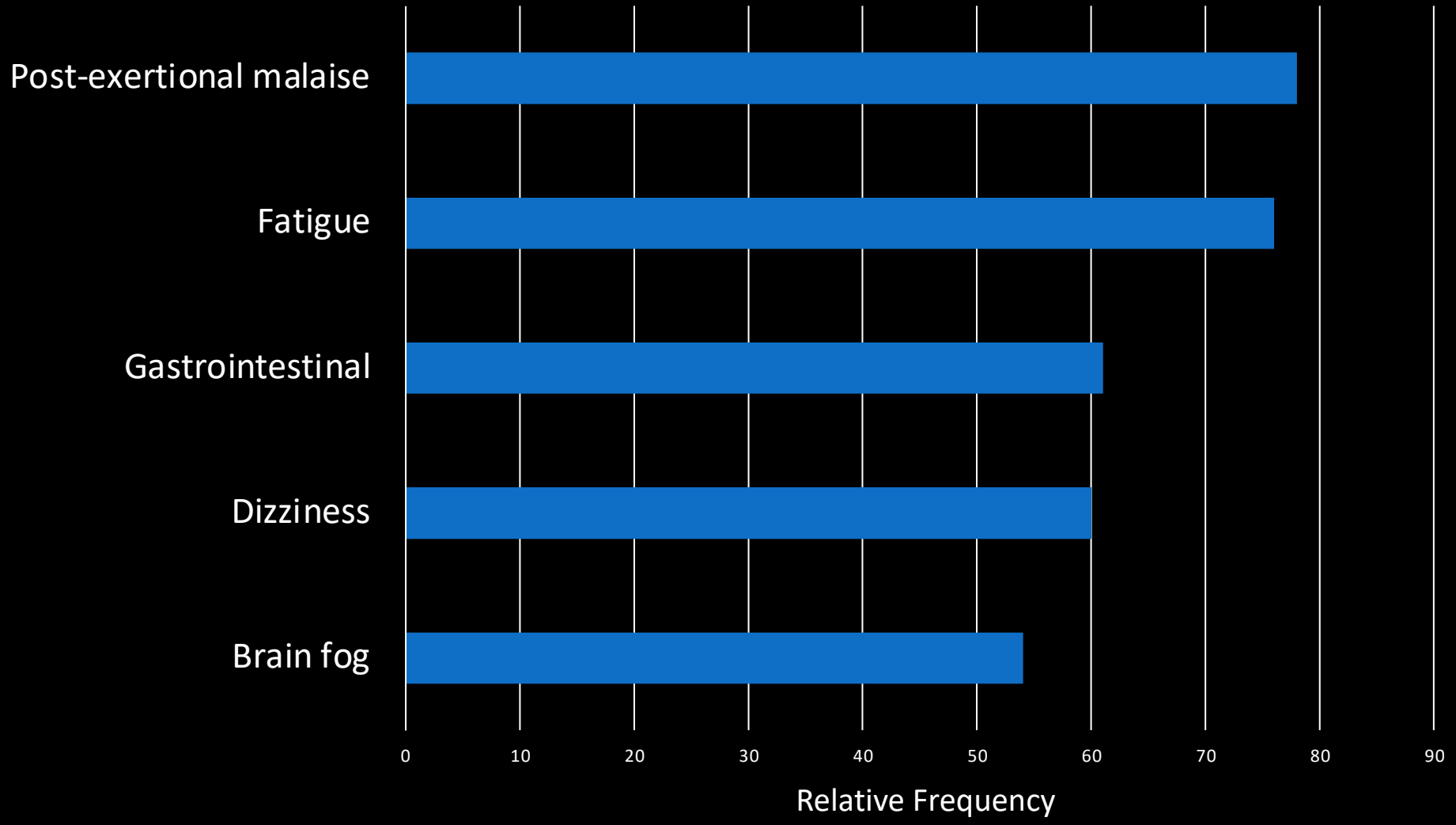
Pregnancy and PASC

- 9.3% (95% CI 7.9-10.9%) met criteria for PASC
- Median time from index date to PASC-defining study visit 10.3 months (IQR 6.1-21.5)



Thaweethai et al JAMA 2023

PASC Symptoms



Risk Factors for PASC

Characteristic	PASC Positive n=139	PASC Indeterminate n=1363	Odds Ratio	Adjusted Odds Ratio
Covering expenses difficult	57%	41%	1.93 (1.36, 2.75)	1.57 (1.05, 2.34)
Obesity	38%	22%	2.19 (1.51, 3.16)	1.65 (1.12, 2.43)
Depression or anxiety	59%	35%	2.61 (1.82, 3.74)	2.64 (1.79, 3.88)
Oxygen for acute infection	12%	6%	2.34 (1.34, 4.09)	1.86 (1.00, 3.44)

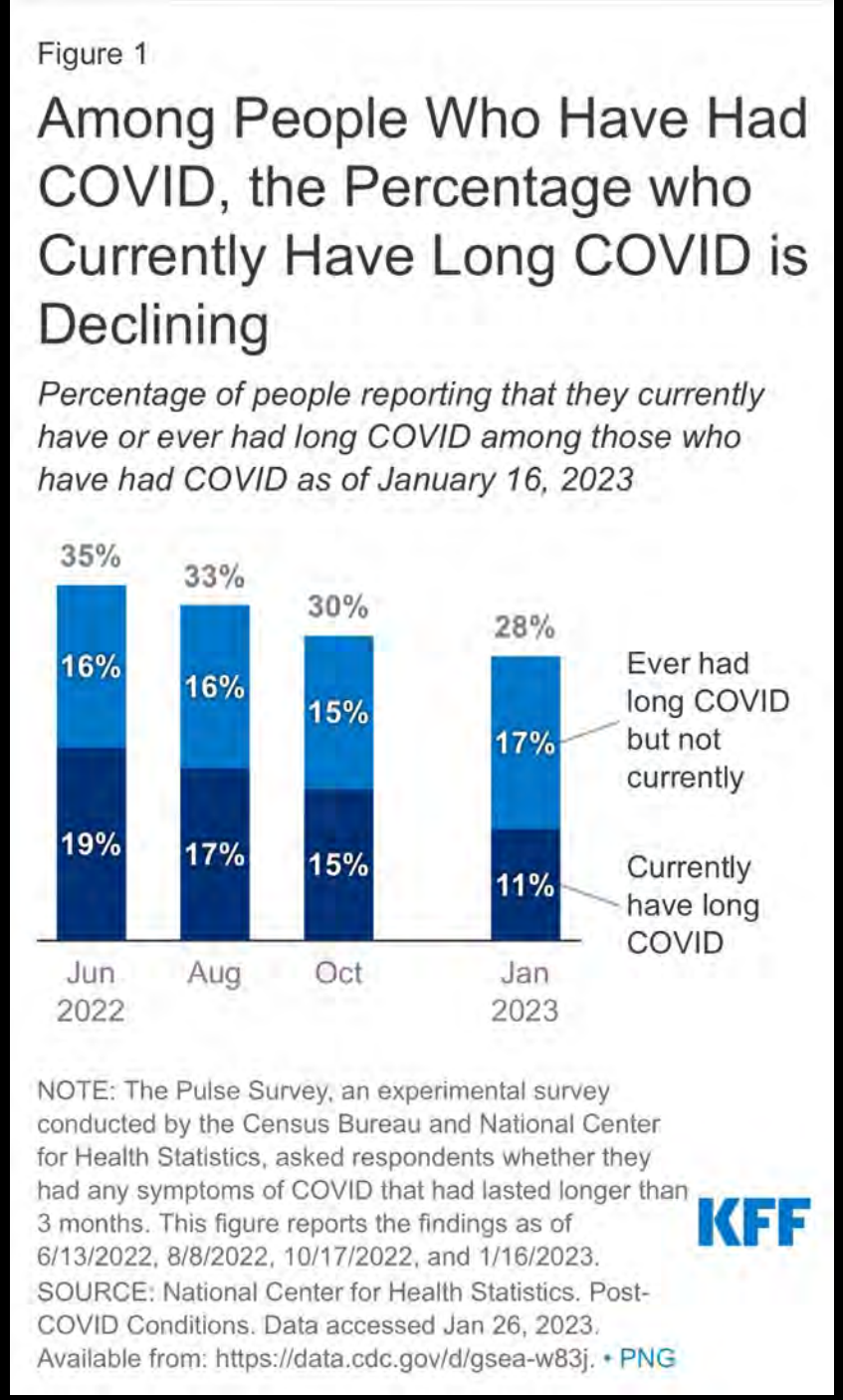
Multivariable logistic regression model also adjusted for age, era of infection, insurance status, discrimination index, vaccination, tobacco use, other medical comorbidities, number prior pregnancies, trimester of infection

RECOVER-Pregnancy Cohort

- 1 in 10 individuals with SARS-CoV-2 during pregnancy will develop PASC
- Symptoms include post-exertional malaise, fatigue and GI symptoms
- Socioeconomic and clinical characteristics associated with development of PASC
- Rates of PASC among pregnant populations may be lower than non-pregnant adults with estimates ranging from 10-25%

Symptom Duration

- Unclear duration and trajectory
- BMJ study (2021) most patients recovered at 1 year
- UK statistics- 30% of patients with PASC having symptoms for ≥ 2 years
- Follow RECOVER participants for 4 years



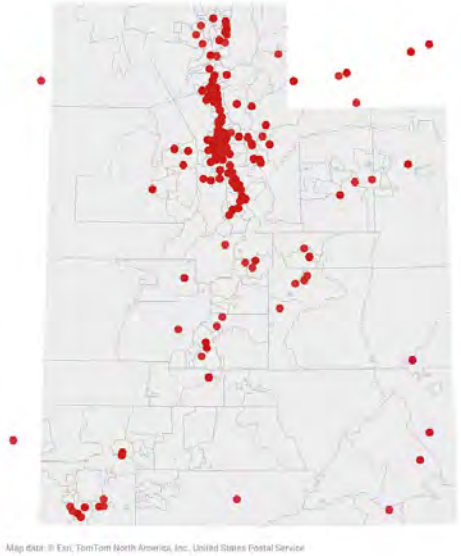
LONG COVID CONTINUES TO IMPACT UTAHN'S HEALTH AND PRODUCTIVITY

HEALTH
UNIVERSITY OF UTAH

Many people who had COVID-19 continue to experience ongoing health problems even after they recovered from the initial infection. These problems can include **respiratory issues, cardiovascular problems, and neurological issues**, among others. **Long-term COVID clinics can provide specialized care and support** to these individuals to help them manage their ongoing health issues.

>1800
PATIENTS SINCE
JULY 2021

U of U Health's Comprehensive COVID Clinic Reach



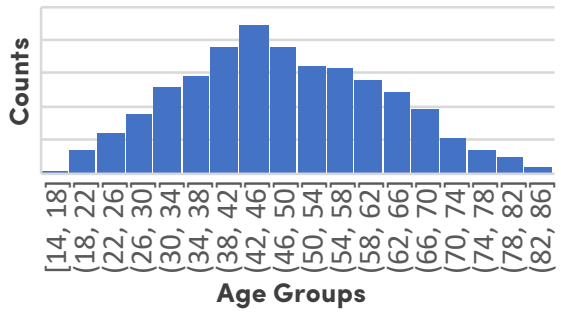
Long COVID affects 1 in 5 adults[1]

- Since July 2021, U of U Health's Comprehensive COVID Clinic cared for **>1,800 patients**
- **67% of patients were female,** 32% were male
- **49% of patients are from rural and underserved areas** with low health equity
- Majority of patients are **between 26 and 62**

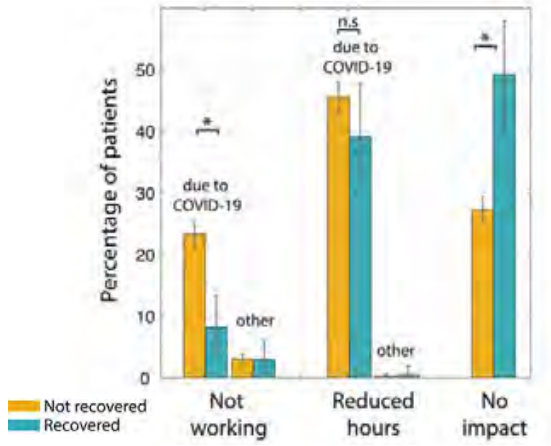
Patients with long COVID:

- Are **less able to work** and **may lose health insurance**
  - **40%** working reduced hours
  - **20%** not able to work
- **Struggle to care for children** and elderly family members

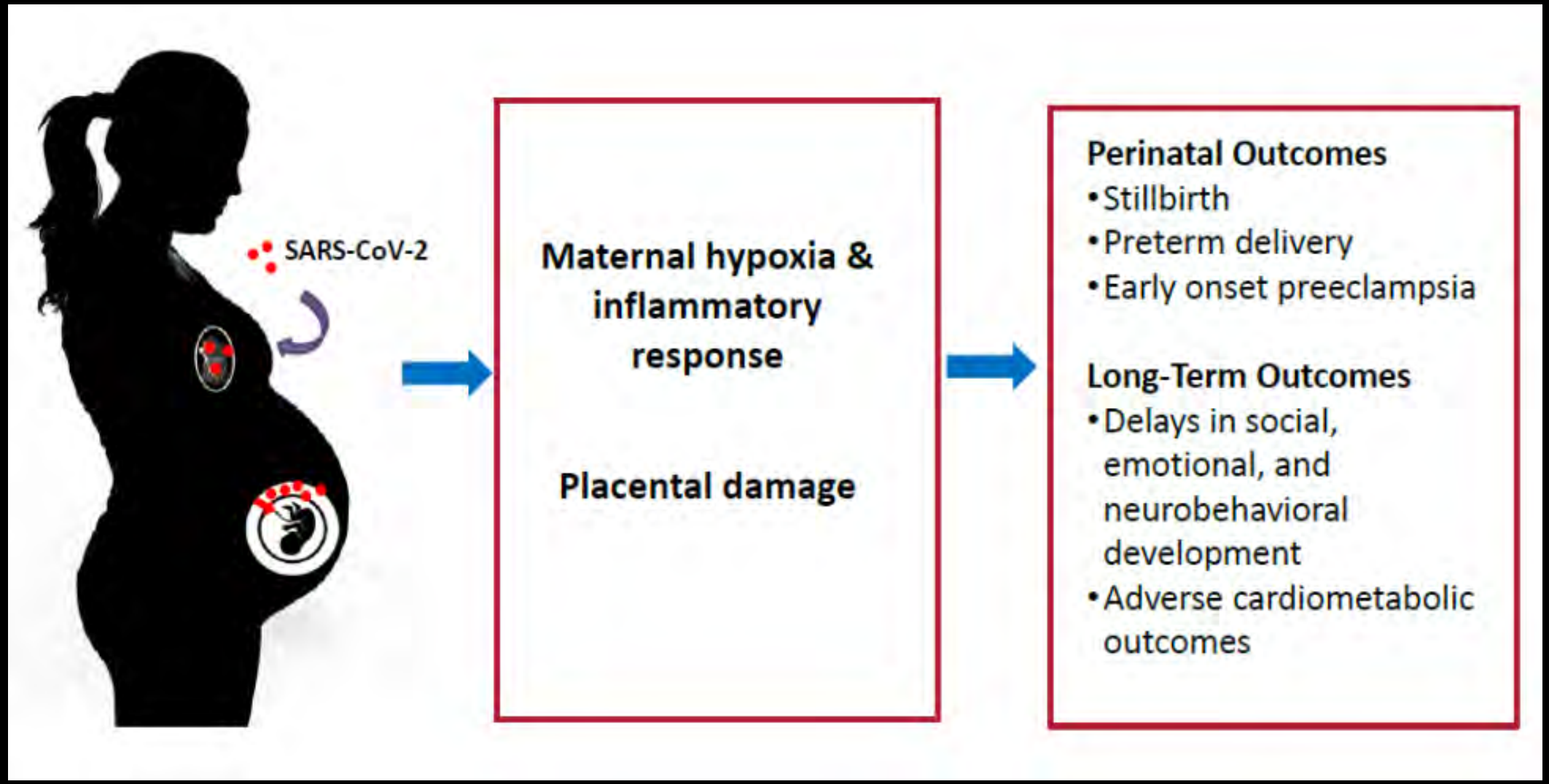
Distribution of ages



d. Long COVID impact on work



Are offspring affected?



Offspring Neurodevelopment

- Prospective cohort N=255
  - 114 exposed to SARS-Cov-2 and 141 unexposed
  - 62 historical cohort pre-pandemic
- Performed ASQ-3 at 6 months
- Birth during pandemic but not in utero exposure associated with difference in ND at 6 months

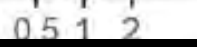
Shuffrey et al JAMA Peds 2022

Offspring Neurodevelopment

- Retrospective cohort N=7772 live births
  - 222 births to SARS-CoV-2 positive mothers
- Queried diagnosis codes and labs for 8 hospitals in the northeast (March- Dec 2020)

Edlow et al JAMA Open 2022

Variable		N	Odds ratio	p
Pregnancy COVID status	COVID negative	7550	Reference	
	COVID positive	222	1.86 (1.03, 3.36)	0.04
Maternal age (years)		7772	1.03 (1.00, 1.06)	0.05
Maternal race	White	5363	Reference	
	Asian	772	1.38 (0.92, 2.07)	0.11
	Black or African American	656	0.51 (0.27, 0.96)	0.04
	Other	733	1.40 (0.82, 2.40)	0.21
	Unknown	248	1.22 (0.61, 2.48)	0.57
Maternal ethnicity	Not Hispanic	6378	Reference	
	Hispanic	1134	1.25 (0.76, 2.06)	0.39
	Unavailable	260	1.51 (0.78, 2.92)	0.22
Maternal public insurance	No	6341	Reference	
	Yes	1431	1.01 (0.68, 1.50)	0.97
Offspring sex	Female	3819	Reference	
	Male	3953	1.39 (1.07, 1.81)	0.01
Pre-term birth	No	7086	Reference	
	Yes	686	3.39 (2.49, 4.62)	<0.001



Remaining Offspring Questions

- Is it exposure to the pandemic and societal changes of the pandemic or the exposure itself?
- Do the findings persist when compared with controls who are unexposed evaluated in the same way?
- Does initial COVID-19 severity matter?

Summary

- COVID-19 had a huge, ongoing societal impact
- Continue to observe excess deaths
- Perinatal morbidity and mortality remain higher with Omicron
- Boosters effective against severe disease
- Vaccines offer neonatal protection
- PASC public health crisis warrants ongoing attention

Research in Pregnant Individuals

"Protection by exclusion of pregnant women from drug development and clinical therapeutic trials, even during epidemics and pandemics, is not unprecedented. Moreover, it is both misguided and not justifiable and may have excluded them from potentially beneficial interventions…pregnant women should be given the opportunity to be included in clinical trials for COVID-19 based on the concepts of justice, equity, autonomy and informed consent."

Costantine et al Obstet Gynecol 2020

Thank you!

- Jeanette Brown, MD
  Medical Director U of Utah Long COVID Clinic

- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development for funding the MFMU GRAVID study

- National Heart, Lung and Blood Institute for funding the RECOVER study

FEBRUARY 24, 2023

Management of Inherited Bleeding Disorders in Obstetrics and Gynecology

Tricia Huguelet, MD
Associate Professor
Section Chief, Pediatric and Adolescent Gynecology
Medical Director, Spots and Dots Clinic, Hemophilia and Thrombosis Center

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Learning Objectives

1. Recognize the **prevalence** of Von Willebrand's Disease and mild platelet function defects in patients presenting for obstetric and gynecologic care
2. Discuss optimal **treatment of acute and chronic heavy menstrual bleeding** in the gynecologic patient with an inherited blood disorder
3. Review best practices in patients undergoing **gynecologic surgery** in the setting of an inherited blood disorder
4. Discuss management strategies for the **laboring patient** with an inherited blood disorder

Prevalence of Inherited Bleeding Disorders in Patients Presenting for ObGyn Care

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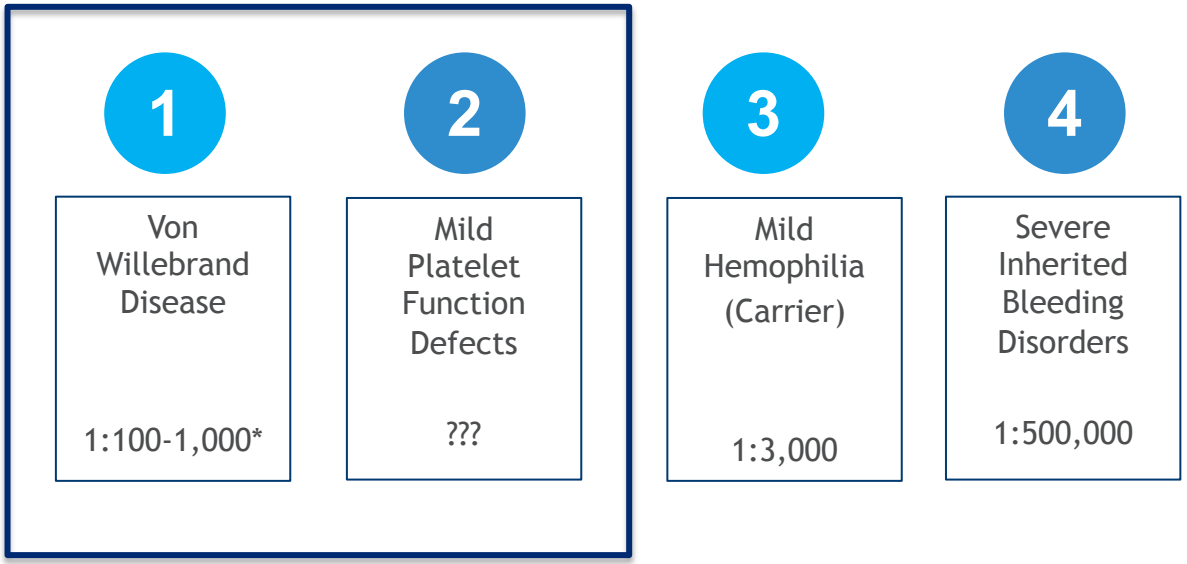
Overview of Bleeding Disorders in Patients with a Uterus

- Inherited Bleeding Disorders affect up to 1% of females in the United States
- 20-30% of women experience heavy menstrual bleeding **and up to 25%** will be diagnosed with an inherited bleeding disorder
- Up to 25% women with severe PPH (> 2liters) will be diagnosed with an IBD

Prevalence of Inherited Bleeding Disorders



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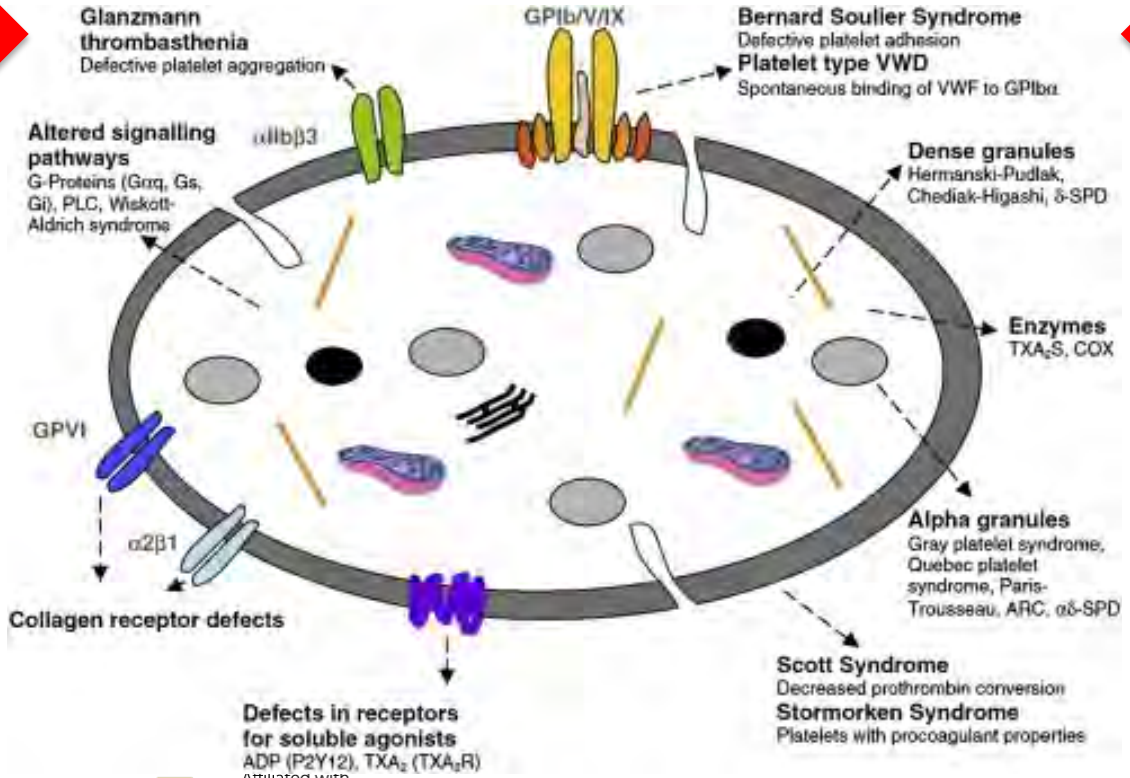
*Type 3 = 1 in 1,000,000

Von Willebrand Disease

Type	Prevalence within VWD	Pathophysiology
Type 1	70–80%	Quantitative defect (reduced absolute amount of VWF) Normal function
Type 2	20%	Qualitative defect (abnormal function)
Type 2A		Loss of high molecular weight multimers
Type 2B		Increased binding of VWF to platelets
Type 2M		Decreased binding of VWF to platelets
Type 2N		Decreased binding of VWF to FVIII
Type 3	Rare (3–5 cases per million)	Quantitative defect (virtual absence of VWF)

Inherited Platelet Disorders



Upwards of 30% of women experience heavy menstrual bleeding in their lifetime

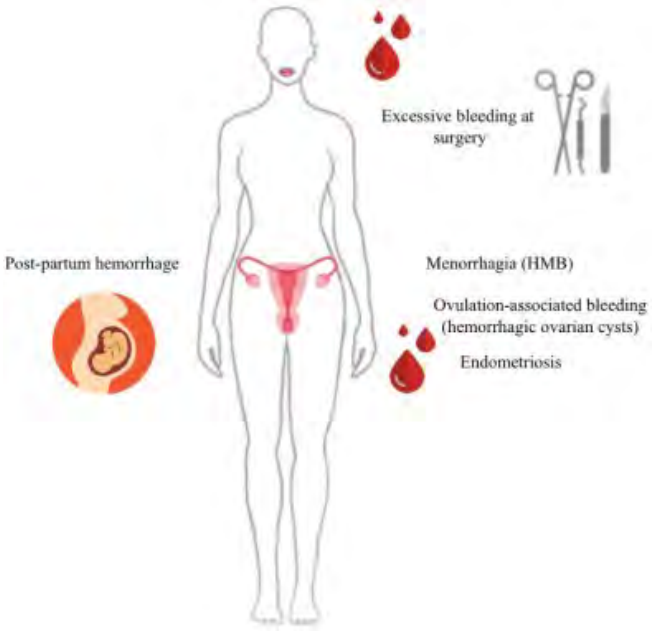
CDC Registry - Symptoms in VWD (n = 319)

Symptoms	Proportion of Patients (%)
Heavy menstrual bleeding	76
Excessive bruising	55
Epistaxis	48
Oropharyngeal bleeding	29
Post-dental procedure bleeding	35
Post-surgical bleeding	37
Excessive bleeding from minor wounds	48
Joint bleeding	16
Muscle bleeding	8

Inherited Platelet Disorders

- Bleeding severity is variable but generally **much more severe** with Glanzmann Thrombasthenia and Bernard-Soulier Syndrome

- Typical clinical symptoms are mucocutaneous bleeding
  - Heavy menstrual bleeding
  - Epistaxis
  - Gum bleeding
  - Ecchymoses (superficial)
  - Surgical bleeding



Lowe, Platelets 2019

Management of Acute and Chronic HMB in Patients with IBDs

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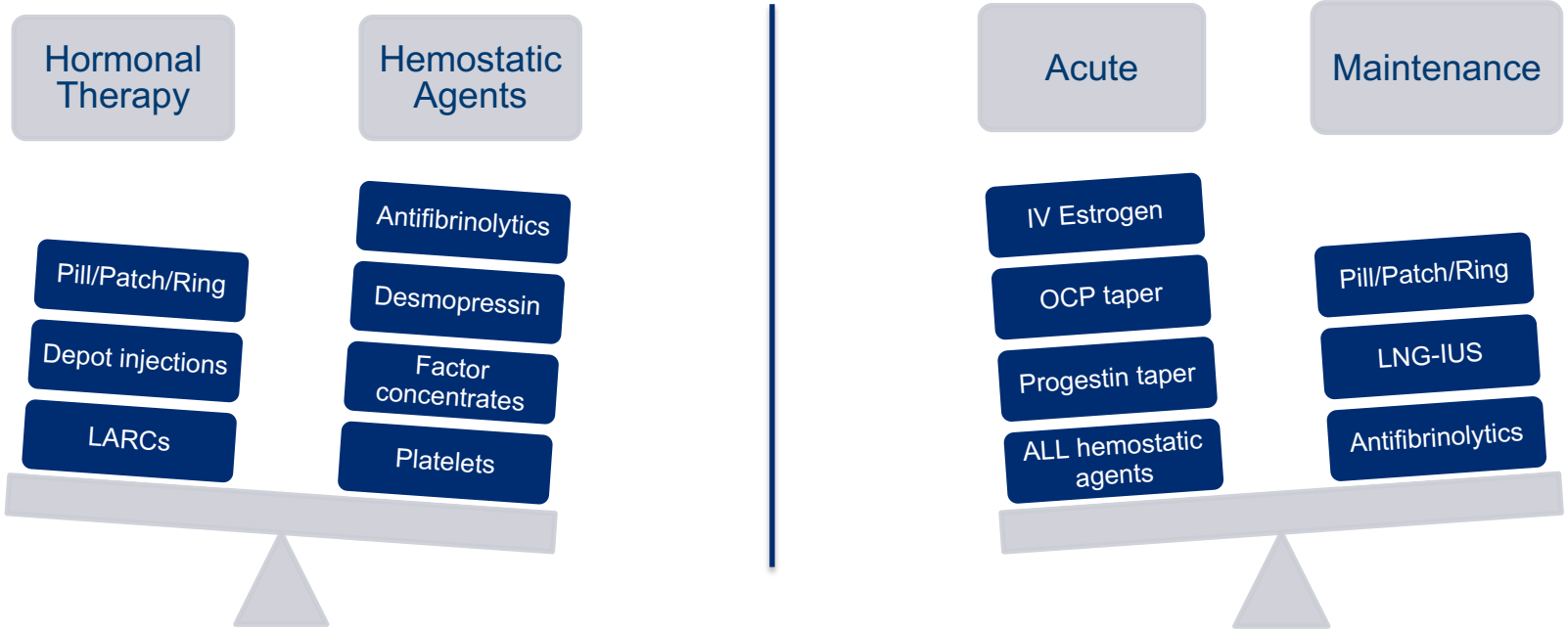
Treatment Approach



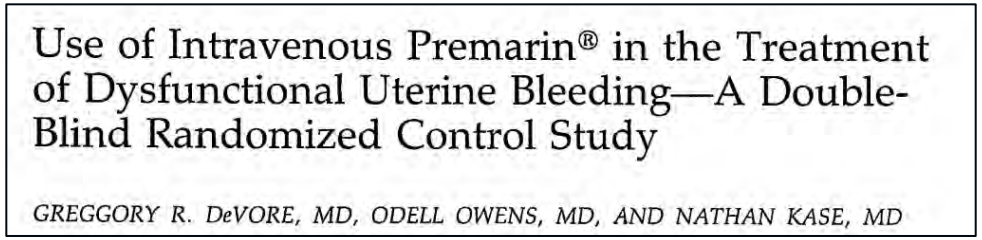
CDC Registry – Treatments for HMB (n= 165)

Symptoms	Prevalence
Oral contraceptives	54.5%
Desmopressin	33.9%
Antifibrinolytics	24.2%
Blood or plasma products	7.3%
Clotting factor products	6.1%
Endometrial ablation	4.2%
Levonorgestrel IUD	3%
Uterine artery embolization	3%
Hysterectomy	10.6%

Acute Management of HMB

Hormonal	Non-Hormonal	IV Iron Therapy
Combined Contraceptive Pill Taper *Ethinyl estradiol 35mcg/norgestimate 0.25mg* *PO*	Tranexamic acid *10mg/kg IV TID* *1300mg PO TID*	Iron Sucrose or Ferric Carboxymaltose
Progestin Taper *Norethindrone acetate TID (15mg)* *Medroxyprogesterone acetate TID (60mg)* *PO*	Aminocaproic acid *100mg/kg IV QID* *500mg PO QID*	
Conjugated equine estrogen *Premarin 25mg q 4hrs x 6 doses* *IV*	Desmopressin *IV, IN or SQ*	
Leuprolide acetate *3.75 or 11.25mg* *IM*	VWF Concentrate *IV*	
** Don't' forget foley balloon tamponade!	Platelet transfusion *IV*	
	Recombinant FVII *IV*	

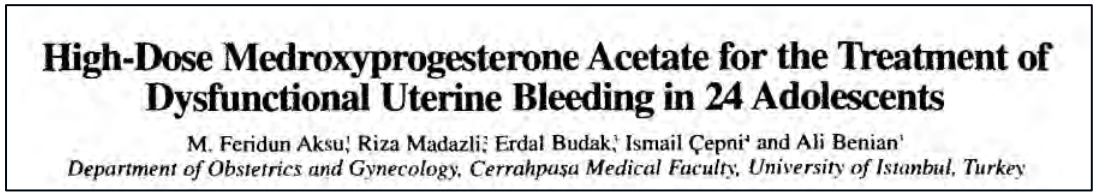
Acute Hormonal Management



Use of Intravenous Premarin® in the Treatment of Dysfunctional Uterine Bleeding—A Double-Blind Randomized Control Study

GREGGORY R. DeVORE, MD, ODELL OWENS, MD, AND NATHAN KASE, MD

- IV CEE 25mg IV q 4 hrs
- Results: 72% vs 38% at 2 doses



High-Dose Medroxyprogesterone Acetate for the Treatment of Dysfunctional Uterine Bleeding in 24 Adolescents

M. Feridun Aksu, Riza Madazli, Erdal Budak, Ismail Çepni and Ali Benian

Department of Obstetrics and Gynecology, Cerrahpaşa Medical Faculty, University of Istanbul, Turkey

- MPA PO 60-120mg Day 1, 20mg QD
- Results: 25% 24 hours, 100% 96 hours

Oral Medroxyprogesterone Acetate and Combination Oral Contraceptives for Acute Uterine Bleeding

A Randomized Controlled Trial

Malcolm G. Munro, MD, Nakia Mainor, MD, Romie Basu, MD, Mikael Brisinger, MD,

- Ortho-Cyclen TID taper vs MPA 20mg TID taper
- Results: Median cessation 3 days, no difference

Maintenance Hormonal Management of HMB

Hormonal	Non-Hormonal	Iron Therapy
Combined contraceptive pill *PO*	Tranexamic acid *PO*	Ferrous sulfate *PO*
Progesterone only pill (norethindrone or MPA) *PO*	Aminocaproic acid *PO*	
Combined contraceptive patch	Desmopressin *IN or SQ*	
Combined ring		
Depot MPA *IM*		
Levonorgestrel intrauterine device		

Treatment of HMB: Levonorgestrel IUS

Cochrane Library

Cochrane Database of Systematic Reviews

Progestogen-releasing intrauterine systems for heavy menstrual bleeding (Review)

- **Cochrane 2020**: 25 RCTs (n=2511) – LNG-IUS *superior* to other medical therapies in reduction in MBL, equal efficacy to ablation, uncertain if better or worse than hysterectomy
- **Cochrane 2022**: 9 systematic reviews in Cochrane Library through July 2021. Reaffirmed LNG-IUS is the best first-line treatment for reducing MBL, followed by antifibrinolytics.

Treatment of HMB + IBD: Levonorgestrel-IUS

Levonorgestrel-releasing intrauterine system for the management of heavy menstrual bleeding in women with inherited bleeding disorders: long-term follow-up☆

Claudia Chi[a,b], Farah Y. Huq[b], Rezan A. Kadir[a,b,*]

→ Significant improvement in PBAC (255 → 35), Hb and QOL

Levonorgestrel-Releasing Intrauterine Device Use in Female Adolescents with Heavy Menstrual Bleeding and Bleeding Disorders: Single Institution Review

Oluyemisi A. Adeyemi-Fowode MD [1,2,*], Xiomara M. Santos MD [1], Jennifer E. Dietrich MD, MSc [1,2], Lakshmi Srivaths MD [1,3]

→ Significant improvement in Hb + Ferritin, 60% amenorrhea

Use of the Levonorgestrel Intrauterine System to Treat Heavy Menstrual Bleeding in Adolescents and Young Adults with Inherited Bleeding Disorders and Ehlers-Danlos Syndrome

Patricia S. Huguelet [1,*], JL Laurin [2], D Thornhill [3], G Moyer [4]

→ 62% amenorrhea Mean continuation 5.08 years

Chi Contraception 2011, AF JPAG 2017, PH JPAG 2022

Non-Hormonal Management of HMB in Patients with IBDs

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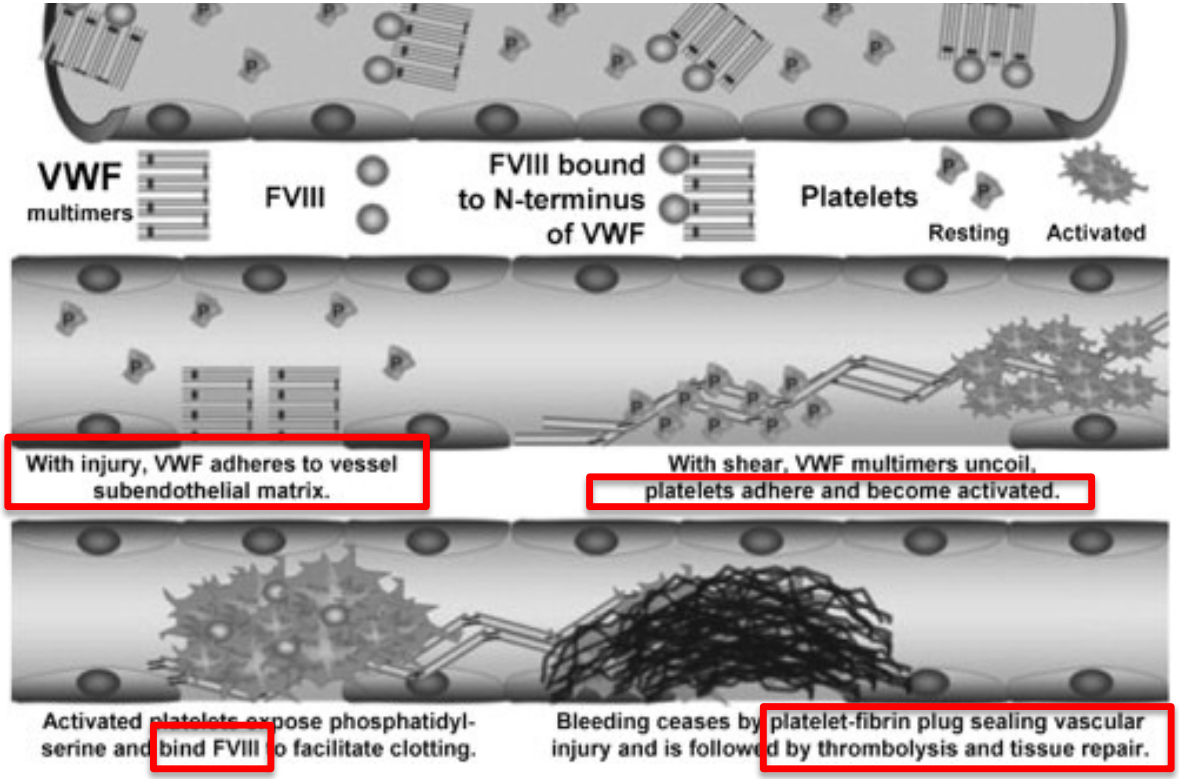
Platelets and VWF in Primary Hemostasis



DDAVP

VWF

Platelets

TXA

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Matthews. Pediatric Clin North Amer, 2013

Maintenance Management of HMB

Hormonal	Non-Hormonal	Iron Therapy
Combined contraceptive pill *PO*	Tranexamic acid *PO*	Ferrous sulfate *PO*
Progesterone only pill (norethindrone or MPA) *PO*	Aminocaproic acid *PO*	
Combined contraceptive patch	Desmopressin *IN or SQ*	
Combined ring		
Depot MPA *IM*		
Levonorgestrel intrauterine device		

Treatment HMB: Antifibrinolytics

Tranexamic Acid Treatment for Heavy Menstrual Bleeding

A Randomized Controlled Trial

Reduction in MBL
40.4% vs. 8.2%

- 196 adult women with HMB (80cc MBL) randomized to TXA vs. Placebo for 6 cycles

- **Cochrane 2018**: 13 RCTs (n=1312) TXA versus placebo, progestins, NSAIDs, and LNG-IUS
- **Conclusion**: TXA more effective than progestins and NSAIDS at reducing HMB, but less than LNG-IUS

Maintenance Management of HMB

Hormonal	Non-Hormonal	Iron Therapy
Combined contraceptive pill *PO*	Tranexamic acid *PO*	Ferrous sulfate *PO*
Progesterone only pill (norethindrone or MPA) *PO*	Aminocaproic acid *PO*	
Combined contraceptive patch	Desmopressin *IN or SQ*	
Combined ring		
Depot MPA *IM*		
Levonorgestrel intrauterine device		

Desmopressin (DDAVP)

- **Treatment option for Mild VWD and Mild Platelet Dysfunction**
- Adjunct to antifibrinolytic therapy

Route	Dose
Intranasal	< 50kg: 150mcg (1 spray) > 50kg: 300mcg (2 sprays)
Subcutaneous	0.3 mcg/kg (max 20mcg)
Intravenous	0.3 mcg/kg (max 20mcg)

- Variable routes of administration
- FVIII and VWF levels increase 2-4 fold
- Maximum levels occur 30-60 minutes after IV and 30-120 minutes after intranasal
- Administer with menses onset
  and repeat at 12-24 hour intervals, for the first 2-3 days of menses

- Side effects include facial flushing, headaches and nausea
- Limit free water intake for 24 hours after administration

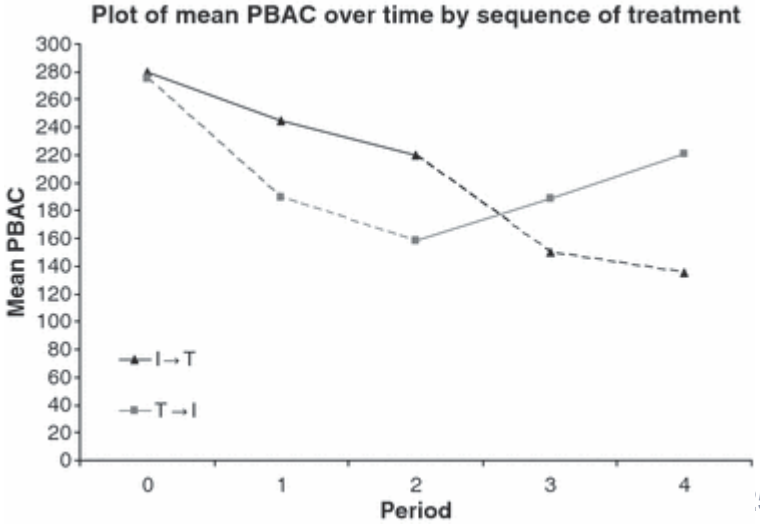
HMB Tx: Oral Tranexamic Acid vs DDAVP

bjh research paper

Multisite management study of menorrhagia with abnormal laboratory haemostasis: a prospective crossover study of intranasal desmopressin and oral tranexamic acid

- RCT Crossover study of 116 women with HMB over 4 menstrual cycles

- Normalization of MBL defined as PBAC < 100
  - 22% DDAVP group
  - 33% TXA group
- Both groups had significant improvement in QOL



Kouides, 2009 BJ Haemotology

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Maintenance Management of HMB

Hormonal	Non-Hormonal	Iron Therapy
Combined oral contraceptive pills	Tranexamic acid oral	Ferrous sulfate
Progesterone only pills	Aminocaproic acid	
Combined patches		
Combined rings		
Progesterone injections		
Levonorgestrel intrauterine device		

Approach to Oral Iron Therapy

IDA Severity	Recommended Dosing
Moderate (Hb 7-10) - Severe (Hb <7)	Ferrous sulfate 2 tablets once daily *(130mg elemental iron)*
Mild (Hb 10-11)	Ferrous sulfate 1 tablet daily *(65mg elemental iron)*
Iron deficiency without anemia (Hb ≥ 12)	Ferrous sulfate 1 tablet every other day

* Continue oral iron therapy for minimum of 3 months and then repeat ferritin

Optimizing Patient Outcome at Time of Gynecologic Surgery

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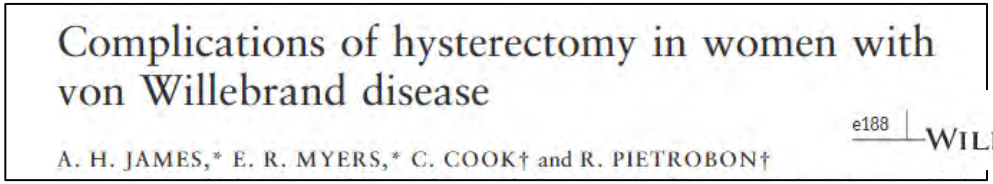
Complications of Hysterectomy in VWD


Complications of hysterectomy in women with von Willebrand disease

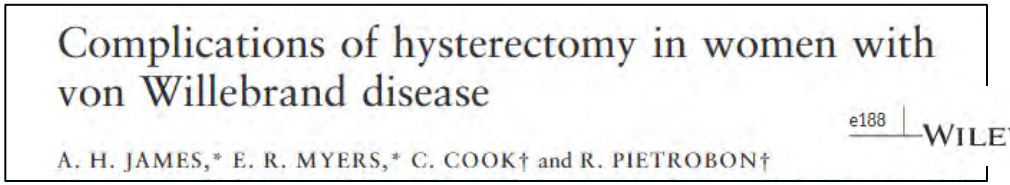
A. H. JAMES,* E. R. MYERS,* C. COOK† and R. PIETROBON†

e188 WILEY–Haemophilia

- Estimate incidence of bleeding and other complications in women with VWD undergoing hysterectomy
- Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project of the AHRQ
- Queried all hospital discharge codes for hysterectomy from 1988-2004

- 545 hysterectomies in women with VWD vs 1,357,588 without VWD
- **VWD women younger, higher rates of HMB**

Complications of Hysterectomy in VWD


Complications of hysterectomy in women with von Willebrand disease

A. H. JAMES,* E. R. MYERS,* C. COOK† and R. PIETROBON†

e188 WILEY–Haemophilia

Outcome	Women with VWD	Women Without VWD	P-value
Intraop or Postoperative Bleeding	15 (2.75%)	11, 678 (0.86%)	< 0.001
Blood Transfusion	40 (7.34%)	28, 957 (2.13%)	< 0.001
Infection	4 (0.73%)	5,203 (0.38%)	0.159
DVT/PE	0	1493 (0.11%)	1.000

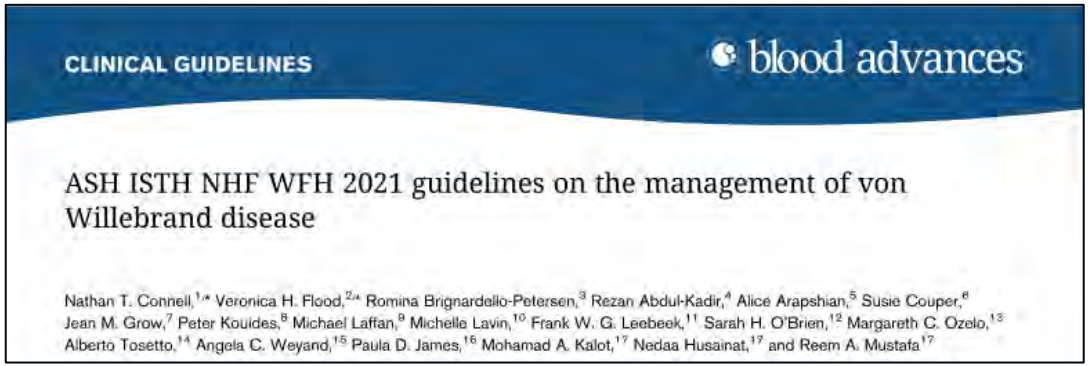
How well do we screen women undergoing surgery for HMB?

- Truven Health MarketScan Research Database (insurance claims database), queried for females age < 40 with HMB undergoing hysterectomy, endometrial ablation, UAE or HSC/D&C
- Excluded patients with fibroids, malignancy of genital tract or previous diagnosis of IBD
- Defined screening as VWF Ag or VWF Activity in prior 12 months
- 8998 women met inclusion criteria
  - 57 women (0.6%) were screened for VWD
  - 1276 women (14%) had coagulation tests (PT, PTT)

Von Willebrand disease screening in women undergoing hysterectomy for heavy menstrual bleeding

e188 WILEY–Haemophilia

Guidelines for Surgery Prophylaxis


CLINICAL GUIDELINES

blood advances

ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease

Nathan T. Connell,[1,*] Veronica H. Flood,[2,*] Romina Brignardello-Petersen,[3] Rezan Abdul-Kadir,[4] Alice Arapshian,[5] Susie Couper,[6] Jean M. Grow,[7] Peter Kouides,[8] Michael Laffan,[9] Michelle Lavin,[10] Frank W. G. Leebeek,[11] Sarah H. O'Brien,[12] Margareth C. Ozelo,[13] Alberto Tosetto,[14] Angela C. Weyand,[15] Paula D. James,[16] Mohamad A. Kalot,[17] Nedaa Husainat,[17] and Reem A. Mustafa[17]

- Limited high-level evidence to guide recommendations
- No clear guidelines to define minor versus major surgery
- Not all bleeding disorders result in same bleeding phenotype
- Risks of VWF Concentrate include inducing inhibitor formation & hypersensitivity reactions
- **Obtaining individualized expert opinion from hematologists and gynecologists with experience managing these patients is critical**

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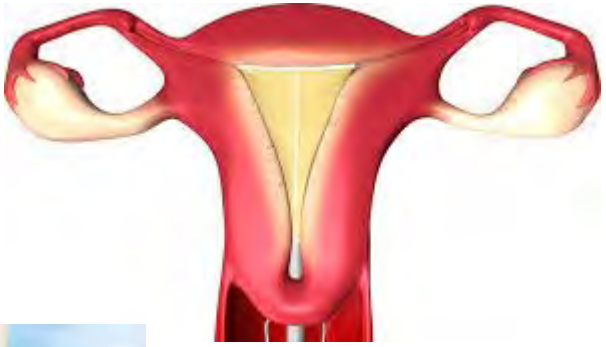
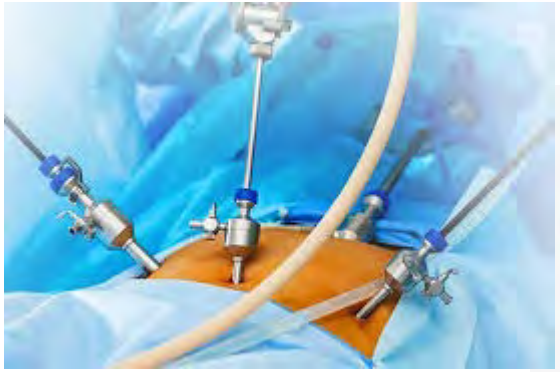
Connell, 2020. Blood Advances.

Surgery Prophylaxis - Minor



- Avoid NSAIDs and Aspirin preoperatively and postoperatively
- Minor Procedures: Type 1 VWD and Type 2 A-N-M
  - **Tranexamic acid**
  - 1300mg PO TID
  - 1000mg IV (10mg/kg)
- Minor Procedures: Type 2 B and 3
  - **TXA and VWF Concentrate**
  - TXA 1300mg PO TID vs IV
  - VWF 40-60 units IV/kg



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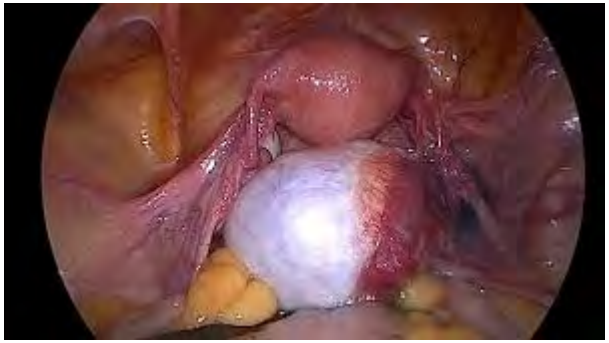
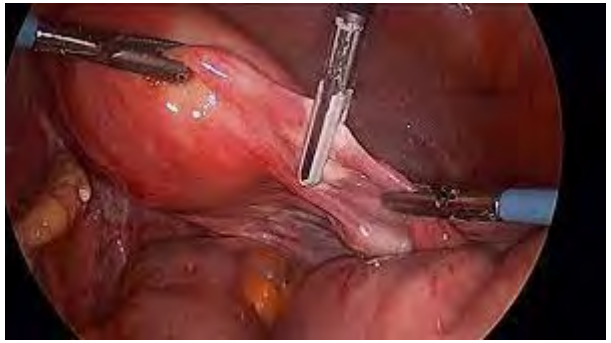
Laffan, 2020. Haemophilia
Connell, 2020. Blood Advances.

Surgery Prophylaxis - Major



- Major Procedures: Type 1
  - **DDAVP**
  - 0.3mcg/kg IV or SQ (max 20mcg)
  - Optimal to confirm DDAVP response before using, but patients likely to respond if VWF > 0.30 IU/mL
  - Limit fluid intake to < 1 Liter given anti-diuretic activity



- Major Procedures: Type 2 and Type 3
  - **VWF Concentrate (Humate-P)**
  - 40-60 units IV/kg

- **Goal: FVIII and VWF Activity ≥ 0.50 for at least 3 days postop**

Laffan, 2020. Haemophilia
Connell, 2020. Blood Advances.

Labor Management

Overview of Bleeding Disorders in Patients with a Uterus

Journal of Thrombosis and Haemostasis, 5: 1165–1169

ORIGINAL ARTICLE

Bleeding events and other complications during pregnancy and childbirth in women with von Willebrand disease

A. H. JAMES and M. G. JAMISON
Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, North Carolina, USA

- National Inpatient Sample (NIS) Database queried for hospital discharges for pregnancy and VWD
- 4067 deliveries with VWD
- **Increased risk for PPH (OR 1.5, CI 1.1-2.0) and 5-fold increased risk of blood transfusion**
- **Maternal mortality rate was 10x higher than controls (5 of 4067)**

Physiologic Coagulation Changes of Pregnancy

1	2	3
INCREASED	DECREASED	UNCHANGED
FACTOR VII	Factor XI	Factor II
FACTOR VIII	Factor XIII	Factor V
Factor IX	Protein S	Factor IX
Factor X		Platelets
Factor XII		
VWF		
Fibrinogen		
PAI-1		

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VWD Management - Antepartum

- Preconception counseling
- Multidisciplinary care with Hematology, Obstetrics and Anesthesiology
- FVIII and VWF levels should be obtained at the following time-points during pregnancy
  - Active bleeding any trimester
  - Planned invasive procedures
  - 34-36 weeks gestation
- Goal: Factor levels > 50% with active bleeding, invasive procedures, and labor

Reynen, James. Semin Thromb & Hemost, 2016
Weyan. Hematol Onc Clin North Amer, 2021

VWD Management – Intrapartum

- VWF Levels < 50% have increased risk of bleeding at delivery and postpartum
- Admit labs: CBC, PT/PTT, VWF Ag, VWF Activity, FVIII level
- Women with factor levels > 50% should be offered the option of regional anesthesia
- Vaginal delivery is generally considered safe for VWD and Mild Platelet Disorders, but a prolonged second stage should be avoided
- Operative delivery and intrapartum invasive procedures should be avoided until the status of the fetus is confirmed

Reynen, James. Semin Thromb & Hemost 2016
Pacheco. Obstet Gynecol 2024

Treatment Options by VWD Type

Type	Recommended initial treatment when FVIII or VWF:RCo is <0.50 IU/mL
Type 1	DDAVP
Type 2	DDAVP factor concentrate
Type 2A	DDAVP factor concentrate
Type 2B	*Avoid DDAVP* First line factor concentrate
Type 2M	DDAVP factor concentrate
Type 2N	DDAVP factor concentrate
Type 3	Factor concentrate

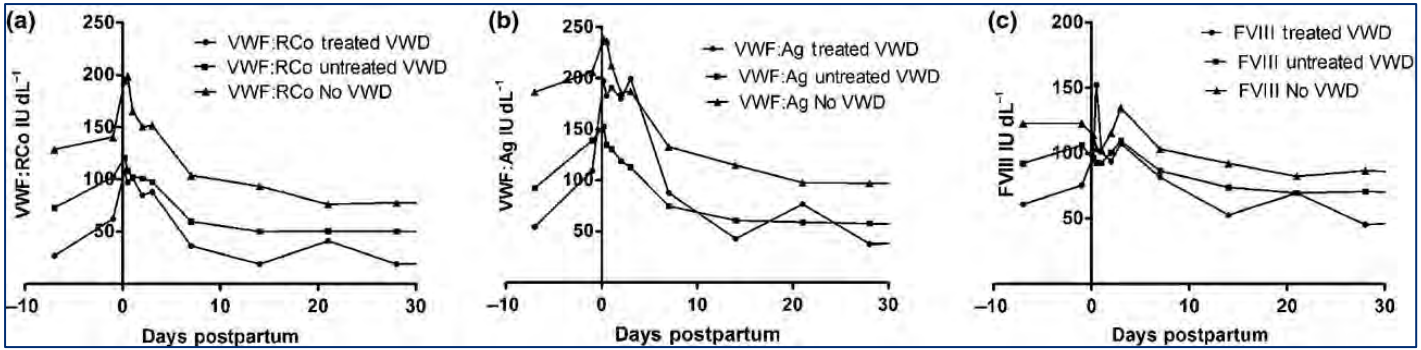
DDAVP

- 0.30 mcg/kg IV over 30 minutes

VWF Concentrate

- 40-80 units/kg IV load
- 20-40 units/kg IV q 12 hours

VWD Management - Postpartum



- VWF and FVIII levels persist until 48hours pp and then began to decline to pre-pregnancy levels
- Levels approach baseline by one week postpartum and reach baseline by 3 weeks pp
- Risk of PPH is elevated in VWD compared to controls, particularly DELAYED PPH

- **Maintain VWF levels > 0.50 IU/mL for 3 days post-SVD and 5 days post-C/S**
- **Prescribe Tranexamic acid 1300mg PO TID for 10-14 days postpartum**

Pacheco. Obstet Gynecol 2024
Reynen, James. Semin Thromb & Hemost 2016
James. Haemophilia 2014

How well do we follow the guidelines?

- Truven Health MarketScan Research Database, queried database for patients with confirmed VWD Diagnosis and Live Delivery
- 2238 pregnant women with VWD, 2009 - 2013
- Aim = Assess frequency of 3rd trimester VWF labs

Laboratory monitoring during pregnancy and post-partum hemorrhage in women with von Willebrand disease

Sarah H. O'Brien[1,2] | Joseph R. Stanek[1] | Dominder Kaur[3] | Katherine McCracken[4] | Sara K. Vesely[5]

How well do we follow the guidelines?

- 32% (n = 714) had 3rd trimester VWF levels monitored
- PPH occurred in 6.4% of the study cohort
- Frequency of PPH lower in monitored (4.9%) versus unmonitored group (7.3%), p = 0.23 (CI -4.4% to -0.3%)

Laboratory monitoring during pregnancy and post-partum hemorrhage in women with von Willebrand disease

Sarah H. O'Brien[1,2] | Joseph R. Stanek[1] | Dominder Kaur[3] | Katherine McCracken[4] | Sara K. Vesely[5]

Platelet Dysfunction - Intrapartum

- Mild Platelet Dysfunction
  - Utilize tranexamic acid with or without DDAVP
  - Avoid operative vaginal delivery
  - Active management of third stage of labor

- Severe Platelet Dysfunction (GT, BS)
  - Consult Hematology
  - Platelet transfusion often needed during labor and up to 2 weeks postpartum
  - Recombinant FVII also use for GT

Take Home Points

- 20-30% of patients with HMB have an underlying inherited bleeding disorder
- Tranexamic acid has wide utility in both obstetric and gynecologic management
- DDAVP is contraindicated in patients with Type 2B and Type 3 VWD
- Multidisciplinary care is critical to optimize patient outcome

Thank you

A Few Comments about Laboratory Monitoring

Factors that increase plasma VWF levels

Hormonal

High-dose estrogen
Pregnancy

Stress

Sepsis
Severe illness
Strenuous exercise
Phlebotomy

Chronic endothelial activation

Cardiovascular disease
Hypertension
Diabetes

Aging

Age-related increases may also be related to comorbidities

Why Check a Ferritin?

Table 2
Conventional test results in the progression of iron deficiency

	Iron Depletion	Iron-Restricted Erythropoiesis	Iron Deficiency Anemia
Hemoglobin concentration	Normal	Normal	Reduced
Mean corpuscular volume	Normal	Normal-Reduced	Reduced
Reticulocyte hemoglobin content[a]	Normal	Reduced	Reduced
Serum iron concentration	Normal	Reduced	Reduced
Serum ferritin concentration	Reduced	Reduced	Reduced
Total iron binding capacity	Normal	Increased	Increased
Soluble transferrin receptor	Normal	Increased	Increased

Why Ferritin?

Original Study

Iron Deficiency without Anemia: A Common Yet Under-Recognized Diagnosis in Young Women with Heavy Menstrual Bleeding

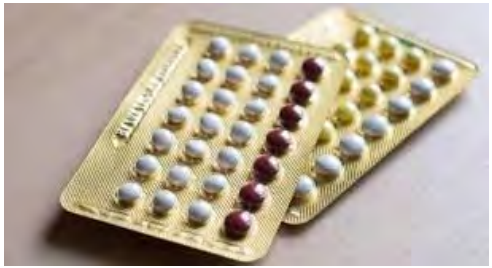
Stephen Johnson MD [1], Abigail Lang BS [2], Mollie Sturm MPH [3], Sarah H. O'Brien MD, MSc [3,4,*]

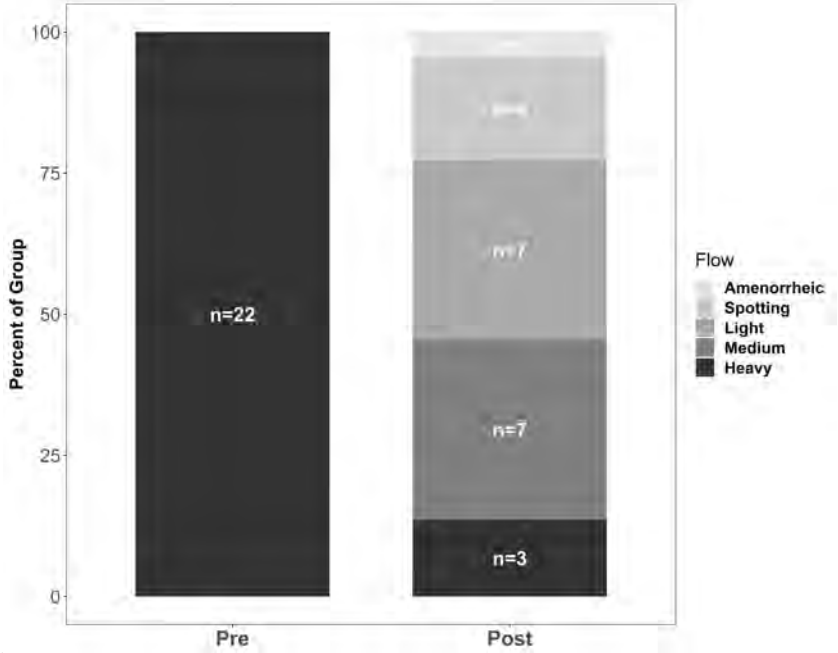
- 114 adolescents, ages 9-19 presenting with heavy menstrual bleeding for outpatient care
- 51% with ferritin < 20 ng/mL: of these, only 41% were anemic and 46% were microcytic

< 50% of Iron Deficiency cases in adolescents detected with screening with Hb or CBC alone

Treatment in IBDs: Antifibrinolytics + OCPS

- Pilot study of 22 adolescents using TXA and OCPs dual therapy as first line therapy
- 90% patient compliance at 6+ months
- No thromboembolic events





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Antifibrinolytics and Thrombotic Risk

- Controversy stems from mechanism of action: tissue plasminogen activator inhibitor and therefore prevents degradation of fibrin

- Observational Data: TXA with 3-fold increased risk for VTE but not statistically significant (CI 0.65 – 15.78)

- Product labeling
  1. Current or past history of thrombosis
  2. Increased risk of thrombosis
  3. Retinal vein or arterial occlusion
  4. ***Concurrent use of combination oral contraceptive pills (U.S. Only)***

Sundstrom, BJOG 2008
Thorne, Contraception 2018

Antifibrinolytics + COCP and Thrombotic Risk

- Sweden: 19 years of prescribing TXA for HMB (238,000 women years of use), **no VTE risk**
- Cochrane Review: 13 RCTs of TXA for HMB, **no VTE risk**
- RCT and PPH: International, randomized placebo-controlled trial of 20,600 women treated with TXA for postpartum hemorrhage, **no VTE risk**
- General Surgery: Large, placebo-controlled trials with use of TXA in major surgery, **no VTE risk**

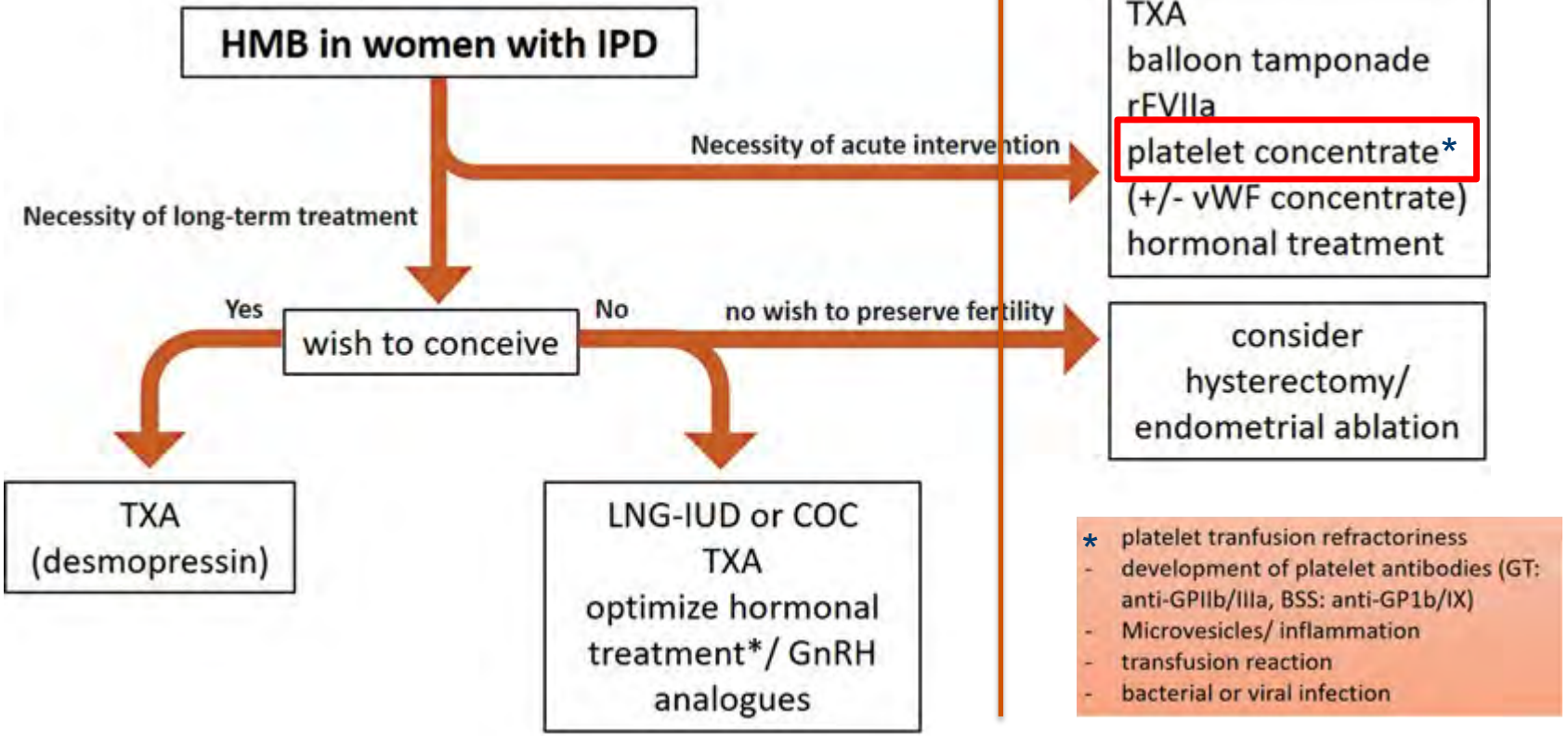
Antifibrinolytics + COCP and Thrombotic Risk

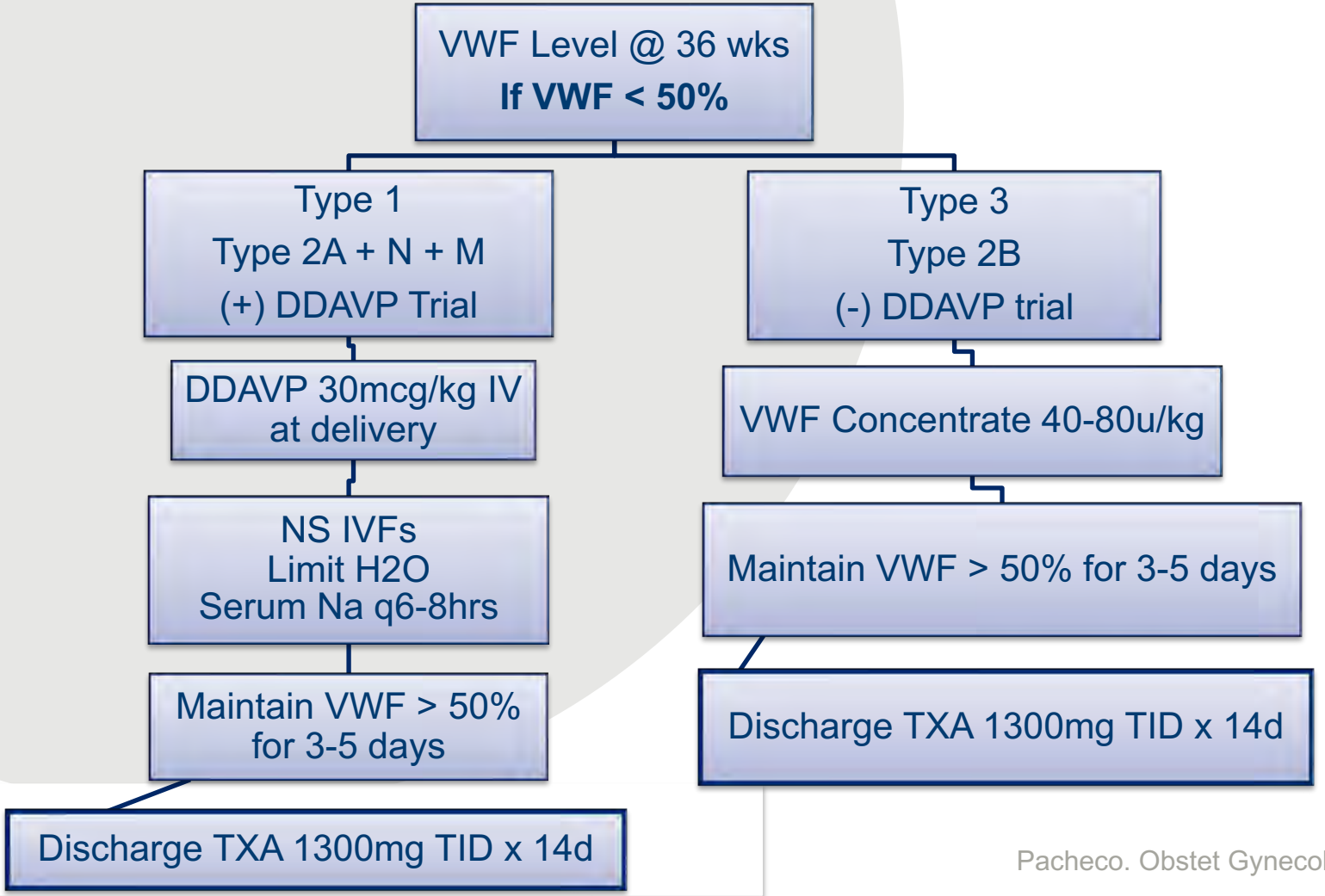
Conclusion:

The extensive clinical experience demonstrating the safety of short-term TXA exposure and its very beneficial effects for acute HMB suggest that the benefits of therapy, even when combined with COCPs, **for most women will outweigh potential risks.**

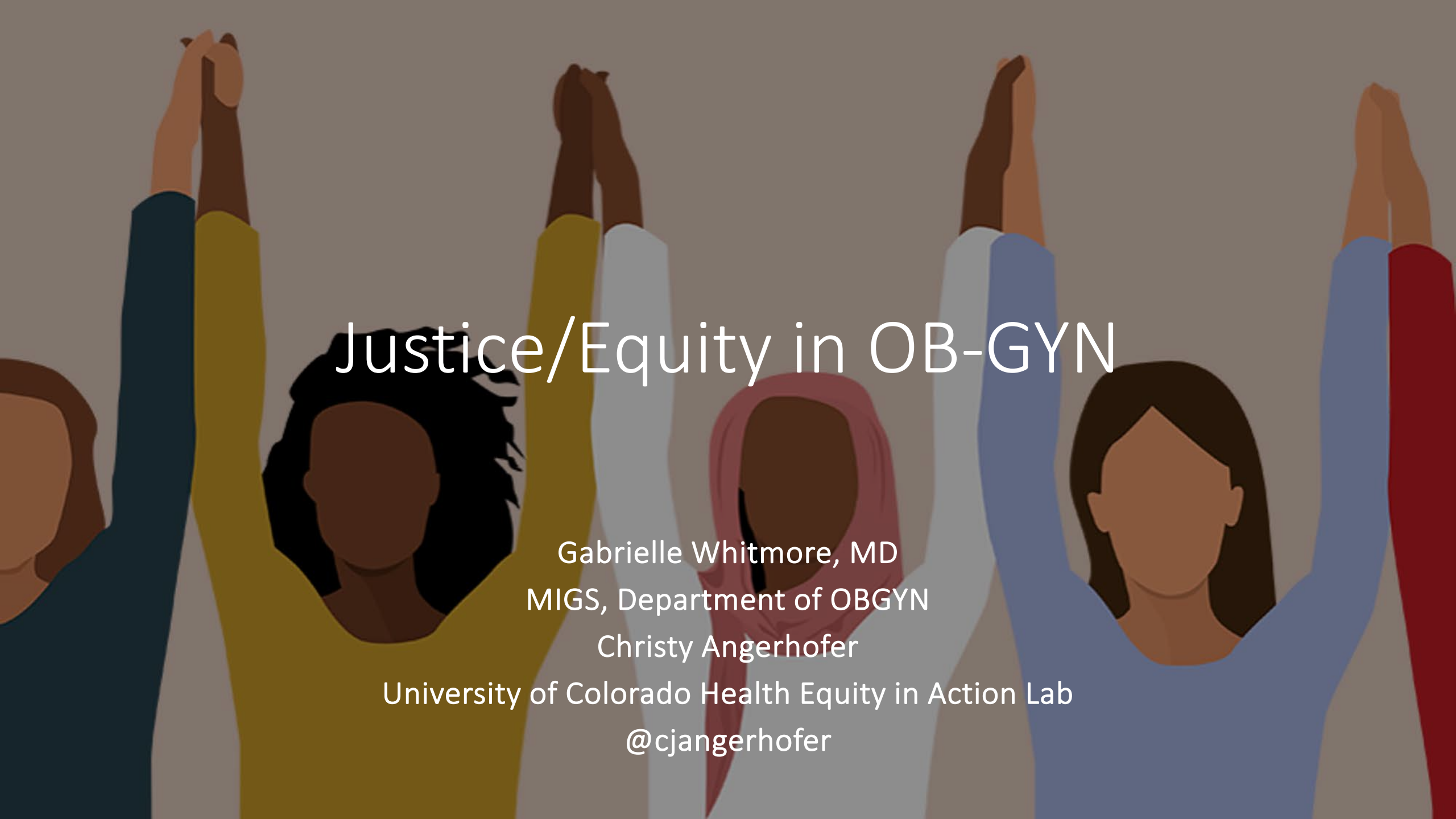
Women with increased risk beyond COCPs should probably avoid this combination therapy.

Platelet Dysfunction





Pacheco. Obstet Gynecol 2024



Justice/Equity in OB-GYN

Gabrielle Whitmore, MD
MIGS, Department of OBGYN
Christy Angerhofer
University of Colorado Health Equity in Action Lab
@cjangerhofer

Objectives

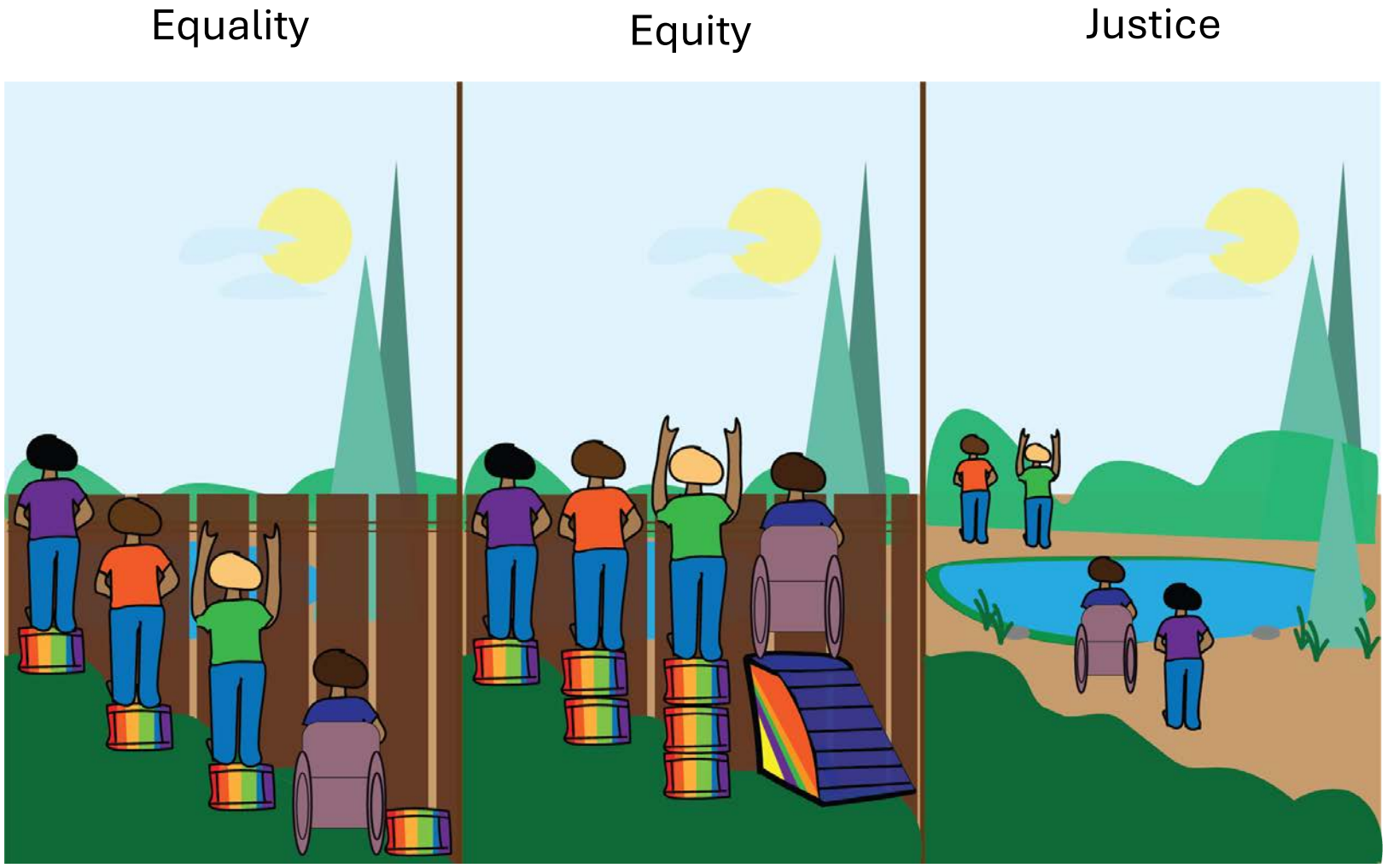
To explore the key concepts and definitions of diversity, equity, inclusion, and justice

Review the history and provide context to understand why reproductive justice and equity is so important today

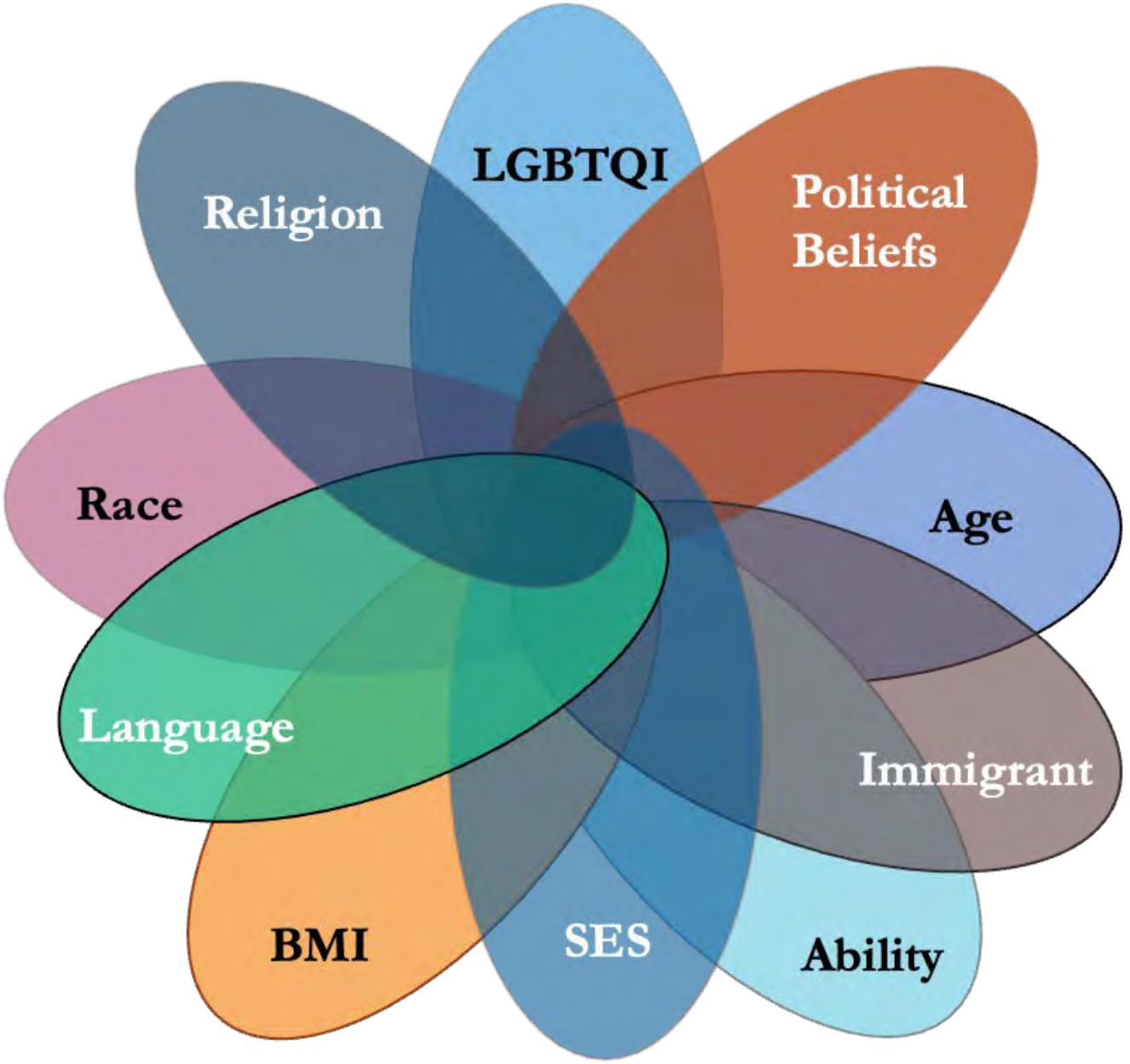
Provide tools to critically analyze ourselves and our working environments to overall improve the healthcare of our patients

What is DEIJB?

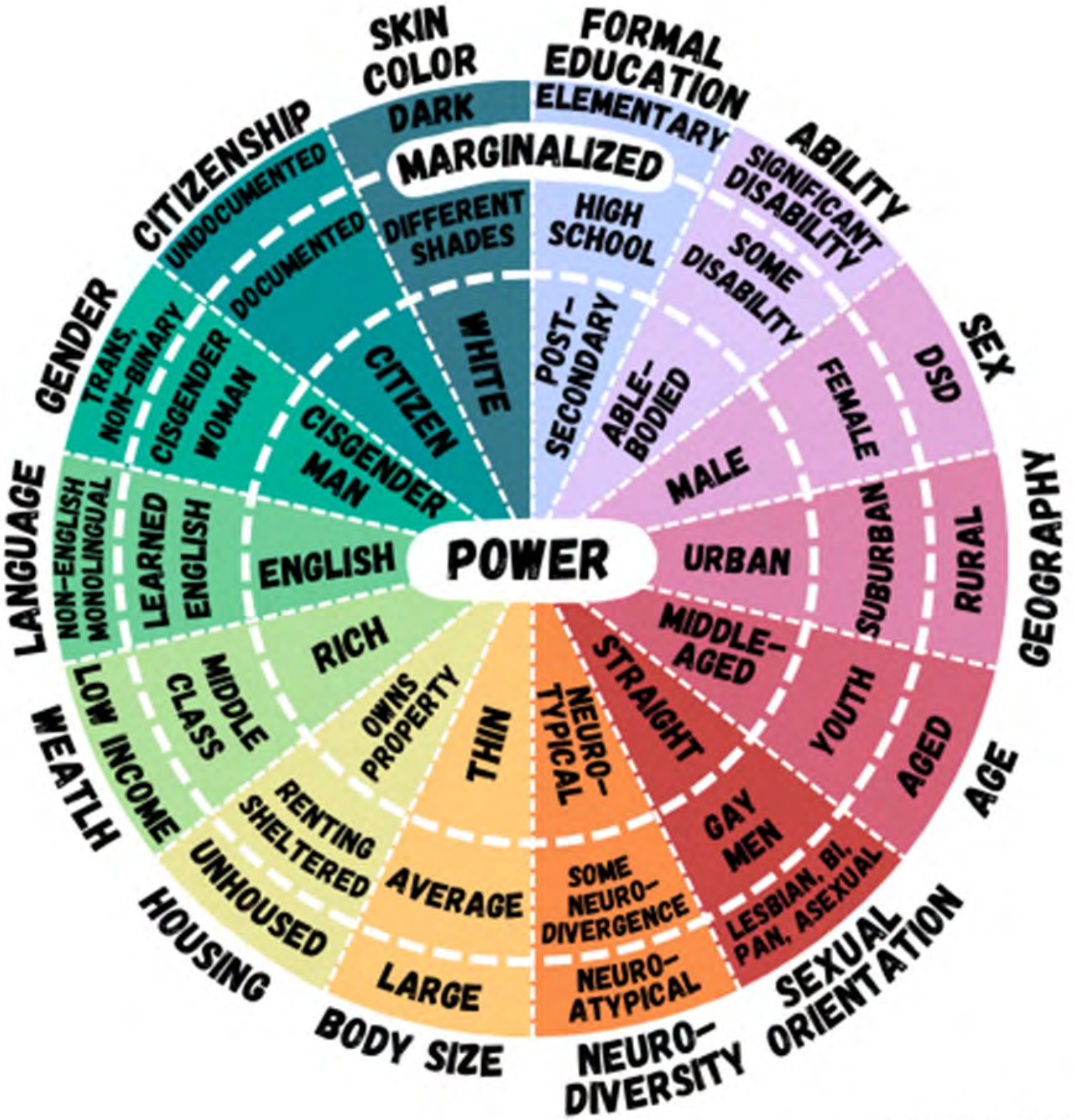
Equality versus Equity



Who are we talking about?

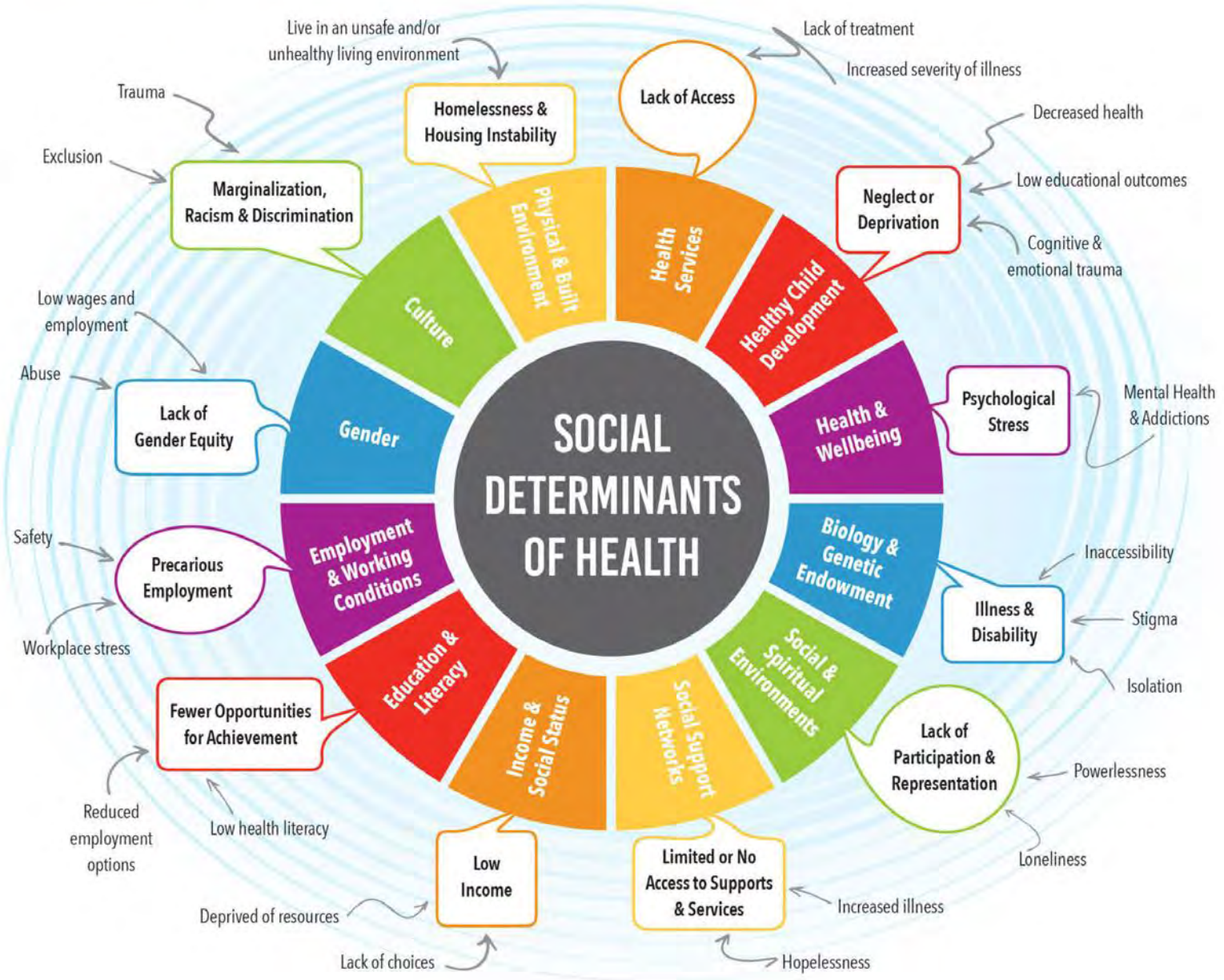


Power


SKIN COLOR
FORMAL EDUCATION
ABILITY
CITIZENSHIP
GENDER
SEX
LANGUAGE
GEOGRAPHY
WEALTH
AGE
HOUSING
SEXUAL ORIENTATION
BODY SIZE
NEURO-DIVERSITY
POWER
MARGINALIZED
DARK
DIFFERENT SHADES
WHITE
ELEMENTARY
HIGH SCHOOL
POST-SECONDARY
SIGNIFICANT DISABILITY
SOME DISABILITY
ABLE-BODIED
UNDOCUMENTED
DOCUMENTED
CITIZEN
TRANS, NON-BINARY
CISGENDER WOMAN
CISGENDER MAN
MALE
FEMALE
DSD
NON-ENGLISH MONOLINGUAL
LEARNED ENGLISH
ENGLISH
URBAN
SUBURBAN
RURAL
RICH
MIDDLE CLASS
LOW INCOME
MIDDLE-AGED
YOUTH
AGED
OWNS PROPERTY
RENTING
SHELTERED
UNHOUSED
THIN
AVERAGE
LARGE
NEURO-TYPICAL
SOME NEURO-DIVERGENCE
NEURO-ATYPICAL
STRAIGHT
GAY MEN
LESBIAN, BI, PAN, ASEXUAL
CREATED BY KAYLA THOMAS

Advantage and Disadvantage

FIGURE 1: SOCIAL DETERMINANTS OF HEALTH AND WELL-BEING[14]

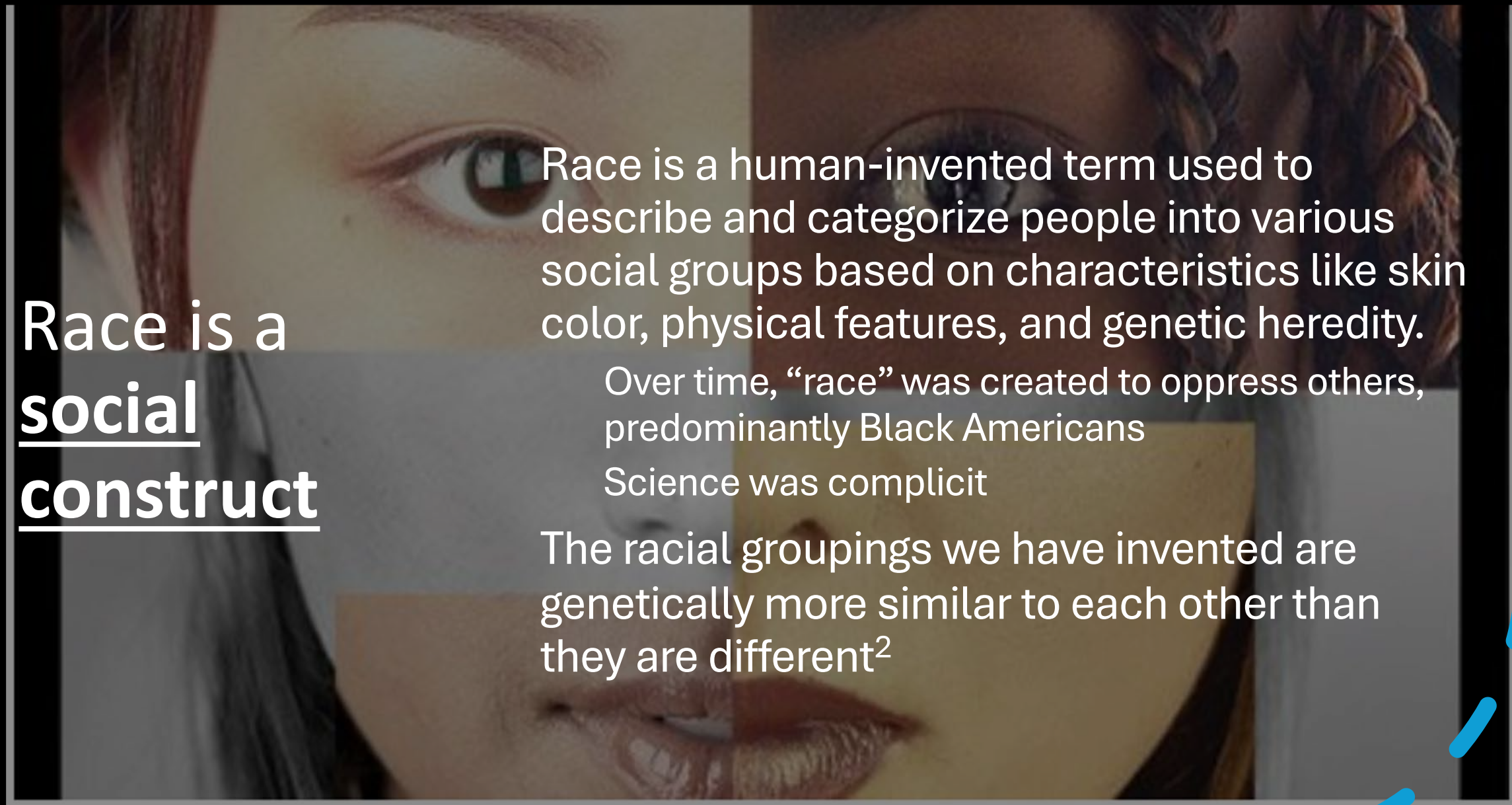


Race is a **social construct**

Race is a human-invented term used to describe and categorize people into various social groups based on characteristics like skin color, physical features, and genetic heredity.

- Over time, “race” was created to oppress others, predominantly Black Americans
- Science was complicit

The racial groupings we have invented are genetically more similar to each other than they are different[2]



Reckoning

Nuriddin A, Mooney G, White AIR. Reckoning with histories of medical racism and violence in the USA. Lancet. 2020 Oct 3;396(10256):949-951. doi: 10.1016/S0140-6736(20)32032-8. PMID: 33010829; PMCID: PMC7529391.

ILLUSTRATION BY DIANA EJAITA

1790 founding father and professor at University of Pennsylvania Benjamin Rush taught that **blackness was a form of leprosy**.

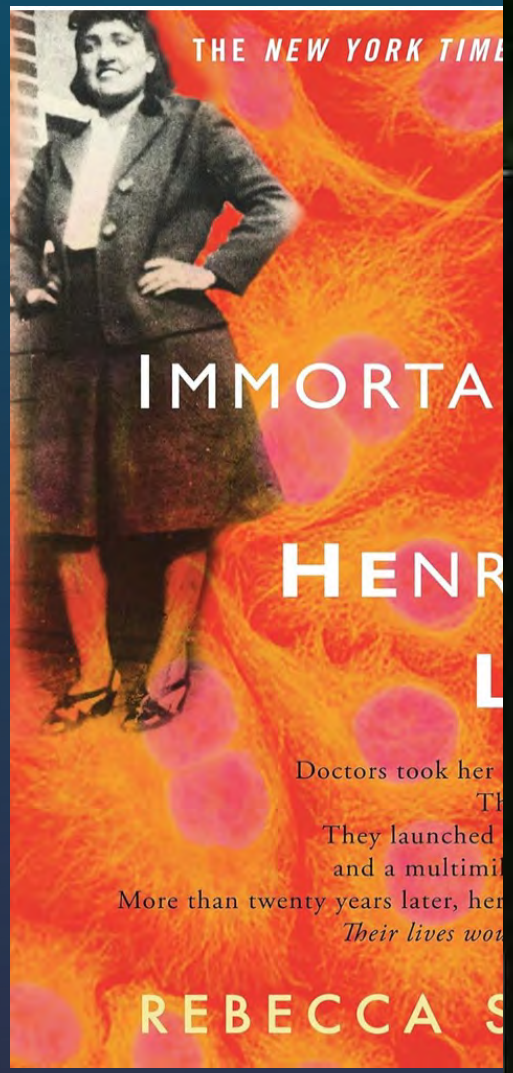
Medical schools relied on enslaved Black bodies as “anatomical material” and recruited students in southern states by advertising its abundance.

The Virginia Medical College employed a Black man named Chris Baker as its “resurrectionist” to steal freshly buried Black bodies to use for dissection.

John Brown, an enslaved man, was **"lent"** to Dr. Thomas Hamilton to experiment on to determine the **thickness of Black skin**.

1875 Essay, Physician Josiah Nott taught that Black people were **immune to tropical disease** such as malaria and yellow fever


SIMS


THE NEW YORK TIME
IMMORTA
HENR
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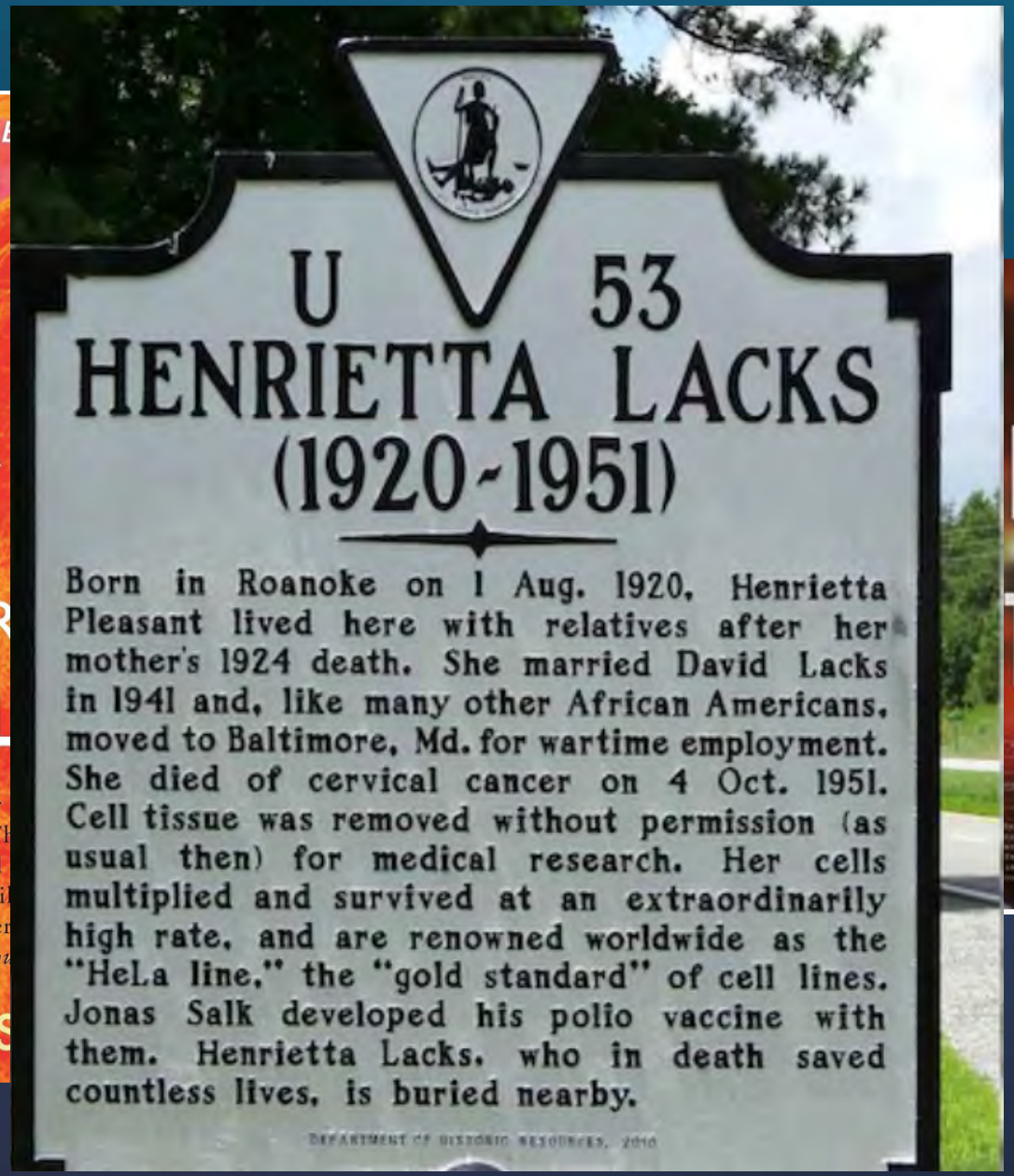

U 53
HENRIETTA LACKS
(1920-1951)
Born in Roanoke on 1 Aug. 1920, Henrietta Pleasant lived here with relatives after her mother's 1924 death. She married David Lacks in 1941 and, like many other African Americans, moved to Baltimore, Md. for wartime employment. She died of cervical cancer on 4 Oct. 1951. Cell tissue was removed without permission (as usual then) for medical research. Her cells multiplied and survived at an extraordinarily high rate, and are renowned worldwide as the "HeLa line," the "gold standard" of cell lines. Jonas Salk developed his polio vaccine with them. Henrietta Lacks, who in death saved countless lives, is buried nearby.

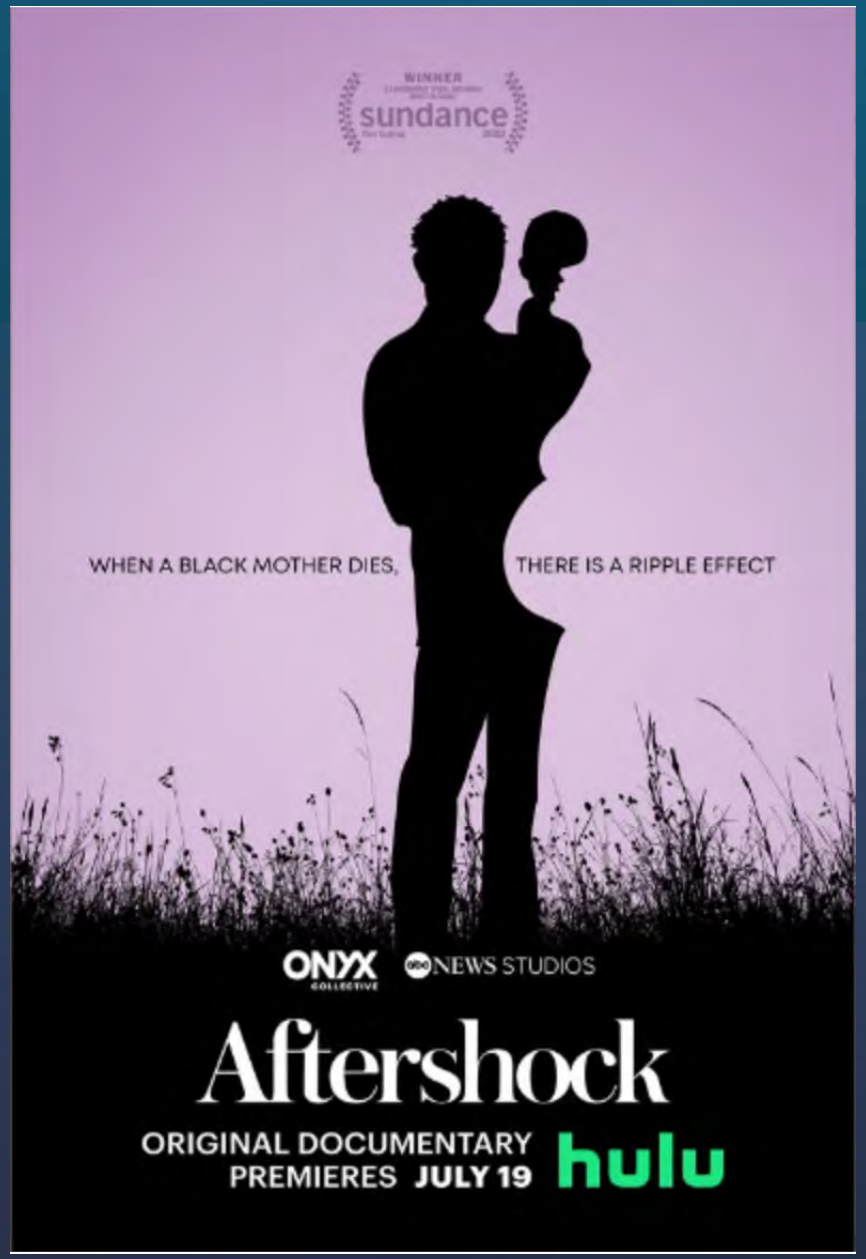

HBO ORIGINAL
L LIFE OF
TTA LACKS

Today

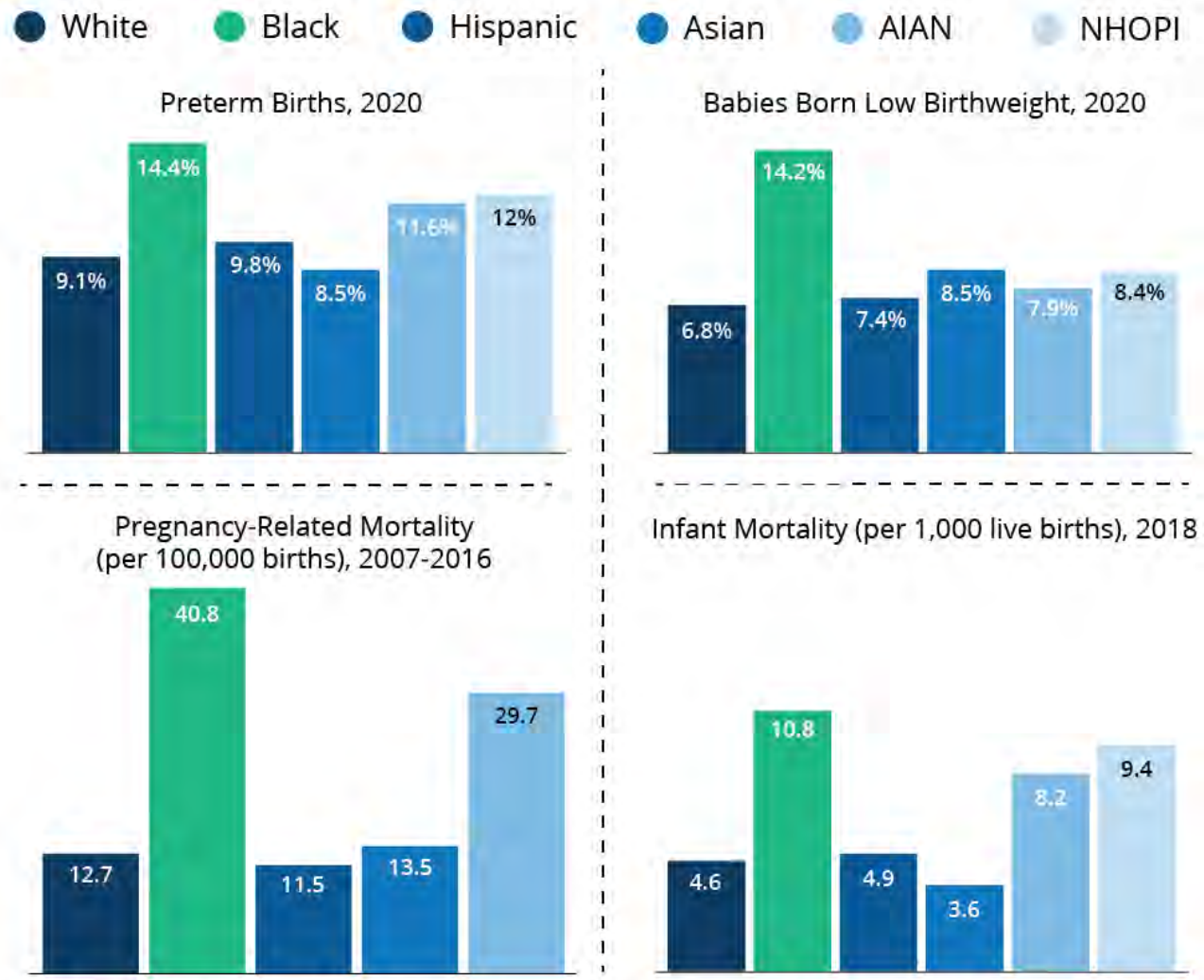
After reports of forced sterilizations in Californian prisons, the state launched an investigation and determined that at least 144 incarcerated women were illegally sterilized between 2005-2013

In 2020, allegations by a whistleblower of involuntary hysterectomies in a US Immigration and Customs Enforcement facility are concerning if confirmed.

The disparity in infant mortality between White and Black people in the USA is even higher now than it was in the Antebellum period; hospitals serving predominantly Black and Latinx patients are underfunded.


WINNER
sundance
WHEN A BLACK MOTHER DIES,
THERE IS A RIPPLE EFFECT
ONYX COLLECTIVE
ABC NEWS STUDIOS
Aftershock
ORIGINAL DOCUMENTARY
PREMIERES JULY 19
hulu

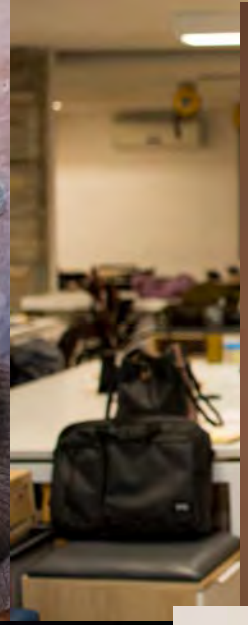
A Look at Key Maternal and Infant Health Disparities Among Black People



NOTE: AIAN refers to American Indian or Alaska Native. NHOPI refers to Native Hawaiian or Other Pacific Islander.
SOURCE: Original source information and data available at www.kff.org/report-section/key-facts-on-health-and-health-care-by-race-and-ethnicity-health-status-outcomes-and-behaviors/

KFF



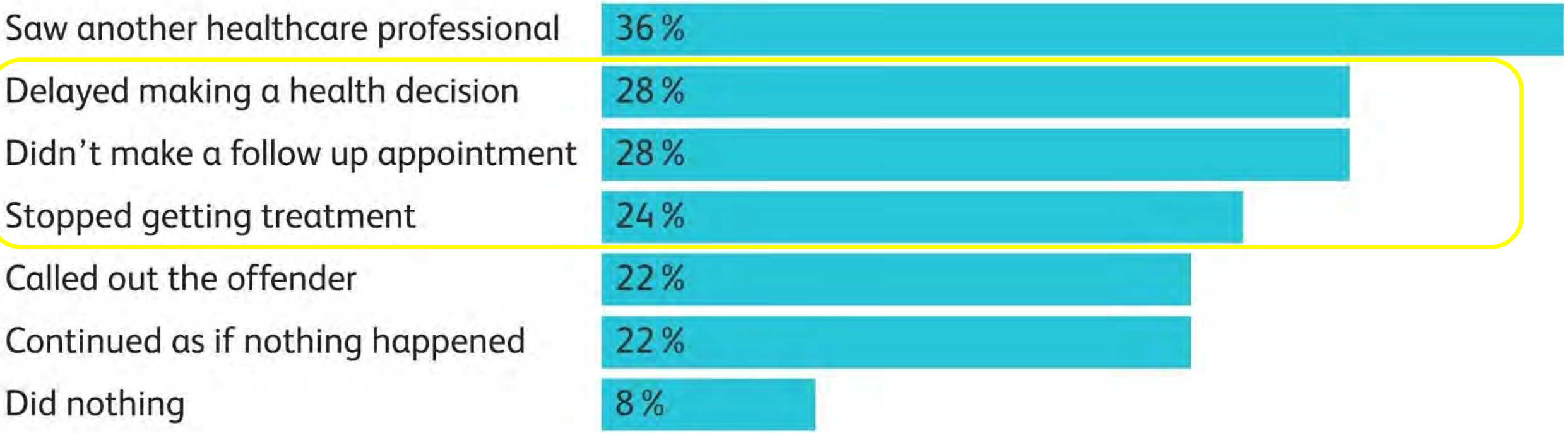






Responding to racism in healthcare can force Black patients to choose between basic respect and continued care

Which of the following have you done because of racism you've experienced while dealing with the healthcare system?



Among Black respondents who reported experiencing racism in a healthcare setting. N=322

verywell

Source: Verywell Black Health Experience Study (January 2022)

VBAC Calculator

VAGINAL BIRTH AFTER CESAREAN

Early Pregnancy | Delivery Admission

Maternal age (range 15-50 years):

Height Unit:

- ○ inches
- ◉ centimeters

Height (range 119-191 cm):

Weight Unit:

- ○ pounds
- ◉ kilograms

Pre-pregnancy weight (range 34-206 kg):

Body mass index: kg/m^2

Obstetric History:

Previous VBAC

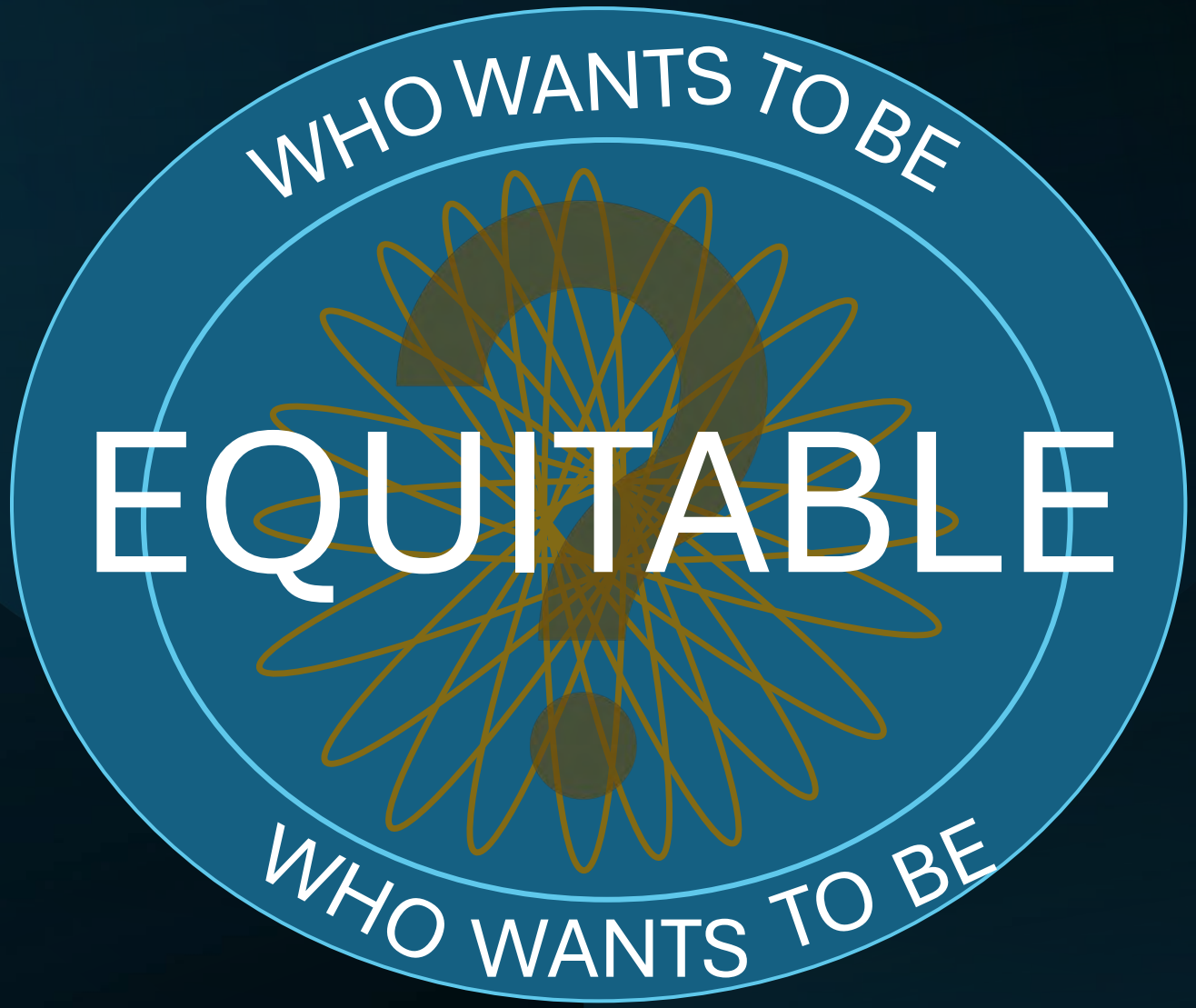
Arrest disorder indication for prior cesarean?

No

Treated chronic hypertension?

No

Who Else?


WHO WANTS TO BE
EQUITABLE
WHO WANTS TO BE

Lesbian and bisexual patients have risk factors that are associated with ovarian and breast cancer

True

False

Lesbian and bisexual patients have risk factors that are associated with ovarian and breast cancer

True

False

Lesbian or transmasculine patients do not require pap testing

True

False

Lesbian or transmasculine patients do not require pap testing

True

False

More than half of transgender patients are denied transition surgery coverage

True

False

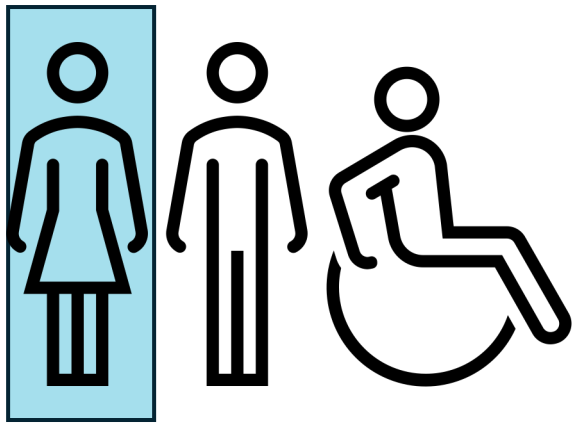
More than half of transgender patients are denied transition surgery coverage

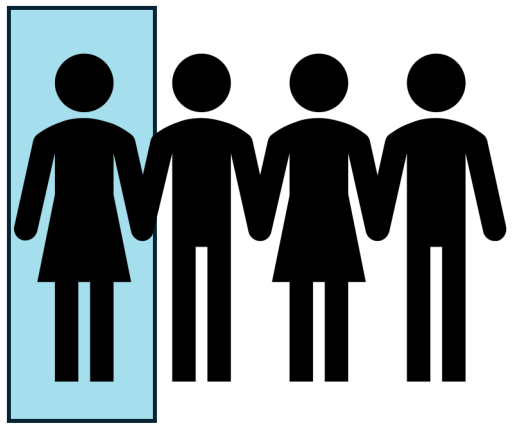
True

False

Health care for lesbians and bisexual women. Committee Opinion No. 525. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;119:1077–80.
Health care for transgender and gender diverse individuals. ACOG Committee Opinion No. 823. American College of Obstetricians and Gynecologists. Obstet Gynecol 2021;137:e75–88.

Health care for transgender and gender diverse individuals. ACOG Committee Opinion No. 823. American College of Obstetricians and Gynecologists. Obstet Gynecol 2021;137:e75–88.





Personal Level

Awareness and Choice

Awareness of core beliefs

Breaking old habits and learning new approaches

Sustainable behavioral change

Accountability

Owning power and privilege

Recognition and mitigation of implicit bias

Cha

- **Commo**
- **Learne**
- **Pervasiv**
- **Unconsci**
- **Conseque**

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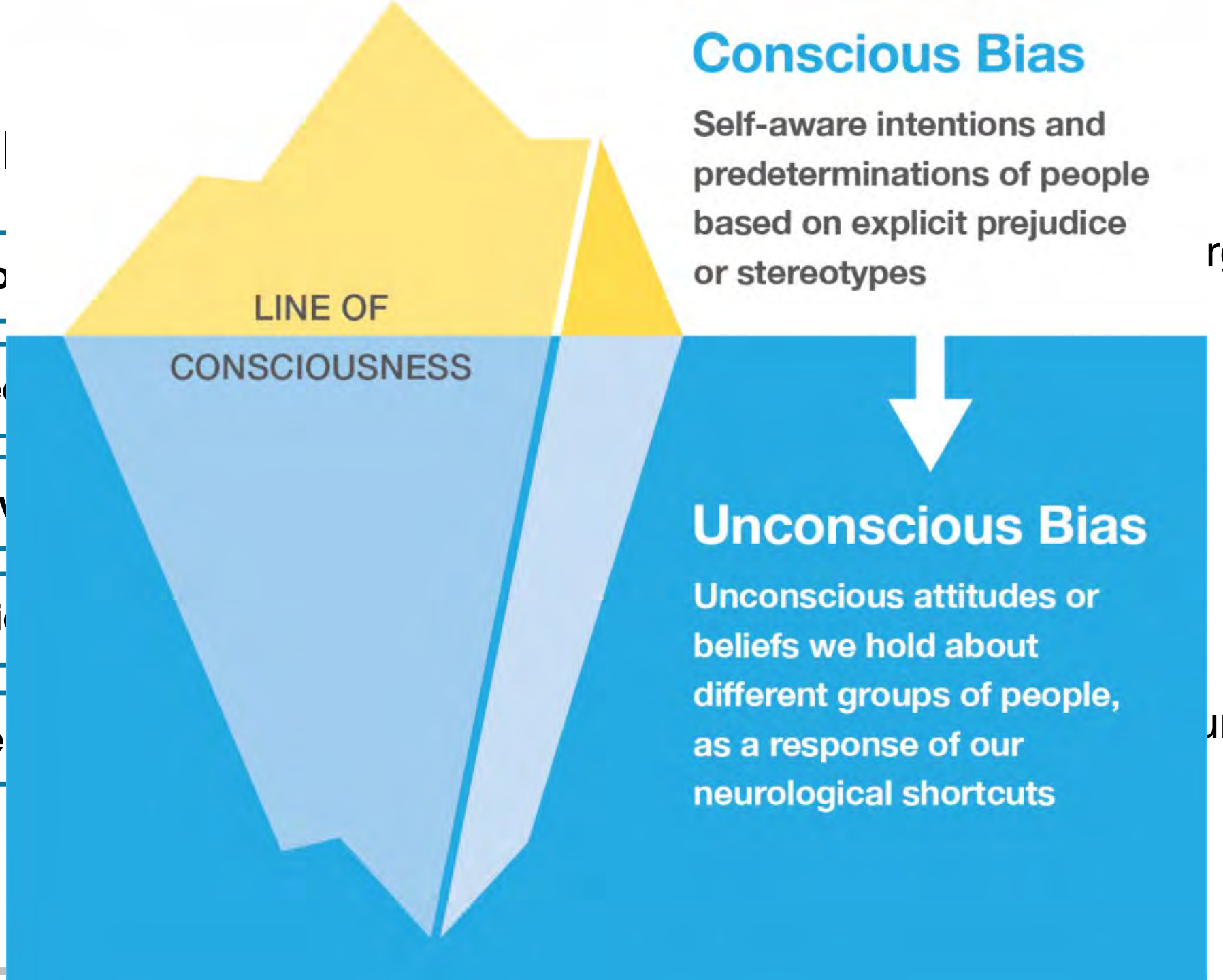
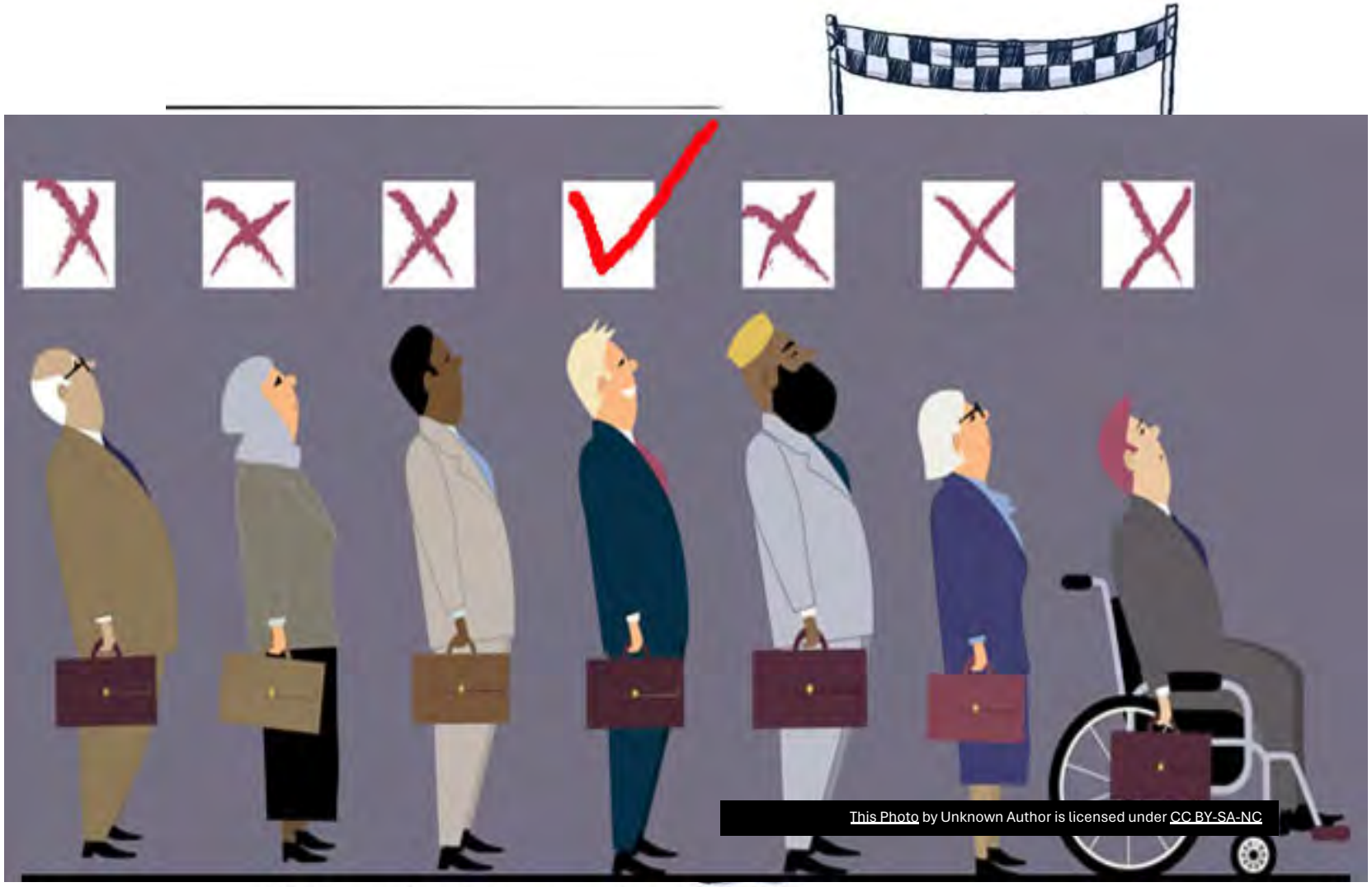


Interpersonal Level

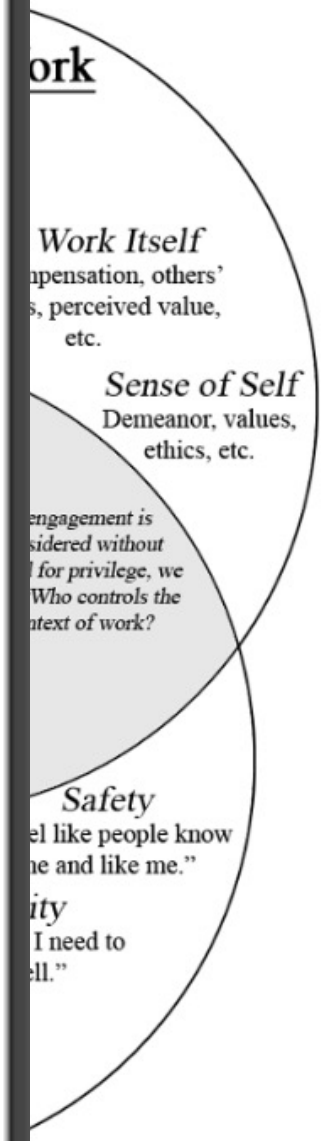


Privilege

It is a form of societ
power that is derive
identity that is part
culture

You are likely to hav
tailwinds because, k
your demographic m
part of the dominan

> "White privilege doesn't mean your life hasn't been hard. It means the color of your skin isn't one of the things making it harder."
>
> — Unknown



Micr

Comments
painful bec
persons ide
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What messa

What's the m


2nd Class
Citizen

Now what?

Take a breath

You can be a good person with positive intentions

Don't make it about you

The weight of historical oppression is heavy

Listen

Give people space to be heard, it's a gift for someone to share their lived experience with you

Learn

Educate yourself

The sincere apology

Address the hurtful comment(s) and acknowledge the impact.

Describe what you will do differently

Allyship and

“The constellation of personal and institutional privilege and power in health care settings provides opportunities to either sustain racial health care privilege gaps or transform these organizations and those who work within them to effectively reduce health care quality disparities between minority and non-minority persons.”

Power-Sharing in Patient Care

Explain that there are two experts in the clinical encounter—describe the different but complementary knowledge

Understanding that physician power is not owned, but activated through relational communication and experience

Being aware of power dynamics that might be hindering communication

Affirming patient autonomy, and empowerment

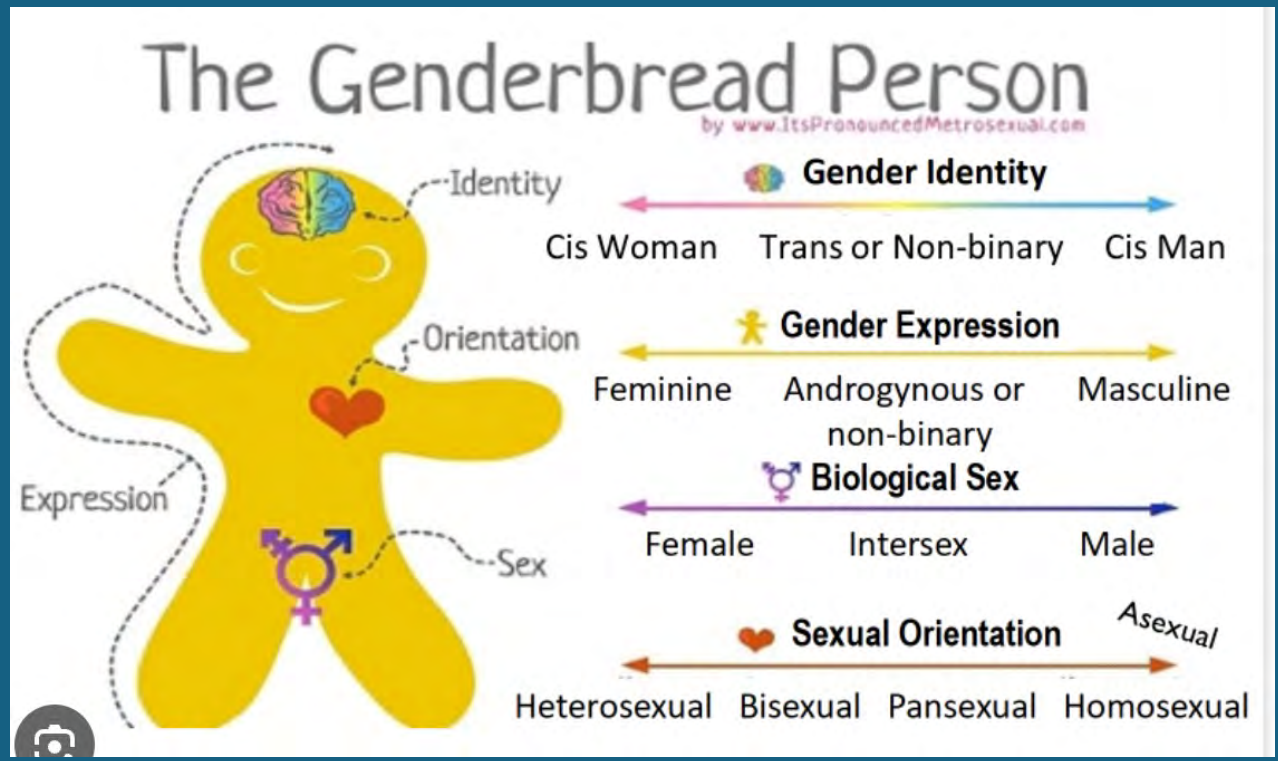
Challenge attitudes that there are right and wrong decisions

Redefine perceptions of a good patient and reassure patients that participation will not result in retribution

Build patients' belief in their ability to take part.

Critical allyship

The "Handling" of power in the physician-patient encounter: perceptions from experienced physicians
Power imbalance prevents shared decision making *Natalie Joseph-Williams,*


The Genderbread Person
by www.ItsPronouncedMetrosexual.com
Identity
Orientation
Expression
Sex
Gender Identity
Cis Woman
Trans or Non-binary
Cis Man
Gender Expression
Feminine
Androgynous or non-binary
Masculine
Biological Sex
Female
Intersex
Male
Sexual Orientation
Asexual
Heterosexual
Bisexual
Pansexual
Homosexual

Create a More Inclusive Environment

Take the time to learn!

Staff education

Utilization of surveys

Inclusive signage and art

Ask yourself- What voices are we missing

Did I consider equity?

“Only when we consider racism and racial inequality to be persistent and implicit in our norms of practice and the ordering of society and not the exception, can we effectively begin to confront this issue.”

Nuriddin A, Mooney G, White AIR. Reckoning with histories of medical racism and violence

Nuriddin A, Mooney G, White AIR. Reckoning with histories of medical racism and violence in the USA. Lancet. 2020 Oct 3;396(10256):949-951. doi: 10.1016/S0140-6736(20)32032-8. PMID: 33010829; PMCID: PMC7529391.

Getting to Justice

- Recognizing t ession are still relevant today, fed by i white dominant culture.
- Affirm racism uctural issues that without interv
- Denounce be indicators of determinants
- Work towards al, interpersonal, institutional a


with gratitude....

THURSDAY

Cannabis Use During Pregnancy and While Breastfeeding: Sorting Through Hazy Evidence

Torri Metz, MD
Associate Professor
Vice-Chair for Research
MFM Division Chief
Feb 22, 2024

HEALTH
UNIVERSITY OF UTAH

Disclosures

- No conflicts of interest related to the content of this presentation

Learning Objectives

- Define prevalence of cannabis use in pregnancy and reported reasons for use.
- Counsel patients regarding the risks of cannabis use during pregnancy and while breastfeeding based on current evidence.
- Recommend and utilize available resources when counseling individuals regarding cannabis use in pregnancy and breastfeeding.

Background

- Cannabis most common illicit drug used in pregnancy
- Crosses the placenta
- Increasing use with increasing legalization of recreational cannabis

Prevalence of Cannabis Use

- Reported prevalence 3-30%
- Data from NSDUH
  - Cross sectional, nationally representative
  - 2.4% past-month use among pregnant patients in 2002
  - 3.9% in 2014
  - 4.9% in 2016

Brown et al JAMA 2016 ; https://www.samhsa.gov/data/report/results-2016-national-survey-drug-use-and-health-detailed-tables

Prevalence

- Retrospective cohort (2009-17)
- Kaiser Permanente Northern California
- N=281,025
- Urine toxicology 4.9%
- Self-report 2.5%
- Being older, of Hispanic ethnicity and lower household income were associated with misclassification of not using cannabis by self-report

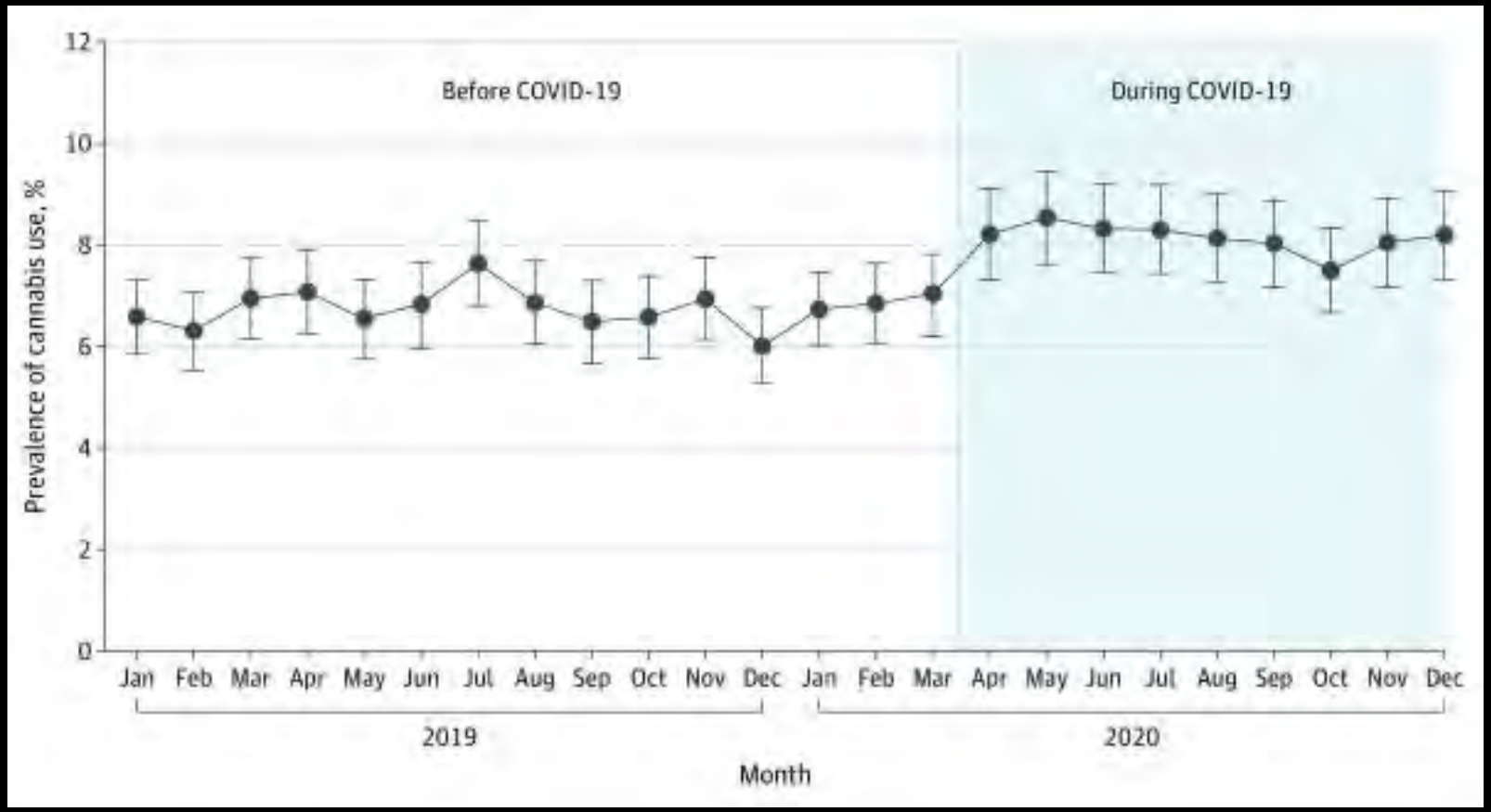
Young-Wolff et al J Addict Med 2020

CCTSI Cross-Sectional Pilot Results

- N=116 paired samples (cord & survey)
- 2.6% reported to healthcare provider
- 6.0% reported use in last 30 days on anonymous survey
- 10.3% THC-A above LOQ (200 pg/g) in the umbilical cord homogenate
- 22.4% THC-A above LOD (100 pg/g)

Metz Obstet Gynecol 2018

What happened during pandemic?



Young-Wolff et al, JAMA 2021

Cannabis Use Disorder

- 2012-13 National Epidemiologic Survey on Alcohol and Related Conditions-III
- 414 pregnant and 902 postpartum individuals
- Prevalence past-year cannabis use 9.8%
- Prevalence cannabis use disorder 3.2%
- Odds of use higher with co-existing mental health disorders

Brown et al Drug Alcohol Depend 2023

What are the reasons for use?

- Tricounty Health Department in CO surveyed clients participating in Special Supplemental Nutrition Program for Women Infant and Children (WIC)
- Monthly caseload of 25,000 clients
- Convenience sample of approx. 1700 individuals

CDPHE, Monitoring Health Concerns Related to Marijuana in Colorado: 2014

Perceived Benefits WIC Survey

Reasons for Use	Use Ever (%, n)	Current Use (%, n)	Past Use (%, n)
Help with depression/anxiety/stress	35% (164)	63% (60)	28% (103)
Help with pain	29% (135)	60% (57)	21% (78)
Help with nausea/vomiting	23% (108)	48% (46)	17% (62)
For fun/recreation	59% (277)	39% (37)	65% (240)
Other reason	16% (75)	14% (13)	16% (58)

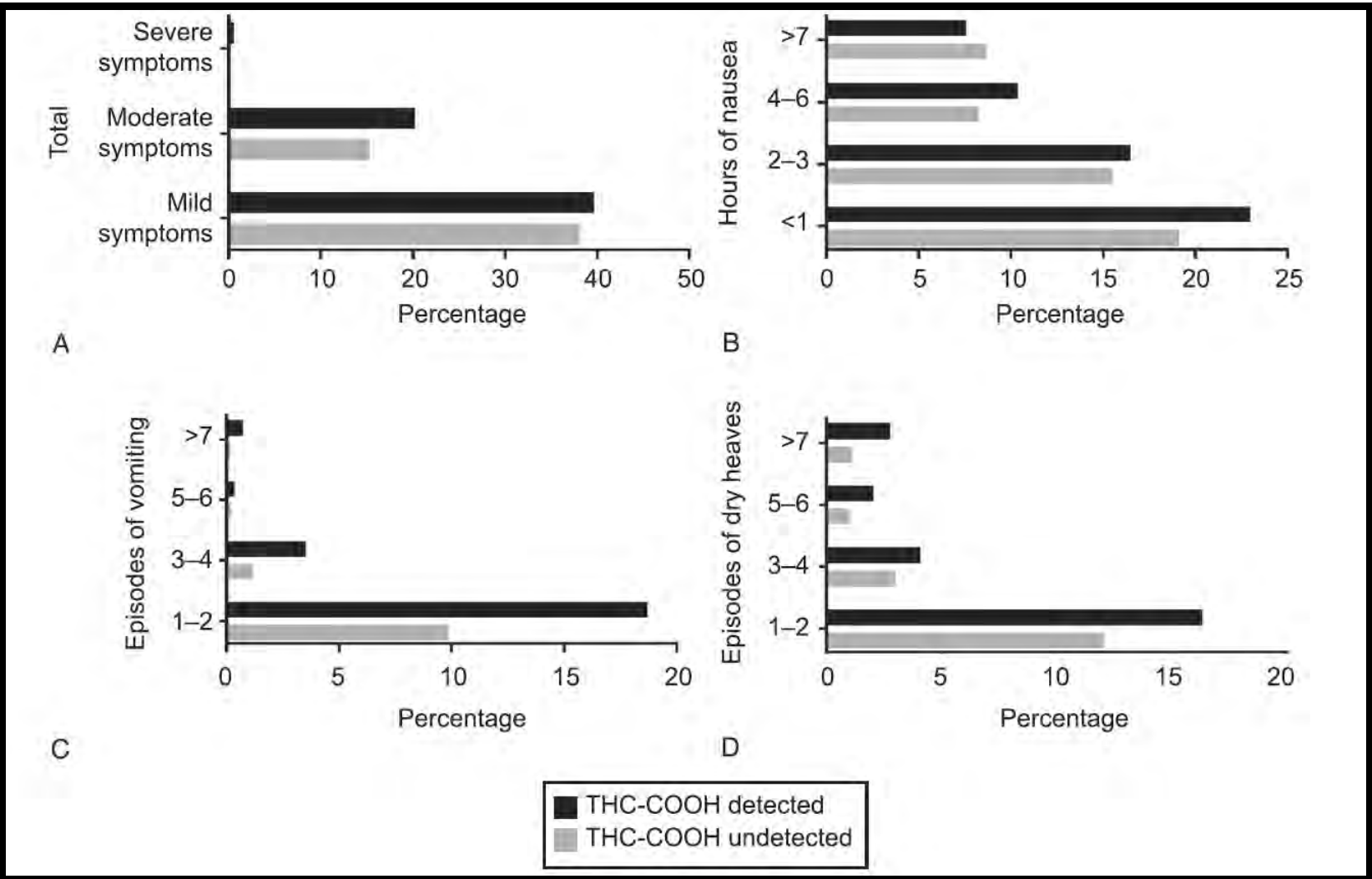
CDPHE, Monitoring Health Concerns Related to Marijuana in Colorado: 2014

Nausea and Vomiting

- Retrospective cohort (N=279,457)
- Kaiser Northern California
- Universal screening with utox and questionnaire
- ICD diagnoses for N/V of pregnancy
- Severe nausea (2.4%), mild nausea (15.2%)
- Individuals with severe NVP (aOR 3.80, 95%CI 3.19-4.52) and mild NVP (aOR 2.37, 95% CI 2.17-2.59) had increased odds of cannabis use

Young-Wolff KC et al JAMA Internal Med 2018

Nausea and Vomiting



Metz et al Obstet Gynecol 2022

Increasing Perceived Safety

- National Survey on Drug Use and Health data

	No past 30 day use, pregnant	No past 30 day use, non-pregnant	Past 30 day use, pregnant	Past 30 day use, non-pregnant
2005	3.5%	3.1%	25.8%	23.7%
2015	16.5%	14.8%	65.4%	62.6

Jarlenski et al 2017

Problems with Existing Studies

- Lack of quantification/timing of exposure
- Difficulty adjusting for tobacco, other drugs, sociodemographic factors
- Reliance on self-report
  - Shiono et al (1995) completed a prospective cohort study with structured interviews and maternal serum toxicology screens
  - 70% of individuals with positive THC on serum tox screen denied use in structured interview

Shiono Am J Obstet Gynecol 1995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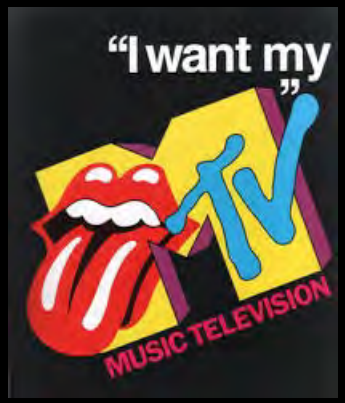

"I want my"
MTV
MUSIC TELEVISION


Top 10 Action Movies of the 1980s
PLAY


DESIGN MUSEUM
FIFTY FASHION LOOKS THAT CHANGED THE 1980s
PAULA REED

Perinatal Outcomes Meta-Analysis

- Gunn et al conducted a systematic review and meta-analysis
  - Primary Outcomes: maternal, fetal or neonatal up to 6 weeks postpartum after cannabis exposure
  - Conducted meta-analyses when 3 or more studies available with same outcome (anemia, LBW, BW, neonatal length, NICU admission, GA at del, head circumference, PTB)
- Increased odds anemia, LBW, NICU admit
- More studies needed

Gunn et al BMC Open, 2016

Neonatal Outcomes: Meta-Analysis

- Conner et al performed systematic review and meta-analysis
- Aim: estimate if marijuana use increases risk of adverse neonatal outcomes
  - Primary outcomes: LBW (<2500gm), PTB (<37 wk)
  - Secondary outcomes: BW, GA at delivery, SGA, level II nursery or greater, stillbirth, SAB, low Apgar, abruption, perinatal death

Conner et al Obstet Gynecol 2016

Neonatal Outcomes: Meta-Analysis

- 31 studies total (12 LBW, 14 PTB)
- Pooled unadjusted data demonstrated an association between THC and LBW/PTB
  - LBW (15.4% vs 10.4%, RR 1.43, 95% CI 1.27-1.62)
  - PTB (15.3% vs 9.6%, RR 1.32, 95% CI 1.14-1.54)
- After adjustment for tobacco and other confounders no longer an association
  - LBW (pooled RR 1.16, 95% CI 0.98-1.37)
  - PTB (pooled RR 1.08, 95% CI 0.82-1.43)

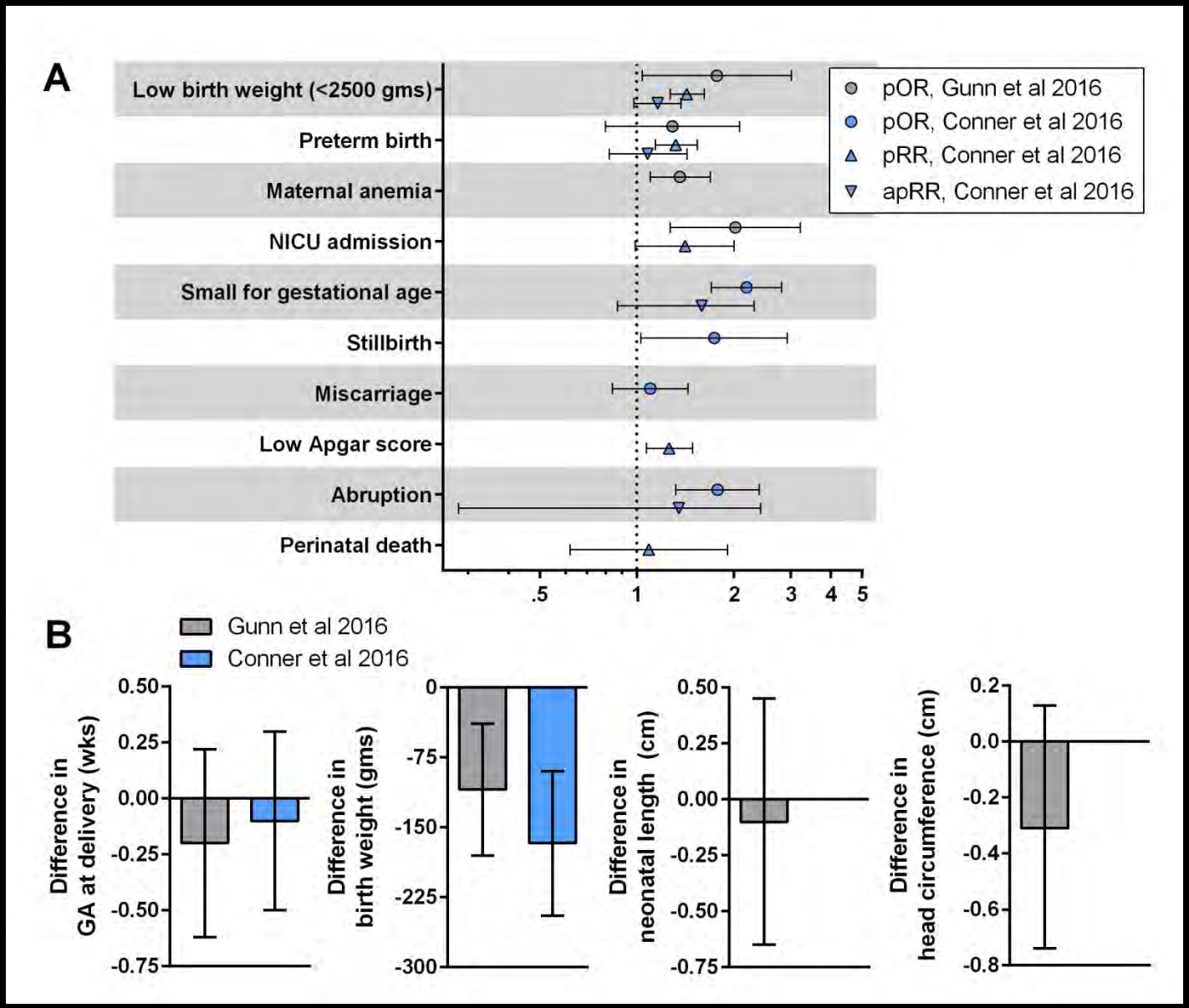
Conner et al Obstet Gynecol 2016

Neonatal Outcomes: Meta-Analysis

- Planned subanalysis of moderate to heavy use (defined as at least once per week)
- Cannabis use associated with low birth weight (RR 1.90, 95% CI 1.44-2.45)
- Cannabis use associated with preterm birth (RR 2.04, 95% CI 1.32-3.17)

Conner et al Obstet Gynecol 2016, ACOG Committee Opinion

Summary Meta-Analyses



Metz and Borgelt Obstet Gynecol 2018

Marchand Meta-Analysis

- Increased risk of LBW, 8 studies, pooled RR 2.06 (1.25-3.42)
- Increased risk of SGA, 6 studies, pooled RR 1.61 (1.44-1.79)
- Increased risk of preterm delivery, 12 studies, pooled RR 1.28 (1.16-1.42)
- Increased risk of NICU admission, 6 studies, pooled RR 1.38 (1.18-1.62)

Marchand et al JAMA Open 2022

Cannabis Use and APOs

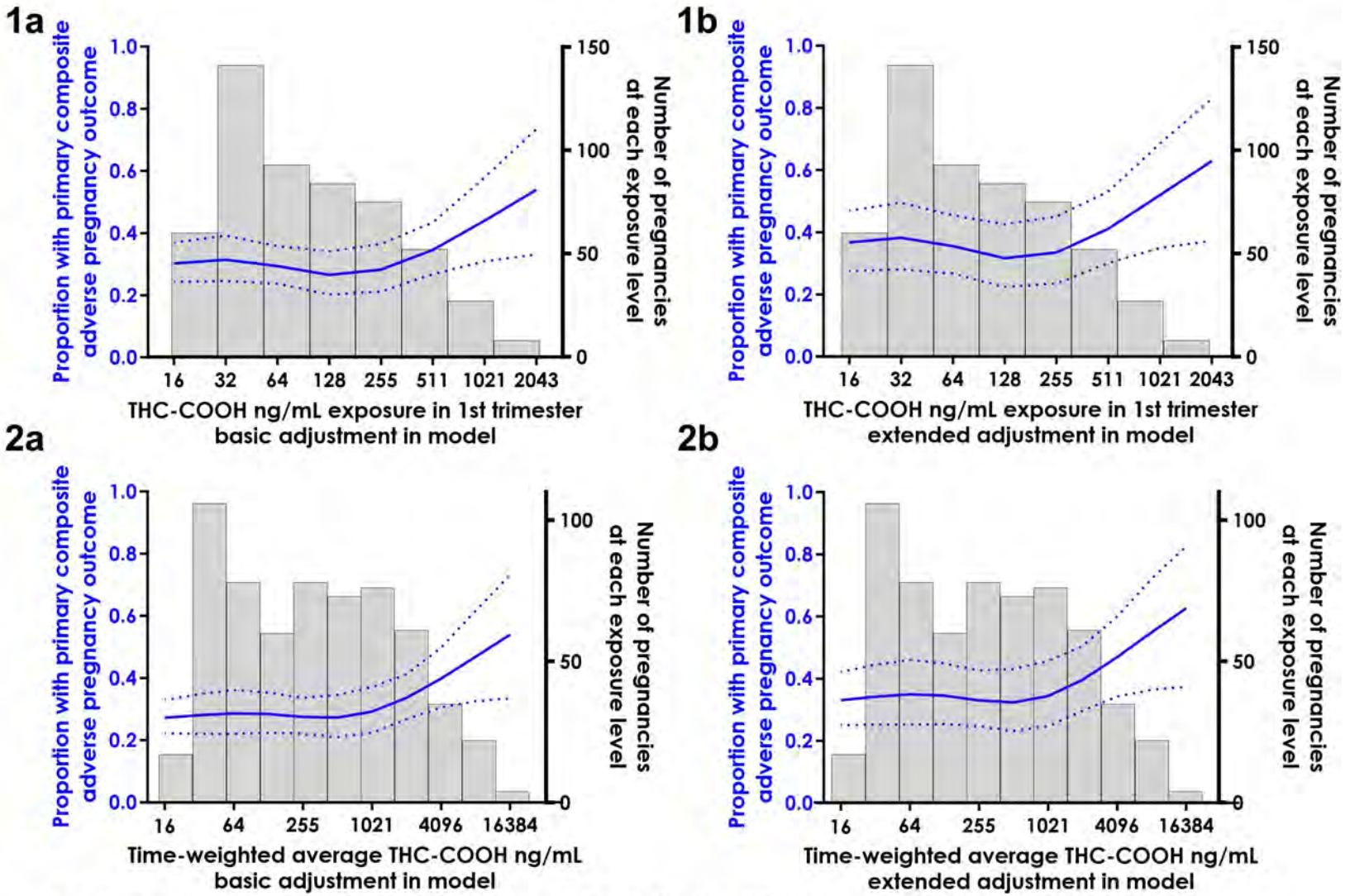
- Ancillary study of NICHD nuMoM2b cohort (2010-13)
- Urine samples from three timepoints in pregnancy assayed for THC-COOH, cotinine and other drugs
- 9,257 participants; 610 (6.6%) exposed to cannabis

Metz et al JAMA 2023

Cannabis Use and APOs

- Cannabis use associated with composite outcome related to placental dysfunction (SGA, HDP, stillbirth, MIPTB)
  - 26% exposed vs 17% unexposed, aRR 1.27, 95% CI 1.07-1.49)
- Not significant when use stopped in first trimester

Metz et al JAMA 2023



Bar indicating instances of zero exposure (1a, 1b n=8717, and 2a, 2b n=8647) omitted from figure.

[a] Basic adjusted model includes tobacco use as detected by urine cotinine ≥ 300 ng/mL at 1st study visit, age ≥ 30 years, body mass index (<20 kg/m^2, 20-29.9 kg/m^2, ≥ 30 kg/m^2), marital status (married, yes/no), public insurance, maternal medical comorbidities (preexisting diabetes or chronic hypertension, yes/no), study site (8 categories).

[b] Extended adjusted model includes all covariates in the basic adjusted model plus Edinburgh Postnatal Depression screen score (≥ 11, yes/no), stress from the Perceived Stress Scale (tertile: low, moderate, high), anxiety from the State-Trait Anxiety Inventory (tertile: none/low, moderate, high), other illicit drug use by urine assay at study visit 1.

Stillbirth

- DATA ARE LIMITED
- Case-control study by Stillbirth Collaborative Research Network
  - Association between stillbirth and cannabis use as demonstrated by cord homogenate positive for THC (OR 2.34, 95% CI 1.13-4.81)
  - Adjusting for cotinine in the maternal serum to account for tobacco use reduced the stillbirth OR for cannabis by approximately 10%

Varner Obstet Gynecol 2014

Congenital Anomalies

- DATA ARE LIMITED AND MIXED
- Linn (1983) found no association with major malformation (OR 1.36, 95% CI 0.97-1.91)
- Large retrospective cohort studies based on birth defects registries
  - Incomplete ascertainment of confounders
  - Potential for recall bias

Linn Am J Public Health 1983, Gibson Aust NZJ Obstet Gynaecol 1983

Congenital Anomalies

- Atlanta Birth Defects Registry
- 122 cases VSD and 3,029 controls
- Adjusted for maternal age, race, overt diabetes, vitamin use
- Periconceptual cannabis associated with VSD (OR 1.90, 95% CI 1.29-2.81)
- More data are needed
- Not adequate evidence of association with any specific congenital birth defect

Williams LJ at el Birth Defects Res A Clin Mol Teratol 2004

Anomalies: Systematic Review

- 11 studies
- Pooled aOR 1.22 (95% CI 1.00-1.50)
- 2 anomalies associated with cannabis use
  - Ebstein anomaly, two studies, aOR 2.19 (95% CI 1.25-3.82)
  - Gastroschisis, five studies, aOR 2.50 (95% CI 1.09-5.74)
- Heterogeneous studies, high risk of bias, inconsistent evidence

Delker at el Obstet Gynecol 2023

Paternal Cannabis Use

- Preconception paternal cannabis use associated with lower birth weight, SAB and SIDS
- Altered sperm DNA methylation in genes involved in neurodevelopment and autism spectrum disorder

Lo et al Am J Obstet Gynecol 2022

Neurodevelopment

- Alterations in neurotransmitters in rat models
  - Especially dopaminergic pathways
- Postmortem human fetal brains (elective terminations 17-22 weeks)
  - Dopamine receptors reduced in marijuana-exposed fetuses
  - Most prominent effect in males
  - Directly correlated with amount of cannabis used during pregnancy

Hurd YL et al Neurotoxicol Teratol 2005; Jutras Aswad et al Eur Arch Psychiatry Clin NeuroSci 2009

Prospective Longitudinal Studies

STUDY AND INVESTIGATOR	INITIATION DATE AND LOCATION	STUDY SIZE (N)	POPULATION
Ottawa Prenatal Prospective Study (OPPS), Fried et al	1978 Ottawa, Canada	180	Low-risk, European-American, middle-class; Exposure to marijuana and cigarettes
Maternal Health Practices and Child Development Study (MHPCD), Day et al	1982 Pittsburgh, Pennsylvania	636	High-risk, mixed ethnicity (57% African American), single (71%), low socioeconomic status; Exposure to marijuana and alcohol
Generation R Study, Hoffman et al	2002 Rotterdam, Netherlands	9778	Multi-ethnic, higher socio-economic status

Drug Alcohol Depend 1980;5:415-24. Neurotoxicol Teratol 1998;20:293-306. Clin Perinatol 1991;18:77-91. Neurotoxicol 13:329-34. Paediatr Perinat Epidemiol 2004;18:61-72. Prog Neuropsychopharmacol Biol Psychiatry. 2014;52:45-52.

Neurodevelopment

- DATA ARE LIMITED BY CONFOUNDING
- OPPS
  - No differences between groups below age 4 years
  - At age 4 years, increased behavioral problems, worse language comprehension, decreased sustained attention and memory difficulties
- MHPCD
  - Decreased verbal reasoning at age 6 years
  - Worse academic performance at age 10 years
  - Increased substance use at age 14 years

Fried Life Sci 1995, Day Neurotoxicol Teratol 1994

Neurodevelopment

- Generation R Study
- Higher aggression scores in cannabis-exposed girls, but not boys at 18 months
- No differences in behavior at 3 years of age
- Ongoing follow-up into adulthood for children born from 2002-2006

Jaddoe et al Eur J Epidemiol 2012

Neurodevelopment

- Cross-sectional study (N=11,489 children)
- Adolescent Brain and Cognitive Development Study
- 5.7% exposed to cannabis prenatally
- Mean age at follow-up 9.9 years
- Cannabis exposure after maternal knowledge of pregnancy associated with greater psychotic-like experiences and externalizing, attention, thought and social problems

Paul SE et al JAMA Psych 2020

Neurodevelopment

- Secondary analysis of two MFMU parallel RCTs related to maternal thyroid function
- 1,197 pregnant individuals; 8.3% positive for cotinine and 3.9% positive for THC-COOH
- No difference in childhood IQ at 60 months of age between exposed to THC and unexposed
- Exposed children worse attention scores at 48 months of age

Smid et al Obstet Gynecol 2022

National Academy of Sciences

- Consistent association between prenatal cannabis use and lower birth weight
- Limited evidence of an association between cannabis use and NICU admission
- Insufficient evidence of an association between cannabis use and neurocognitive outcomes
  - Cannot adjust for subtle environmental differences

Committee on the Health Effects of Marijuana, http:www.nap.edu/246252017

Breastfeeding

- THC passes to the neonate in breastmilk
- Letter to the editor NEJM of two patients
  - Chronic heavy use can result in levels up to 8x plasma

Perez-Reyes NEJM 1982

Breastfeeding

- Observational study of 8 women
  - Purchased product with known concentration of THC
  - Abstained from use for 24 hrs prior
  - Inhaled cannabis then collected breast milk at 20 minutes, 1, 2 and 4 hours
  - Exclusively breastfed infant ingests mean of 2.5% of maternal dose

Baker Obstet Gynecol 2018

Breastfeeding

- 54 samples from milk donors
- Delta-9-THC detectable 63% samples up to 6 days after last reported use
- Median concentration 9.47 ng/mL
- Number of daily uses and time from sample collection to analysis were predictors of THC concentration in breastmilk

Bertrand et al Pediatrics

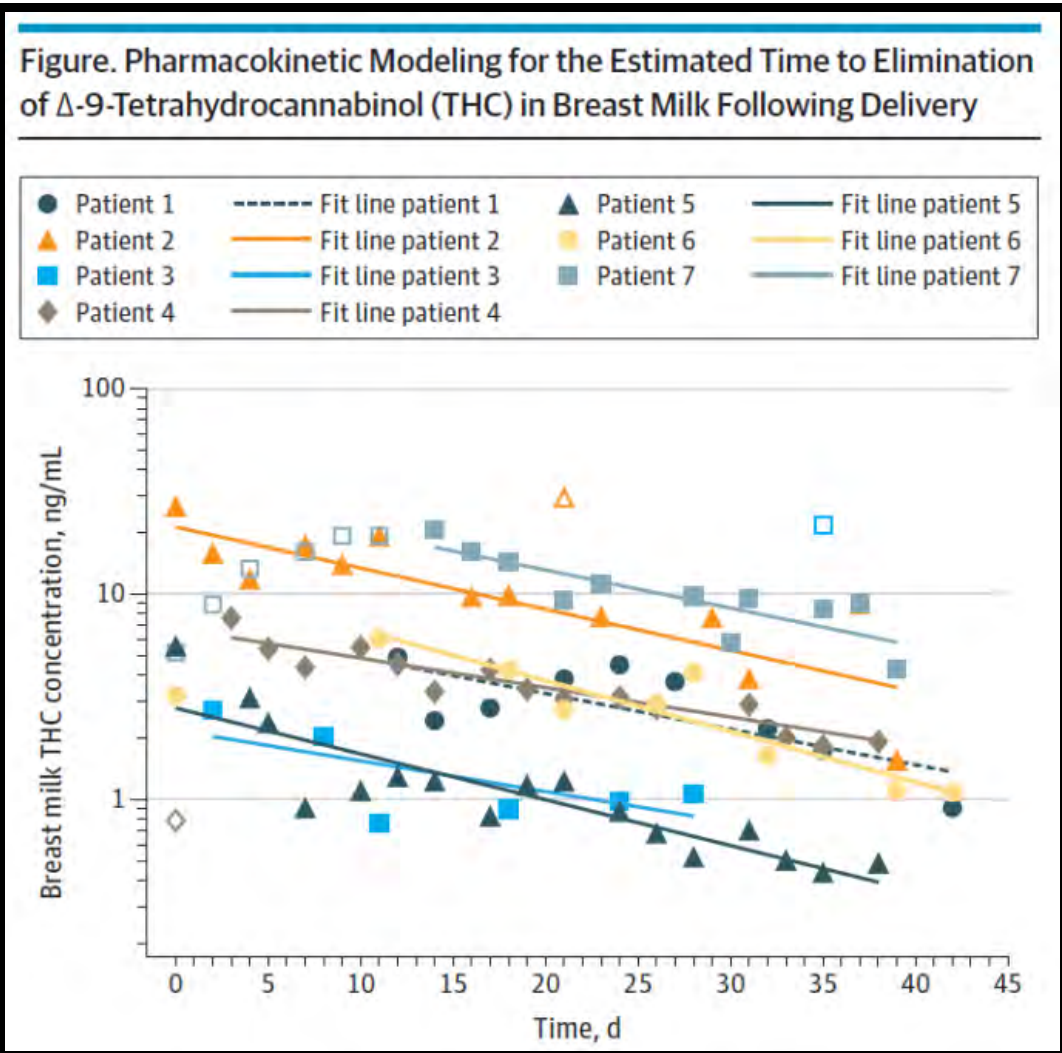
Breastfeeding

- Prospective cohort study to estimate time to elimination of marijuana metabolite from breastmilk (N=25)
- Inclusion criterion of plan for abstinence
  - 12/25 abstinent by plasma sampling
- Primarily inhalation consumption during pregnancy (more than 2 times weekly)
- Detectable THC in breastmilk in all participants during 6- week study period

Wymore et al JAMA Peds 2021

Breastfeeding

- 402 serial samples obtained and analyzed
- Half-life 17 days
- Projected elimination > 6 weeks
- Cannot "pump and dump"



Wymore et al JAMA Peds 2021

ACOG Committee Opinion

- People should not use marijuana during pregnancy or while lactating
  - Ob-gyns should not prescribe for medicinal purposes to pregnant or lactating individuals
  - Insufficient evidence for effects on nursing infant

ACOG, Committee Opinion No. 637, Marijuana Use During Pregnancy and Lactation, Obstet Gynecol 2015

How are we doing now?

- Holland et al recorded patient encounters and evaluated obstetric provider response to disclosure of cannabis use
- 90/460 (19%) reported use at OB intake
- 47 different health care providers
- 48% of the time provider did not respond to cannabis disclosure
- When discussed, response non-specific and focused on tox screens and social services

Holland et al, Obstet Gynecol 2016

Dispensary Project

- Mystery shopper study (400 randomly selected dispensaries)
- Caller was 8 weeks pregnant with nausea
- Nearly 70% had product recommendations
  - Predominantly recommended edibles
  - 65% based recommendation on personal opinion
  - Only 32% recommended discussion with healthcare provider without prompting

Dickson et al Obstet Gynecol 2018

How are we doing now?

- Cross-sectional study 2017-2019 PRAMS
- Prenatal care visits 8 states
  - 2 with legal cannabis
- N=10,696
- 37.2% not asked about cannabis use
- 62.7% not advised against cannabis use
- Of those reporting cannabis use, 49.8% advised not to use in pregnancy
- 7.7% advised to use cannabis at PNV

Skelton et al, Am J Obstet Gynecol 2023

What do we tell patients?

- No known benefits of cannabis use in pregnancy
- Possible risks of cannabis use in pregnancy
- Advise patients not to use cannabis during pregnancy
- No known “safe” amount of cannabis in pregnancy and while breastfeeding

Grant Support

- University of Colorado CCTSI Child-Maternal Health Junior Pilot Program
- Women's Reproductive Health Research Scholar K12HD001271
- NIDA R01DA049832

Thank you!

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Cannabidiol

- Cannabidiol (CBD) component of *Cannabis sativa* plant
- Not psychoactive, sedative, ? therapeutic
- Little known about CBD in isolation in pregnancy
- In vitro models demonstrate adverse effects on trophoblasts and placental remodeling

Alves P et al Arch Toxicol 2021

Cannabidiol

- Zebra fish embryos
- Neural activity decreased more by CBD than THC
- Both decreased neural activity
- Possible synergistic effect with more pronounced effect of CBD in presence of THC

Kanyo R et al Sci Report 2021

Cannabidiol

- Biologically plausible effect on placentation and trophoblast invasion
- Endocannabinoid system active in early pregnancy with placentation
- Active in late pregnancy during fetal neurodevelopment
- Essentially no data specific to CBD in humans

Female Sexual Medicine

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Assistant Professor
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University of Colorado Anschutz Medical Campus

February 22, 2024, 7:55 – 8:35 AM

Conflict of Interest Disclosure

None

Learning Objectives

1. Describe the **diagnostic criteria** and **etiologies** for common sexual function concerns in females.
2. Recommend **treatments** for common sexual function concerns.
3. Discuss **medications** used to support sexual function, with an emphasis on mechanism of action, side effects and clinical utility.

Acknowledgements

- Sexual health care historically and currently operates in gender binaries, heteronormative systems, and tends to cater care to those who identify as heterosexual and cisgender within monogamous relationships.
    - Restrictive binaries in DSM language
    - Lack of meaningful research of diverse gender and sexual groups
    - References to partnerships, and omission of ethically non-monogamous relationships/polyamorous relationships, and other types of sexual engagement
    - Women’s Sexual Health Clinics

"'In high-quality health-care provision, sexual health should be integrated with all aspects of patient [...] care and should hold equal status with physical, spiritual, social, and emotional care.' [1] Thus, it should be as natural to ask about sexual orientation as it is to ask about bowel habits." [2]

MARGARET R.H. NUSBAUM, D.O., M.P.H., AND CAROL D. HAMILTON, ED.D., P.A.-C.

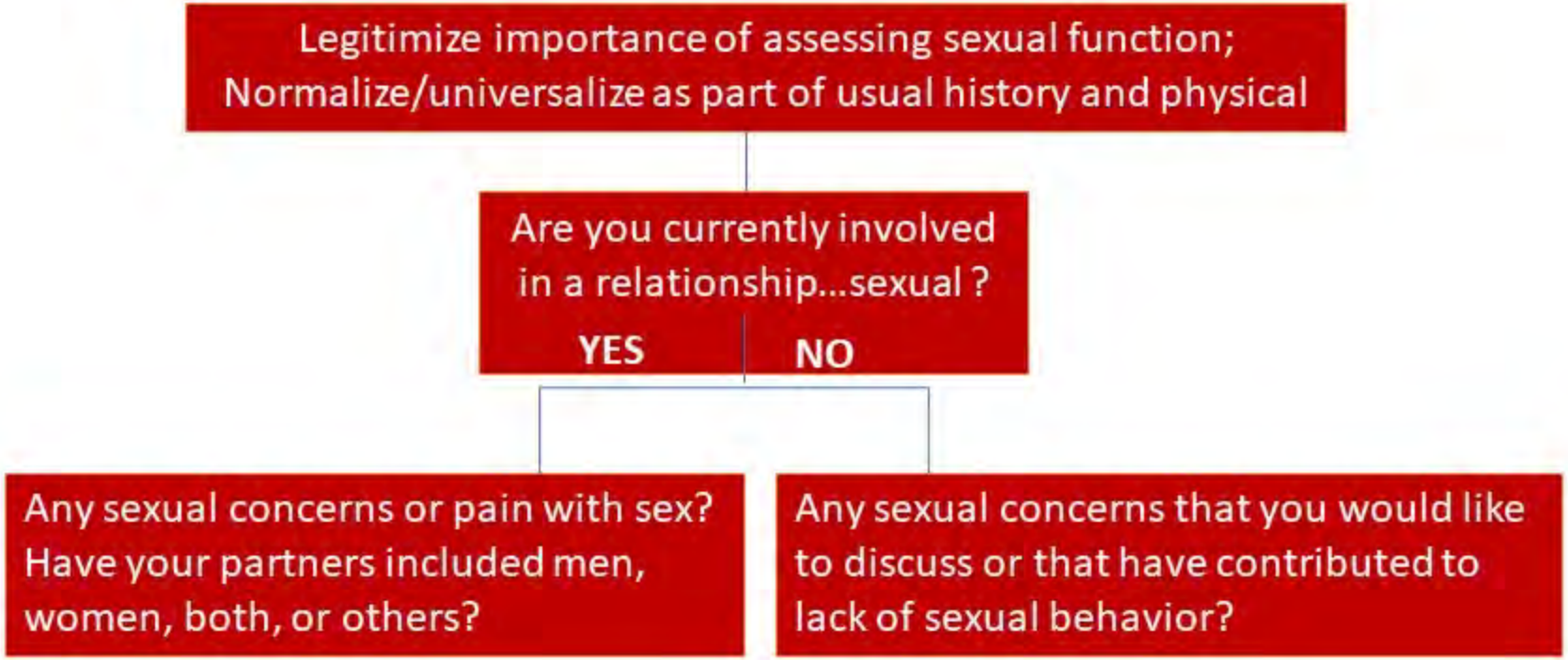
[1] Wilson H, McAndrew S. Sexual health: foundations for practice. New York: BaillièreTindall, 2000:xi.
[2] Nusbaum MR, Hamilton CD. The proactive sexual health history. Am Fam Physician 2002; 66: 1705– 12.

Taking a Sexual History

- Why?
  - 43% of American women report sexual problems
  - Symptom of systemic disease
  - Medication side effect
  - Associated with longevity
  - Your patients want you to
  - If not you… who?!
- Barriers
  - Embarrassment
  - Ill-prepared
  - Not relevant
  - Time constraints

Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress in United States women: prevalence and correlates. Obstet Gynecol 2008; 112: 970– 8
Nusbaum MR, Hamilton CD. The proactive sexual health history. Am Fam Physician 2002; 66: 1705– 12.
Palmore EB. Predictors of the longevity difference: a 25-year follow-up. *Gerontologist.* 1982;22:513-8

Screening for Sexual Function



Adapted from Kingsberg S. Sex, Urol Clin N Am. 2000;34:497-506.

ISSWSH
International Society for the Study of Women's Sexual Health

Female Sexual Function Index (FSFI)

- 6 domains:
  - Desire
  - Arousal
  - Lubrication
  - Orgasm
  - Satisfaction
  - Pain
- Composite score: 0 – 36
  - Score ≤26.55 = Female sexual dysfunction

Female Sexual Function Index (FSFI)

Name: Date:

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential.

In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation, and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how often did you feel sexual desire or interest?

- ☐ 5 = Almost always or always
- ☐ 4 = Most times (more than half the time)
- ☐ 3 = Sometimes (about half the time)
- ☐ 2 = A few times (less than half the time)
- ☐ 1 = Almost never or never

2. Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?

- ☐ 5 = Very high
- ☐ 4 = High
- ☐ 3 = Moderate
- ☐ 2 = Low
- ☐ 1 = Very low or none at all

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how often did you feel sexually aroused ("turned on") during sexual activity or intercourse?

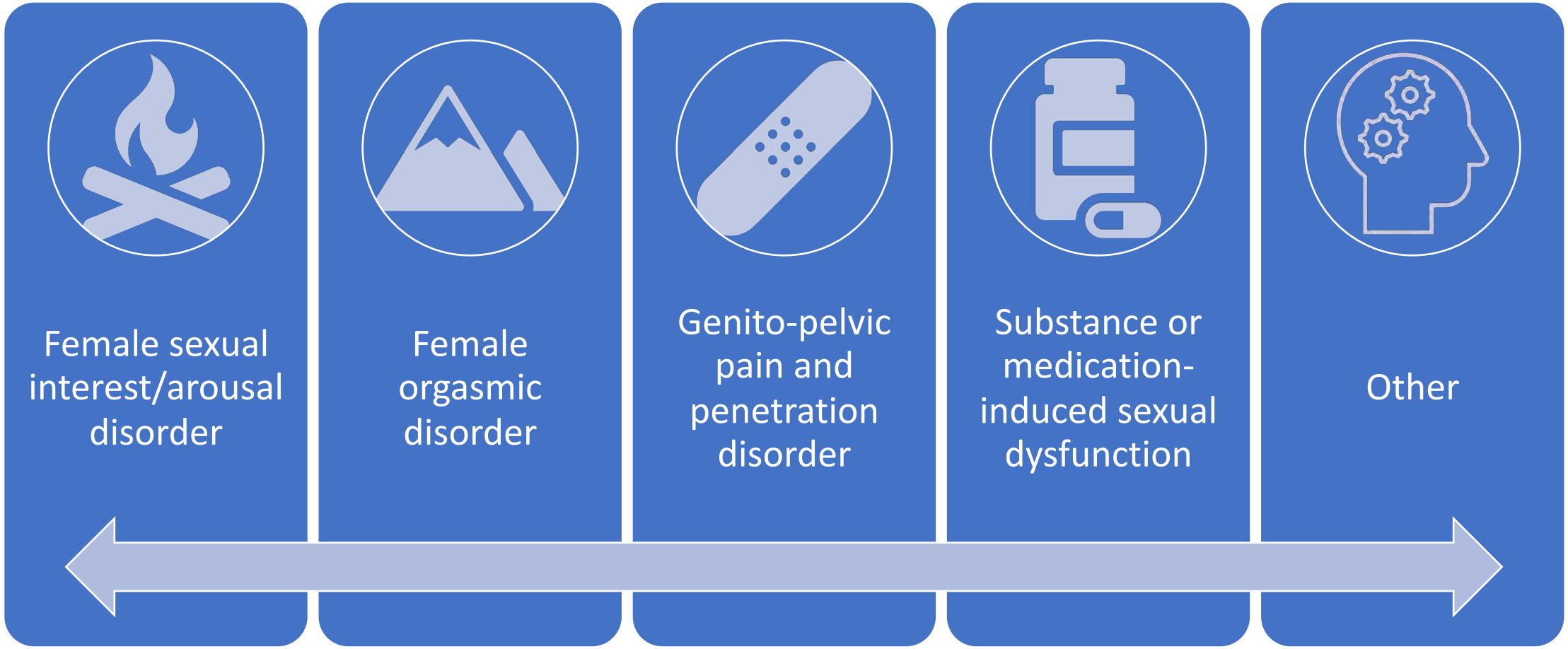
- ☐ 0 = No sexual activity
- ☐ 5 = Almost always or always
- ☐ 4 = Most times (more than half the time)
- ☐ 3 = Sometimes (about half the time)
- ☐ 2 = A few times (less than half the time)
- ☐ 1 = Almost never or never

4. Over the past 4 weeks, how would you rate your level of sexual arousal ("turn on") during sexual activity or intercourse?

- ☐ 0 = No sexual activity
- ☐ 5 = Very high
- ☐ 4 = High
- ☐ 3 = Moderate
- ☐ 2 = Low
- ☐ 1 = Very low or none at all

Rosen R, Brown C, Heiman J, et al. The female sexual function index (FSFI): A multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000;26:191-208.

Classifications of Female Sexual Dysfunction



American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington (VA): APA; 2013.

Sexual Interest and Arousal Disorder

- *Lack of / decrease in ≥3 of the following:*
  - *Interest in sexual activity*
  - *Sexual or erotic thoughts / fantasies*
  - *Initiation of sexual activity / responsiveness to partner's initiation*
  - *Excitement or pleasure during (almost) all sexual activity*
  - *Interest or arousal in response to sexual or erotic cues (e.g. written, visual)*
  - *Genital or non-genital sensations during sexual activity*
- *≥6 months*
- *Distress*

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington (VA): APA; 2013.

Spontaneous Desire

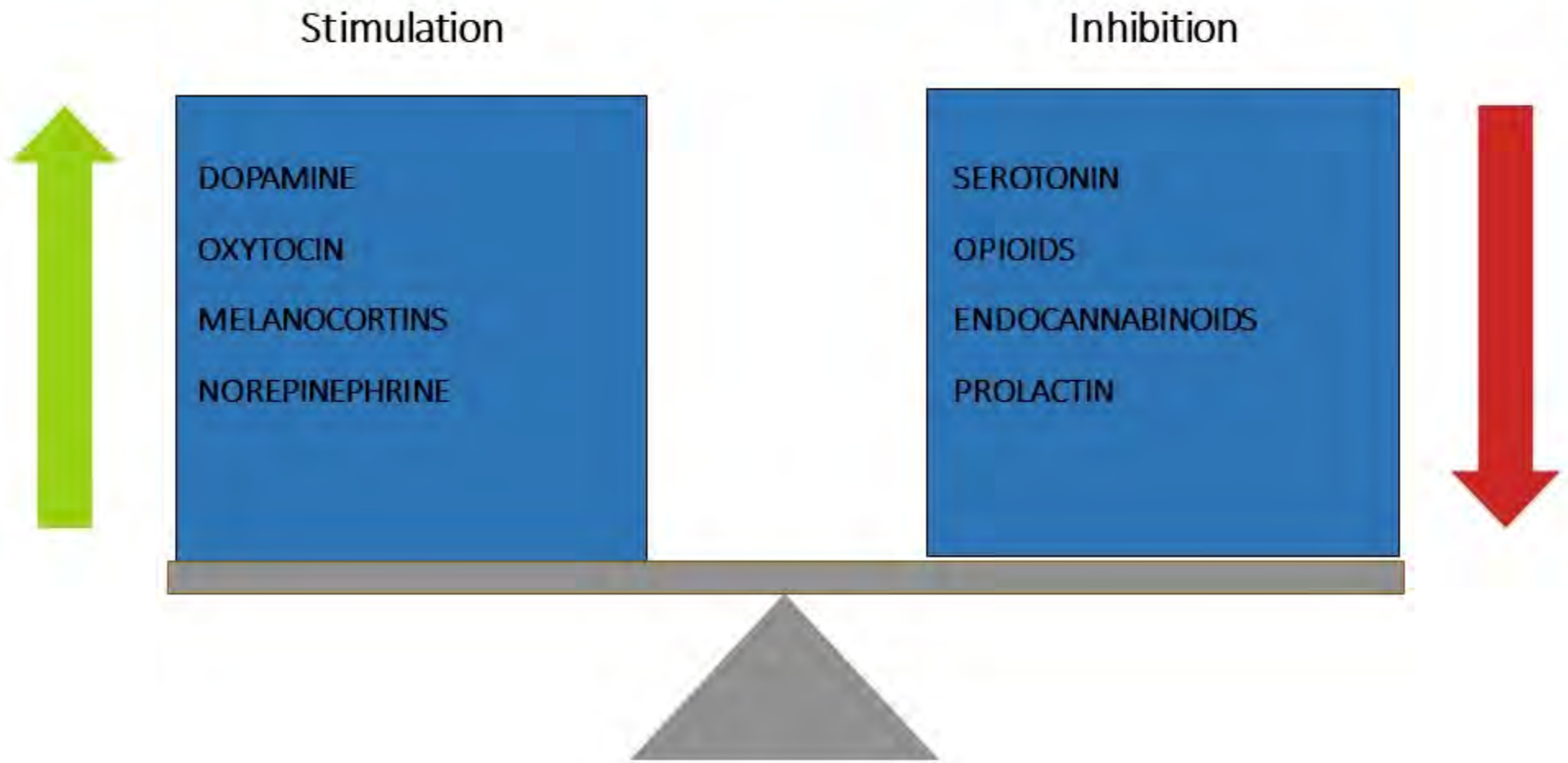
- Desire that seems to erupt out of nowhere
- Urge precedes sexual activity
- Desire starts in the mind
- Type of desire you often see on TV / movies
- **Normal and healthy**

Responsive Desire

- Desire that occurs in context of consensual sexual play, touch, conversation, flirtation, reading, watching
- Urge starts after stimulation
- Intentional, gradual desire
- Pathologized incorrectly as low desire
- **Normal and healthy**

Nagoski, E. (2015). Come as you are: the surprising new science that will transform your sex life. New York, Simon & Schuster Paperbacks.

Dual Control Model



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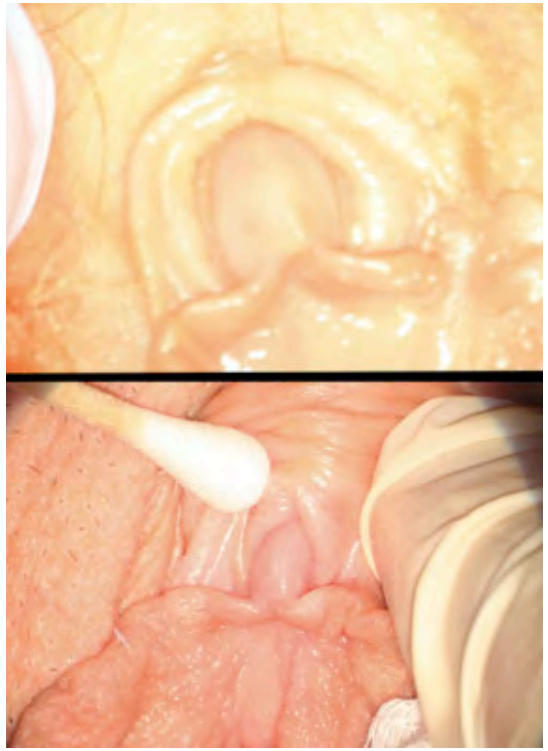
Nagoski, E. (2015). Come as you are: the surprising new science that will transform your sex life. New York, Simon & Schuster Paperbacks.

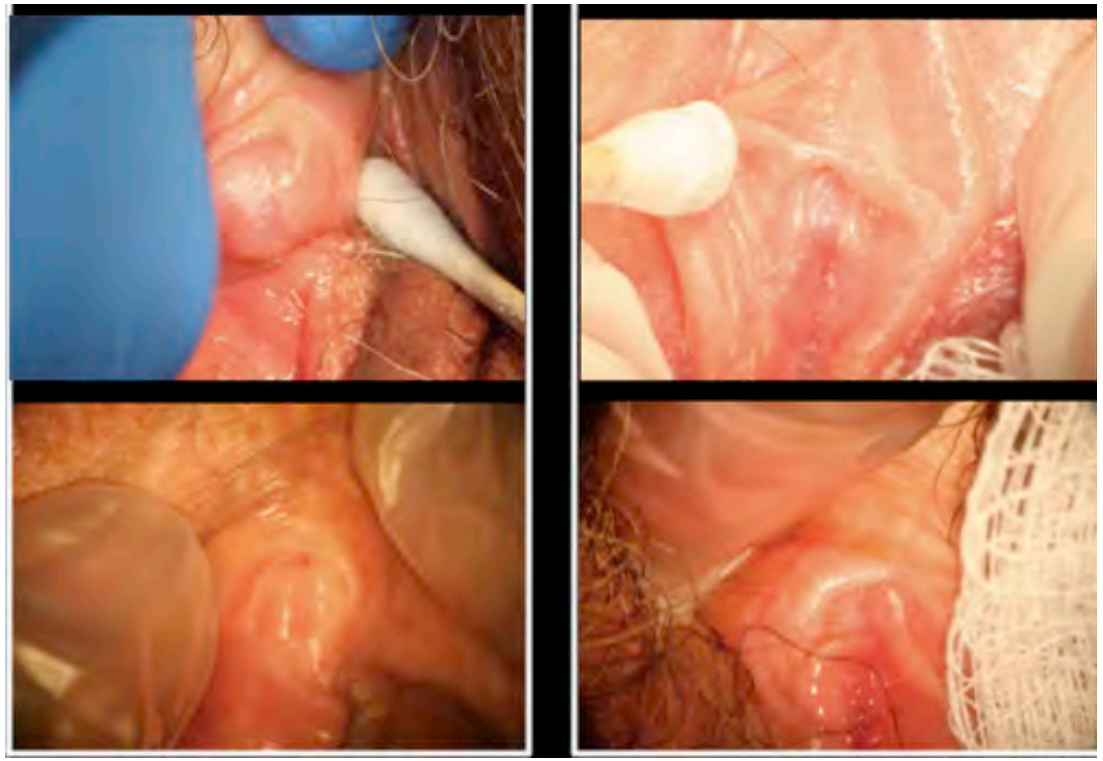
Female Orgasmic Disorder

- *Orgasm that is*
  - ***Absent***
  - ***Delayed***
  - ***Infrequent***
  - ***Reduced intensity***
- *>6 months*
- *Distress*

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington (VA): APA; 2013.

Female Orgasmic Disorder

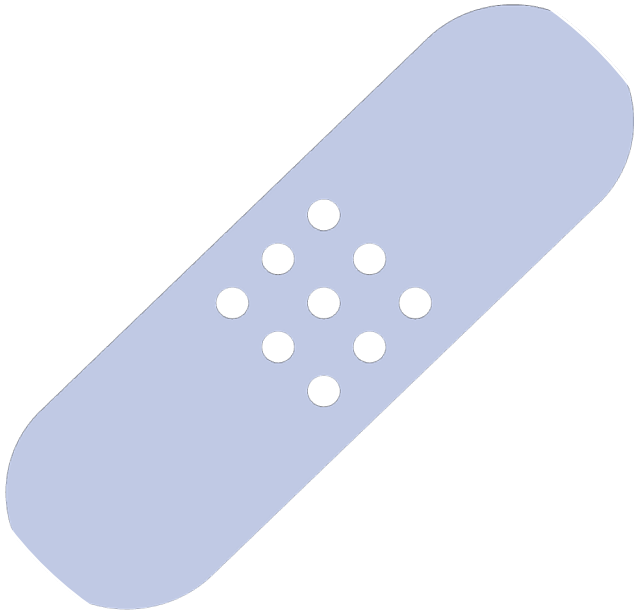




- *Often acquired*
  - *Clitoral adhesions / phimosis (GSM, lichen* sclerosus*)*
  - *Neurologic condition*
  - *Iatrogenic: pelvic surgery, radiation*
  - *FGM*
  - *Psychosocial: trauma, shame, anxiety*

Aerts L, Rubin RS, Randazzo M, et al. Retrospective Study of the Prevalence and Risk Factors of Clitoral Adhesions. Sex Med 2018;6:115–122.

Genitopelvic Pain and Penetration Disorder



- *Persistent / recurrent presence of ≥1 during activity:*
  - *Vulvovaginal or pelvic pain*
  - *Fear / anxiety about pain*
  - *Tensing or tightening of pelvic floor muscles*
  - *Difficulty with penetration*
- *≥6 months*
- *Distress*

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington (VA): APA; 2013.

Genitopelvic Pain and Penetration Disorder

Common causes:

- High tone pelvic floor myalgia
- Genitourinary syndrome of menopause
- Trauma
- Endometriosis
- Vulvodynia
- Vulvar dermatoses

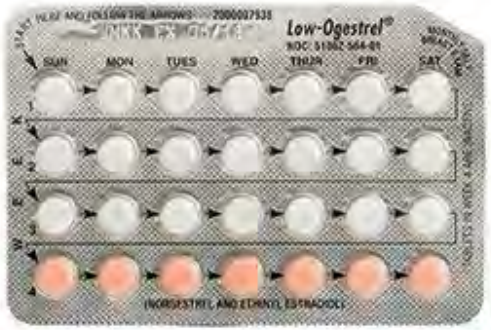
American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington (VA): APA; 2013.

Substance/Medication-Induced Dysfunction

- Disturbance in sexual function
- Temporal correlation with:
  - Substance / medication initiation or discontinuation
  - Dose increase
- Distress

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington (VA): APA; 2013.

Substance/Medication-Induced Dysfunction



- Hormonal
- Psychiatric medications
- Anticholinergic
- Cardiovascular
- Alcohol, marijuana, narcotics

Female Sexual Dysfunction. ACOG Practice Bulletin No. 213. American College of Obstetricians and Gynecologists. Obstet Gynecol 2019;134:e1-18.

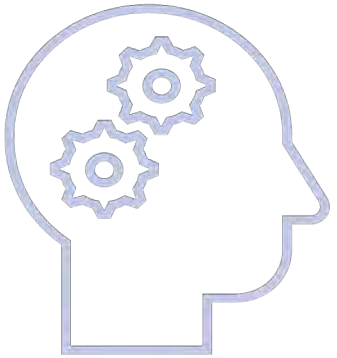
Other: Peripartum, Menopause

- Peripartum
  - Obstetric laceration
  - Lactational hypoestrogenism
  - Postpartum mood disorders
  - Intimate partner violence
  - Sleep deprivation
  - Relationship strain
  - Stress
  - Body image
- Genitourinary Syndrome of Menopause
  - Vaginal dryness, burning, irritation
  - Decreased lubrication

Female Sexual Dysfunction. ACOG Practice Bulletin No. 213. American College of Obstetricians and Gynecologists. Obstet Gynecol 2019;134:e1-18.

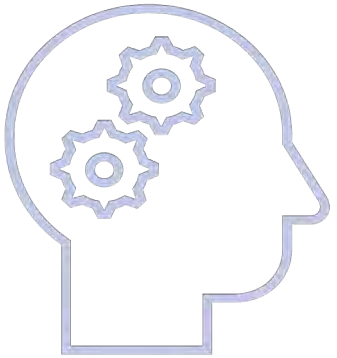
Other: Mental Health

- Depression
  - Anhedonia
  - Avolitional
- Anxiety
  - Anxious rumination
  - Perfectionistic expectations
- ADHD
  - Focus, motivation
- Post-traumatic stress, childhood maltreatment/neglect
  - Power and consent
  - Pleasure and the body



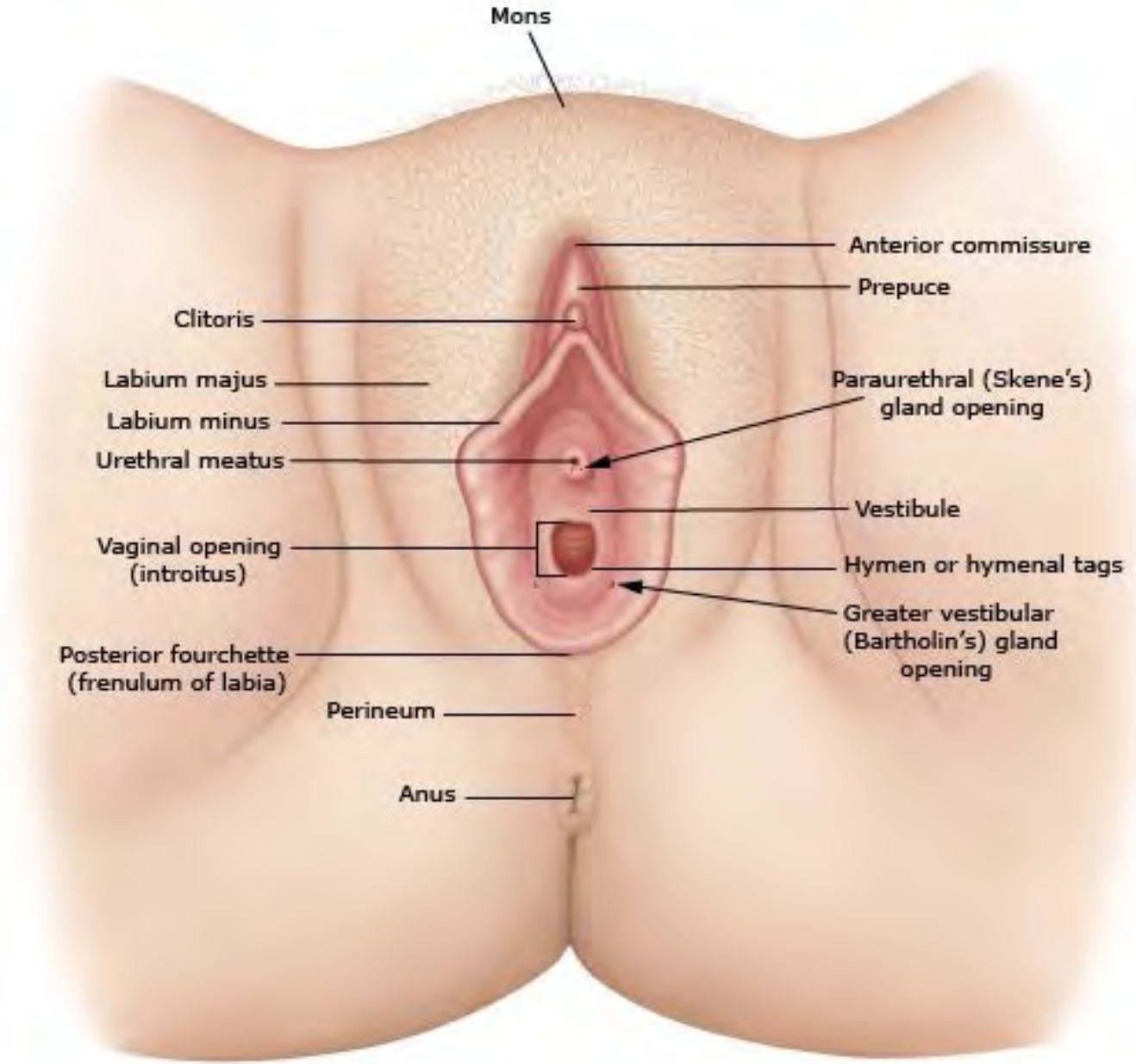
Other: Psychosocial Factors

- Sexual/relational factors
  - Partner sexual dysfunction
  - Lack of novelty/repetition
  - Poor attention/focus on sexual stimulation
  - Pain or diminished arousal
  - Partner sexual awkwardness
- Cultural/Relational factors
  - Attachment styles
  - Religious/cultural/familial values, beliefs, taboos
  - Relational Discord
  - Partner Psychiatric Issues
- Secondary to medical issues
  - Infertility
  - Changes to body image/mobility/accessibility



Exam

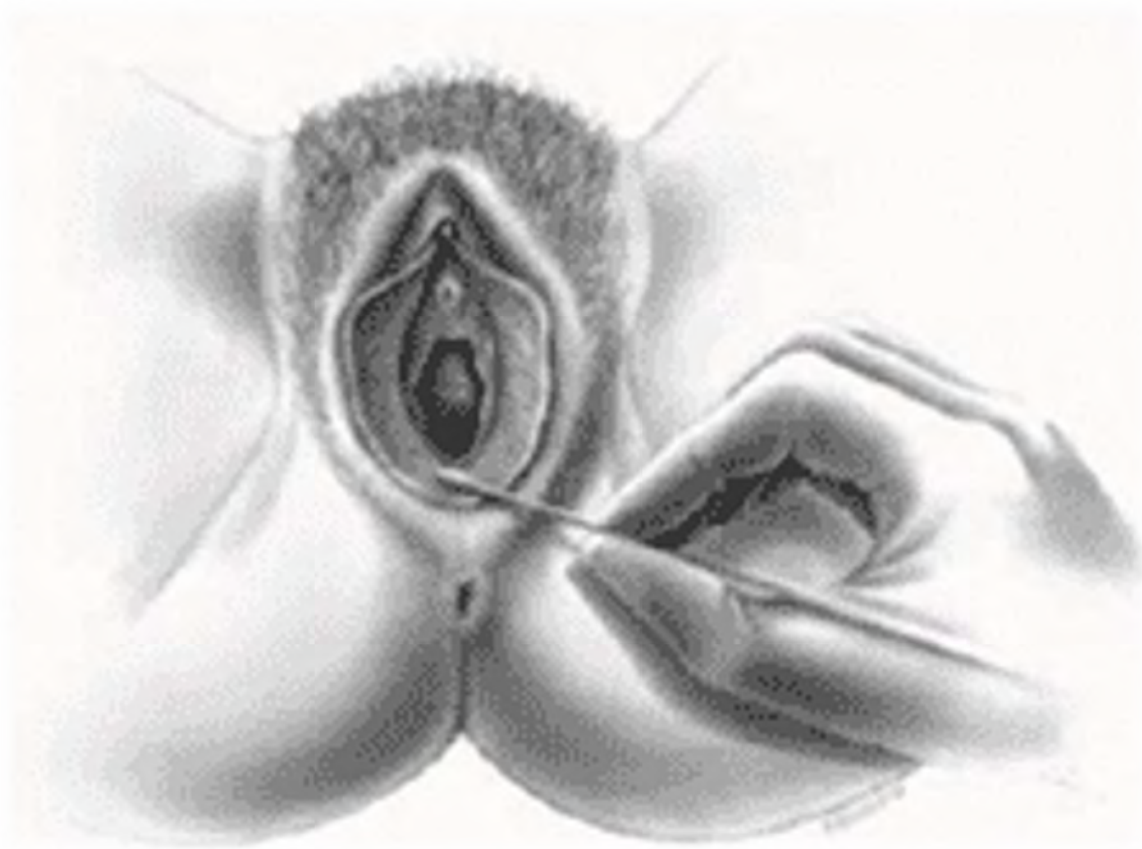
- Adhesions
- Atrophy
- Inflammatory changes

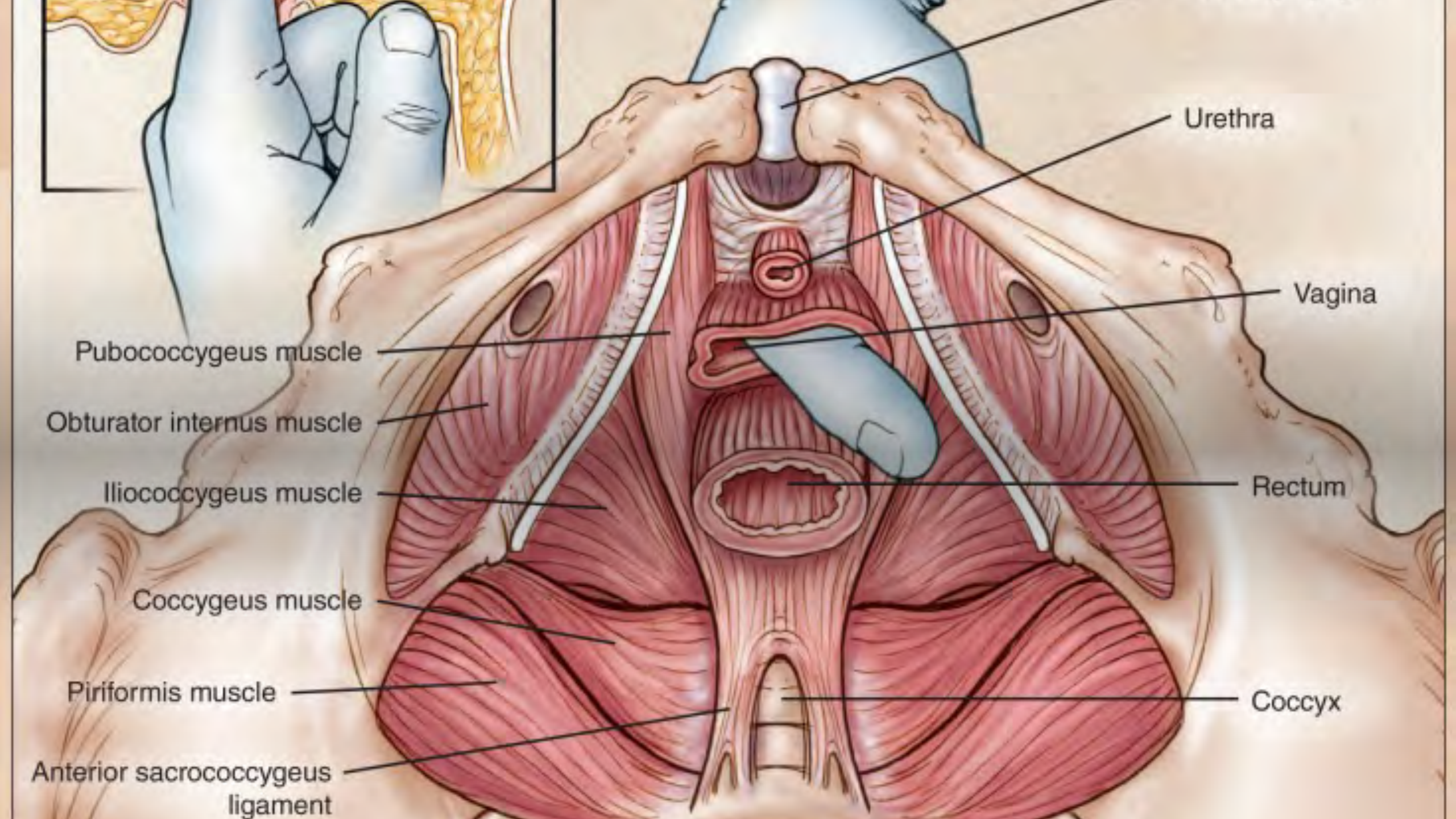


Exam

Test for dysesthesia on:

- Inner thigh
- Labia majora
- Interlabial sulcus
- Vestibule
- Clitoris




Urethra
Vagina
Pubococcygeus muscle
Obturator internus muscle
Iliococcygeus muscle
Rectum
Coccygeus muscle
Piriformis muscle
Coccyx
Anterior sacrococcygeus ligament

Treatment

Moving beyond….

“Have a glass of wine or two to relax.”

“Go on vacation.”

“This is what happens after you’ve been partnered for 15 years.”

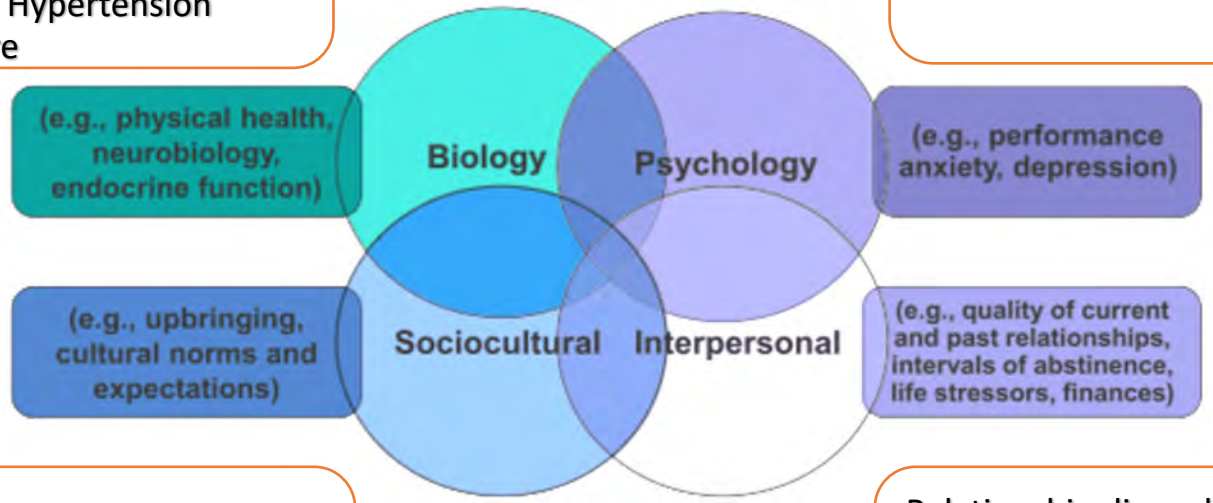
“Biology didn’t intend for females to be sexually active after menopause.”

Treatment

Multimodal, multidisciplinary, biopsychosocial approach

Menopause
Cancer
Childbirth
Endometriosis
Premature ovarian failure
Obesity
Neurologic disease
Diabetes
Hypertension

Trauma
Mood disorders
Substance use disorder
Shame



Religious upbringing
Messaging about sex/sexuality
Sexual education
Comfort with body/sexuality
FGM

Relationship discord / trust
Fatigue (work hours, children)
Sexual satisfaction
Sexual communication

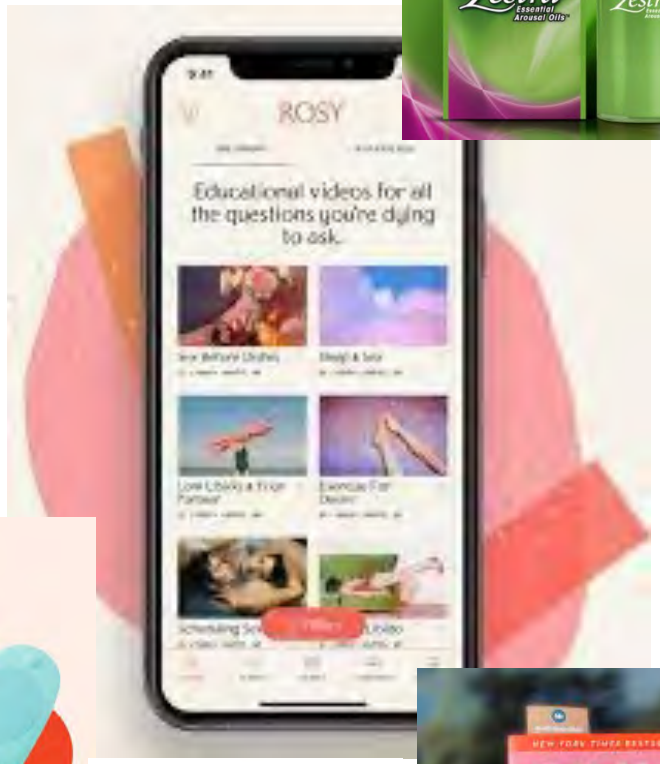
Treatment: Interest/Arousal Disorder

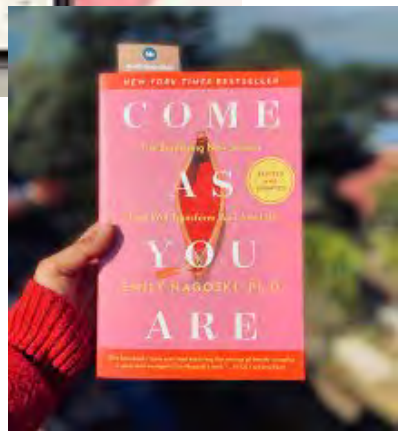
- Psychological therapy
  - Mindfulness therapy
  - Cognitive behavioral therapy
  - Sex therapy
- Exercise

Female Sexual Dysfunction. ACOG Practice Bulletin No. 213. American College of Obstetricians and Gynecologists. Obstet Gynecol 2019;134:e1-18.

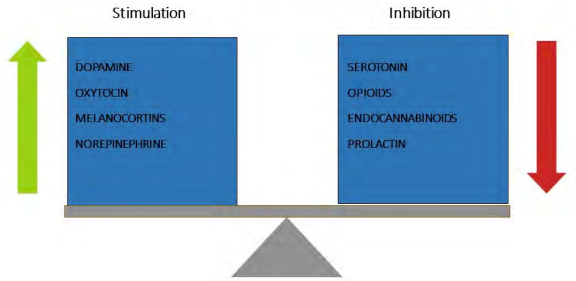
Treatment: Interest/Arousal Disorder

- Education
  - Rosy App
  - *Come As You Are* by Emily Nagoski, PhD
  - *Better Sex Through Mindfulness* by Lori Brotto, PhD
- Increase satisfaction
  - Lubricants (silicone-based)
  - Zestra
  - Devices
- Over-the-counter supplements
  - L-Arginine
  - Ristella (Bonafide)
  - ArginMax
  - StronVivo





Treatment: Interest/Arousal Disorder



Flibanserin "Addyi"

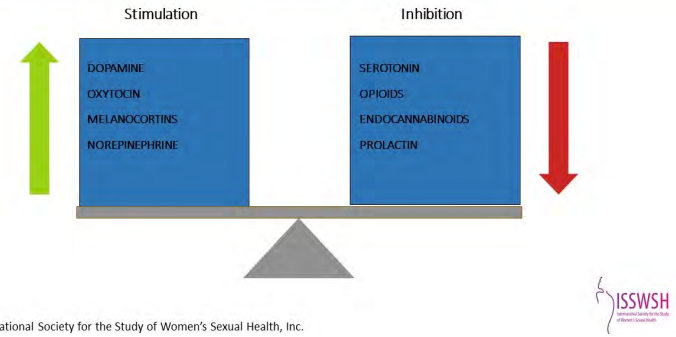
- FDA approved in 2015 for pre-menopausal women.
- Post-synaptic 5HT1A receptor agonist and 5HT2A receptor antagonist.
  - Lowers serotonin and raises dopamine and norepinephrine in prefrontal cortex
  - Increases excitation, decreases inhibition
  - Average of one additional satisfying sexual event per month.
- Daily qHS dosing. 8 week trial.
- Side effects: Dizziness, somnolence, nausea, fatigue.
  - EtOH: Wait 2hr after EtOH.
  - Boxed warning.
- High cost, variable insurance coverage. PhilRx.

Female Sexual Dysfunction. ACOG Practice Bulletin No. 213. American College of Obstetricians and Gynecologists. Obstet Gynecol 2019;134:e1-18.

Treatment: Interest/Arousal Disorder

Bremelanotide "Vyleesi"

- FDA approved in 2019 for pre-menopausal women.
- Melanocortin receptor agonist.
- Use PRN (subcutaneous injection).
  - Works within 45 min, and lasts 8-10 hours
  - Safe to use with ETOH
- Side effects: Nausea. Rx with Zofran.

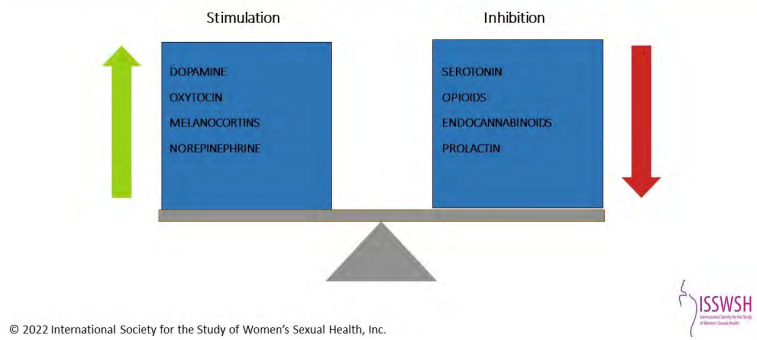


Female Sexual Dysfunction. ACOG Practice Bulletin No. 213. American College of Obstetricians and Gynecologists. Obstet Gynecol 2019;134:e1-18.

Treatment: Interest/Arousal Disorder

<u>Buproprion</u> “Wellbutrin”

- Off-label (no FDA approval).
- Consider as adjunct therapy for women with SSRI-induced low desire.
- Increases norepinephrine and dopamine.
- Reliable insurance coverage, low cost.



Female Sexual Dysfunction. ACOG Practice Bulletin No. 213. American College of Obstetricians and Gynecologists. Obstet Gynecol 2019;134:e1-18.

Treatment: Interest/Arousal Disorder

Post-menopausal women

- Flibanserin or Bremelanotide “off-label”
- Systemic estrogen therapy (low dose, transdermal)
- Systemic testosterone therapy (low dose, transdermal)

Female Sexual Dysfunction. ACOG Practice Bulletin No. 213. American College of Obstetricians and Gynecologists. Obstet Gynecol 2019;134:e1-18.

Treatment: Female Orgasmic Disorder

- Lysis of clitoral adhesions
- Pelvic floor PT
- Psychotherapy, sex therapy, sex skills training
  - Tools
  - Mindfulness
  - Pleasure mapping

Treatment: Genitopelvic Pain & Penetration Disorder

- Pelvic floor PT
    - Myofascial release of muscle tension in pelvic floor, thighs, and abdomen
    - Biofeedback
- Dilators
    - Re-train the muscles not to contract with something in the vagina!
- Trigger point injections
- Muscle relaxants (systemic or local)
- Neuromodulators (systemic or local)
- Pain desensitization through therapy

Treatment: Genitopelvic Pain & Penetration Disorder

Address comorbid conditions:

- Low estrogen
  - Menopause OR breastfeeding
  - **<u>Vaginal estrogen</u>** is VERY effective and LOW risk.
  - Vaginal DHEA / prasterone
  - Vaginal moisturizers (non-hormonal, hyaluronic-acid based)

HyaloGyn

Revaree

Replens

To learn more….

- International Society for Study of Women's Sexual Health (ISSWSH)
- Books:
  - *Come As You Are* by Emily Nagoski
  - *When Sex Hurts* by Irwin and Andrew Goldstein & Caroline Pukall
  - *Mindfulness for Better Sex* by Lori Brotto
- *You are Not Broken Podcast* by Kelly Casperson, MD
- Rosy App
- Websites:
  - OMGYes.com
  - Prosayla.com (ISSWSH patient-facing website)

Sexual Problem Assessment

- Nature of the problem
- Phases of sexual response affected and pain
- Single vs. combined (sequence)
- Lifelong vs. acquired (timeline)
- Generalized vs. situational
- Sudden vs. gradual (predisposing, precipitating, maintaining factors)
- Inhibition, performance anxiety, anger
- Stimulation (technique, satisfaction)
- Contributing factors (psychological, biological, socio-cultural, relational, lifecycle)
- Depression, anxiety, trauma, substances
- Impact and distress
- Exacerbating and alleviating factors
- Partner response/sexual function, communication
- Treatments and their efficacy
- Motivation for therapy (why now?)

ISSWSH

Validated Tools

Validate Tool	Assessment Area
Decreased Sexual Desire Screener (DSDS)	Brief diagnostic tool for Hypoactive Sexual Desire Disorder (HSDD)
Female Sexual Function Index (FSFI)*	Desire, arousal, orgasm, pain
Female Sexual Distress Scale-Revised (FSDS-R)	Distress

ISSWSH
International Society for the Study of Women's Sexual Health

Primary HPV Screening:

Is it coming? Is that OK? Should we do it? Do we have a choice? Does it matter? What next?

49th Annual Vail Ob/Gyn Course

L. Chesney Thompson MD

University of Colorado

Feb 22, 2024

Vail, Colorado

No COI

- Probably
- Yes
- Yes
- Maybe not
- Probably not
- Something else or at least more changes sooner than later

Learning objectives:

- Review current guidelines for Cx CA screening
- Explain HPV as primary screening method
- Appreciate benefits and limitations of primary screening
- Apply HPV as primary screening

REMEMBER

- These are guidelines and meant to suggest a pathway for evaluation and management
- The recommendations are for screening populations without risks. This does not include Immune-compromised individuals, DES exposure nor follow-up to high grade dysplasia or cancer, or pts without a cervix
- Not so comprehensive as to apply to all clinical situations. Not a substitute for clinical judgment
- Individualized approach should be considered and include shared decision making with the patient to determine best strategy

Cervical Cancer Rates

Global

604,000 (470,600) **cases per year**

342,000 *(233,400)* **deaths per year**

Rates > 40/100,000 women (similar to Anal CA in MSM in US)

4th most common Ca in women and 3rd cause of Ca death

United States

13,800 *(13,000)* **cases per year**

(Oropharyngeal most common HPV-linked cancer)

4290 *(4,100)* **deaths per year- 65% higher in black women**

Rates <5/100,000 women

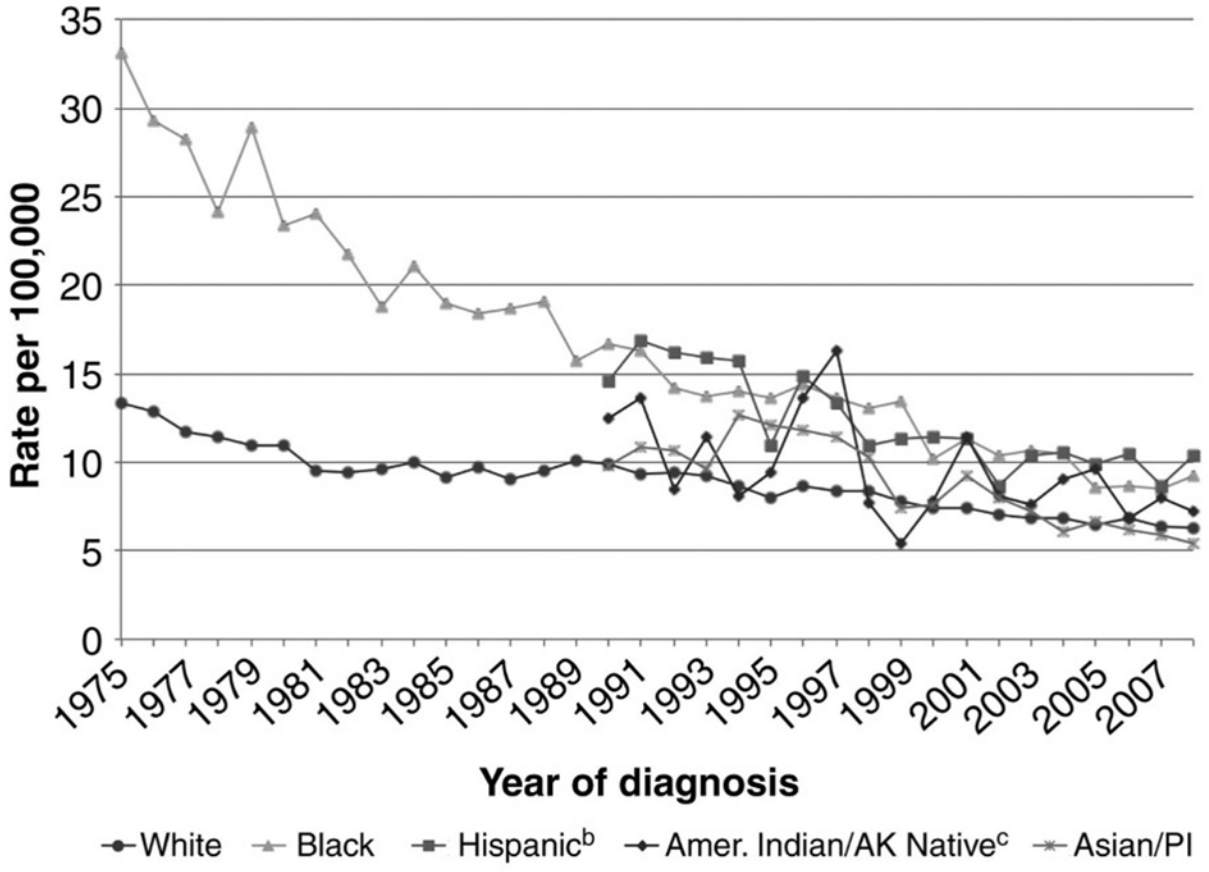
Ranks 18th cancer in women

100,000 Tx'd for Precancer

WHO Health Topics cervical Cancer Nov 2023
Fontham et al. CA: Cancer J Clin. 70,5 2020

Screening Prevents Cervical Cancer

Since screening has been introduced in the United States, the rate of cervical cancer has decreased by 80%.



Pierce Campbell CM, et al. Prevention of invasive cervical cancer in the United States: Past, present, and future. *Cancer Epidemiology, Biomarkers & Prevention*. 2012;21(9):1402–8.

Peto J, et al. The cervical cancer epidemic that screening has prevented in the UK. *Lancet*. 2004;364(9430):249-56.

Management Guidelines: *We've come a long way…. or have we?*

- **1980s Class system: I II III IV and V**
- **1990s Bethesda System: 3 revisions, ASC-US thank you much**
- **2000 Liquid Based Cytology**
- **2003 ALTS data released**
- **2006 ASCCP incorporates HPV management**
- **2011 ASCCP/ACS/ASCP & USPSTF guidelines**
- **2014 FDA approval HPV for primary screening**
- **2015 ASCCP/SGO Interim Guidance for HPV**
- **2016 ACOG endorsed SGO guidelines**
- **2018 USPSTF includes Primary HPV screening**
- **2020 ASCCP "risk based" guidelines**

Additional changes

- Start pap screen w/ sexual debut, 3 yrs after, 18, 20, 21.
- Stop screening 65 or Hysterectomy and no Hx HSIL in low risk population with appropriate screening
- Extended screening intervals 2, 3 and 5 yrs

- Now recommend Primary HPV screening
  - Not HPV only
  - “Reflex Cytology and genotyping”

Traditional fixed cytology slide vs. Liquid Based Cytology

- Historically “old fashioned pap smear” performed well, decreased Cx Ca rates and morbidity 80%
- New liquid-based technology improved screening performance
  - Sensitivity
  - Unsatisfactory/obscured result
  - Readability and efficiency
- In hindsight conventional pap not as sensitive as proposed
- Improved performance with frequent screening
- Splitting hairs? ***Something > Nothing, Any Screen > No Screen***

Risks for Cx CA?

- Early sexual activity, exposure to HPV
- Multiple partners
- HPV infected partners
- No condoms
- Immune compromised
- Lack of vaccine
- Smoking

- Length of time since last pap
- No pap Hx

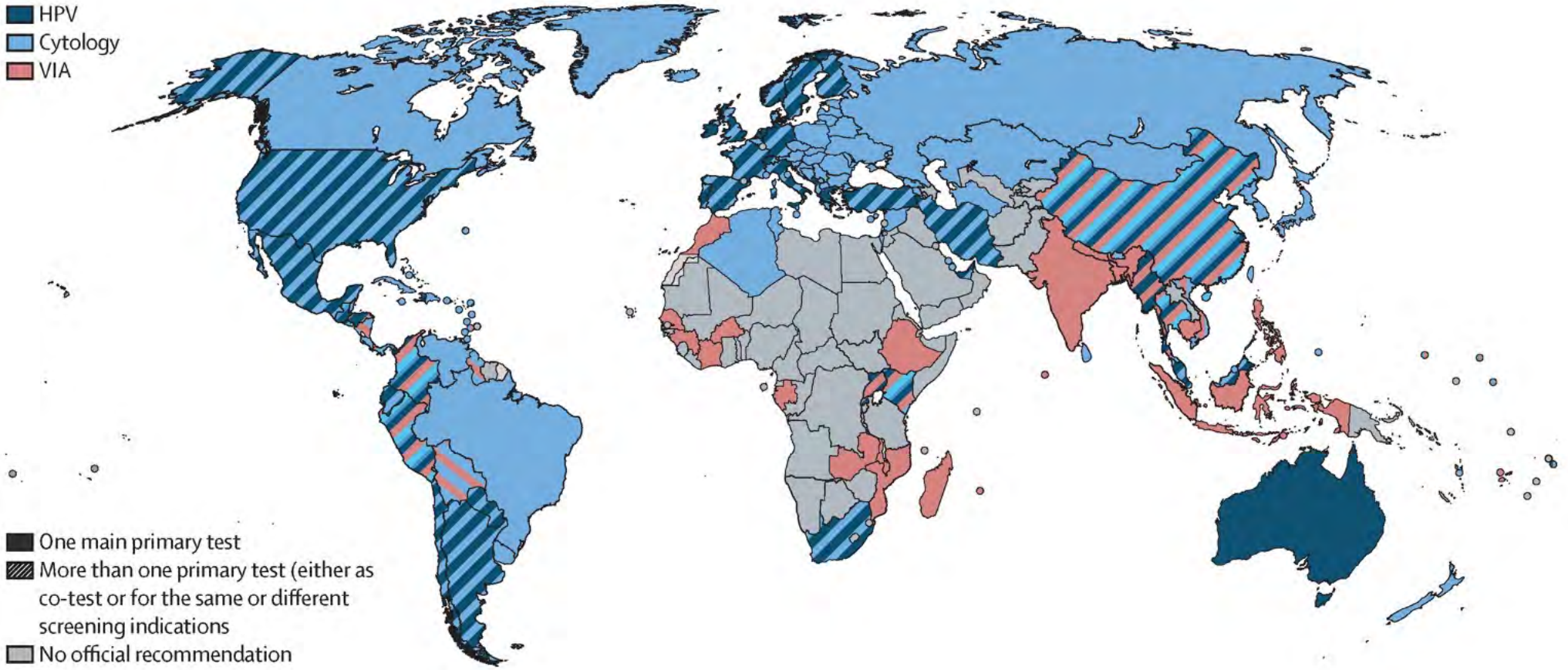
Who recommends Primary HPV Screening?

- **ACS 2020 Outright recommendation Primary HPV Screening Preferred**
- Support/Endorse
  - ASCCP "Supports ACS guidelines. Recognizes the need to transition to Primary HPV Screening"
  - ACOG "ACOG, ASCCP, SGO advise Primary HPV screen may start 25 but initiate Cx CA screen at 21"
  - SGO
  - USPSTF
  - AAFP
  - WHO
  - FIGO
  - ASCO

ASCCP Cx CA Screening Task Force. Jrnl Low Gen Tract Dis. 25,3,July 2021
ACOG.org Cervical cancer Screening Guidelines April 2021

Countries that Recommend Primary HPV Screening

48/139 countries (35%) recommend primary HPV screening as of August 2022



Bruni L, et al. Cervical cancer screening programmes and age-specific coverage estimates for 202 countries and territories worldwide: a review and synthetic analysis. *Lancet Global Health*. 2022;10(8):E1115-E1127.

Cervical cancer screening recommendations from United States professional organizations*[1-6]

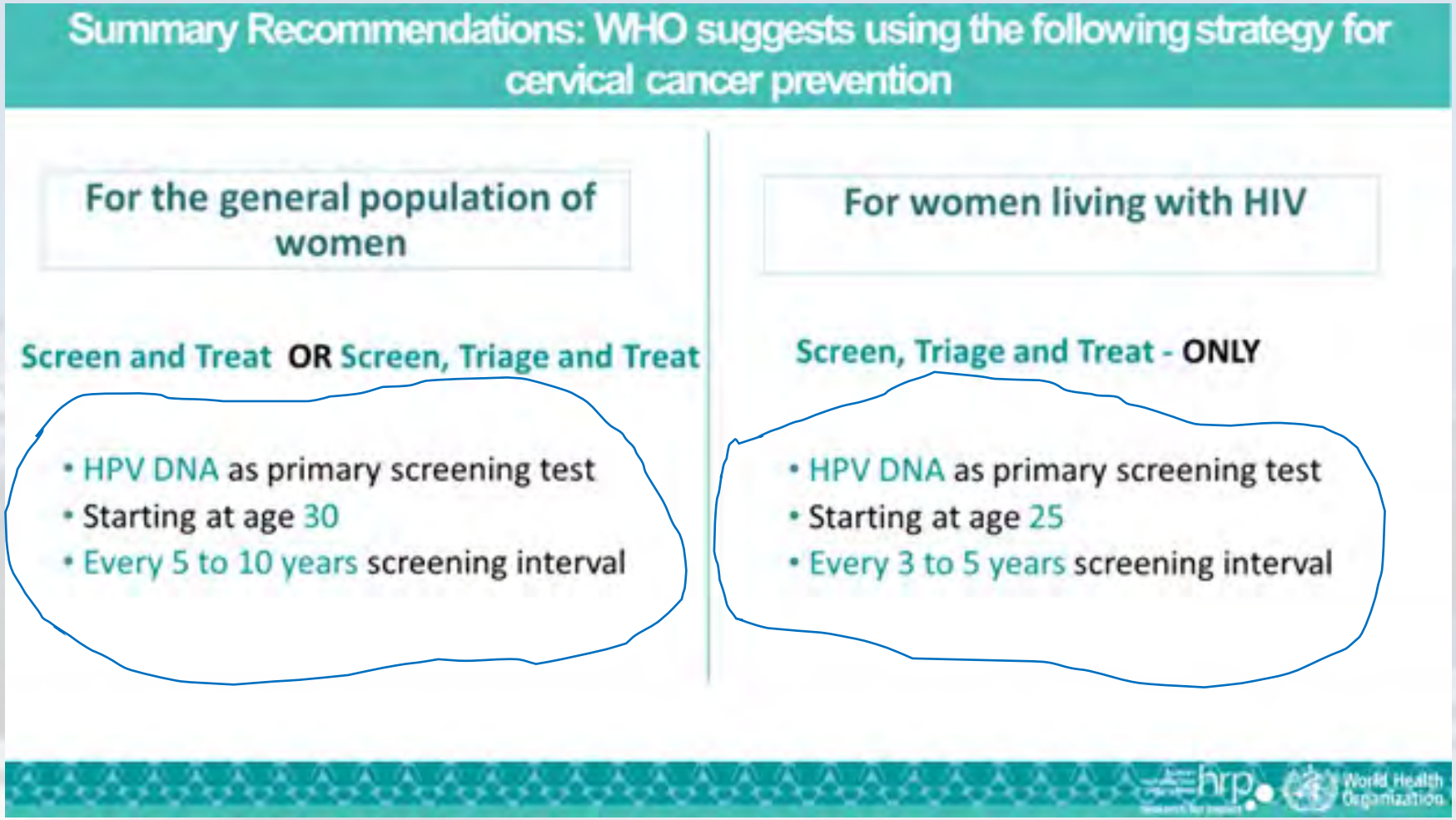
Organization	Age to initiate (years)¶	Age to discontinue (years)	Recommended screening test and frequency		Post-hysterectomy	HPV vaccination
In our practice, we use the following guidelines, in order of preference:						
USPSTF (2018)	21	65Δ	**Age 21 to 29 years** Pap test every 3 years	**Age ≥30 years** One of these methods: •Pap test every 3 years •Primary HPV testing◊ alone every 5 years •Co-testing (Pap test and HPV testing) every 5 years	Not indicated§	Same recommendations as unvaccinated patients
ACS (2020)	25	65¥	**Age ≥25 years** One of these methods: •Primary HPV testing◊ every 5 years (preferred) •Co-testing (Pap test and HPV testing) every 5 years •Pap test every 3 years		Not indicated‡	Same recommendations as unvaccinated patients
ACOG (2021)	21	65Δ	**21-29** pap test every 3 years	**≥30** One of these methods: •Pap test every 3 years •Primary HPV testing◊ alone every 5 years •Co-testing (Pap test and HPV testing) every 5 years	Not indicated§	Same recommendations as unvaccinated patients
ACP (2015)	21	65Δ	Pap test every 3 years	One of these methods: •Pap test every 3 years •Alternative: Co-testing (Pap test and HPV testing) every 5 years	Not indicated§	N/A
ASCCP/SGO (2015 interim guidelines)	21	N/A	Can consider primary HPV testing◊ every 3 years for patients age ≥25	Can consider primary HPV testing◊ every 3 years	N/A	N/A
ACS/ASCCP/ASCP (2012)	21¶	65†	Pap test every 3 years (preferred)	One of these methods: •Co-testing (Pap test and HPV testing) every 5 years (preferred) •Pap test every 3 years	Not indicated**	Same recommendations as unvaccinated patients

Curry SJ. Screening for cervical cancer: United States Preventive Services Task Force recommendation statement. JAMA 2018; 320:674.
Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. CA Cancer J Clin 2020.
Updated Cervical Cancer Screening Guidelines. The American College of Obstetricians and Gynecologists. Available at: www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/04/updated-cervical-cancer-screening-guidelines (Accessed on February 16, 2023).
Sawaya GF, Kulasingam S, Denberg TD, et al. Cervical Cancer Screening in Average-Risk Women: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med 2015; 162:851.
Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: Interim clinical guidance. Gynecol Oncol 2015; 136:178.
Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin 2012; 62:147.

2020 ACS Recommendations

	2020 ACS	2012 ACS	2018 USPSTF
Age 21–24	No screening	Pap test every 3 years	Pap test every 3 years
Age 25–29	HPV test every 5 years (preferred) HPV/Pap cotest every 5 years (acceptable) Pap test every 3 years (acceptable)	Pap test every 3 years	Pap test every 3 years
Age 30–65	HPV test every 5 years (preferred) HPV/Pap cotest every 5 years (acceptable) Pap test every 3 years (acceptable)	HPV/Pap cotest every 3 years (preferred) Pap test every 3 years (acceptable)	Pap test every 3 years, HPV test every 5 years, or HPV/Pap cotest every 5 years
Age 65 and older	No screening if a series of prior tests were normal	No screening if a series of prior tests were normal	No screening if a series of prior tests were normal and not at high risk for cervical cancer

WHO


Summary Recommendations: WHO suggests using the following strategy for cervical cancer prevention
For the general population of women
Screen and Treat OR Screen, Triage and Treat
• HPV DNA as primary screening test
• Starting at age 30
• Every 5 to 10 years screening interval
For women living with HIV
Screen, Triage and Treat - ONLY
• HPV DNA as primary screening test
• Starting at age 25
• Every 3 to 5 years screening interval
hrp
World Health Organization

Why Primary HPV Screen? *Advantages*

- HPV screening better sensitivity for CIN and CA compared to Cytology
- Objective, less labor, efficient throughput, reproducible
- Comparable sensitivity to Cotesting for detecting CIN and no difference for CA
- More efficient, fewer tests to detect same pathology, fewer exams
- Better detection glandular lesions
- Cost efficient (in the long run)

- Potential for self collection
- Potential improve access and reduce disparities
- Simpler algorithm

Einstein et al. ObGyn.142,5 Nov 2023.
Fontham et al. CA: Cancer J Clin. 70,5 2020

Why Not Cytology Alone? *Pros and cons*

- Cons
  - Costly, labor intensive and subjective
  - Requires skilled cytopathologists, shrinking pool
  - Decreased sensitivity requires increased frequency
- Pros
  - Better specificity than HPV
  - Additional infections- Yeast, trich, BV
  - Endometrial cells
  - Tadpoles
  - Confirm specimen adequacy. What if scant cellularity- trust negative HPV?

Einstein et al. ObGyn.142,5 Nov 2023.
Fontham et al. CA: Cancer J Clin. 70,5 2020

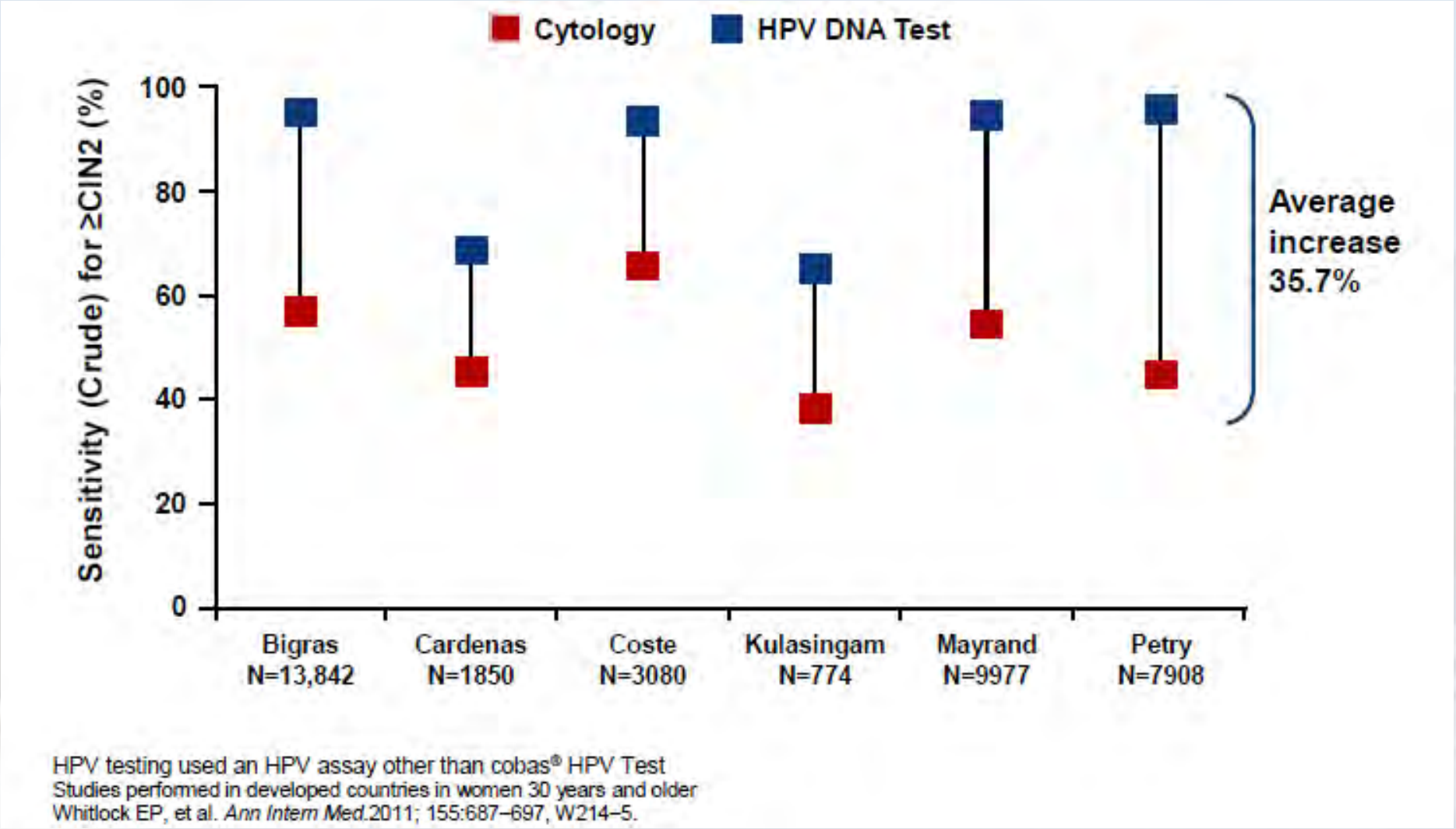
What About CoTesting? *Pros and cons*

- Pros
  - Improves specificity of HPV screen
  - Increase sensitivity of HPV screen (Any additional screening test increases sensitivity), by how much?
  - Detect Non-HPV tumors?
  - Provider and pt acceptability

- Cons
  - Increase test #
  - Increase costs

Einstein et al. ObGyn.142,5 Nov 2023.
Fontham et al. CA: Cancer J Clin. 70,5 2020

Sensitivity of Cytology vs. HPV to Detect HSIL Incident Disease



HPV testing used an HPV assay other than cobas® HPV Test
Studies performed in developed countries in women 30 years and older
Whitlock EP, et al. *Ann Intern Med.*2011; 155:687–697, W214–5.

Far Fewer Cases of CIN3+ over 6 Years in Women Screened with HPV-based Tests than Cytology

Cytology vs. HPV to Detect Future HSIL Disease

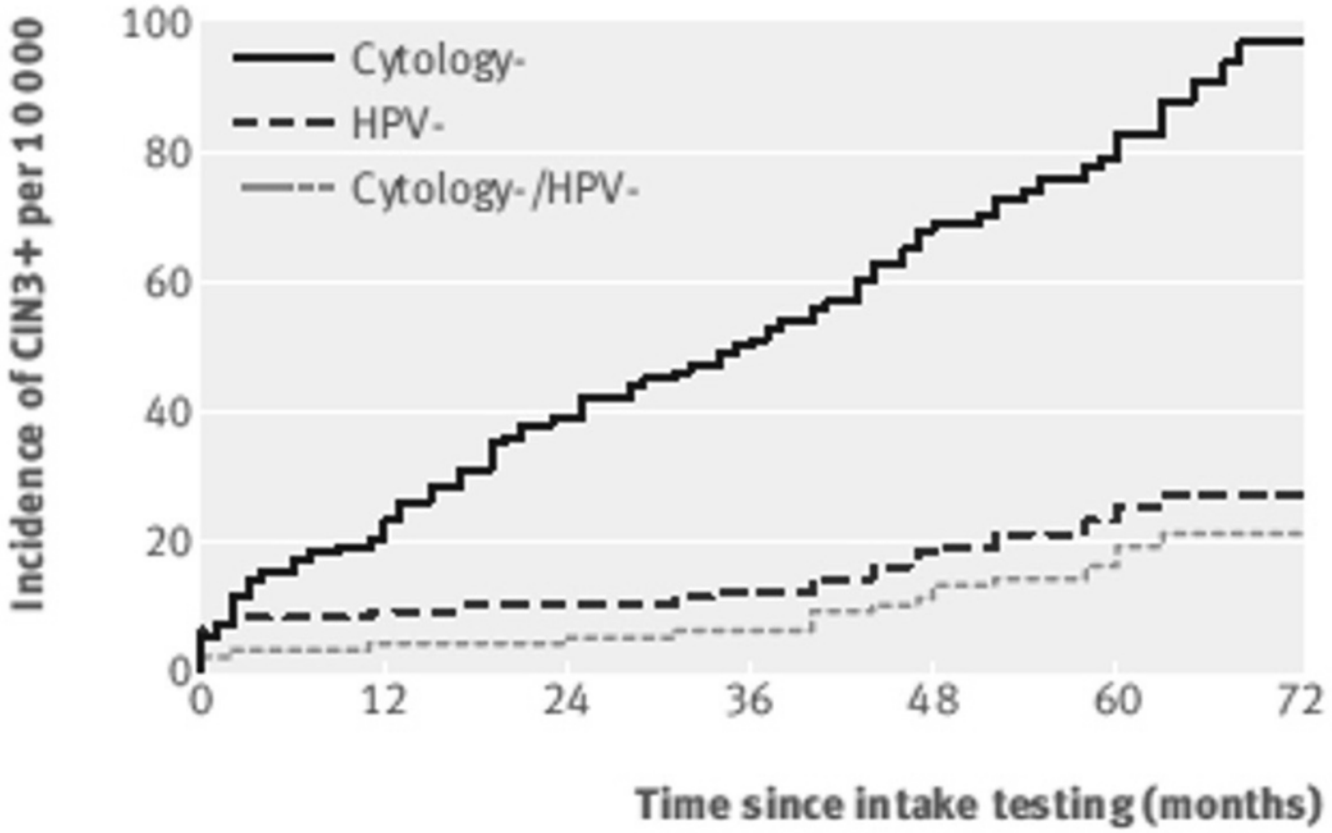


Fig 2 | Kaplan-Meier plots of cumulative incidence rate for CIN3+ for women according to baseline test results in first 72 months of follow-up, excluding Denmark and Tübingen

Dillner J, et al. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: Joint European cohort study. *BMJ.* 2008;337:a1754.

Primary HPV Screening Compared to Cotesting

Primary HPV screening results in similar reduction in cancer rates compared to cotesting, with far fewer tests.

Strategy	Total Tests	Colpos	CIN 2,3	Cancer Cases	Cancer Deaths
No screening	0	0	0	18.86	8.34
Cyto q 3 y age 25-65	13,313	564	142	2.60	0.86
Cyto q 3 y from age 21 then Co-test q 5 y age 30-65	19,806	1,630	201	1.08	0.30
HPV q5 y age 25-65	10,954	1,775	195	0.94	0.28

*Per 1,000 persons with a cervix, screened over a lifetime

Fontham ETH, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2020;70(5):321-346.

Primary HPV Screening is the Most Cost-Effective Approach

Screening Modality	Cases of CIN3+ Detected	Number of Colposcopies	Cost
Primary HPV Screening	294	2422	$3.47 M
Primary Cytology	285	2966	$4.80 M
Cotesting	308	2988	$5.85 M

Modeling study based on 99,549 patients with cotesting followed over 3 years.

Jin XW, et al. Cost-effectiveness of primary HPV testing, cytology and co-testing as cervical cancer screening for women above age 30 years. *J Gen Intern Med.* 2016;31(ii):1338-1344.

Limitations for Primary HPV Screening

- Decreased specificity
- Change in workflow, Implementation challenges, initial costs
- Requires specific laboratory testing, 3 FDA approved platforms
  - Roche Cobas®
  - BD Onclarity ™
  - Abbott Alinity m
- Liquid based, Workflow depends on lab, Clinicians coordinate with labs
- Coding and EMR adaptation
- Patient Provider satisfaction

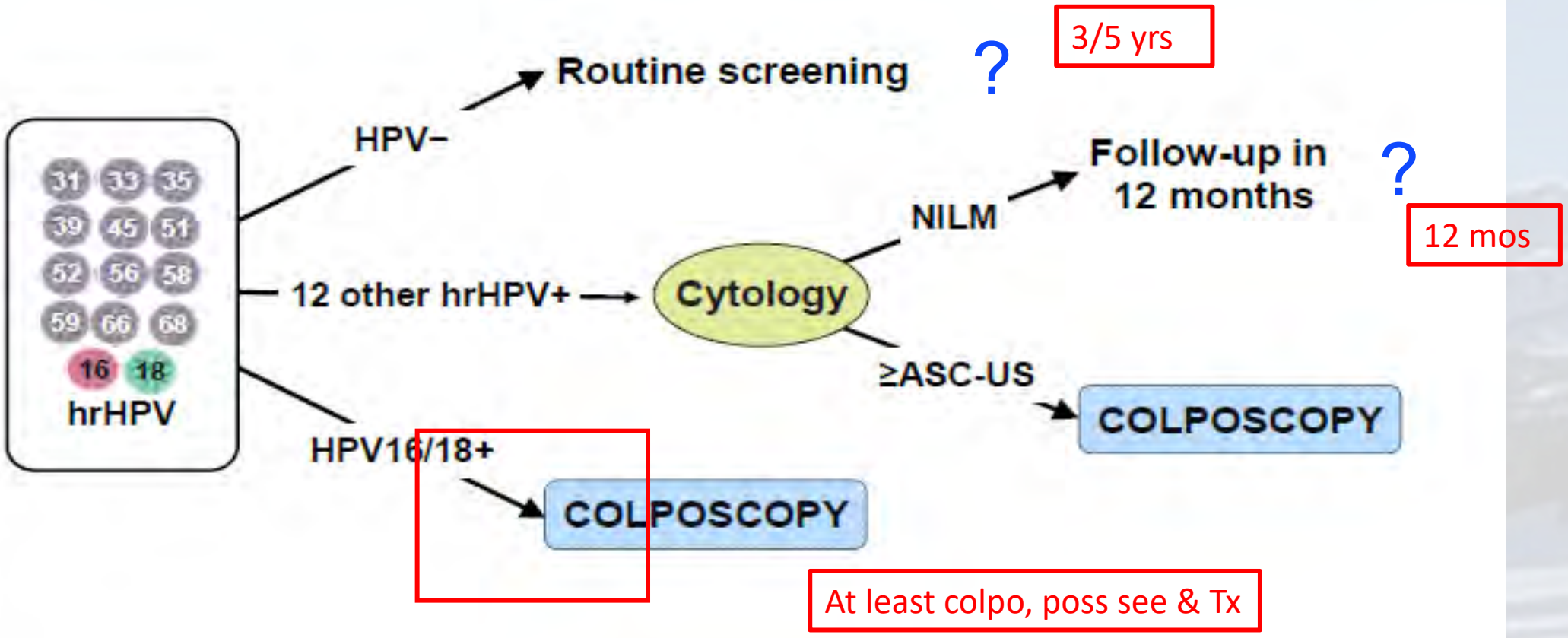
Primary HPV

- Very good test to eliminate pts from close surveillance
- good test for screening pts to identify those at risk of significant dysplasia or cancer

- Not so good at specifically identifying pts needing treatment

- Need additional testing to decide who needs further evaluation and management

Primary HPV Screening – Candidate
HPV with 16/18 Genotyping and Reflex Cytology



hrHPV=high risk HPV

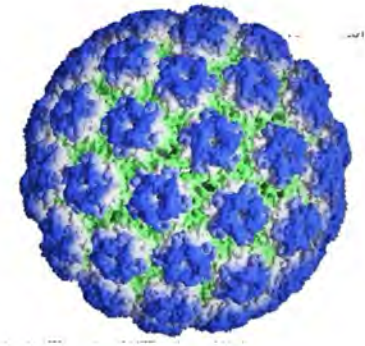
Huh et al. GynOnc. 136, 2015

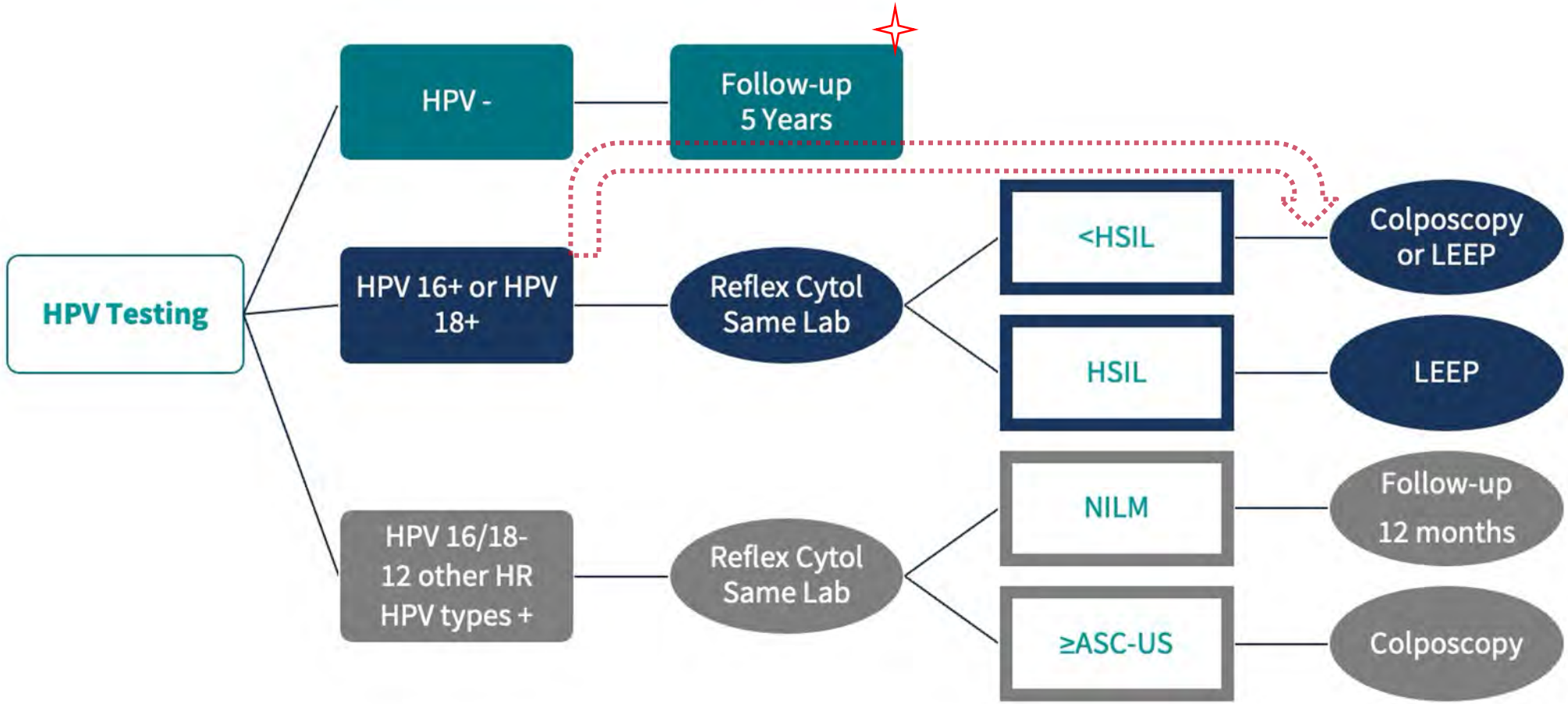
HPV as Primary Screening: SGO/ASCCP Interim Guidelines

- **Initiate at 25**
- **With negative results rescreen no sooner than 3 yrs**
- **Stop at 65 if appropriately screened and negative**
- **Roche COBAS® only system approved originally- now BD and Abbott**
- **Not for use in women s/p hysterectomy**
- **No guidance for immunocompromised or HIV+**
- **How screen HPV+ (Other/Intermediate) but negative 16/18 w/ normal cytology in 12 mos? CoTest reasonable**

Huh et al. GynOnc. 136, 2015

Algorithm for Primary HPV Screening





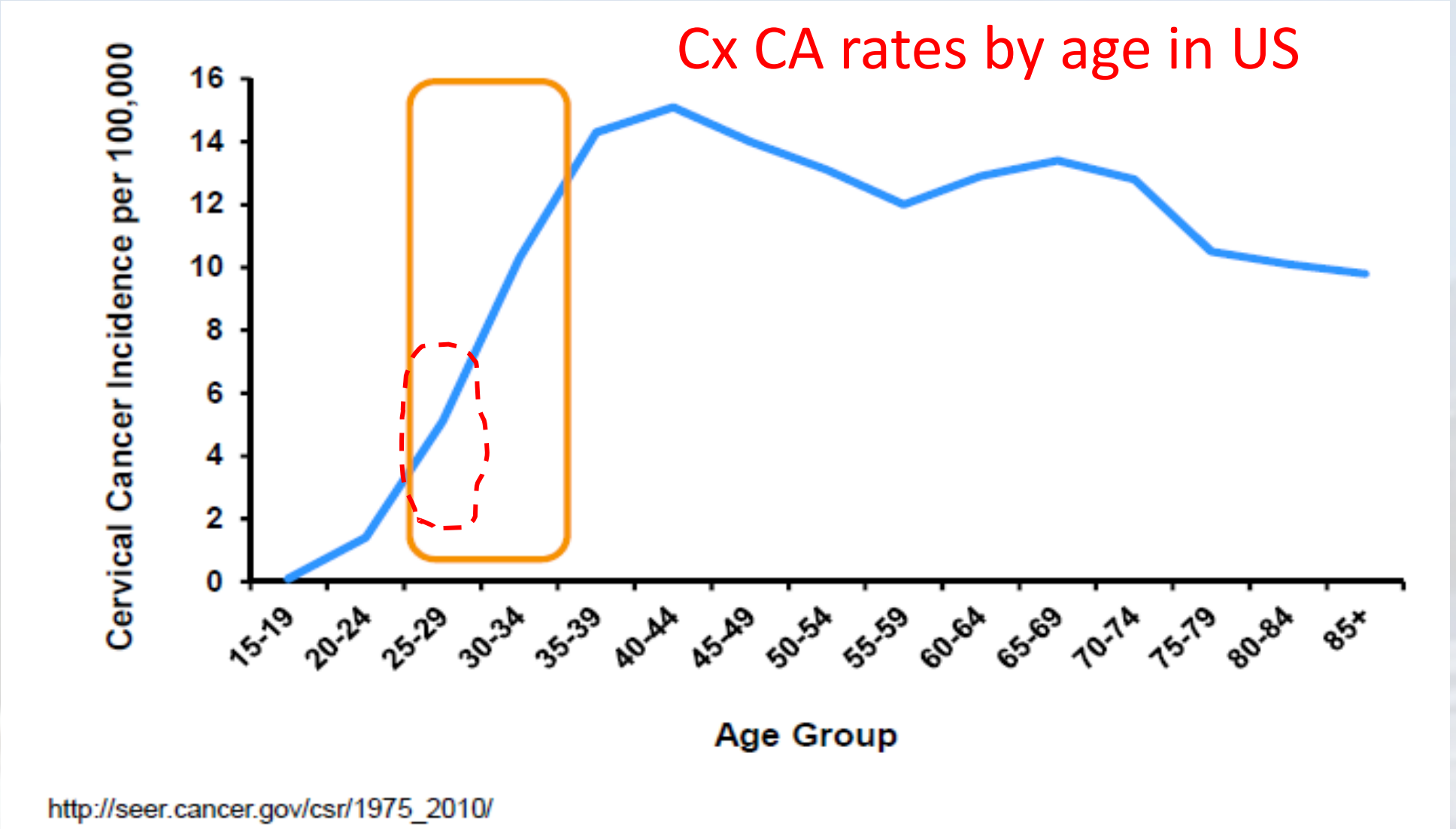
Huh WK, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: Interim clinical guidance. *Obstet Gynecol*. 2015;125(2):330-337.

Perkins RB, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. *J Low Genit Tract Dis*. 2020;24(2):102-131.

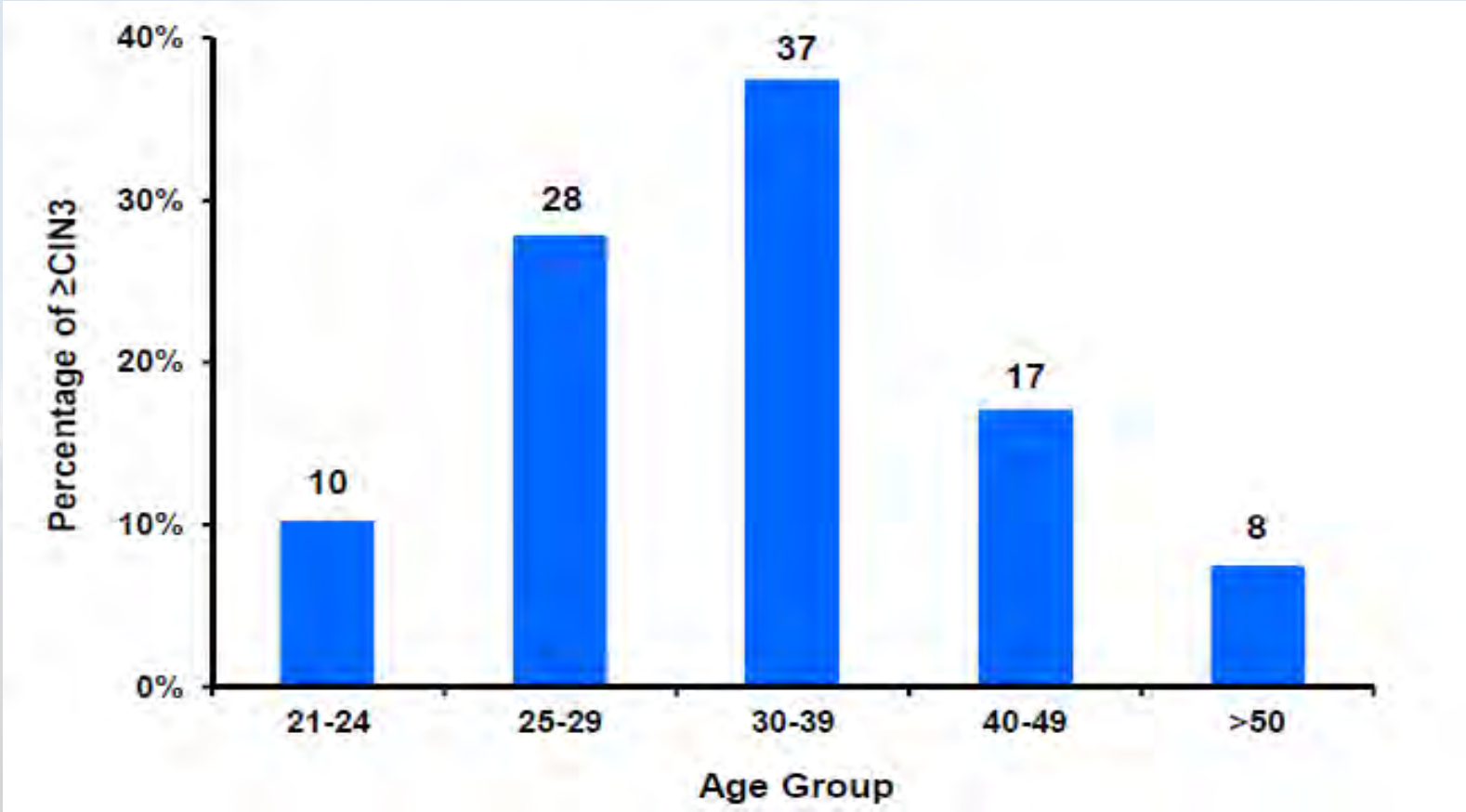
Reflex Cytology for All HPV Tests

- If reflex cytology not available Colposcopy recommended for + 16 or 18
- 16 and 18 pose greatest risk of CIN III so additional procedures recommended (Colposcopy with bx for NILM and Low-Grade Cytology and + 16 or 18 and Tx for HSIL cytology which is + HPV 16) Action threshold exceeds 60% for CIN III therefore expedited Tx recommended
- If reflex cytology not available from HPV sample then collecting cytology at colposcopy recommended. If HSIL still consider Excision even if Bx not HSIL

When start screening?



Rate of CIN III or Greater by Age in ATHENA



Percentages shown are for hrHPV+ women with ≥CIN3, N=252
Huh W, et al. 27th International Papillomavirus Conference, Berlin, Germany, September 17–22, 2011, OP-229.

Wright et al. *Am J Obst Gynecol*, 2011.

What next? *If Hx any indication 1^0 HPV aint the last stop*

- Dual Stain p16/Ki-67
  - Indicator of cell dysregulation
  - Improved sensitivity and reproducibility compared with cytology
  - Improved specificity combined with HPV typing vs. CoTesting
  - Very high NPV
  - Automated, could lead to completely molecular pap
- Extended Genotyping
  - e.g. 16, 31, 18, 33/58, 52, 45, 51 (Roche) 16, 18, 45, 31/33/52/58 (Abbott)
  - Predicts HSIL lesions with good sensitivity and specificity
  - Persistent and multiple HPV infection increases risk for dysplasia and progression
- DNA Methylation
  - Biomarker for clinically relevant HPV infection
  - Methylation accumulation can predict risk for progression to HG disease
  - >sensitivity cytology, < CoTest, but > specificity than both. Needs validation

Einstein et al. ObGyn.142,5 Nov 2023

What next?

- Self-Sampling
  - Gaining popularity in Europe and Australia
  - Similar performance to clinician obtained specimen
  - Reduce barriers to screening
  - NCI SHIP Trial across US representing racial, socioeconomic & ethnic diversity

- What about vaccinated populations?
  - No current recs
  - Evidence of decreased HPV, dysplasia and cancer
  - Test performance changes significantly with decreasing prevalence
  - PPV of cytology declines significantly

Self-collection

- Not yet FDA approved in US
- Multiple effectiveness studies and patient acceptability studies have shown that self-collection is effective, is cost-effective and is acceptable to women, especially among under-screened populations
  - Sensitivity comparable to clinician-obtained samples with PCR-based HPV tests.
  - A positive test requires a physician collected specimen for triage

Arbyn M, et al. Detecting cervical precancer and reaching underscreened women by using HPV testing on self-samples: Updated meta-analyses. *BMJ*. 2018;363:k4823

Bottom line

- Primary HPV screening works comparably to CoTesting
- Less complicated
- Potentially fewer exams and tests
- Potential to increase access and improve patient participation- Self collection.
- Can be cost efficient
- Need transition and preparation before widely available
- Any screen is better than no screen
- If you don’t like (like) the weather……. Just wait a minute


Thank you
Safe travels
&
Looking forward to the 50th!
See you then

University of Colorado **Anschutz Medical Campus**

Postpartum Laceration Complications and Management

Lauren G. Rascoff, MD
Division of Female Pelvic Medicine and Reconstructive Surgery

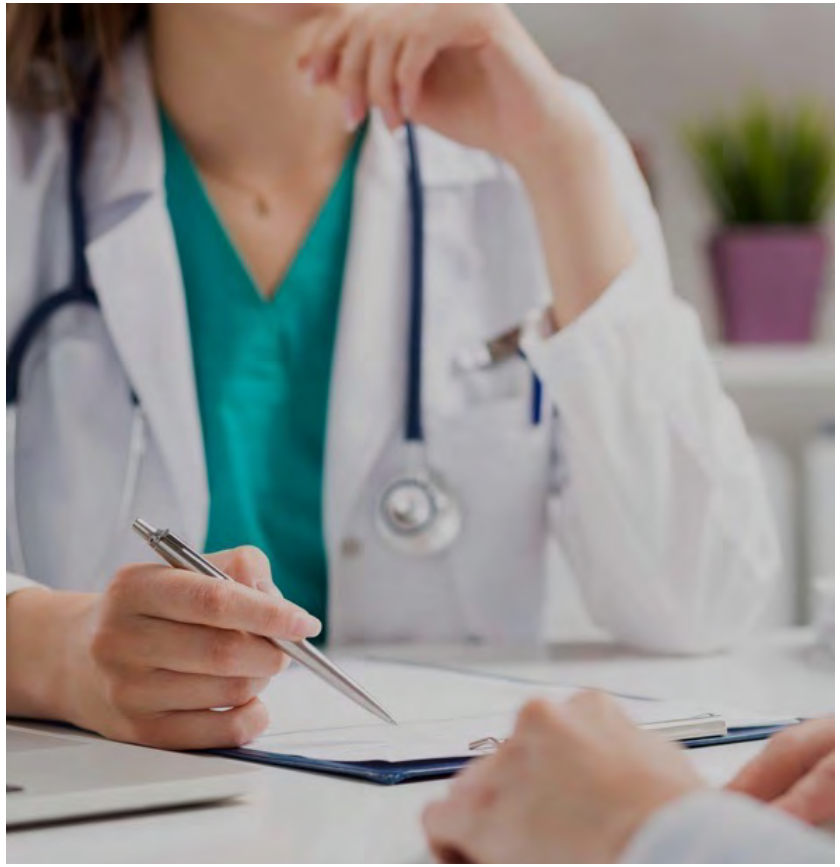
I have nothing to disclose

Learning Objectives

1) Identify the incidence of OASIS tears and the association of OASIS and pelvic floor disorders

2) Understand postpartum pelvic floor complications in the immediate postpartum period

3) Understand management of postpartum pelvic floor complications



Incidence of OASIS injuries

Overall OASIS risk: 6.3%

Risk of OASIS in the first delivery: 5.7%

Risk in parous women with no previous OASIS: 1.5%

Risk factors for OASIS Injuries

- Vaginal delivery
- Operative vaginal delivery
- Episiotomy
- Fetal macrosomia
- Prolonged second stage
- Fetal occiput posterior presentation
- Increasing maternal age

Operative vaginal delivery

- Forceps is associated with a greater risk of OASIS than vacuum delivery, but the data are conflicting
- In one study, OASIS occurred in 24% of vacuum-assisted deliveries compared to 4% NSVD
- In a study of over 100,000 spontaneous vaginal deliveries, OASIS occurred in 8.6% of forceps deliveries, 3.7% of vacuum-assisted vaginal deliveries, and 1.3% of NSVD
- Small cohort studies have reported the diagnosis of delayed OASIS in over 80% of women with forceps-assisted deliveries

Oasis injuries and pelvic floor disorders

OASIS increases the risk of subsequent loss of bowel control

Studies have reported postpartum fecal incontinence rates up to 28% in women with OASIS, compared with rates of 1 to 10% for women delivered without OASIS

Additional long-term sequelae

- Perineal pain
- Dyspareunia
- Defecatory dysfunction
- Urinary incontinence

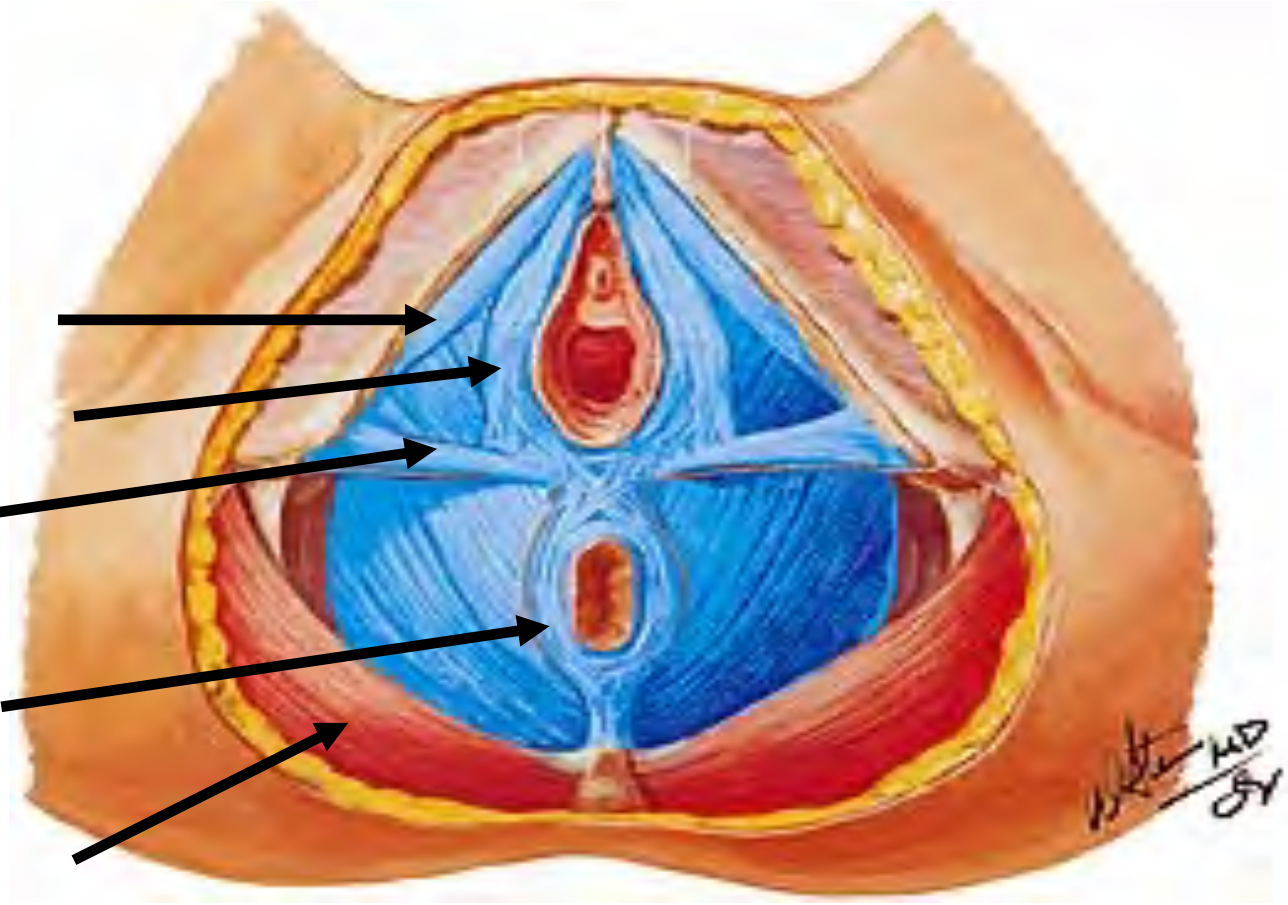
Prognosis

For women with primary OASIS, the risk of repeat OASIS in a future vaginal delivery is approximately 3 to 5%

Women with two prior OASIS have been reported to have a 10-fold increased risk for sphincter injury in next pregnancy

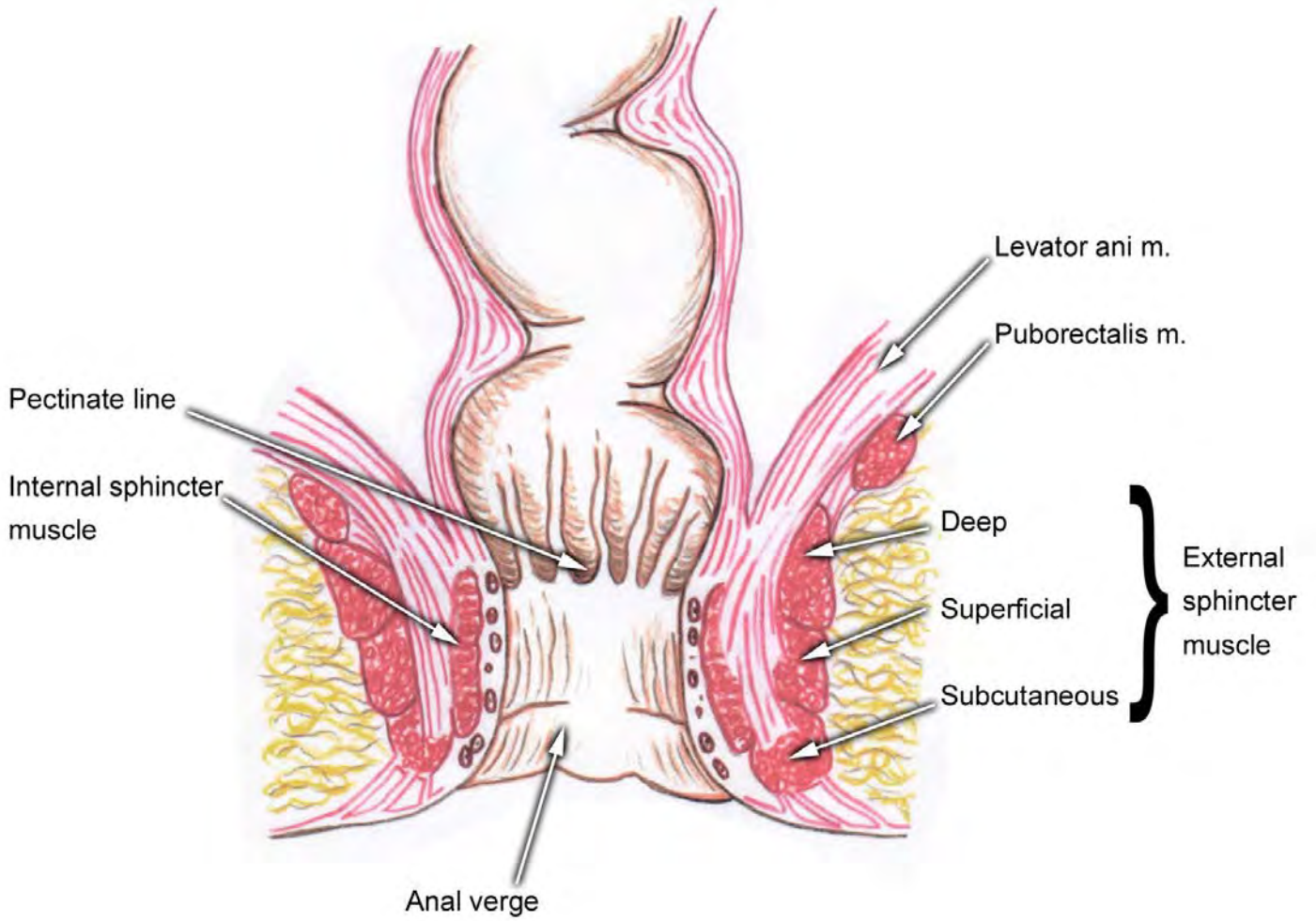
Pelvic floor muscles!

- Ischiocavernosis
- Bulbocavernosus
- Transverse perineii
- External anal sphincter
- Gluteus maximus



Anorectal Anatomy!

Internal anal sphincter is responsible for 85% of continence



Perineal Lacerations

Box 1. Classification of Perineal Lacerations

First degree: Injury to perineal skin only

Second degree: Injury to perineum involving perineal muscles but not involving anal sphincter

Third degree: Injury to perineum involving anal sphincter complex

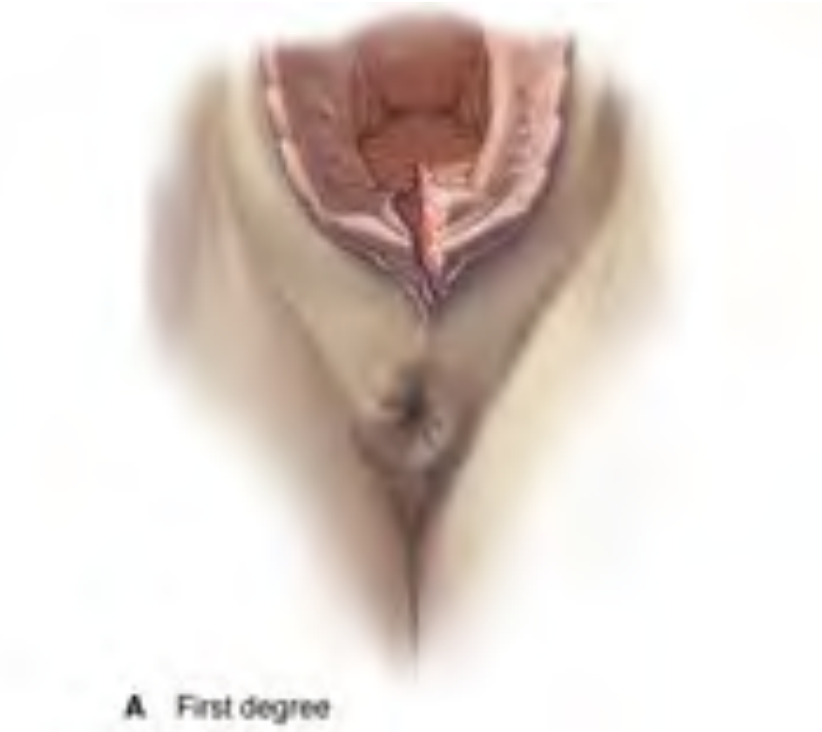
- 3a: Less than 50% of external anal sphincter thickness torn
- 3b: More than 50% external anal sphincter thickness torn
- 3c: Both external anal sphincter and internal anal sphincter torn

Fourth degree: Injury to perineum involving anal sphincter complex (external anal sphincter and internal anal sphincter) and anal epithelium

Modified from American College of Obstetricians and Gynecologists. Obstetric data definitions (version 1.0). Washington, DC: American College of Obstetricians and Gynecologists; 2014. Available at: http://www.acog.org/-/media/Departments/Patient-Safety-and-Quality-Improvement/2014reVITALizeObstetricDataDefinitionsV10.pdf. Retrieved April 29, 2016. ⇦

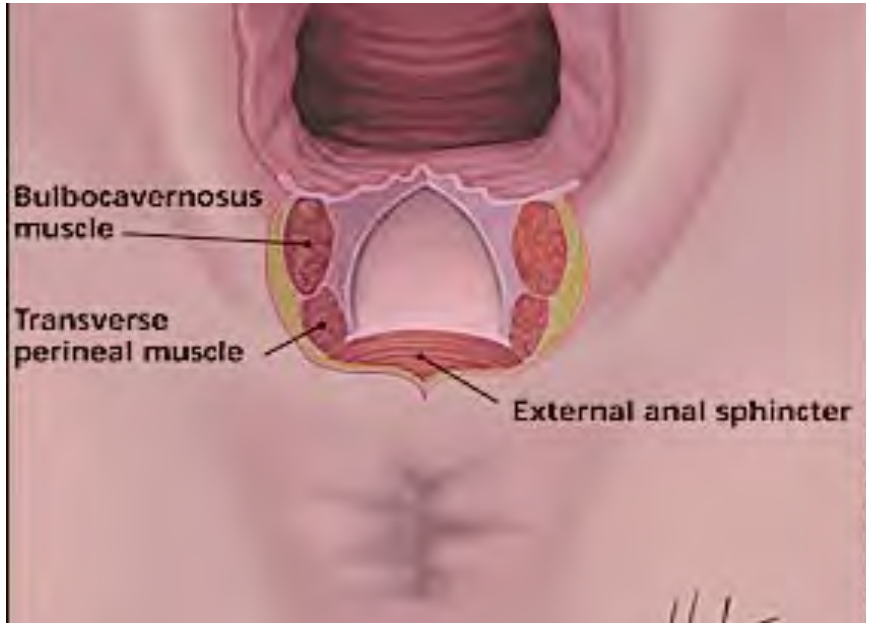
First degree laceration

Laceration of the vaginal epithelium or perineal skin only



Second degree laceration

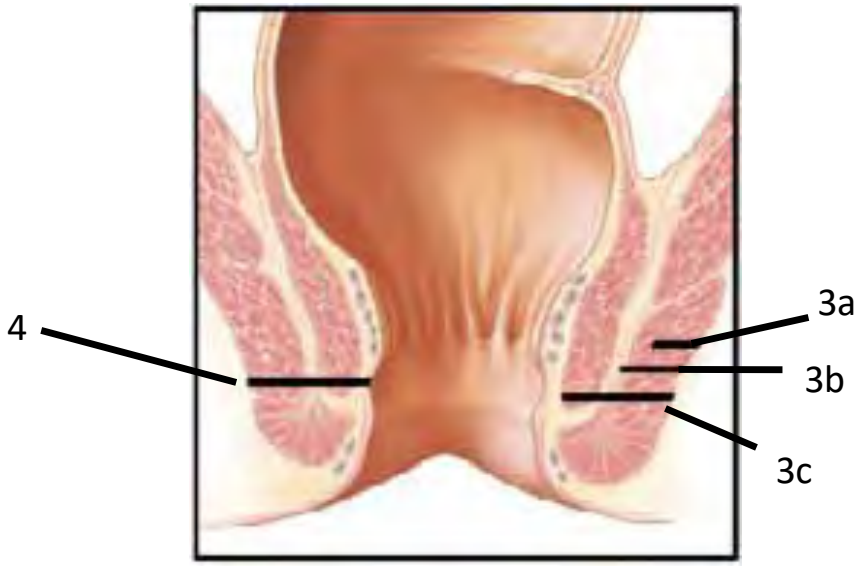
Laceration of the perineal muscles, but not the anal sphincter complex



Third degree laceration

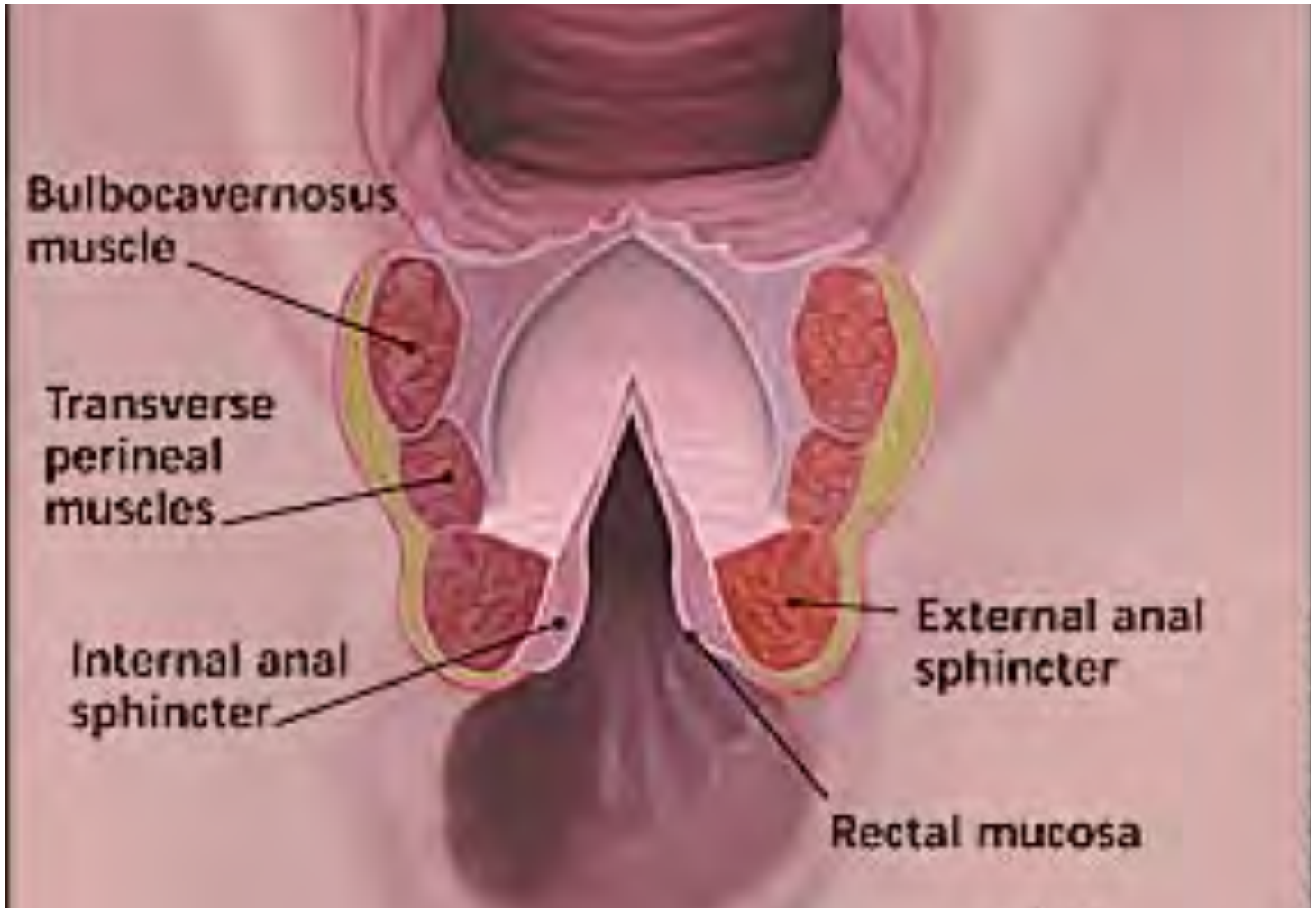
Disruption of the anal sphincter muscles

- 3a – <50% thickness of EAS
- 3b – >50% thickness of EAS
- 3c – IAS also involved



Fourth degree laceration

Disruption of the anal sphincter complex with involvement of the anal epithelium



Immediate repair versus delayed repair after delivery

Factors that may favor waiting 8-12 hours to repair…

- Lack of anesthesia services
- Lack of OR availability
- Inadequate training of OB provider

In one study, women were randomly assigned to immediate repair or delayed repair. Rates of fecal incontinence at 1 year were comparable

Antibiotics – recommendations from ACOG

01

In a randomized controlled trial in which patients received a single dose of a second-generation cephalosporin versus placebo, there were significantly lower rates of postpartum wound complications at 2 weeks (8% versus 24%, P=.04)

02

A single dose of antibiotic at the time of repair is recommended in the setting of OASIS

03

Unclear if patients need oral dose after repair

Aseptic technique during initial repair

May be the most important factor to prevent breakdown

In one study, aseptic technique at the time of initial repair with povidone-iodine powder was associated with decreased risk of breakdown – 3.5% vs. 13.5%

The 2007 National Institute for Health and Clinical Excellence guidelines as well as the Royal College of Obstetricians and Gynaecologists recommend using aseptic techniques during perineal repair

Perineal care after OASIS injury to prevent infection and/or breakdown

- Hygiene
- Pain management
- Constipation prevention
- Delay of sexual activity

When to see patients postpartum?

Expert opinion recommends close follow up: 1-2 weeks postpartum

Our practice routinely see all patient with OASIS injuries without breakdown at 8 weeks postpartum and immediately if they have a breakdown

Role of pelvic floor physical therapy

Pelvic floor physical therapy has been shown to improve urinary and fecal incontinence at 12 months postpartum

The addition of biofeedback physiotherapy has been suggested as a way to improve motor and sensory function

We routinely refer postpartum patients with a history of OASIS injury to pelvic floor physical therapy at 8 weeks postpartum

Now onto cases…

31 year old 11 days s/p NSVD complicated by a 3c laceration presents for a perineal check to her OB

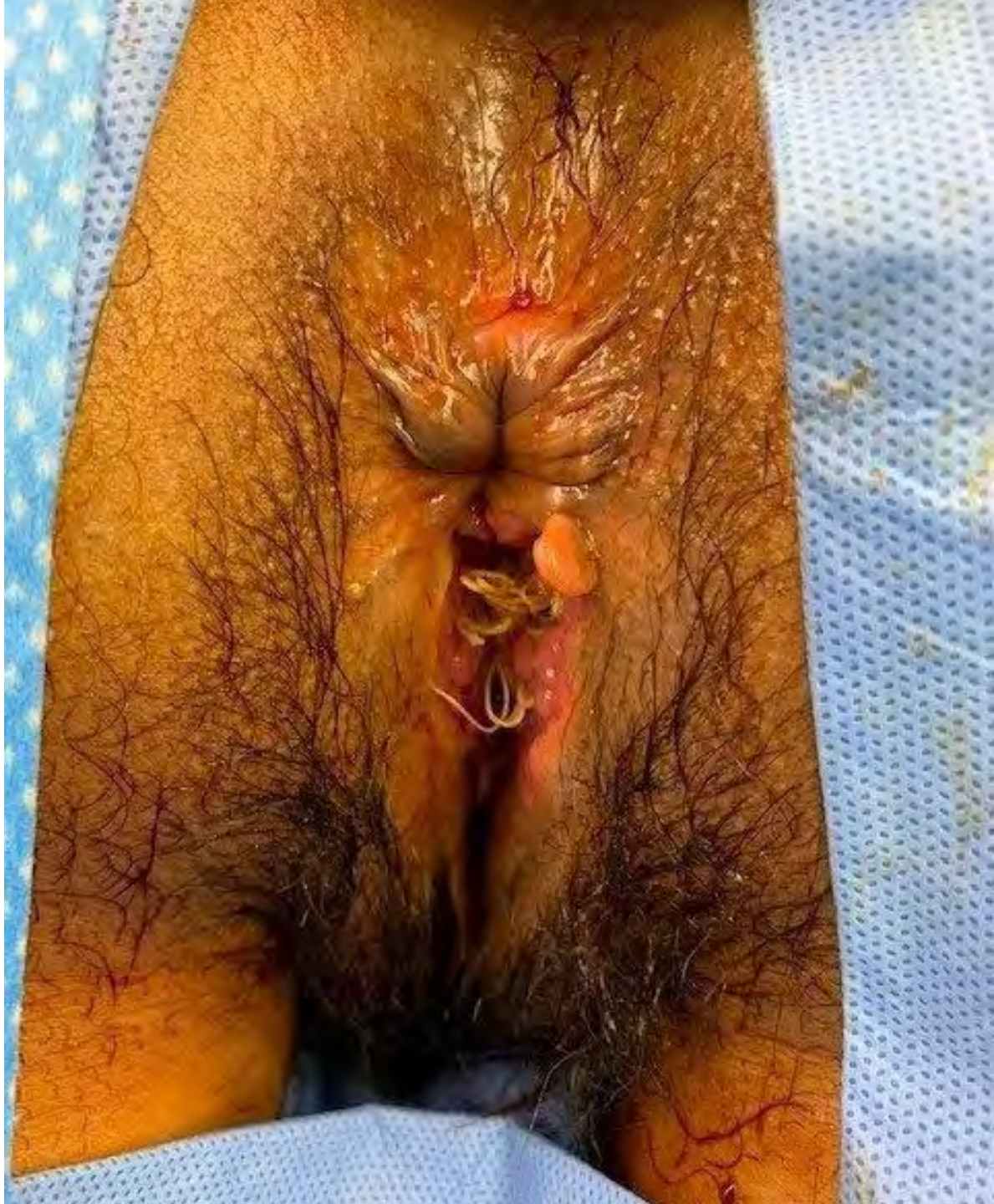
Patient states she felt “a pop down there”

No fevers at home, no foul-smelling discharge

Exam shows breakdown of her perineal laceration

3c breakdown 11 days postpartum

Preoperative



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Risk of wound complications following OASIS injury

- **25%** - wound breakdown
- **20%** - wound infection
- Most complications occur in the first 2 weeks

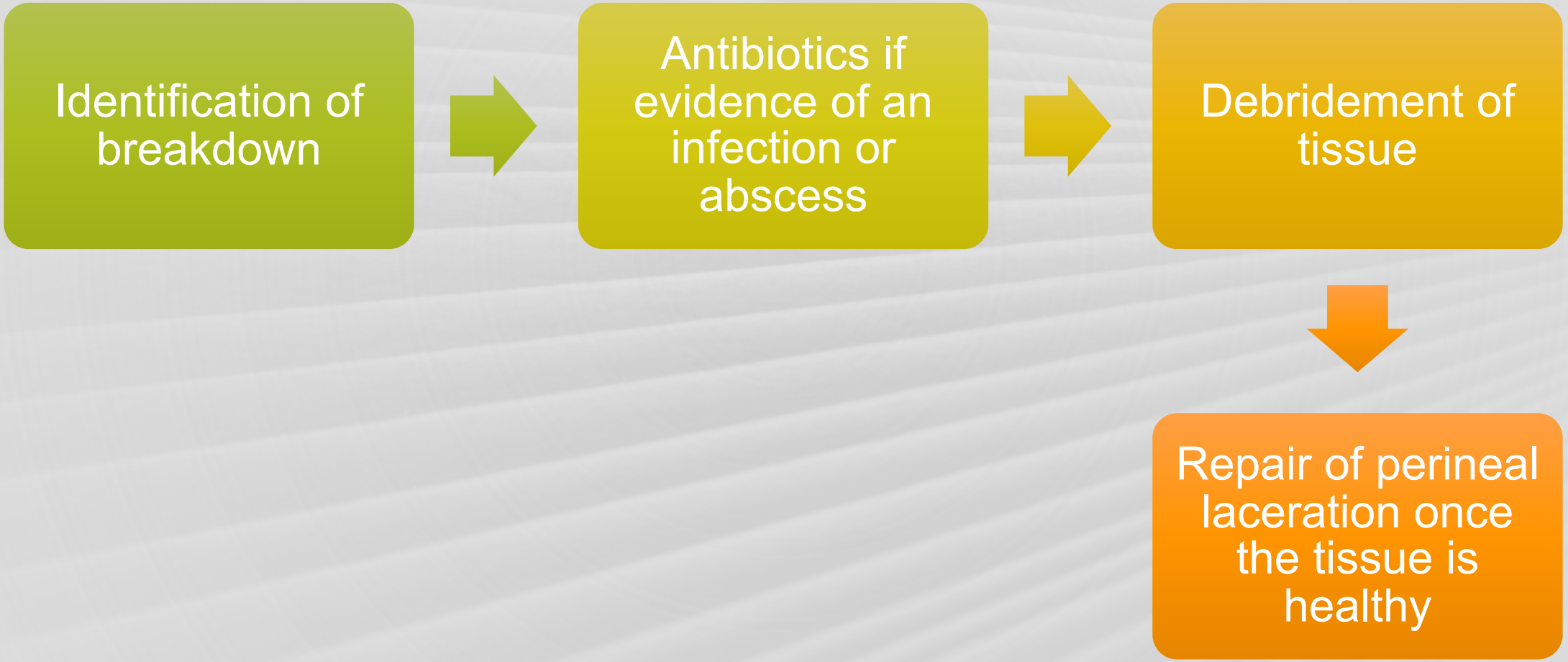
Risks factors for perineal laceration breakdowns

- Infection is the biggest risk factor
- Hematoma (usually occurs within 24 hours of delivery)
- Operative vaginal delivery
- Sexual activity

Symptoms requiring evaluation

- Severe pain
- Foul smelling discharge
- Fecal incontinence

Approach to repair of perineal laceration breakdown



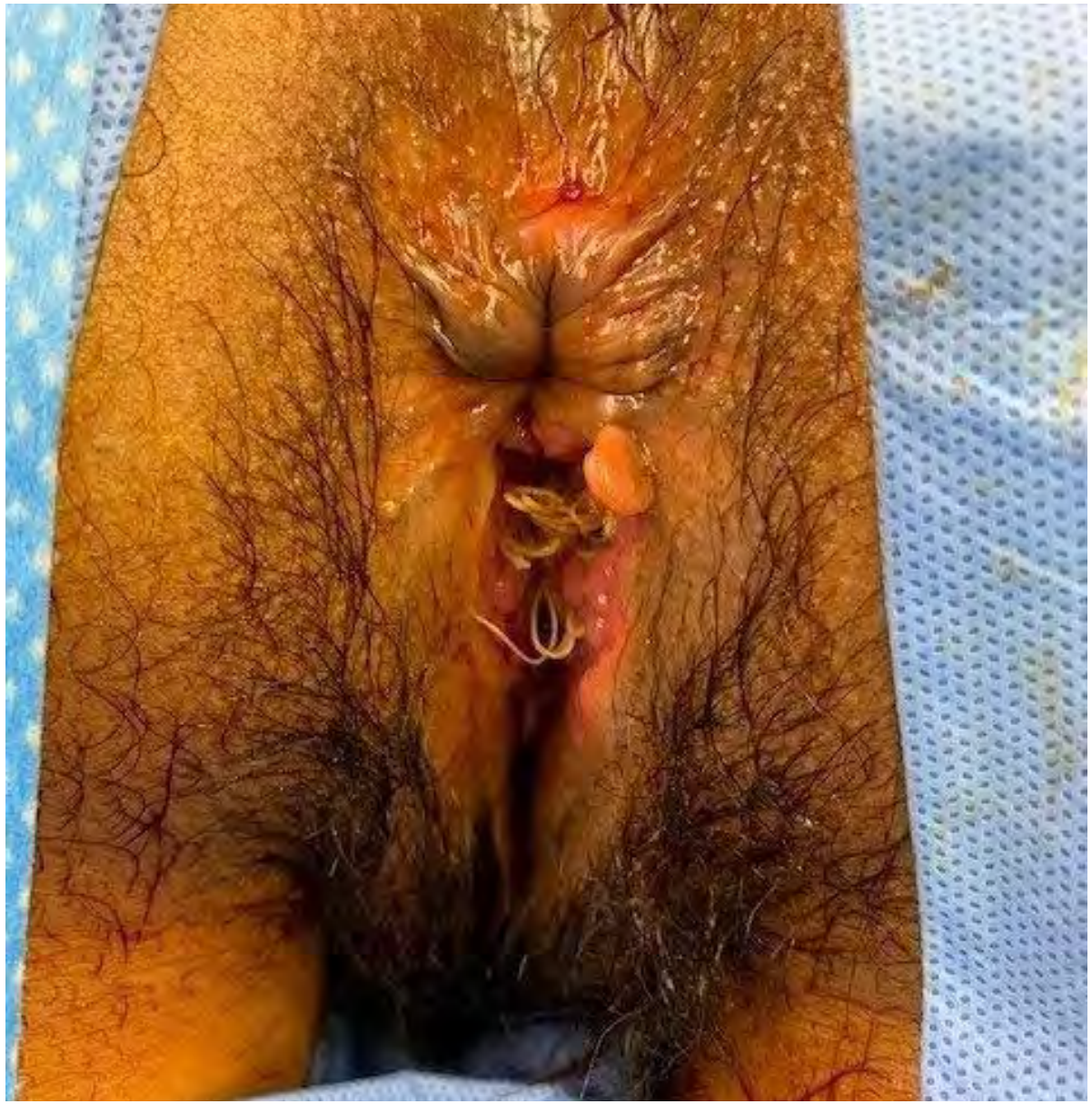
Timing of Repair?

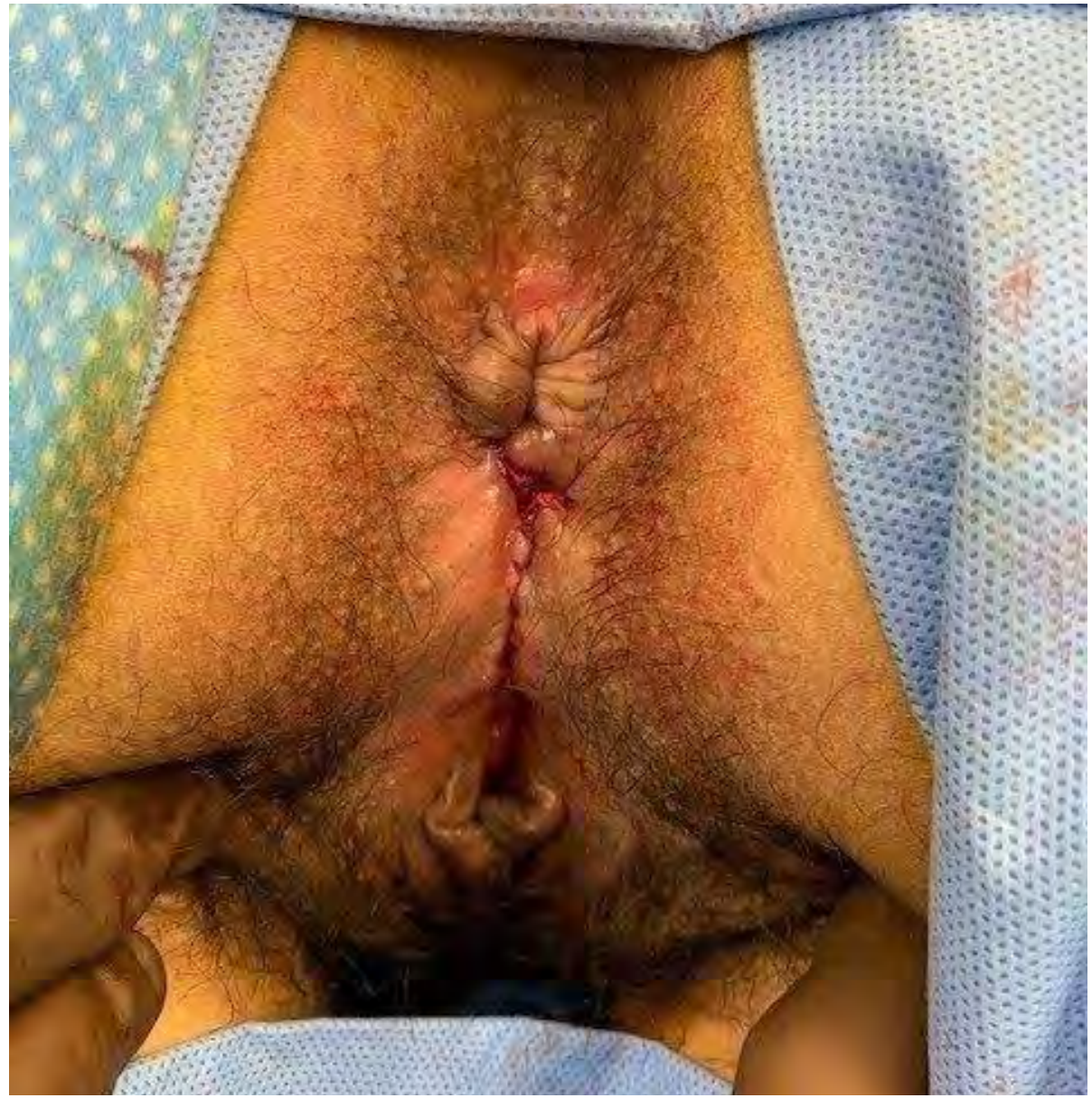
- ACOG does not give specific recommendations
- From Pearls of Exxcellence: “Controversy exists regarding immediate versus delayed repair of all perineal breakdown...Conventional practice has been to delay repair for two to three months to ensure complete tissue recovery prior to attempted repair and allow for possible spontaneous healing. Delayed repair is challenging for patients who often suffer from anal incontinence, inability to resume sexual activity, and pain…Once all signs of infection had completely resolved, a repair was performed. In these series, perineal repair was attempted as early as 7 to 10 days following delivery. There is currently insufficient evidence to provide a definitive recommendation for early or delayed repair for perineal wound dehiscence.”
- Many studies in the 1990s showed similar outcomes of early repairs of the anal sphincter complex after laceration breakdown versus the traditional 3-4 month delayed repair
- One study performed between 2013 and 2018 showed successful early repair of anal sphincter laceration breakdown versus delayed repair

Timing of repair?

Main factor is treatment of infection

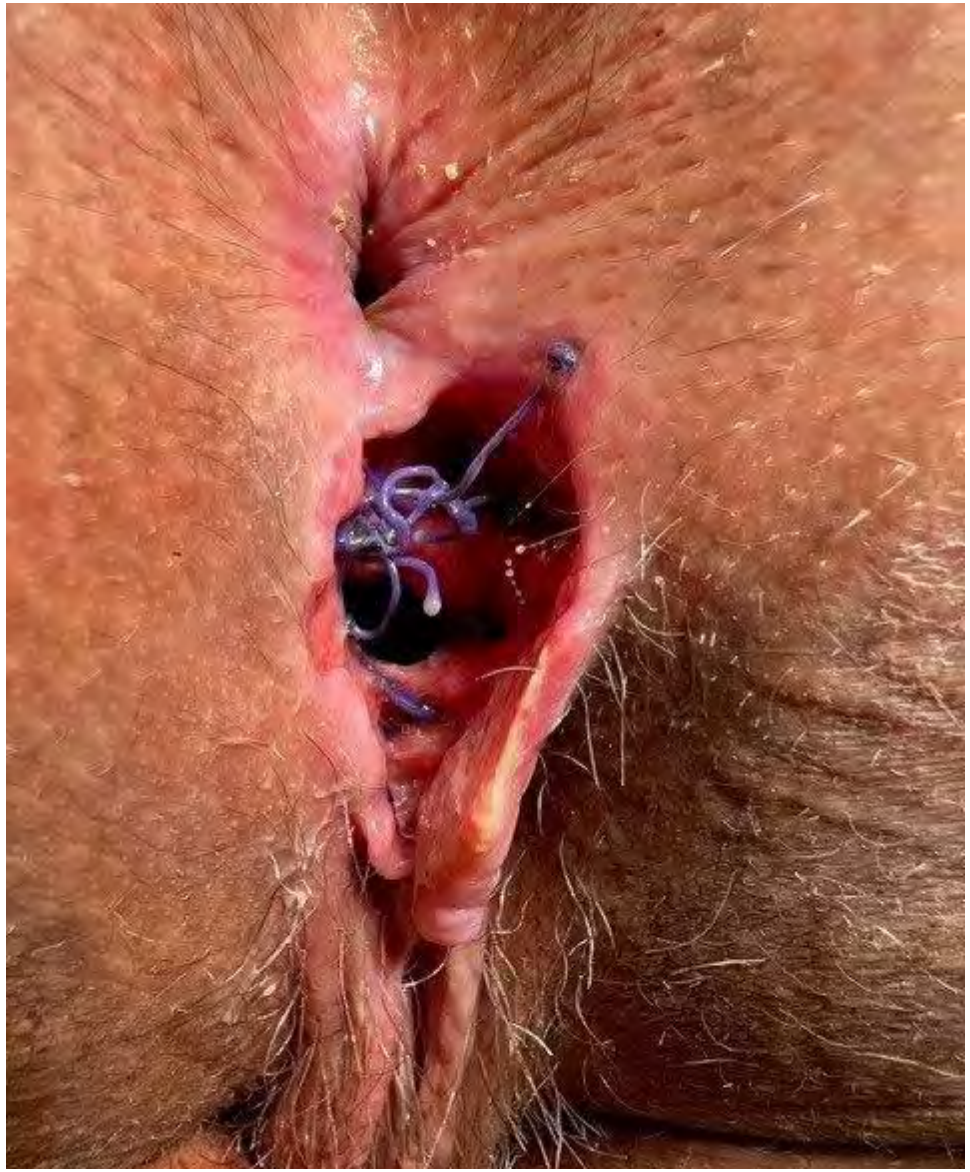
Once the infection is treated, the laceration can be repaired



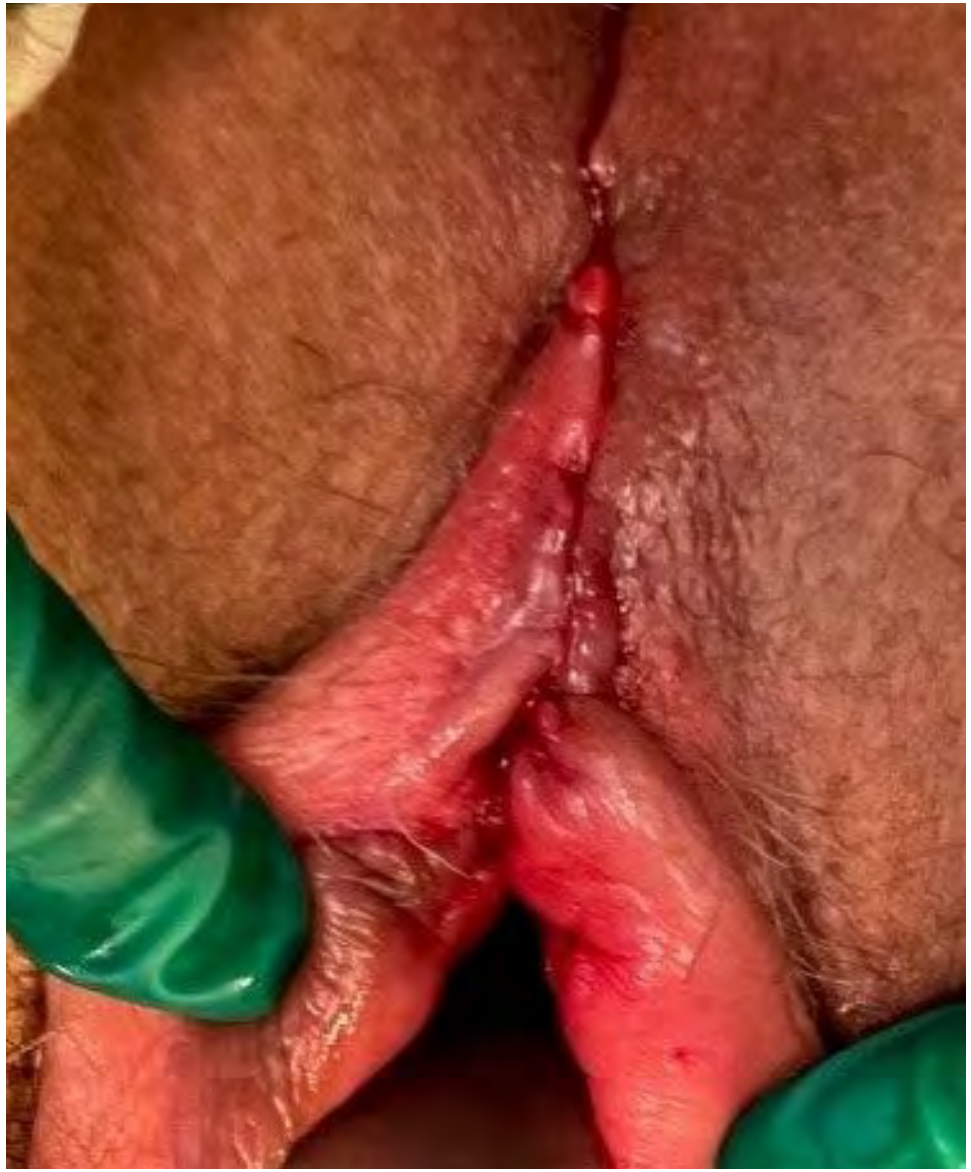


3c breakdown 6 weeks postpartum

Preoperative

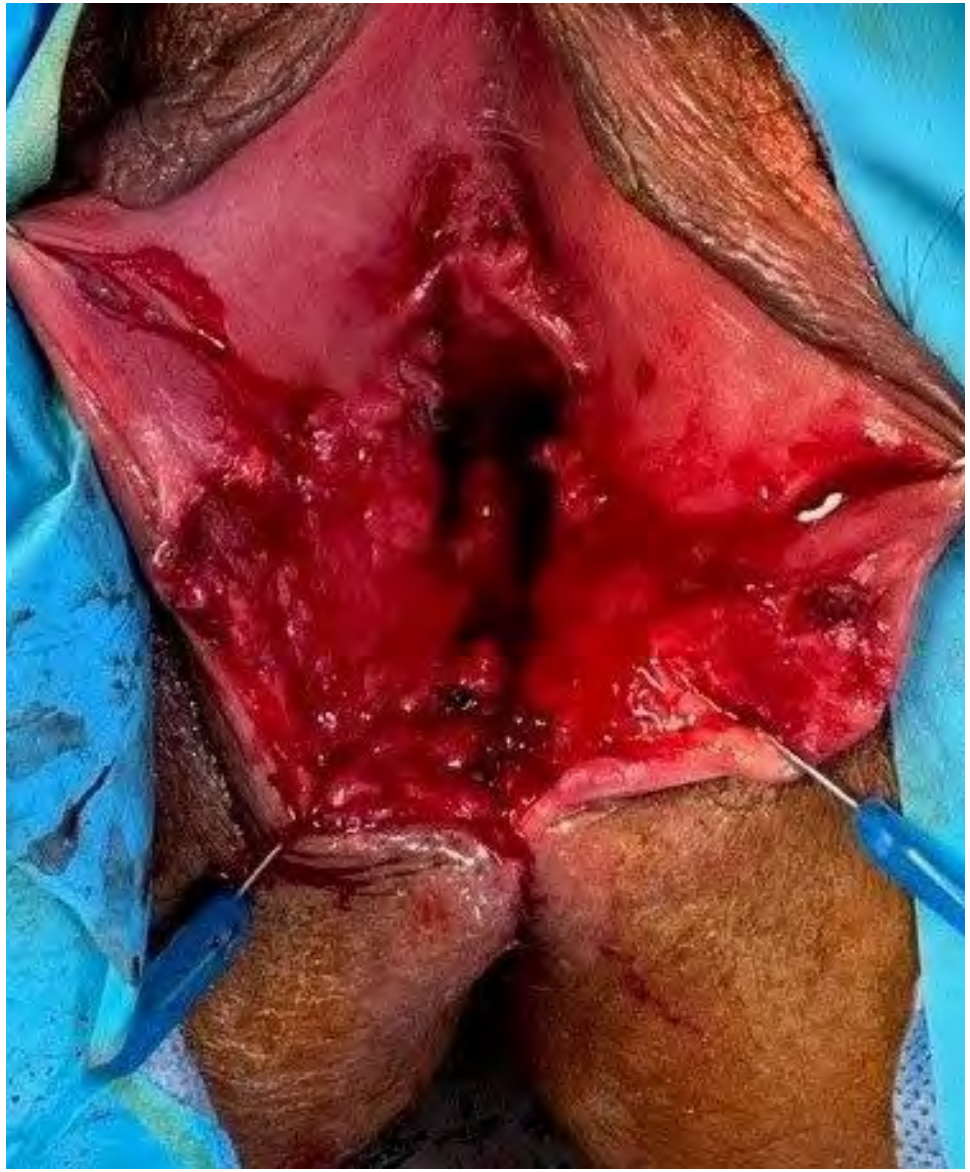


Postoperative – Vaginal Repair



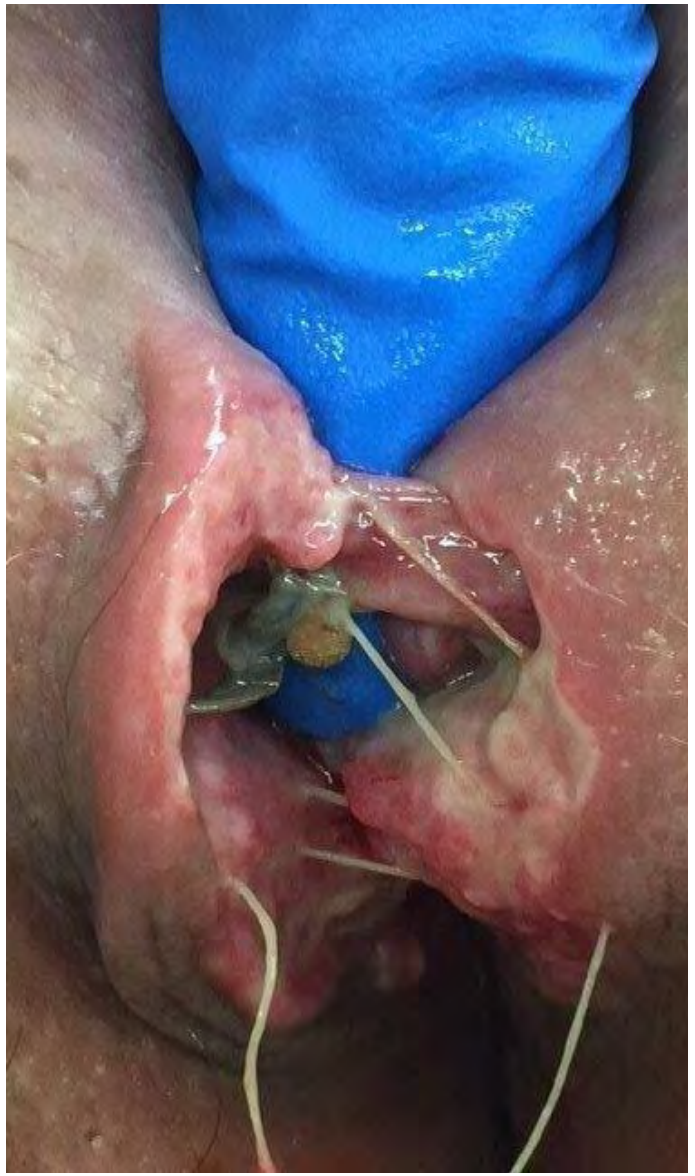
Postoperative – Sphincter Repair

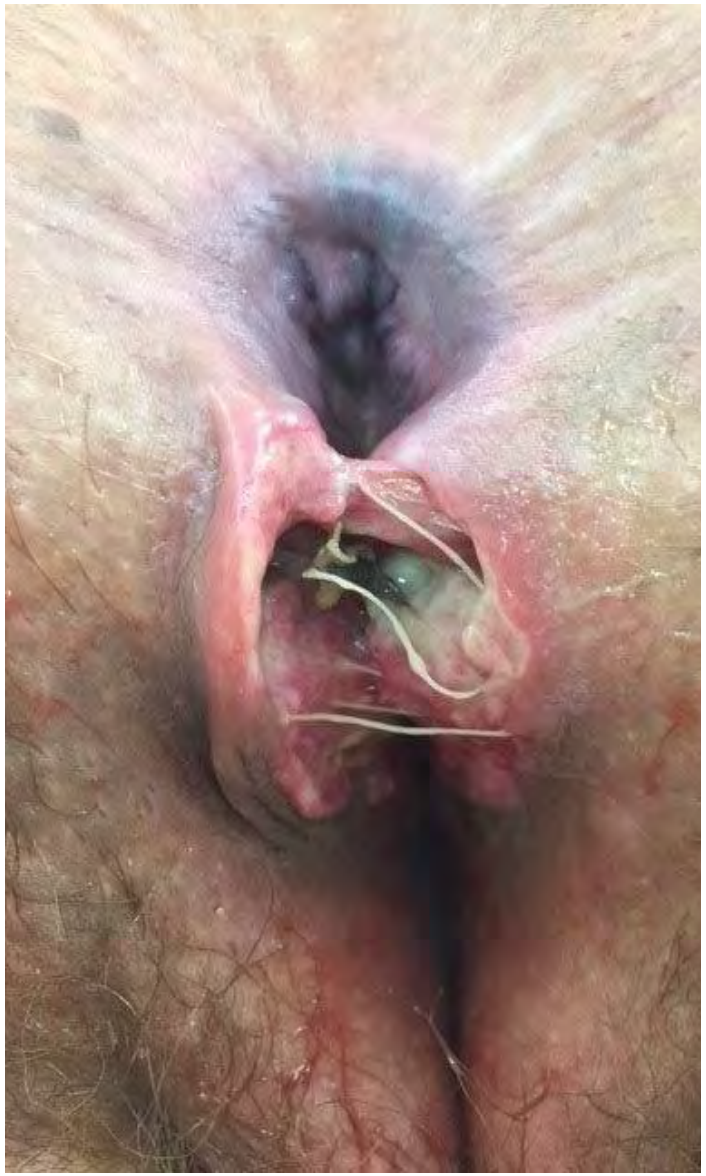
3c breakdown – Preoperative



4th Degree breakdown

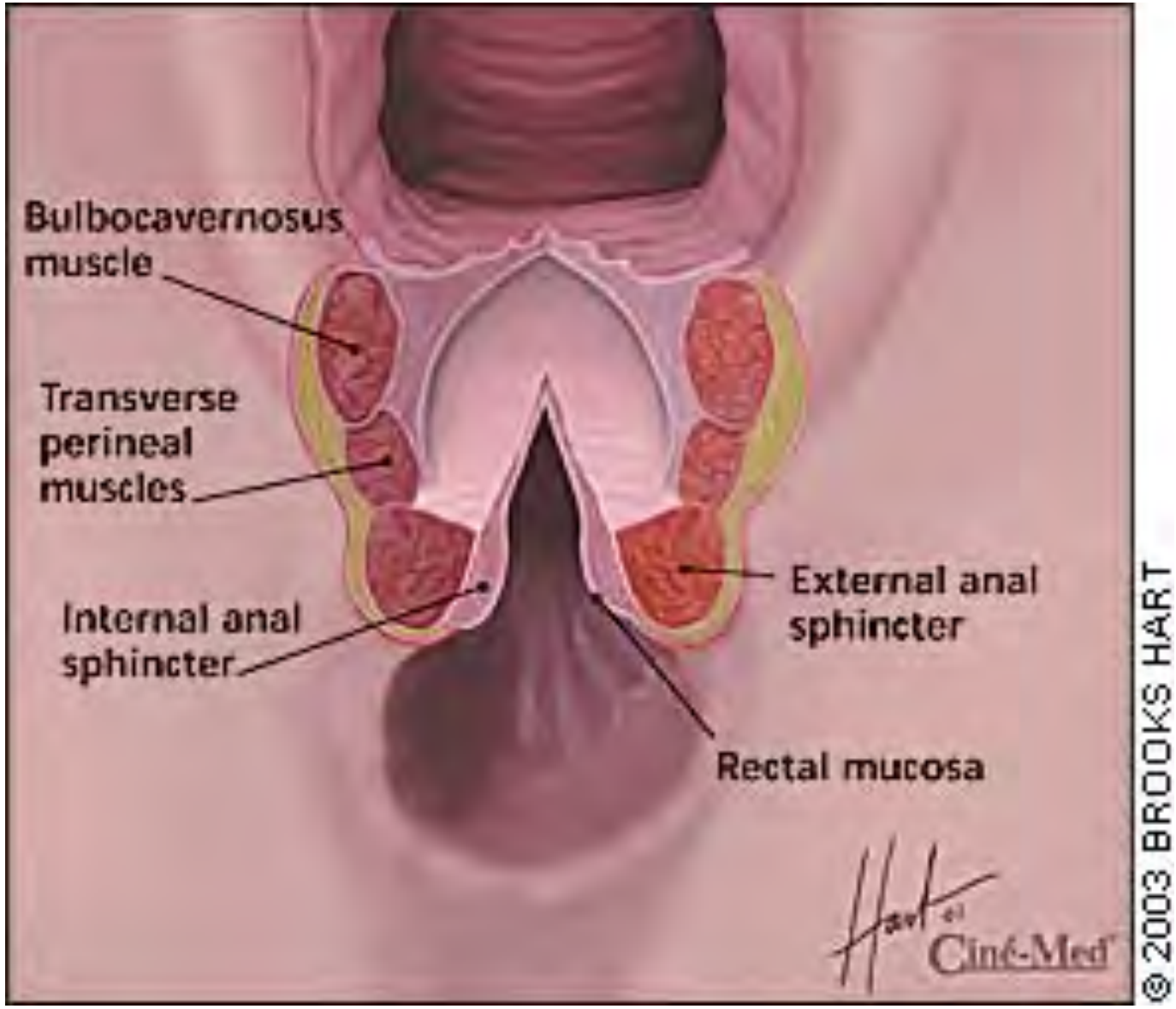
Preoperative





Fourth Degree Laceration Repair

- Rectal Mucosa
  - Reapproximate anal mucosa with 4-0 vicryl interrupted or running suture
  - Place first suture 1cm above apex

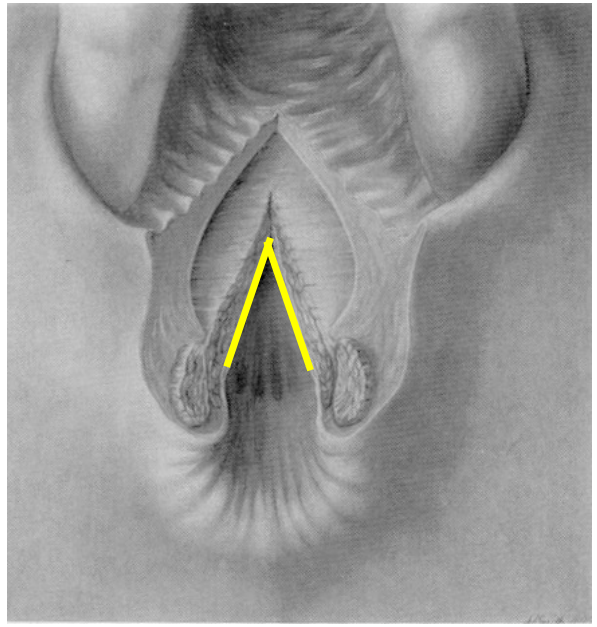


Internal Anal Sphincter

The IAS is the rubbery layer overlying the rectal mucosa

Repair with interrupted sutures

Use delayed absorbable suture material (2-0 PDS)

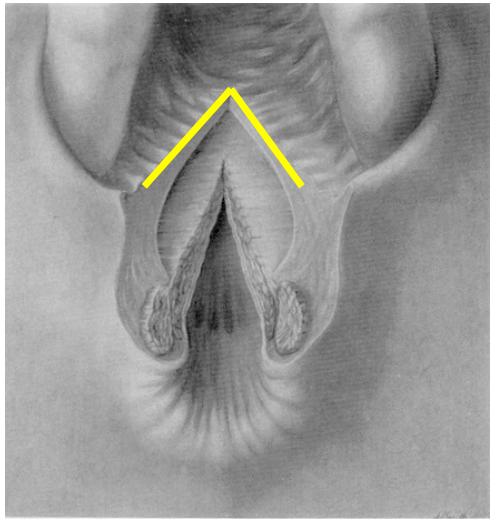


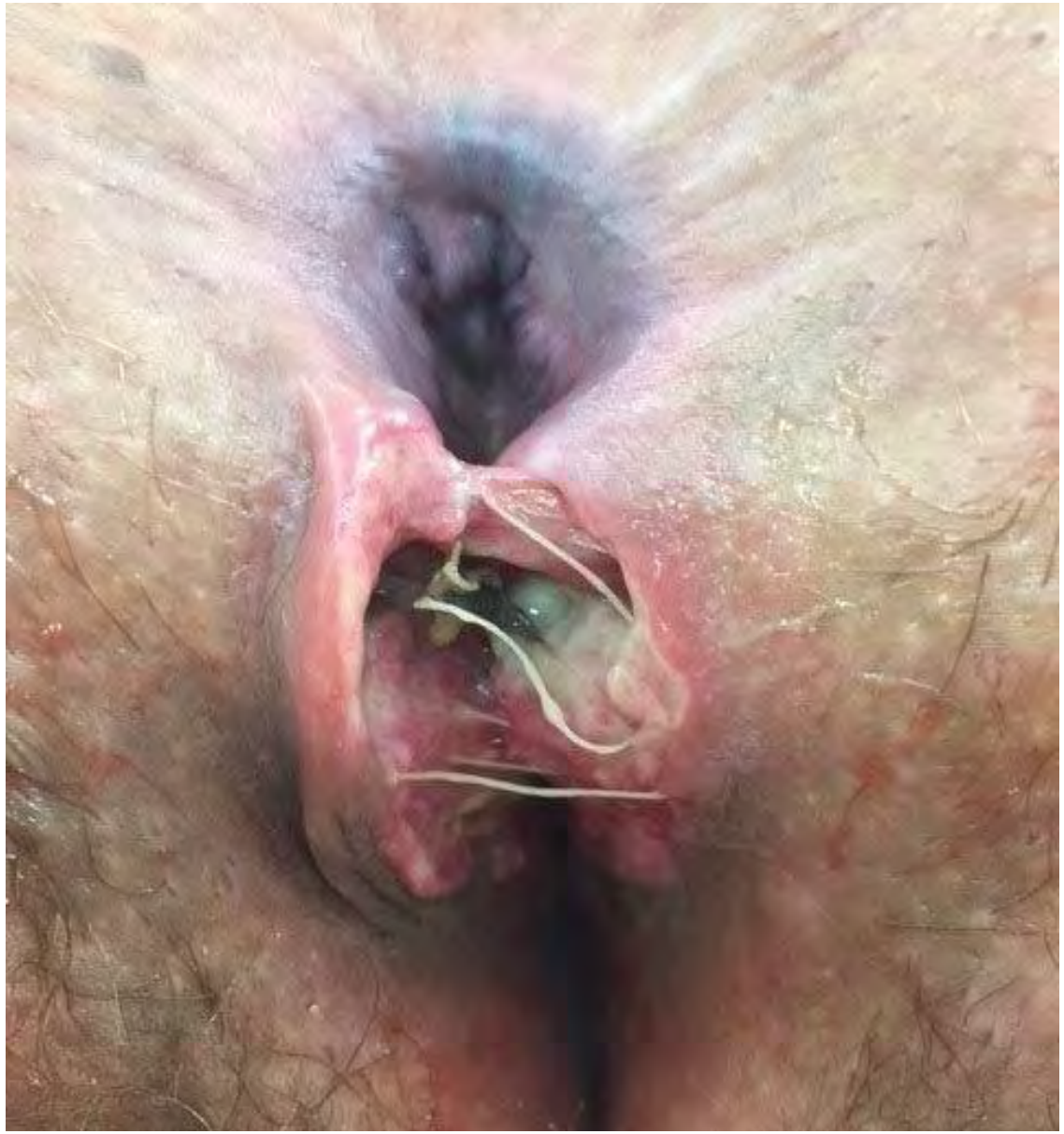
External Anal Sphincter

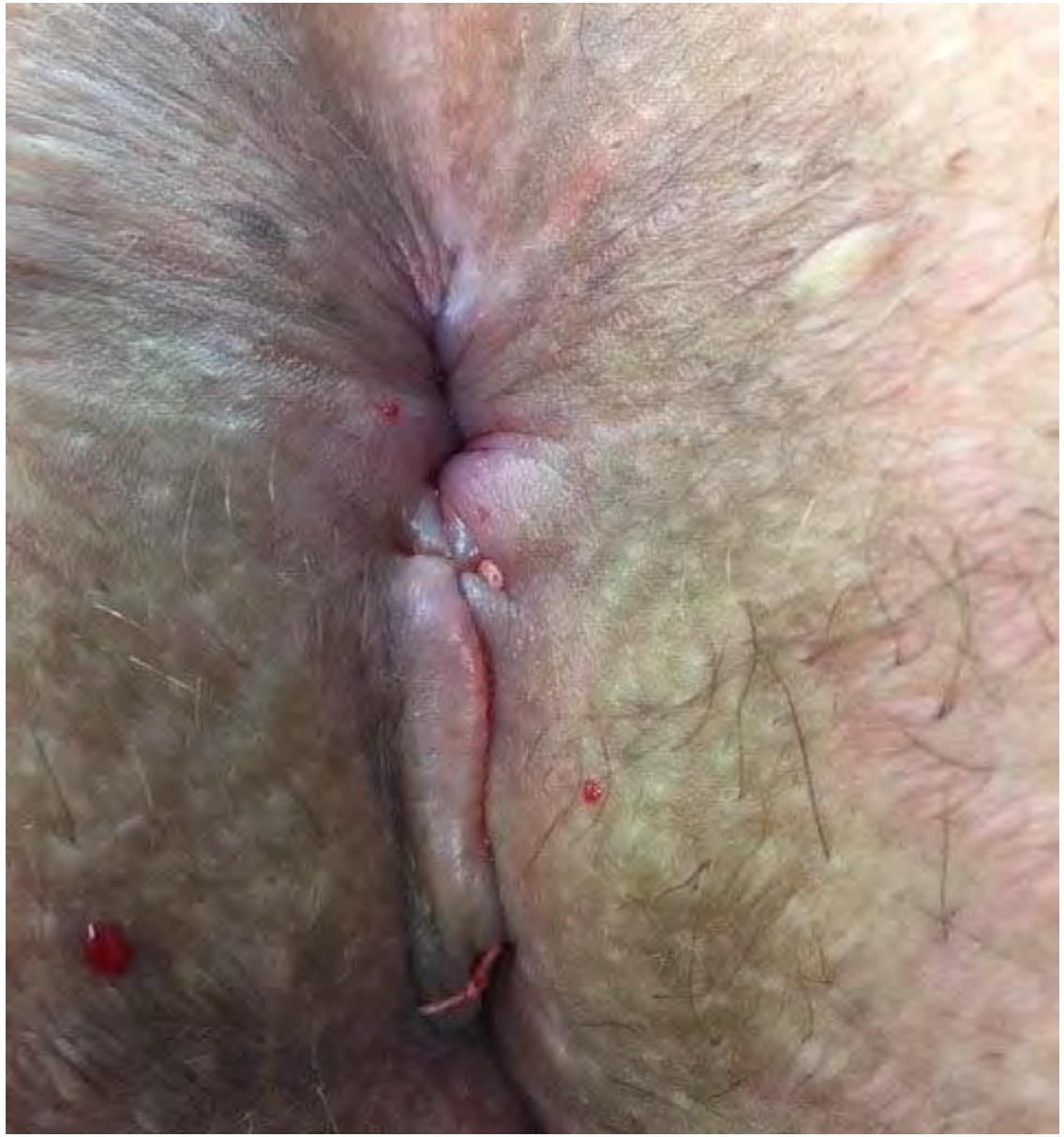
Repair EAS with interrupted sutures (PISA)

No clear data on suture type

- Vicryl
- PDS/Delayed absorbable







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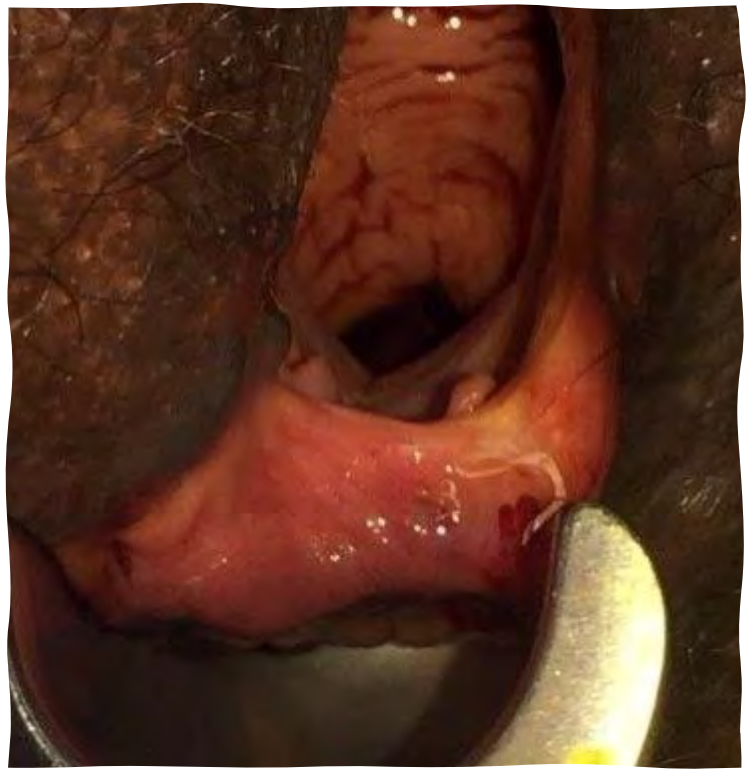

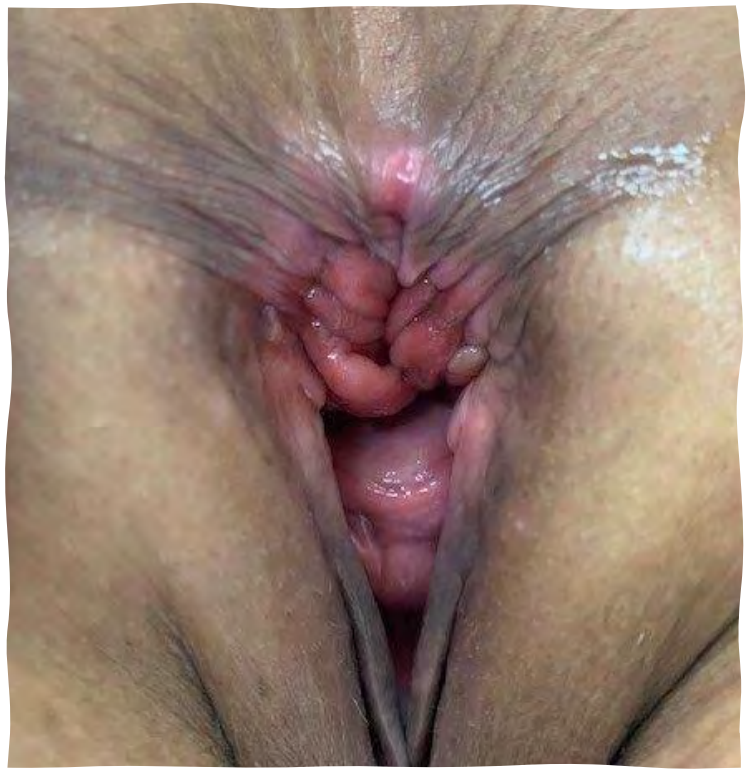

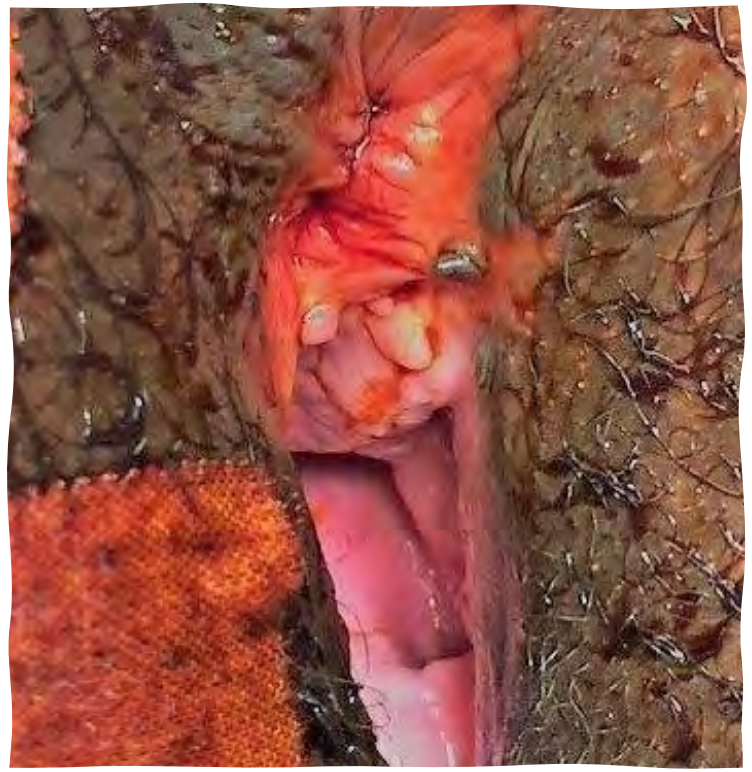

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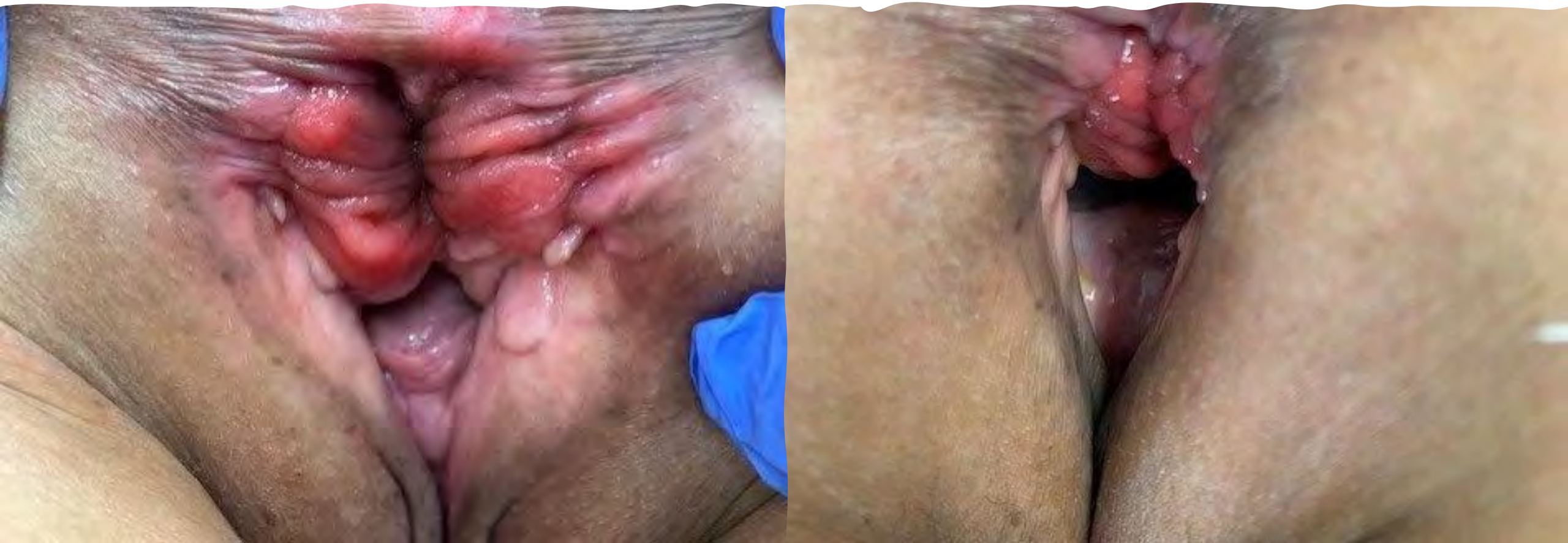
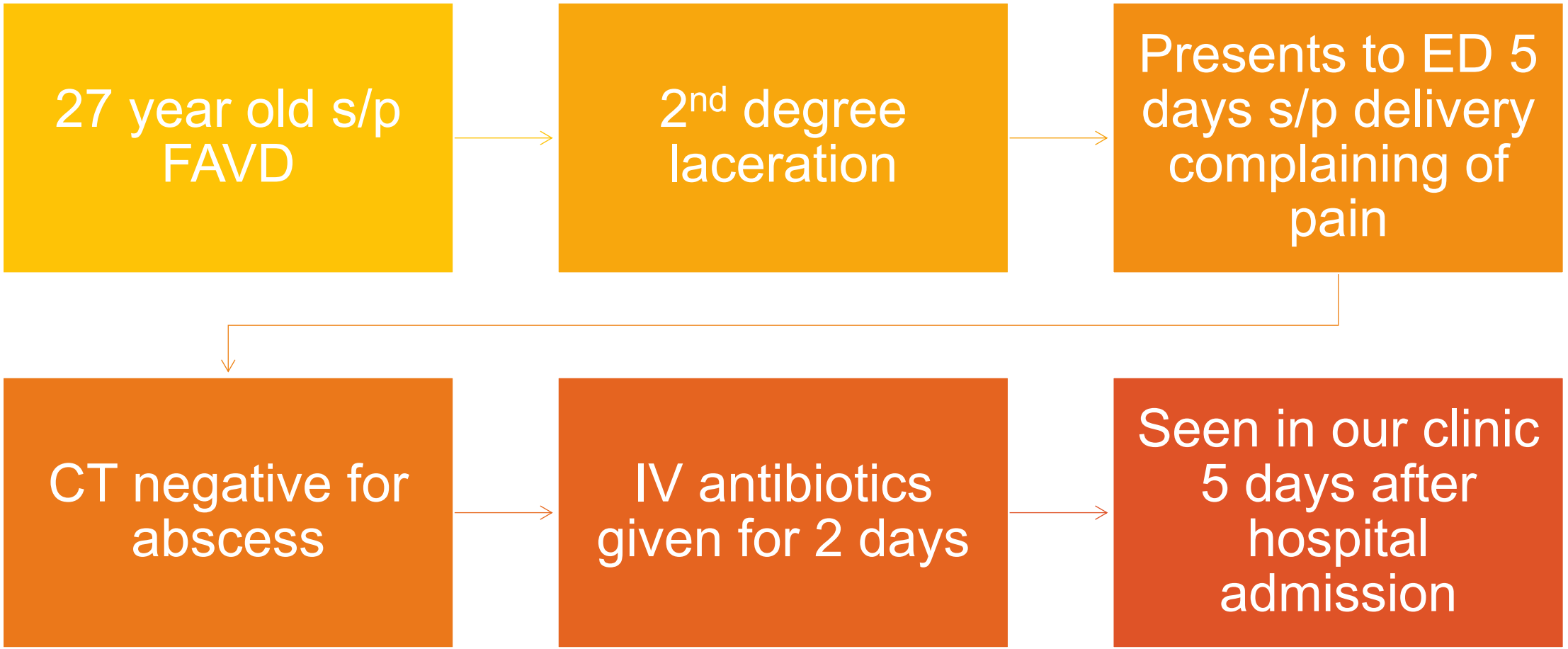
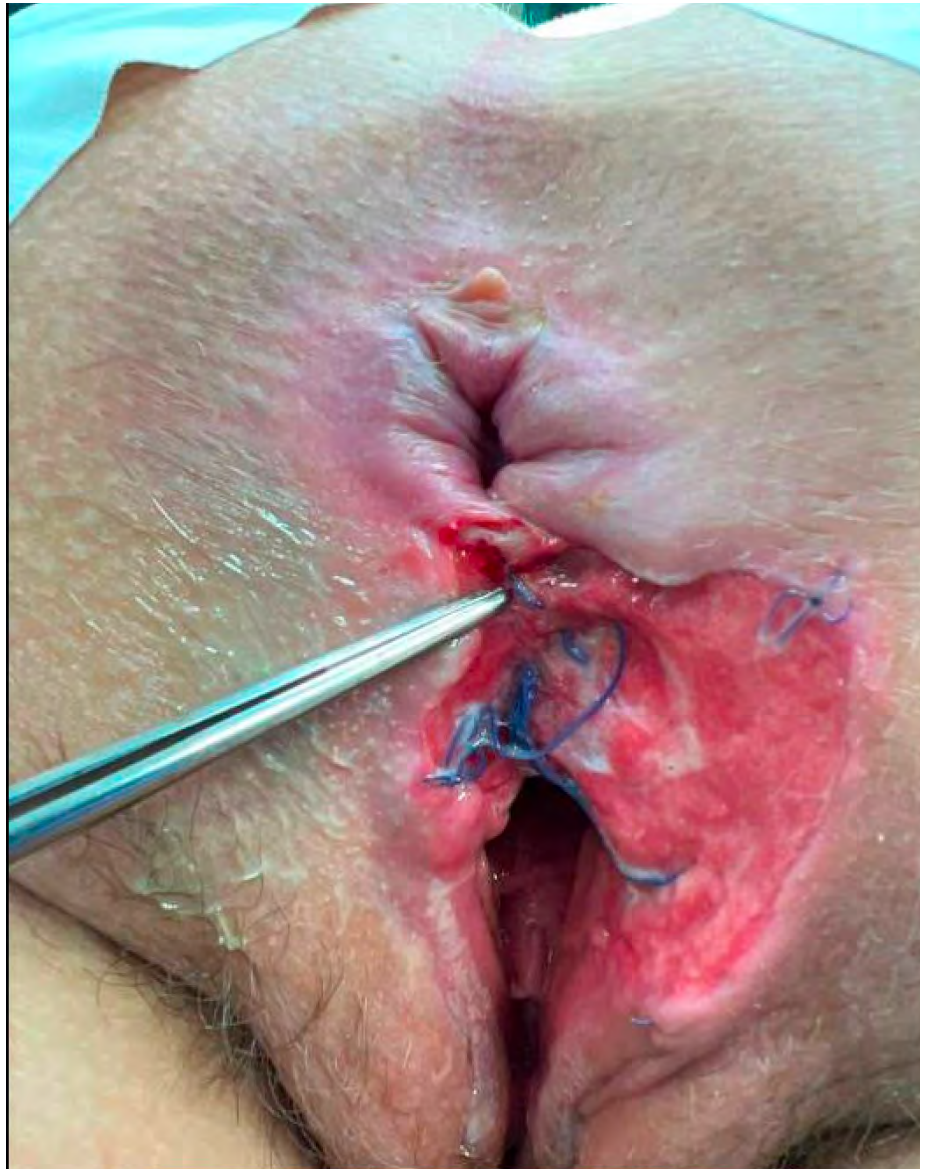


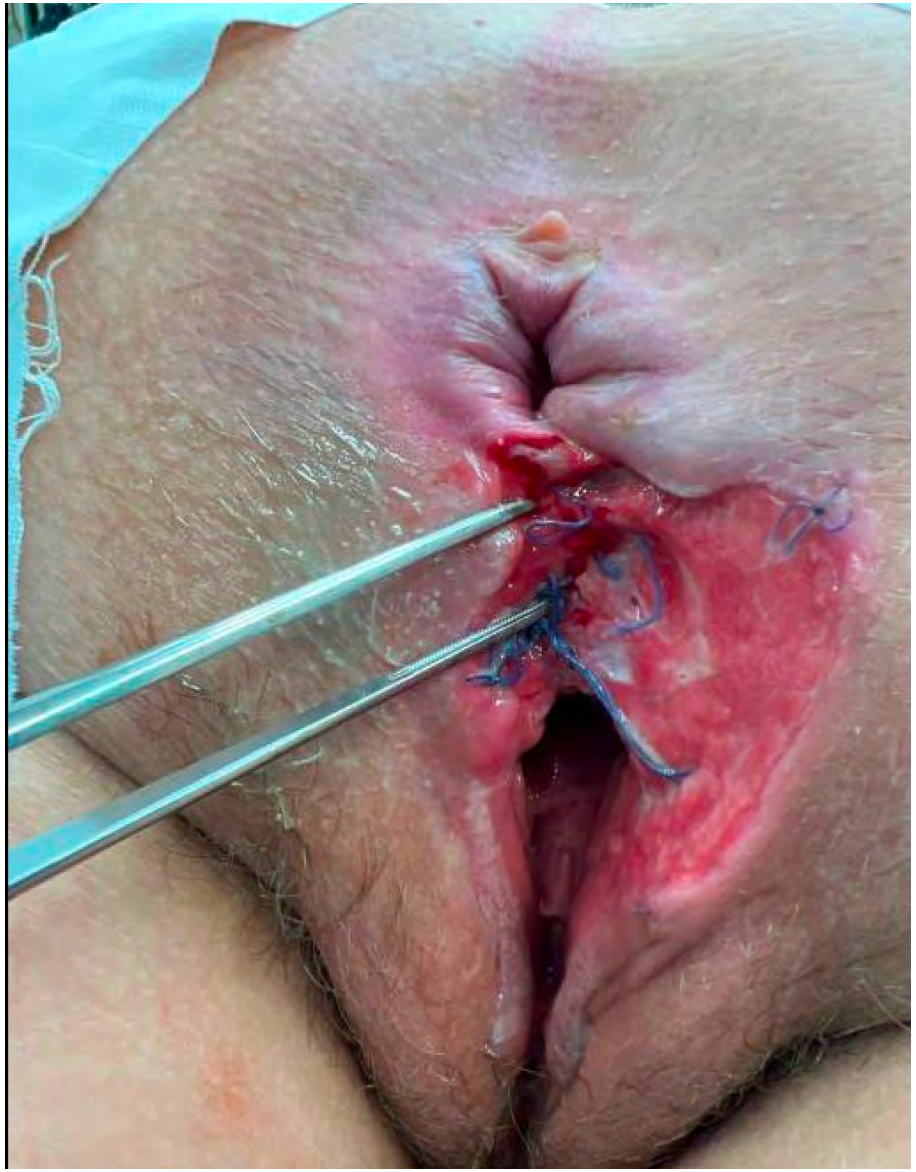

27 year old s/p FAVD
2nd degree laceration
Presents to ED 5 days s/p delivery complaining of pain
CT negative for abscess
IV antibiotics given for 2 days
Seen in our clinic 5 days after hospital admission

Preoperative

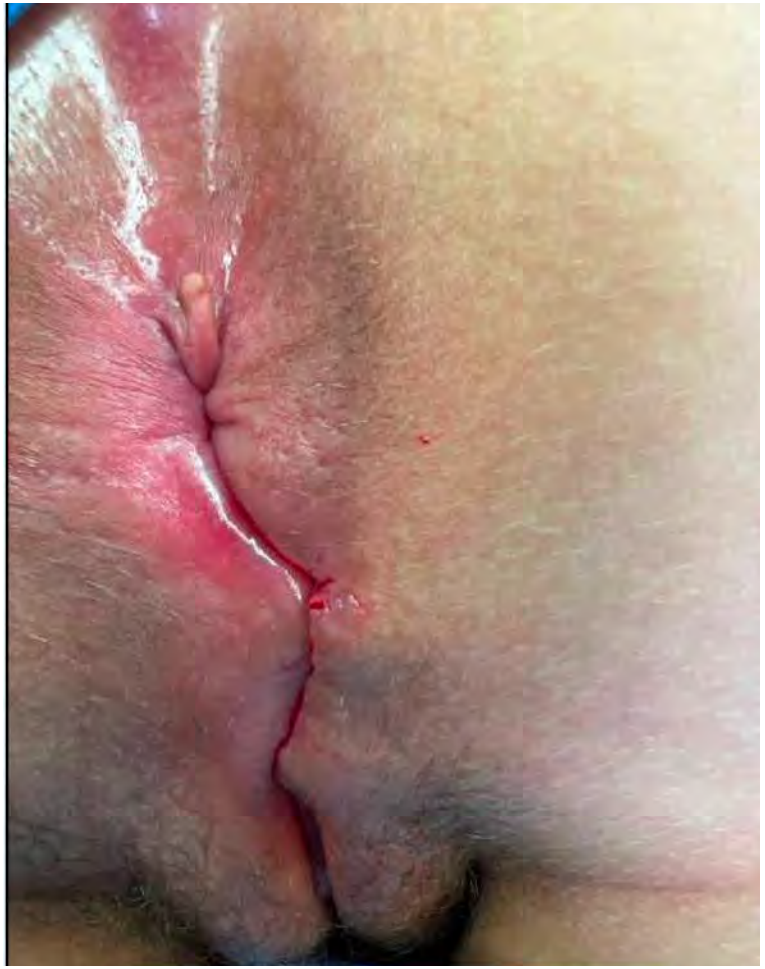
Preoperative – Internal anal sphincter

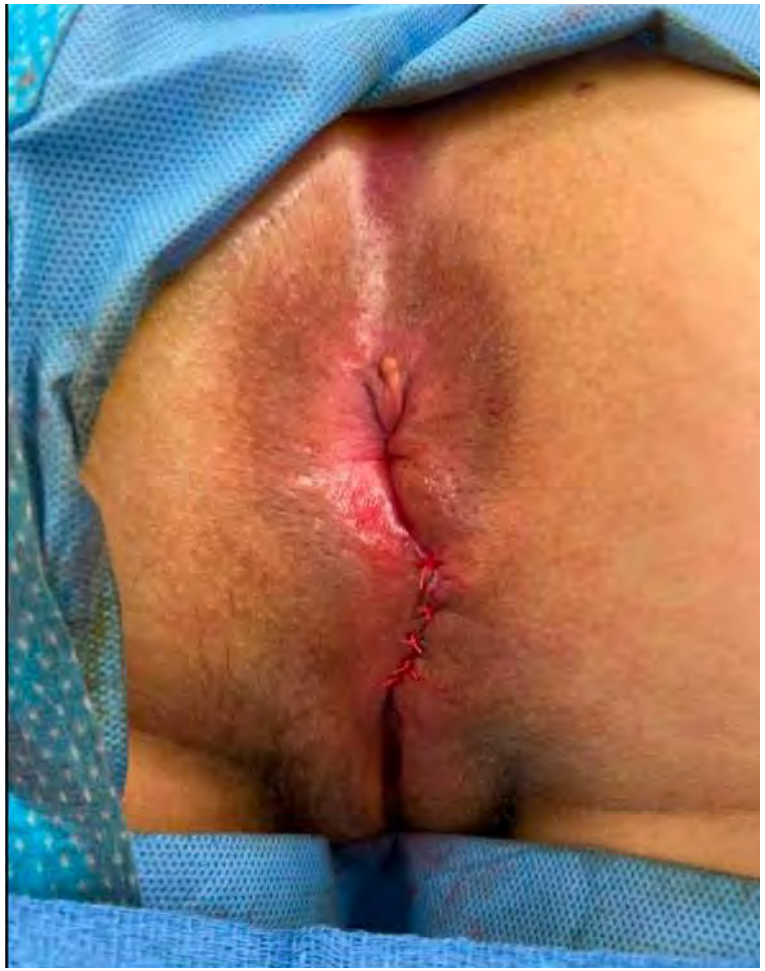


Preoperative – External Anal Sphincter



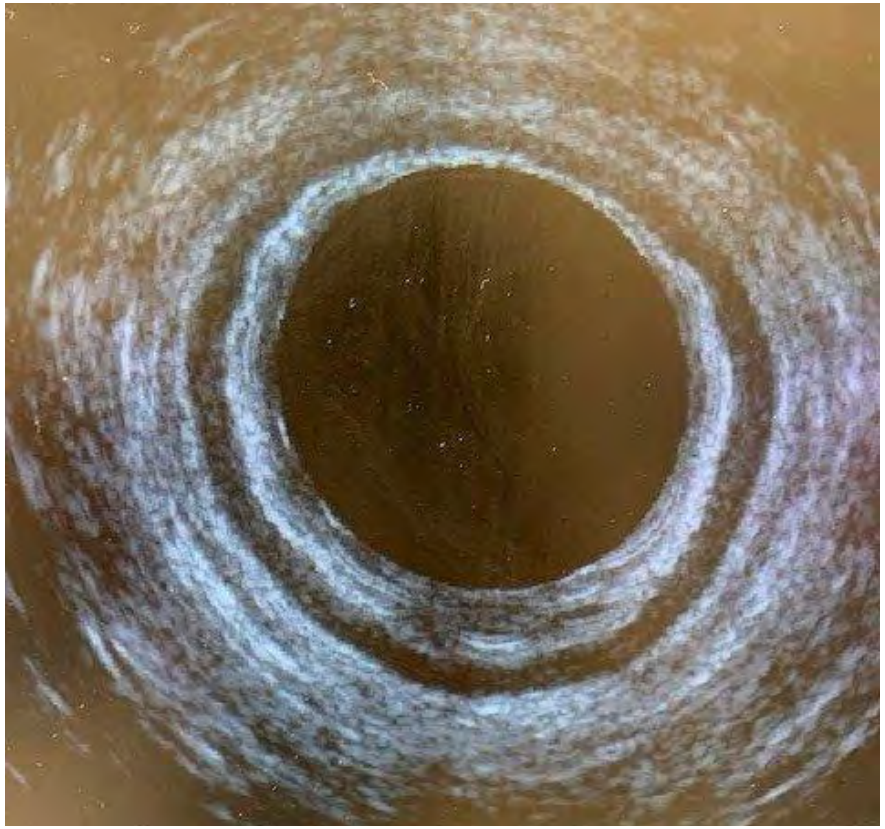
Postoperative

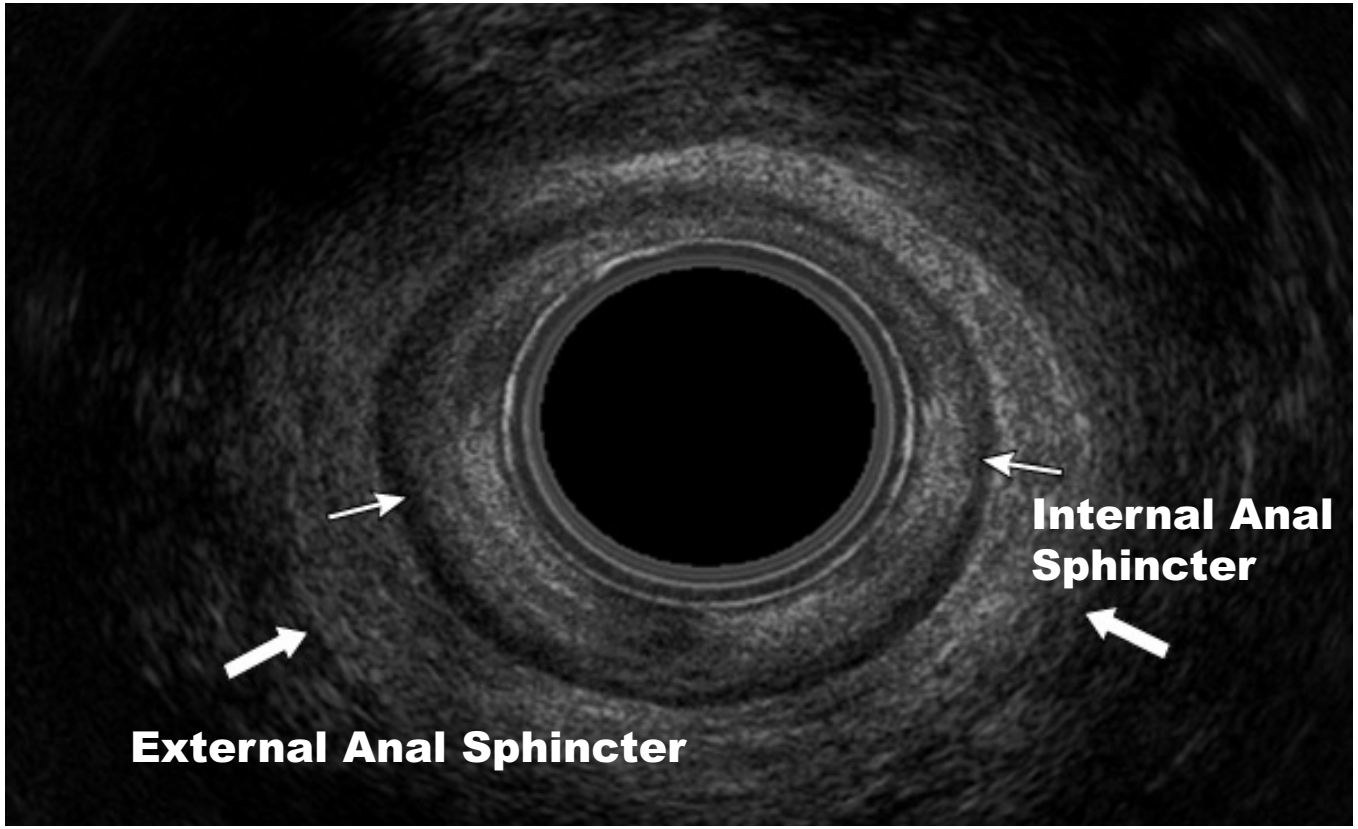




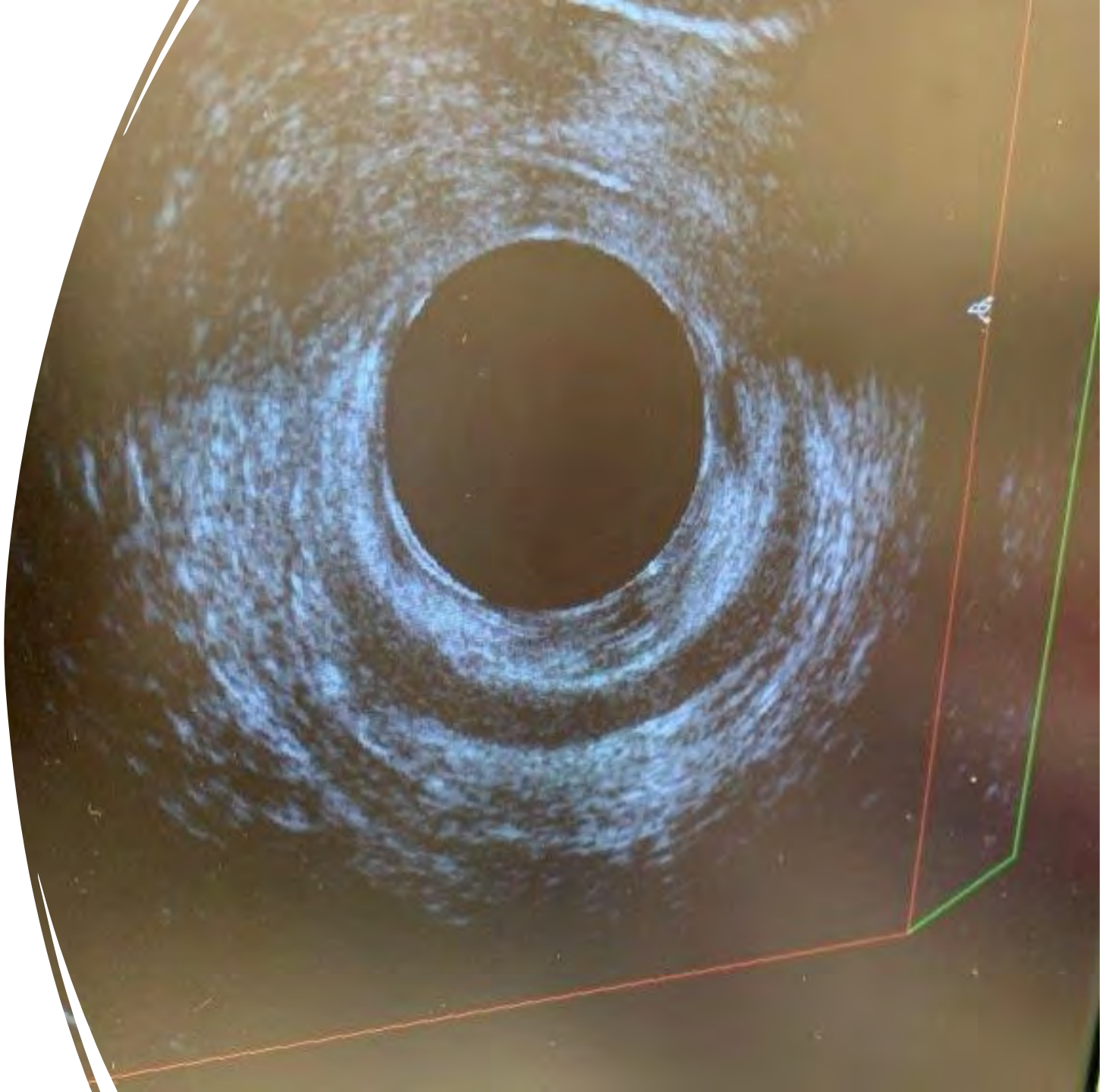
Endoanal Ultrasound

- Useful in diagnosing internal and external anal sphincter defects
- May be useful immediately postpartum or for undiagnosed injuries later in life





Endoanal ultrasound – anterior defect



Endoanal ultrasound – should we perform on all patients?

- In a randomized controlled trial, women with lacerations were allocated to either clinical examination and laceration repair or endoanal ultrasound and laceration repair.
- No differences reported in fecal incontinence symptoms at 3 months or 1 year postpartum
- In one study, 24% of women diagnosed with a sphincter tear by endoanal ultrasound did not have confirmation of anal sphincter damage at the time of surgery, which may describe a high false positive rate for sphincter injury
- Not routinely performed in postpartum population

What to do in subsequent pregnancies?

- Expert opinion recommends that if a woman had a breakdown of her laceration repair, suffered fecal incontinence post delivery, or expressed suffering psychological trauma from her birthing experience that it is reasonable to offer her a planned cesarean section
- Decision made based on clinical presentation and symptoms

Takeaway points

- Overall incidence of OASIS injury is 6.3%
- Operative delivery is a major risk factor for OASIS injuries
- Fecal incontinence occurs in 28% of women after OASIS injuries
- Aseptic technique and antibiotics at the time of initial repair decreases risk of breakdown
- Infection is the main risk factor for breakdown of laceration repair
- Once infection has been treated, immediate repair of laceration may be warranted
- Pelvic floor physical therapy has been proven to improve urinary and fecal incontinence at 1 year postpartum
- Refer to urogynecology!!

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THANK YOU!

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HYPOVENTILATION, HYPOXIA, AND HYPERCAPNIA OH MY! PULMONARY DISORDERS IN PREGNANCY

Jake Hirshberg
Assistant Professor MFM and PCCM

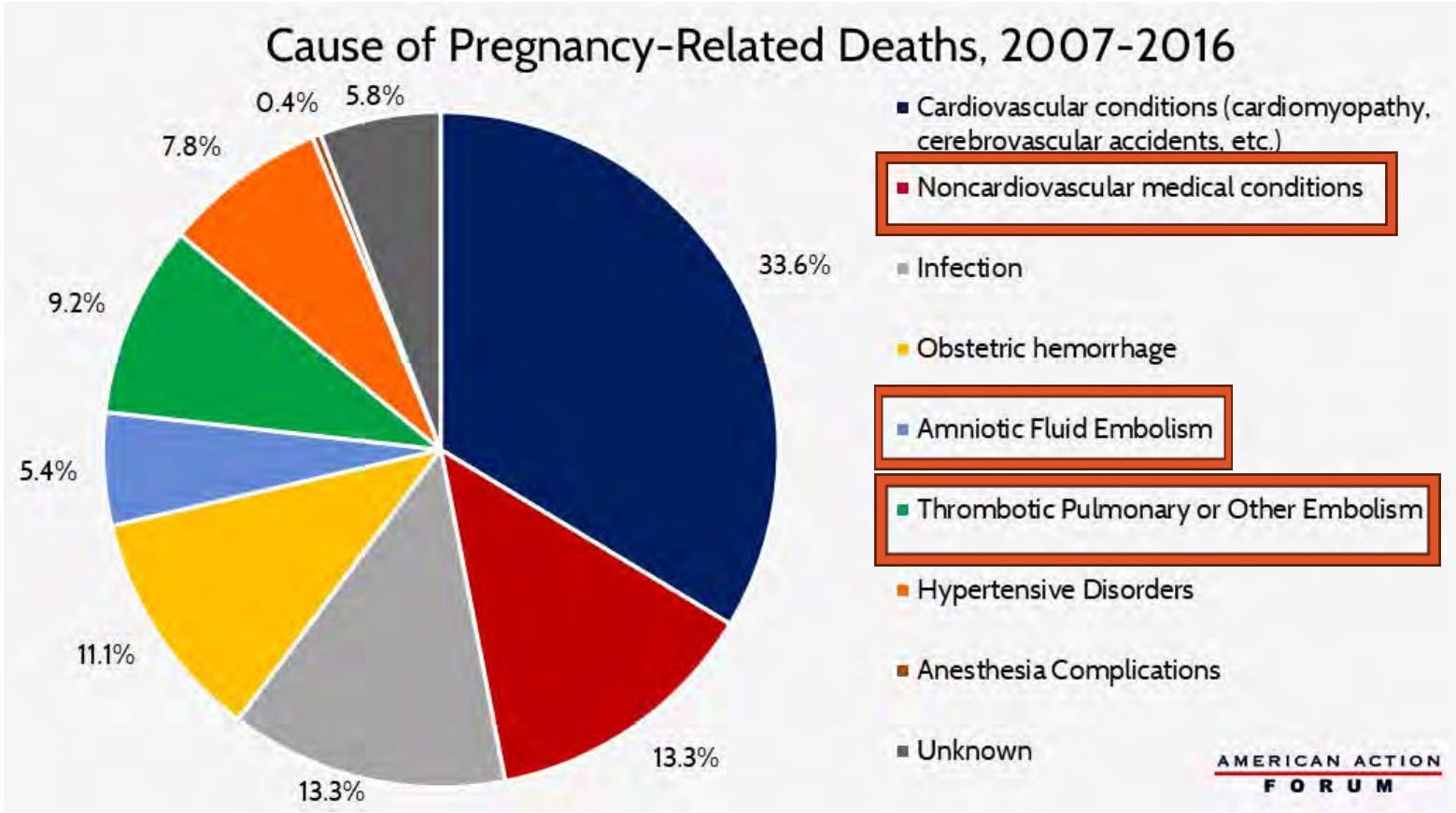
Disclosures

- None

Objectives

- Impact on maternal morbidity and mortality
- Physiologic pulmonary adaptations in pregnancy
  - Oxygenation
  - Ventilation
  - Placental gas exchange
- Pathophysiology of pulmonary disease in pregnancy
  - Asthma
  - Pulmonary embolism
  - Pneumonia
  - ARDS
  - Tuberculosis
  - Cystic fibrosis
  - Pulmonary hypertension

Maternal Mortality

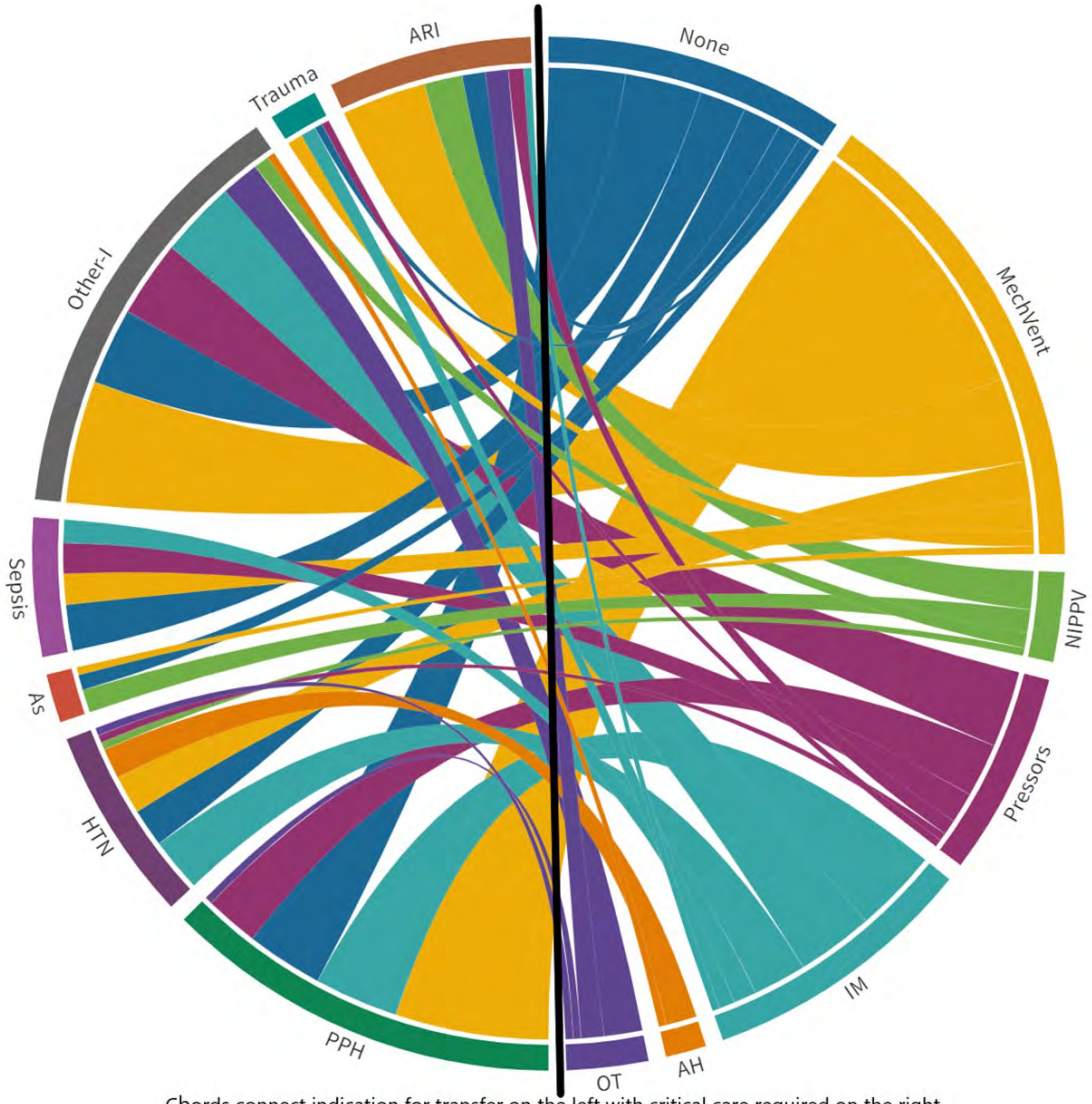


Indications for ICU admission

102 ICU admissions over a 5-year period at a single center

Indication for transfer	N=102 (%)	Critical Care Required	N=102 (%)
Hemorrhage	32 (31)	None	29 (28)
Hypertension	16 (16)	Invasive Ventilation	48 (47)
Respiratory Insufficiency	20 (20)	Non-Invasive Ventilation	9 (9)
Sepsis	15 (15)	Vasopressor infusion	19 (19)
Trauma	4 (4)	Antihypertensive infusion	4 (4)
Other	34 (33)	Invasive Hemodynamic Monitoring	28 (28)
		Other	7 (7)

Figure 1: Indication for transfer and critical care provided



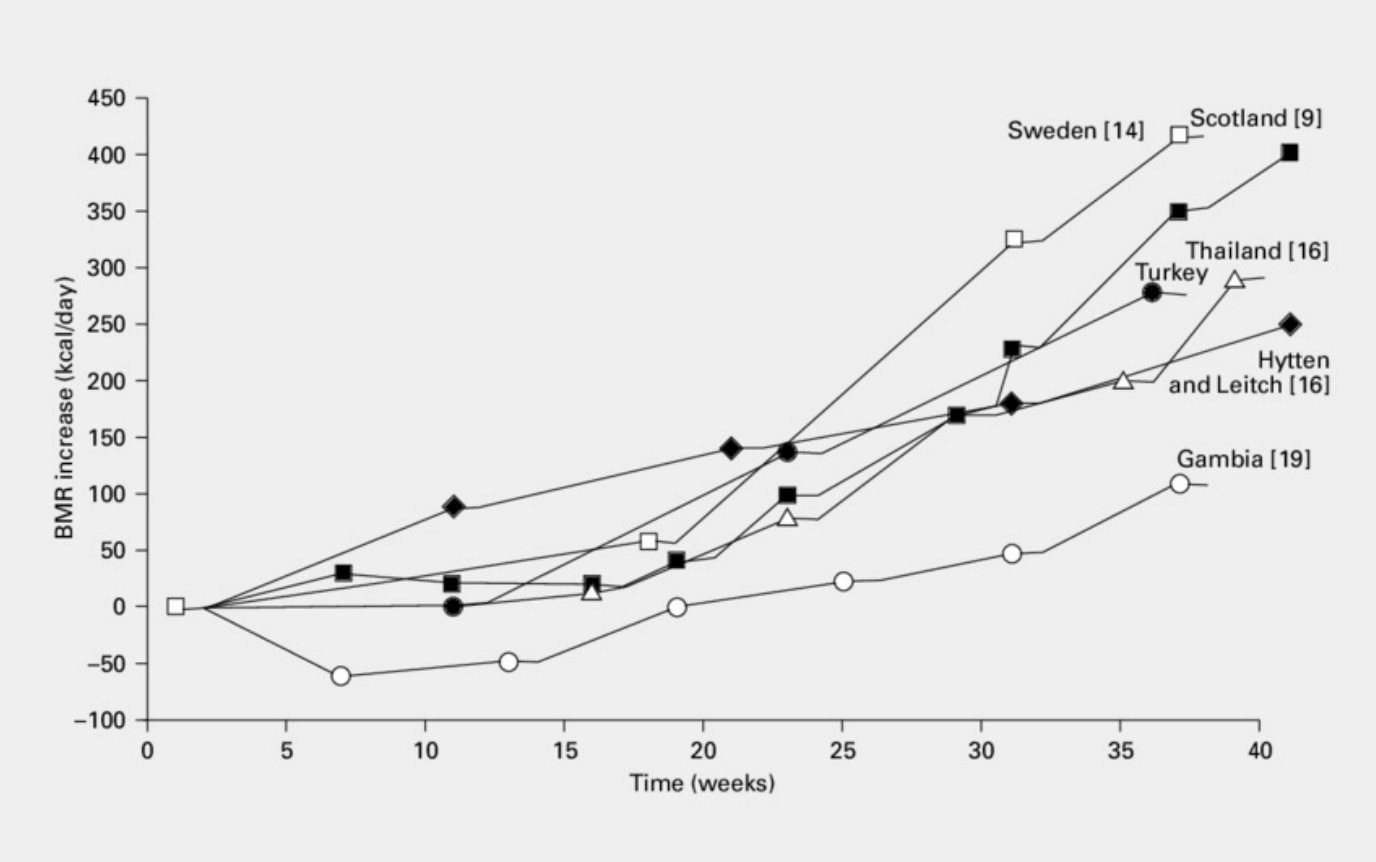
Chords connect indication for transfer on the left with critical care required on the right

ARI=Acute respiratory insufficiency, Other-I=Other indication for transfer, As=Asthma, HTN=Hypertension, PPH=Hemorrhage, OT=Other treatment, AH=Antihypertensive infusion, IM=Invasive monitoring, NIPPV=Non-invasive positive pressure ventilation

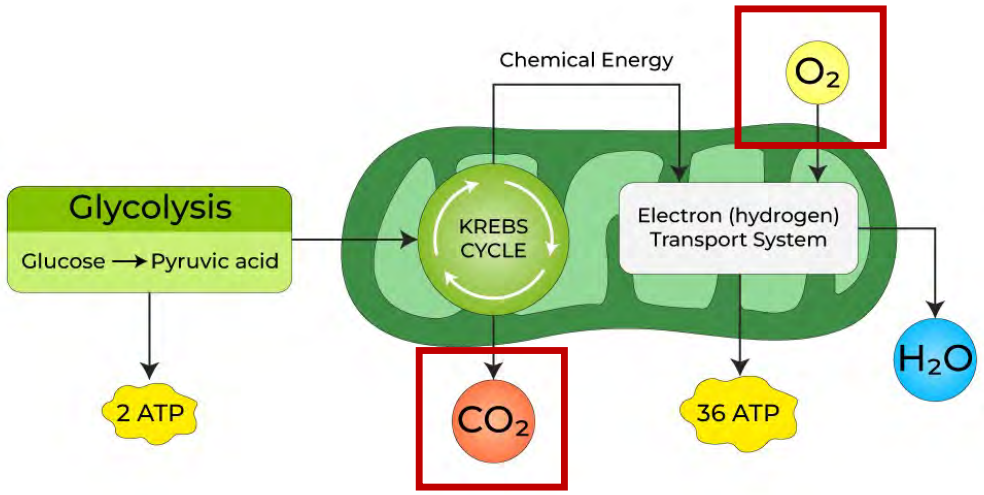
Metabolic demands of pregnancy

Basal metabolic rate

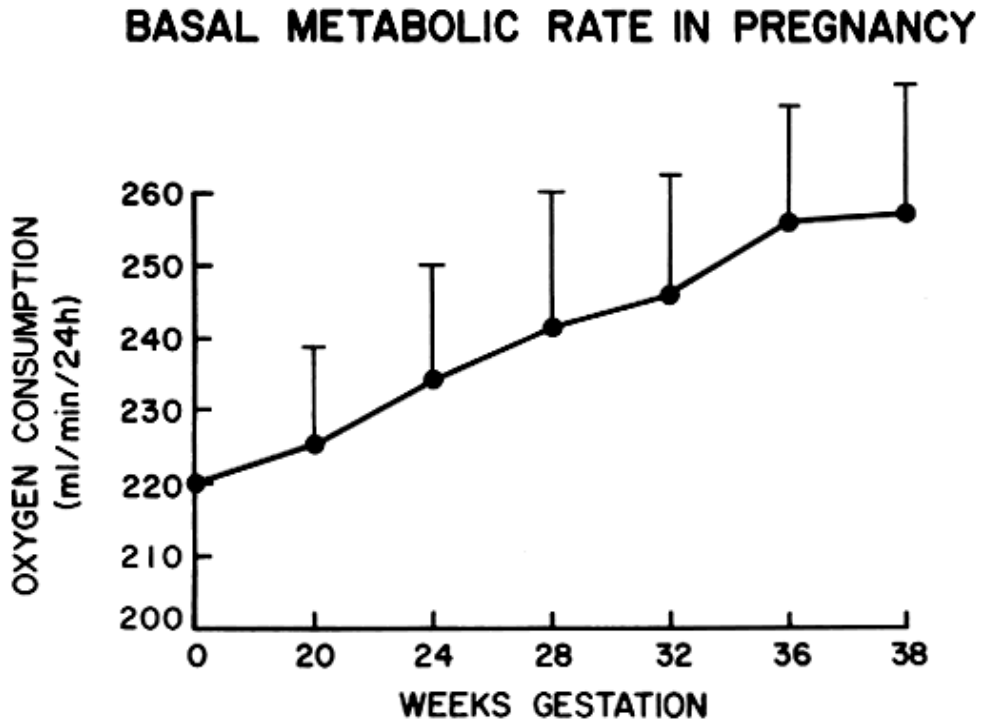
- BMR increases by 20-60% in pregnancy
- “Metabolism for two”



Metabolic demands of pregnancy



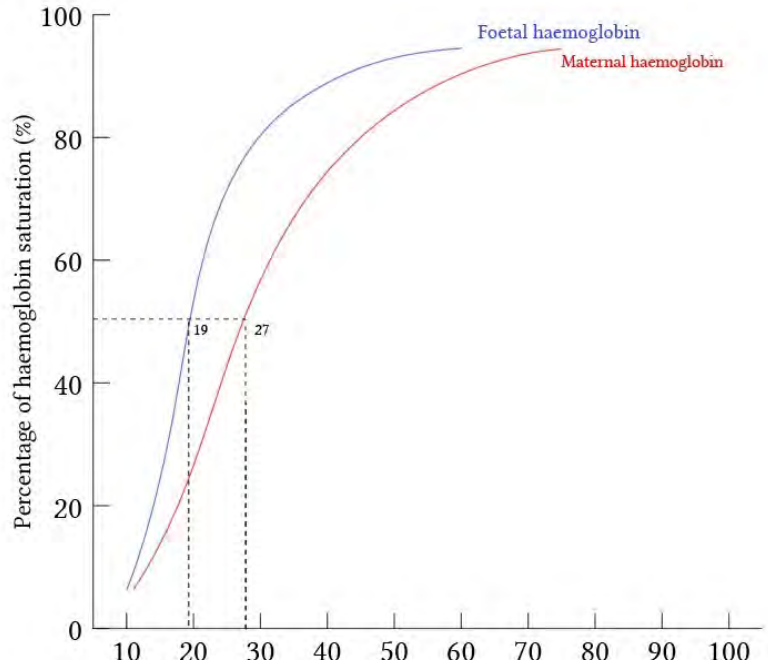
"Breathing for two"

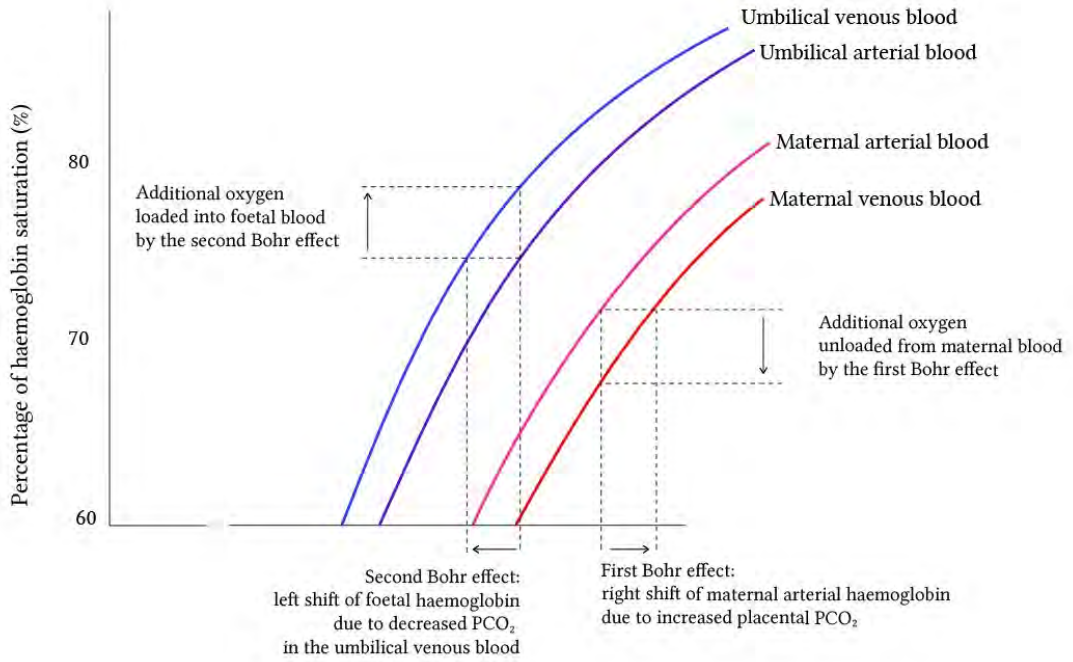


Oxygen delivery

Fetal cheat codes

- Fetal Hgb has higher O2 affinity
- Resp alk increases 2-3 DPG aiding O2 offloading
- Fetal Hgb averages 15g/dL at term
- Oxygen delivery is largely driven by SpO2 not PaO2

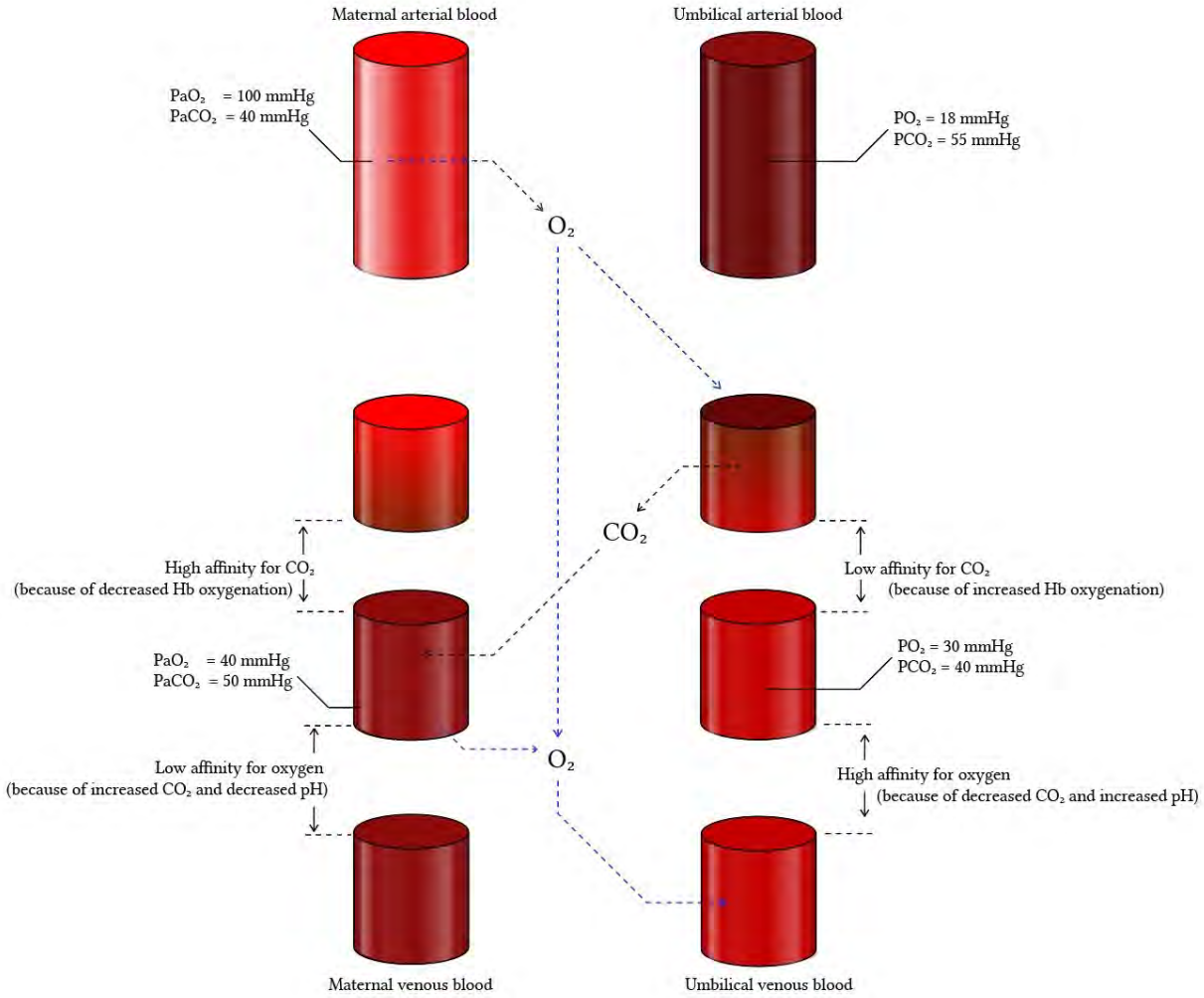




Carbon dioxide offloading

Gradient dependent

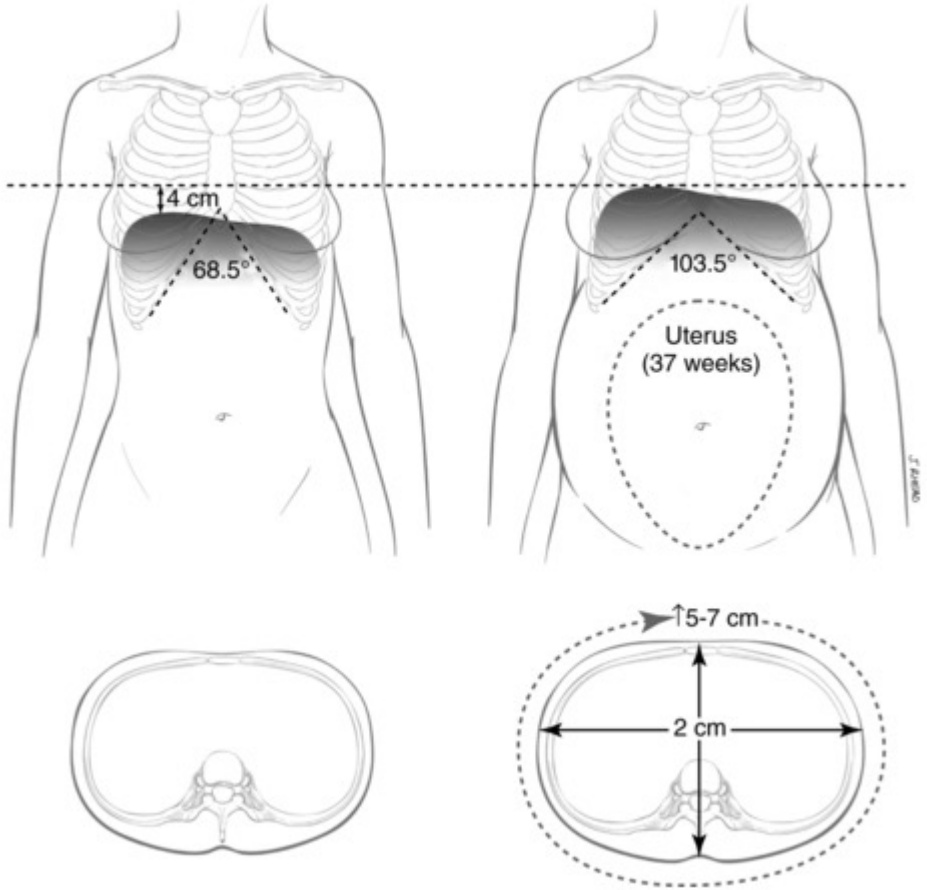
- CO2 must move from high to low concentration
- Increased maternal ventilation leads to decreased PCO2 levels
- Compensated respiratory alkalosis



Respiratory Alkalosis

Blood gas measurement	Non-pregnant adult	Third trimester
pH	7.38–7.44	7.39–7.45
Arterial partial pressure of oxygen (mmHg [kPa])	80–100 (11–13)	92–107 (12.3–14.3)
Arterial partial pressure of carbon dioxide (mmHg [kPa])	35–45 (4.7–5.9)	25–33 (3.3–4.4)
Bicarbonate (mmol/L or mEq/L)	21–30	16–22

Physiologic changes in pregnancy



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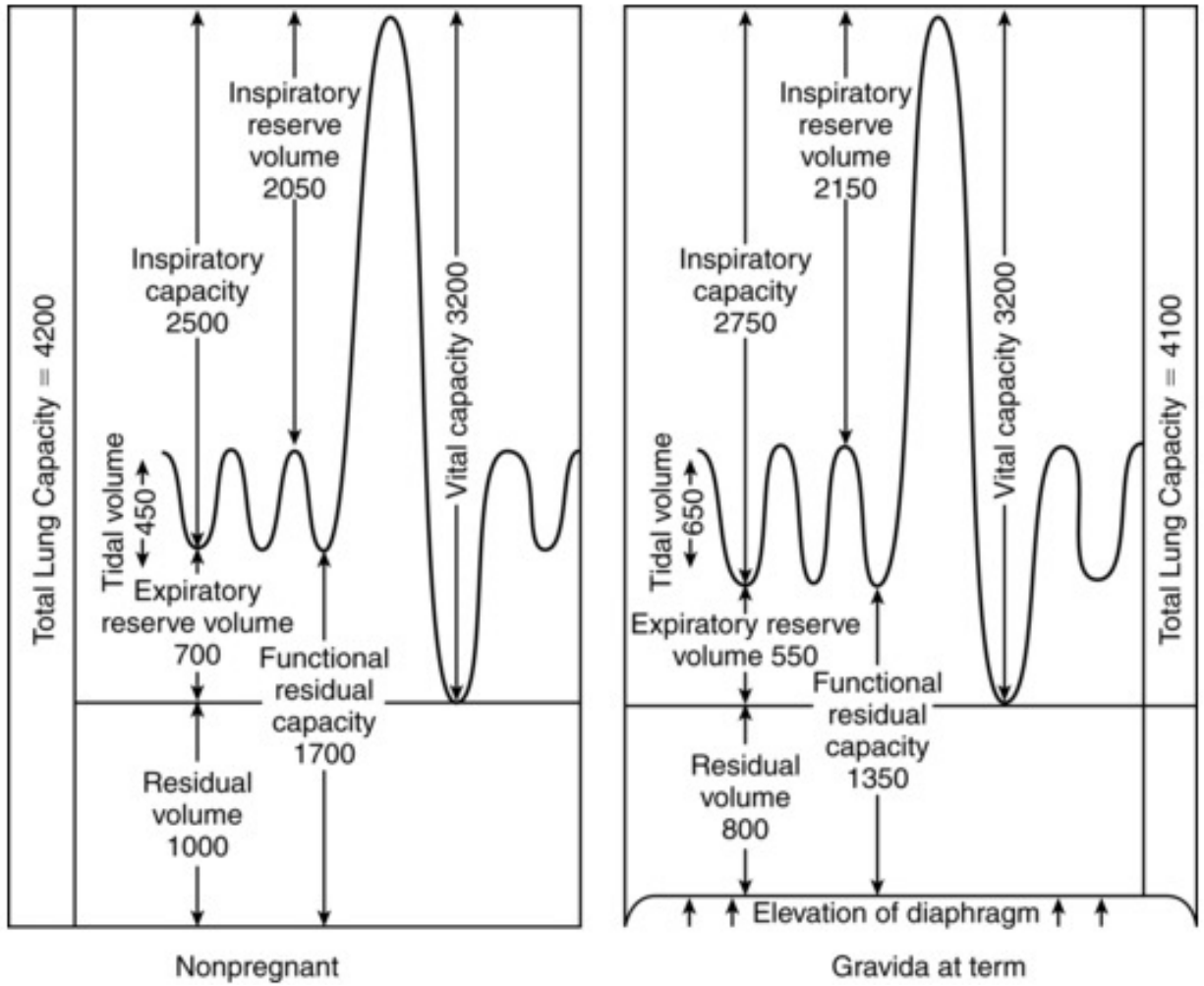
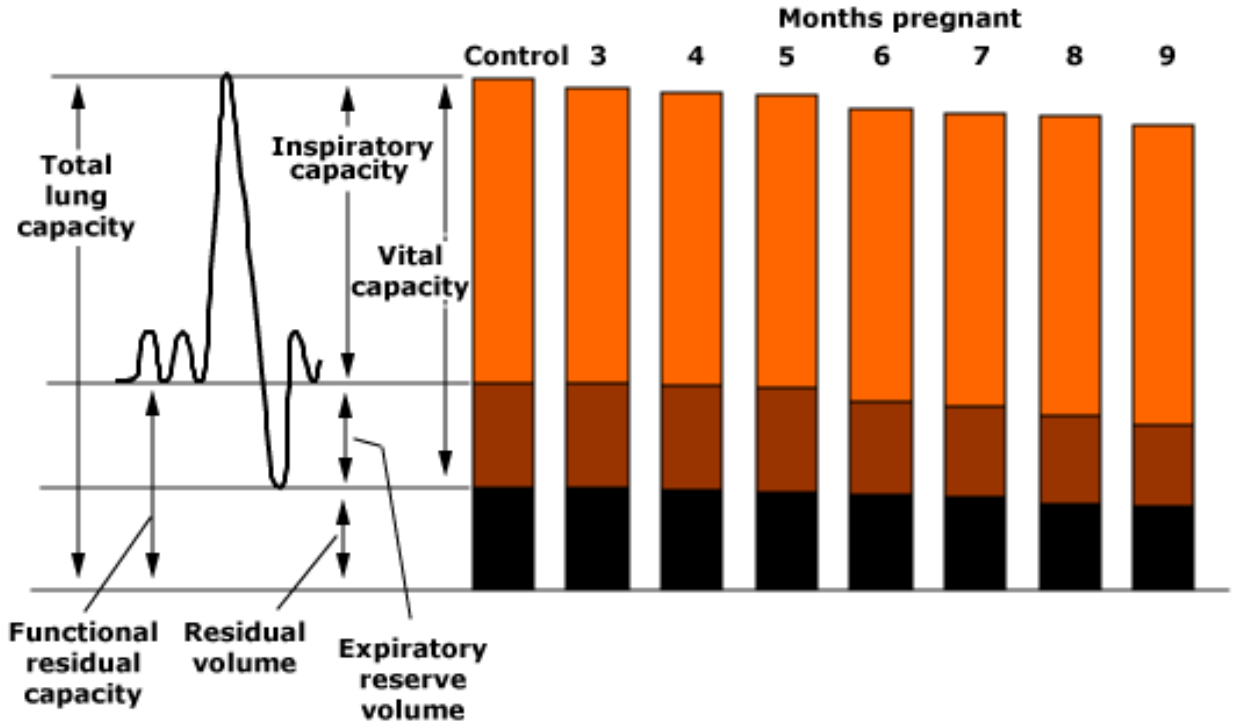


Thorax	
Chest wall compliance	Decreased
Thoracic diameter	Increased
Diaphragm	Elevated
Lung compliance	Unchanged
Lung Volumes	
Total lung capacity	Slightly increased
Vital capacity	Slightly increased
Inspiratory capacity	Slightly increased
Functional residual capacity	Decreased
Residual volume	Slightly decreased
Expiratory reserve volume	Decreased
Spirometry	
FEV1, FVC, FEV1/FVC	Unchanged
Ventilation	
Minute ventilation	Increased
Tidal volume	Increased
Respiratory rate	Unchanged
Blood gas	
pH	Normal
PaO2	Slightly elevated (100-105 mmHg)
PaCO2	Slightly decreased (32-34 mmHg)
Bicarbonate	Slightly decreased (15-21 mmHg)

Changes in pulmonary function tests during pregnancy



Serial measurements of lung volume compartments during pregnancy. Functional residual capacity decreases approximately 20 percent during the latter half of pregnancy, due to a decrease in both expiratory reserve volume and residual volume.

Redrawn from Prowse, CM, Gaensler, EA, Anesthesiology 1965; 26:381.

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Respiratory disease in pregnancy

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Asthma

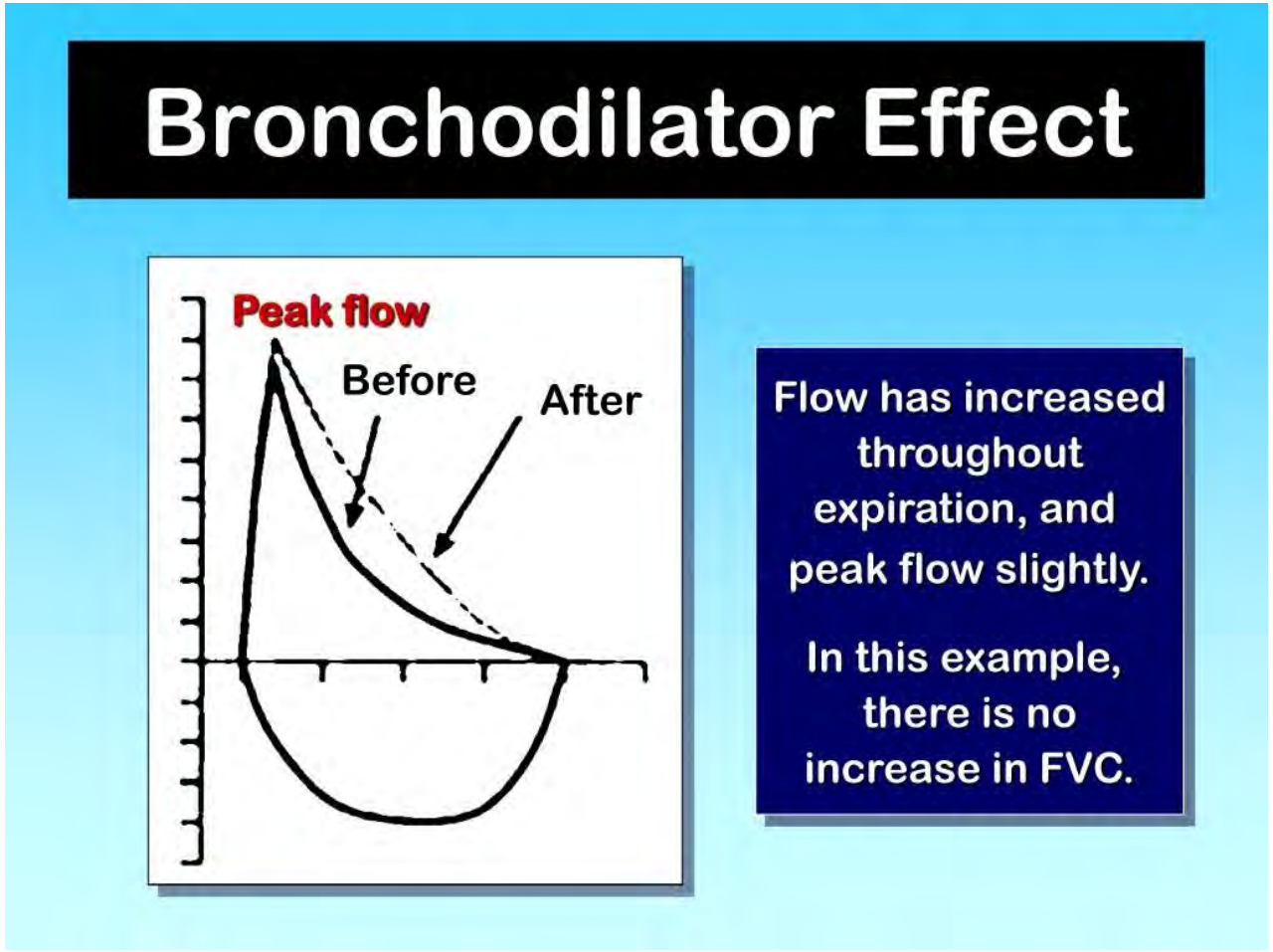
Reactive airway disease

- Chronic airway inflammation with increased responsiveness to stimuli leading to airway obstruction
- Complicates 4-8% of pregnancies
- Increasing prevalence and morbidity

Asthma

Diagnosis

- Signs and symptoms: Cough, wheezing, chest tightness, dyspnea
- Typically enter pregnancy with a diagnosis
- Dx is made when FEV1 is reduced at baseline but improves by greater than 12% with bronchodilator administration
- PFTs are safe in pregnancy
- Methacholine testing is not advised
- Consider testing for IgE antibodies to specific triggers

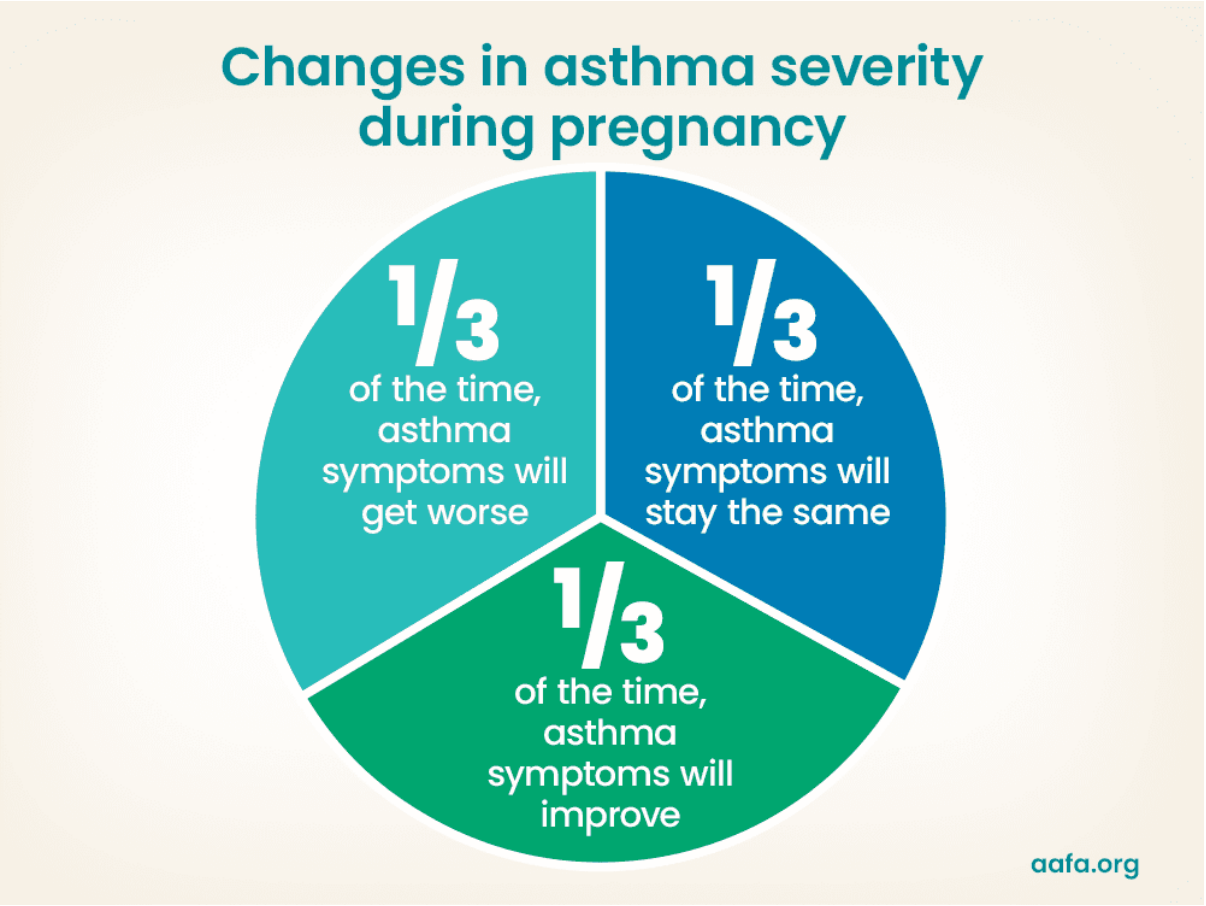


Components of Severity		Classification of Asthma Severity (Youths ≥12 years of age and adults)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment **Normal FEV_1/FVC:** **8–19 yr 85%** **20–39 yr 80%** **40–59 yr 75%** **60–80 yr 70%**	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not >1x/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 ≥80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV_1			

Asthma

Effects of pregnancy on asthma

- Mild
  - 12.6% exacerbation
  - 2.3% hospitalization
- Moderate
  - 25.7% exacerbation
  - 6.8% hospitalization
- Severe
  - 51.9% exacerbation
  - 26.9% hospitalization



Asthma

Effects of asthma on Pregnancy

TABLE 3
Singleton pregnancy complications among US women with asthma

Outcomes	No asthma n = 206,468 n (%)	Asthma n = 17,044 n (%)	Site-adjusted *P* value[a]	Site-adjusted odds ratio (95% CI)[a]	Fully adjusted odds ratio (95% CI)[a,b]
Hypertensive disorders of pregnancy					
Superimposed preeclampsia	1680 (0.8)	213 (1.3)	< .0001	1.54 (1.33–1.79)	1.34 (1.15–1.56)
Eclampsia	207 (0.1)	33 (0.2)	.01	1.61 (1.10–2.36)	1.41 (0.96–2.07)
Preeclampsia	9628 (4.7)	924 (5.4)	< .0001	1.24 (1.16–1.33)	1.14 (1.06–1.22)
Gestational hypertension	5523 (2.7)	557 (3.3)	.0003	1.18 (1.08–1.30)	1.08 (0.98–1.19)
Maternal seizure					
All maternal seizures	176 (0.1)	33 (0.2)	.0008	1.93 (1.32–2.83)	1.79 (1.21–2.63)
Maternal seizure without hypertension noted	93 (0.05)	14 (0.09)	.19	1.45 (0.83–2.55)	1.35 (0.77–2.37)
Maternal seizure with hypertension noted	83 (0.05)	19 (0.12)	.0006	2.51 (1.48–4.25)	2.37 (1.40–4.02)
Other pregnancy complications					
Gestational diabetes	10,420 (5.1)	927 (5.4)	.06	1.07 (1.00–1.15)	1.11 (1.03–1.19)
Chorioamnionitis	6415 (3.1)	504 (3.0)	.32	1.05 (0.95–1.16)	1.06 (0.96–1.17)
Placenta previa	1444 (0.7)	141 (0.8)	.06	1.19 (0.99–1.42)	1.30 (1.08–1.56)
Complications of labor and delivery					
Prelabor cesarean delivery	23,688 (11.5)	2193 (12.9)	< .0001	1.15 (1.10–1.21)	1.16 (1.09–1.23)
Spontaneous labor	111,523 (54.0)	8921 (52.3)	< .0001	0.86 (0.84–0.89)	0.87 (0.84–0.90)
Cesarean delivery after spontaneous labor	18,835 (9.1)	1749 (10.3)	.0003	1.10 (1.05–1.16)	1.06 (1.00–1.12)
Induction	71,257 (34.5)	5930 (34.8)	< .0001	1.10 (1.06–1.13)	1.10 (1.06–1.14)
Cesarean delivery after induction	14,746 (7.1)	1381 (8.1)	< .0001	1.22 (1.15–1.29)	1.17 (1.10–1.24)
All vaginal delivery	149,199 (72.3)	11,721 (68.8)	< .0001	0.84 (0.81–0.87)	0.84 (0.80–0.87)
PPROM	4596 (2.2)	516 (3.0)	< .0001	1.23 (1.12–1.36)	1.18 (1.07–1.30)
PROM	14,379 (7.0)	1212 (7.1)	.98	1.00 (0.94–1.07)	0.99 (0.93–1.05)
Breech presentation	8785 (4.3)	811 (4.8)	.01	1.10 (1.02–1.19)	1.13 (1.05–1.22)
Placental abruption	3242 (1.6)	380 (2.2)	< .0001	1.27 (1.14–1.42)	1.22 (1.09–1.36)
Maternal hemorrhage	13,423 (6.5)	1292 (7.6)	.001	1.11 (1.04–1.18)	1.09 (1.03–1.16)
Maternal pulmonary embolism	114 (0.06)	20 (0.12)	.008	1.90 (1.18–3.07)	1.71 (1.05–2.79)
Maternal postpartum fever	5531 (2.7)	532 (3.1)	.35	1.05 (0.95–1.15)	0.99 (0.90–1.09)
Maternal ICU admission	902 (0.6)	73 (0.6)	.01	1.38 (1.08–1.76)	1.34 (1.04–1.72)
Maternal death	18 (0.01)	1 (0.01)	.70	Not calculated	Not calculated
Low birthweight, <2500 g	16,551 (8.1)	1815 (10.7)	< .0001	1.26 (1.19–1.33)	1.16 (1.10–1.23)
Preterm birth, <37 wk	23,618 (11.4)	2526 (14.8)	< .0001	1.25 (1.19–1.31)	1.17 (1.12–1.23)
Intrauterine fetal death	1148 (0.6)	110 (0.7)	.26	1.12 (0.92–1.38)	1.07 (0.87–1.32)

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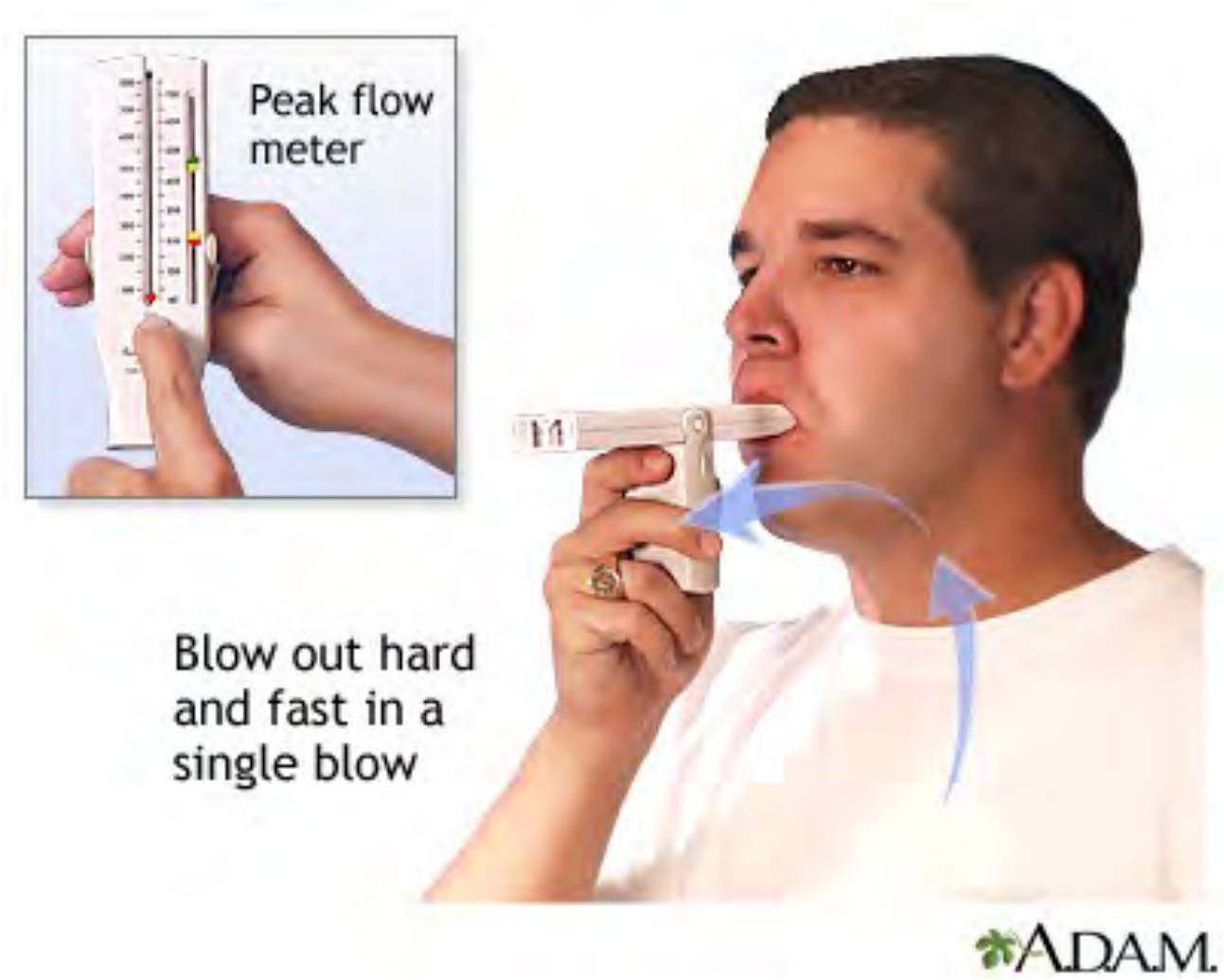
Asthma

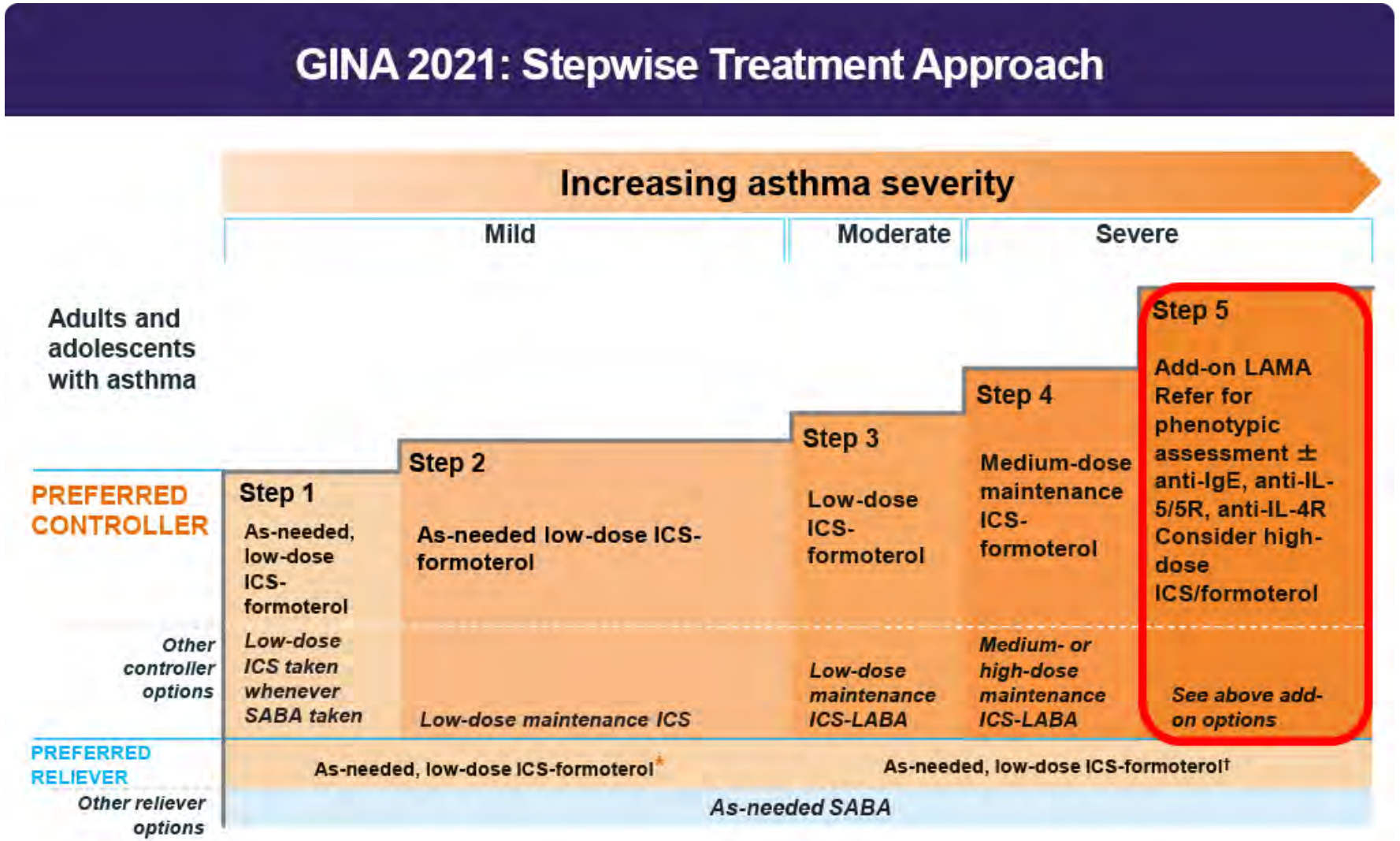
Treatment

- Avoiding triggers
- Continuing prepregnancy meds
  - Known decrease in Rx fills in the first trimester
- Establish a baseline
  - FEV1 requires PFTs
  - PEFR (peak flows) do not
    - Establish a PEFR when healthy
    - Green zone >80%
    - Yellow zone 50-80%
    - Red zone <50%



Asthma

Chronic Pharmacotherapy



FDA = US Food and Drug Administration; ICS = inhaled corticosteroid; Ig = immunoglobulin; IL = interleukin; □LABA = long-acting β2-agonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroid; SABA = short-acting β2-agonist.

Adapted from GINA. Global Strategy for Asthma Management and Prevention. Updated 2021 (https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf). Accessed 7/25/21.

Medication	Low dose	Medium dose	High dose
ICS-SABA combination			
Budesonide-albuterol HFA (Brand name: Airsupra)*			
NOTE: Not used for maintenance therapy. Acute symptom relief: Budesonide-albuterol (80 mcg/90 mcg) 2 inhalations as needed (usual maximum: 12 inhalations/day).			
ICS-LABA combinations			
Beclomethasone [beclometasone]-formoterol DPI or HFA (Not available in United States or Canada, but available elsewhere [sample brand names: Formodual, Fostair, Foster])¶ Δ			
100 mcg/6 mcg	1 inhalation twice a day	2 inhalations twice a day	
200 mcg/6 mcg			2 inhalations twice a day
Budesonide-formoterol HFA (Brand names: Symbicort, Breyna)¶			
80 mcg/4.5 mcg	2 inhalations twice a day		
160 mcg/4.5 mcg		2 inhalations twice a day	
Fluticasone furoate-vilanterol DPI (Brand name: Breo Ellipta)Δ			
NOTE: Inhaled fluticasone furoate has a greater anti-inflammatory potency per microgram than fluticasone propionate inhalers. Thus, fluticasone furoate is administered at a lower daily dose and used only **once** daily.			
50 mcg/25 mcg◇	1 inhalation once daily		
100 mcg/25 mcg		1 inhalation once daily	
200 mcg/25 mcg			1 inhalation once daily
Fluticasone propionate-formoterol MDI (Not available in United States or Canada, but available elsewhere [sample brand name: Flutiform])			
50 mcg/5 mcg	2 inhalations twice daily		
125 mcg/5 mcg		2 inhalations twice daily	
250 mcg/10 mcg			2 inhalations twice daily
Fluticasone propionate-salmeterol DPI (Brand names: Advair Diskus, Wixela Inhub)Δ			
100 mcg/50 mcg	1 inhalation twice a day		
250 mcg/50 mcg		1 inhalation twice a day	
500 mcg/50 mcg			1 inhalation twice a day
Fluticasone propionate-salmeterol HFA (Brand name: Advair HFA)			
45 mcg/21 mcg	2 inhalations twice a day		
115 mcg/21 mcg		2 inhalations twice a day	
230 mcg/21 mcg			2 inhalations twice a day

Asthma

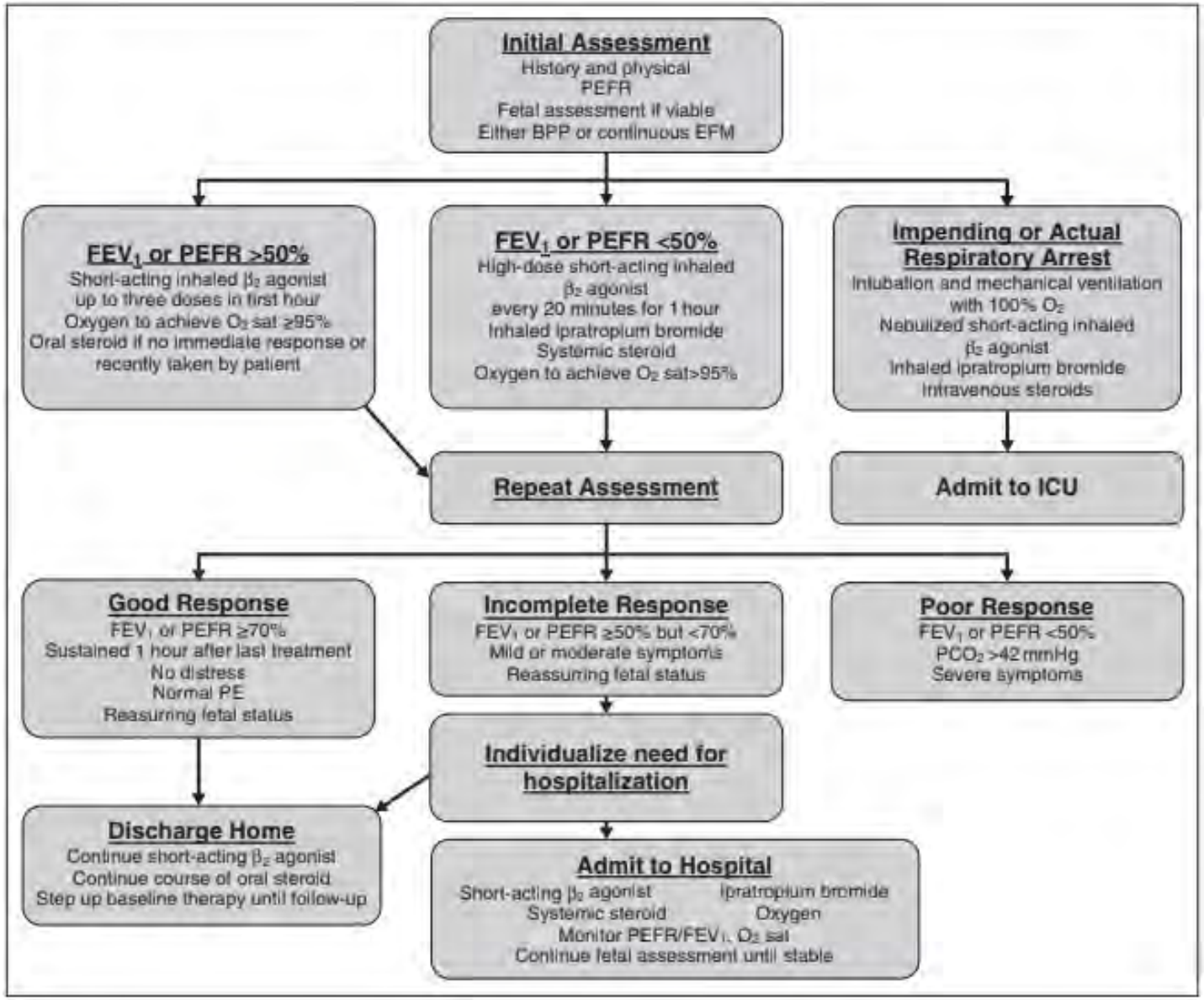
Less common meds in pregnancy

- Theophylline
  - Phosphodiesterase and adenosine receptor blocker
  - Lots of side effects
  - Requires blood level monitoring
- Leukotriene modulators (motelukast)
  - Blocks leukotrienes from causing bronchospasm
  - Used in aspirin mediated bronchospasm
  - Probably safe in pregnancy
- Omalizumab
  - Monoclonal antibody against IgE
  - No observed harm in limited data

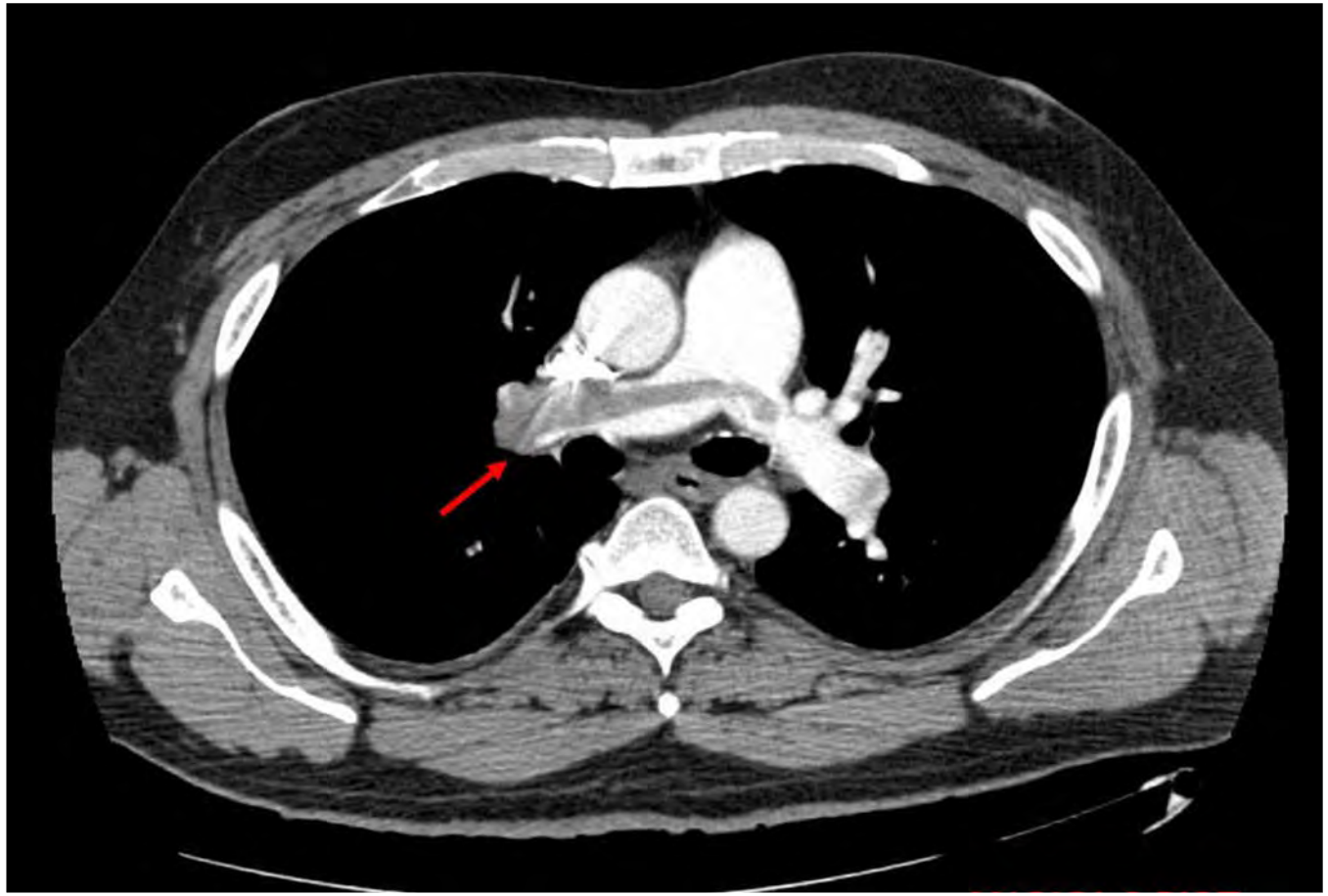
Asthma

Treating an acute exacerbation

- Alterations to typical asthma care:
  - Consider fetal monitoring
  - Higher SpO2 goals
  - Lower CO2 threshold
  - Less reserve



Pulmonary embolism



Pulmonary embolism

Epidemiology

- 6th leading cause for maternal mortality in U.S.
- 10-30% of maternal deaths
- Absolute incidence 0.1%
- 14% increase in VTE-associated pregnancy hospitalizations 1994-2009

Pulmonary embolism

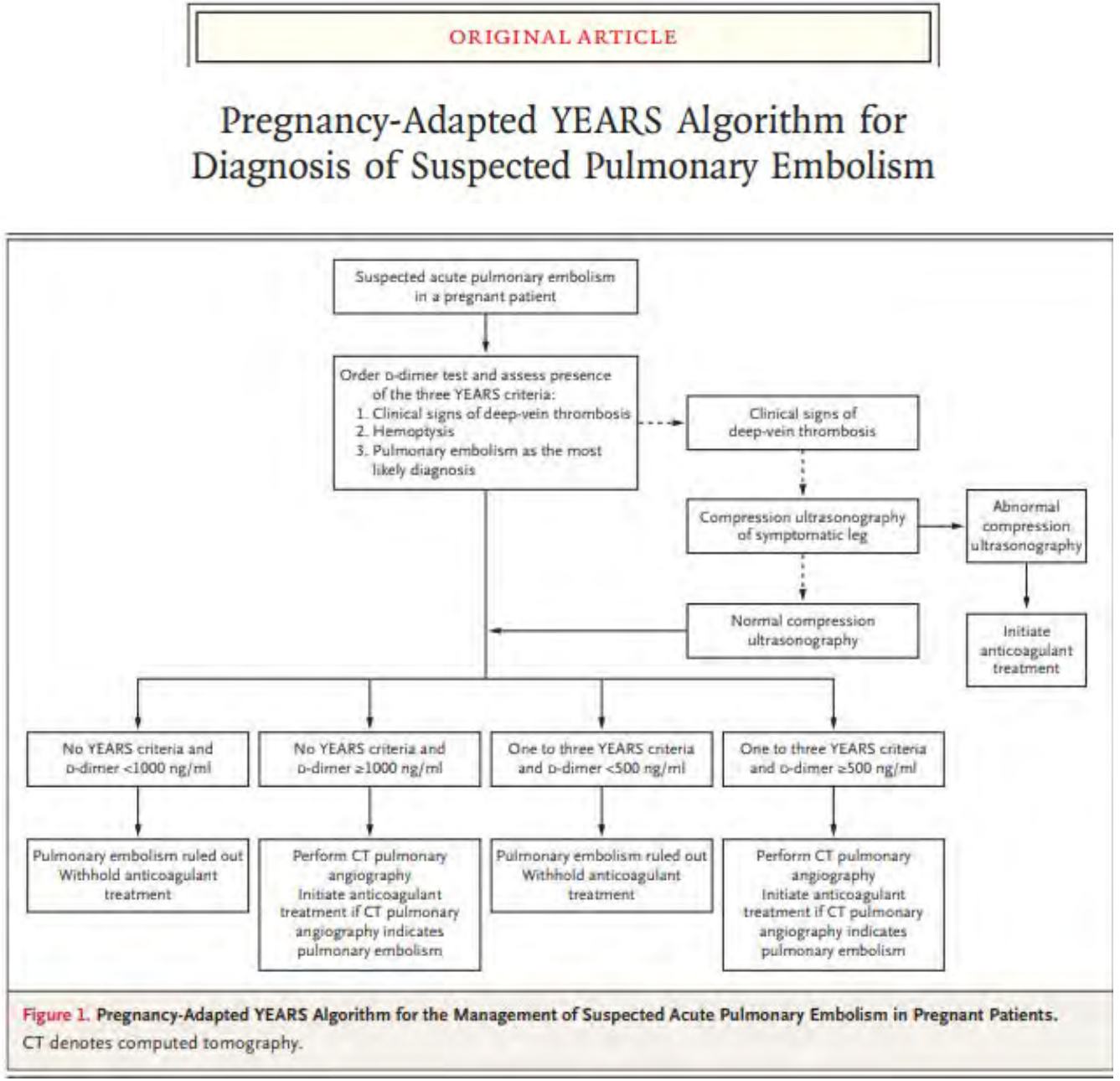
Presentation

- Ranges from asymptomatic to sudden death
- Overlap with normal physiologic symptoms of pregnancy
- Small case series of 38 patients
  - 62% dyspnea
  - 55% pleuritic chest pain
  - 24% cough
  - 18% sweating

Pulmonary embolism

Workup

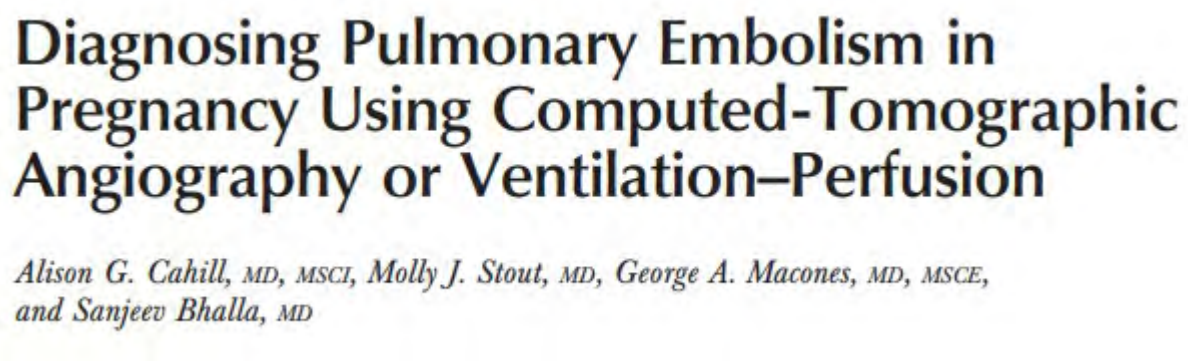
- Arterial blood gases not useful
  - 59% patients with normal a-a gradient
- D-dimer not typically used
  - Lack of normal reference in pregnancy
  - Sensitivity of 73%: so not too useful when negative
- Well's criteria not useful
  - High prevalence of tachycardia



Pulmonary embolism

Workup

- VQ scan: test of choice with normal CXR
  - High rate of indeterminate scans in general population
    - Due to CXR anomalies
  - 75-93% diagnostic VQ scans in pregnancy
  - "Normal:" 0-6% chance of PE
  - "High:" 56-96% chance of PE
- CT pulmonary angiography
  - High negative predictive value in pregnancy
  - BUT, up to 30% nondiagnostic in pregnancy (U-King-Im, 2008)
  - Consider when VQ scan not available or indeterminate
  - Is comparable or inferior to VQ scan in pregnancy


Diagnosing Pulmonary Embolism in Pregnancy Using Computed-Tomographic Angiography or Ventilation–Perfusion

Alison G. Cahill, MD, MSCI, Molly J. Stout, MD, George A. Macones, MD, MSCE, and Sanjeev Bhalla, MD

Pulmonary embolism

Radiation exposure

- What is the radiation risk?
  - CTPA has lower fetal radiation than VQ
    0.003-0.131 mGy vs 0.32-0.74 mGy
  - CTPA has higher maternal radiation than VQ
    - 7.3 vs 0.9 mSv
  - VQ delivers 150-fold lower breast/lung radiation
  - CXR + VQ scan + CTPA is still less than 0.5 rad

Table 1:
Potential Health Effects (Other Than Cancer) of Prenatal Radiation Exposure

Acute Radiation Dose* to the Embryo/Fetus	Time Post Conception Up to 2 weeks	Time Post Conception 3rd to 5th weeks	Time Post Conception 6th to 13th weeks	Time Post Conception 14th to 23rd weeks	Time Post Conception 24th week to term
< 0.10 Gy (10 rads)†	Non-cancer health effects NOT detectable				
0.10–0.50 Gy (10–50 rads)	Failure to implant may increase slightly, but surviving embryos will probably have no significant (non-cancer) health effects.	Growth restriction possible	Growth restriction possible	Non-cancer health effects unlikely	
> 0.50 Gy (50 rads) The expectant mother may be experiencing acute radiation syndrome in this range, depending on her whole-body dose.	Failure to implant will likely be high, depending on dose, but surviving embryos will probably have no significant (non-cancer) health effects.	Probability of miscarriage may increase, depending on dose. Probability of major malformations, such as neurological and motor deficiencies, increases. Growth restriction is likely	Probability of miscarriage may increase, depending on dose. Growth restriction is likely.	Probability of miscarriage may increase, depending on dose. Growth restriction is possible, depending on dose. (Less likely than during the 6th to 13th weeks post conception) Probability of major malformations may increase	Miscarriage and neonatal death may occur, depending on dose.

Pulmonary embolism

Treatment

- Therapeutic anticoagulation
  - Lovenox > heparin gtt
- Suction thrombectomy?
- Catheter directed lytics?
- Systemic lytics?
  - Complication rate similar to non-pregnant population: 1% mortality, 8% maternal hemorrhage
  - PPH risk highest if used within 8 hours of delivery
  - 6% fetal loss rate possibly causal by thrombolytic therapy
  - No issues in liveborn children

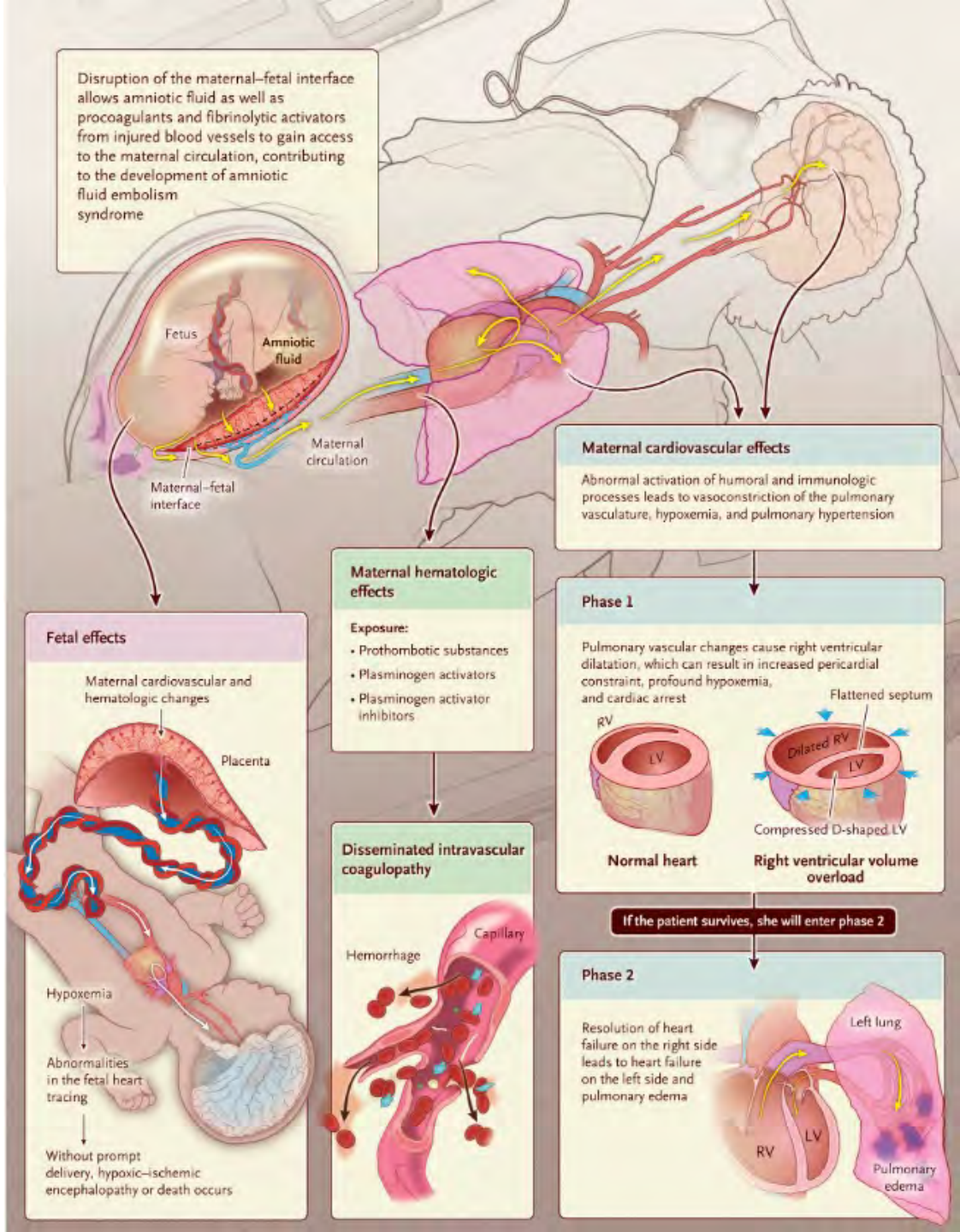
American Heart Association Definitions of Massive, Submassive, and Low-Risk PE and Associated Mortality

PE Classification	Definition	Mortality
Massive	Acute PE with sustained hypotension (< 90 mm Hg systolic) > 15 minutes or requiring inotropic support	25%–65% (62)
Submassive	Systolic pressure > 90 mm Hg and either: (a) RV dysfunction (CT, BNP/proBNP, ECG changes) or (b) myocardial necrosis (elevated troponins)	3% (20)
Low risk	Absence of hypotension, RV dysfunction, and myocardial necrosis	<1% (20)

Note.—BNP = brain natriuretic peptide, ECG = electrocardiography.

Amniotic fluid embolism

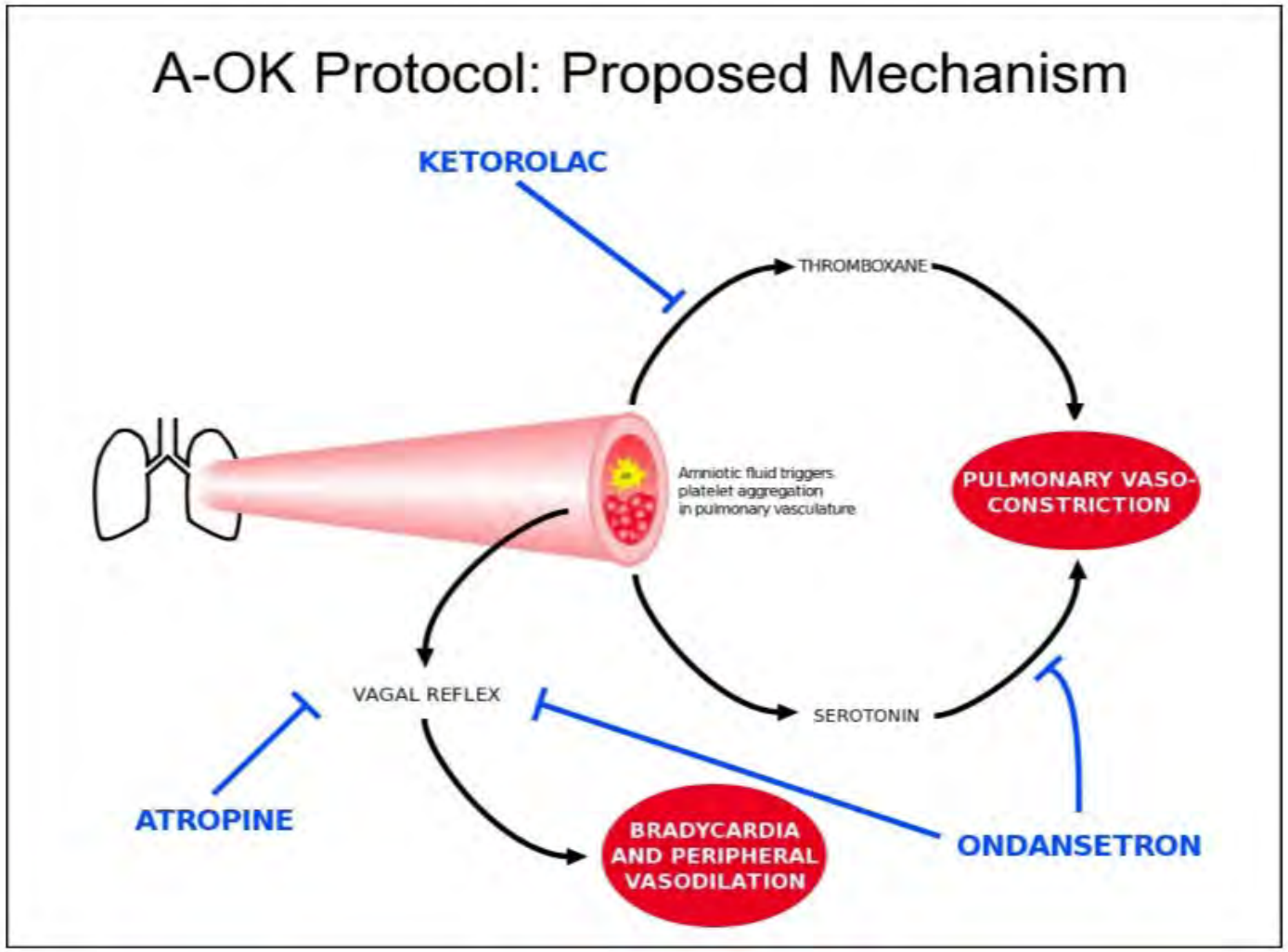
- 1:16,000 to 1:50,000 deliveries
- Disruption of maternal fetal interface
- Most commonly at the time of delivery
- Bad luck->bad heart-> bad blood
  - Acute pulm vasoconstriction
  - Acute RV failure-> arrest (87%)-> LV failure
  - Prothrombotic substance-> DIC
- 20-60% mortality
  - 60% of survivors have neurologic impacts



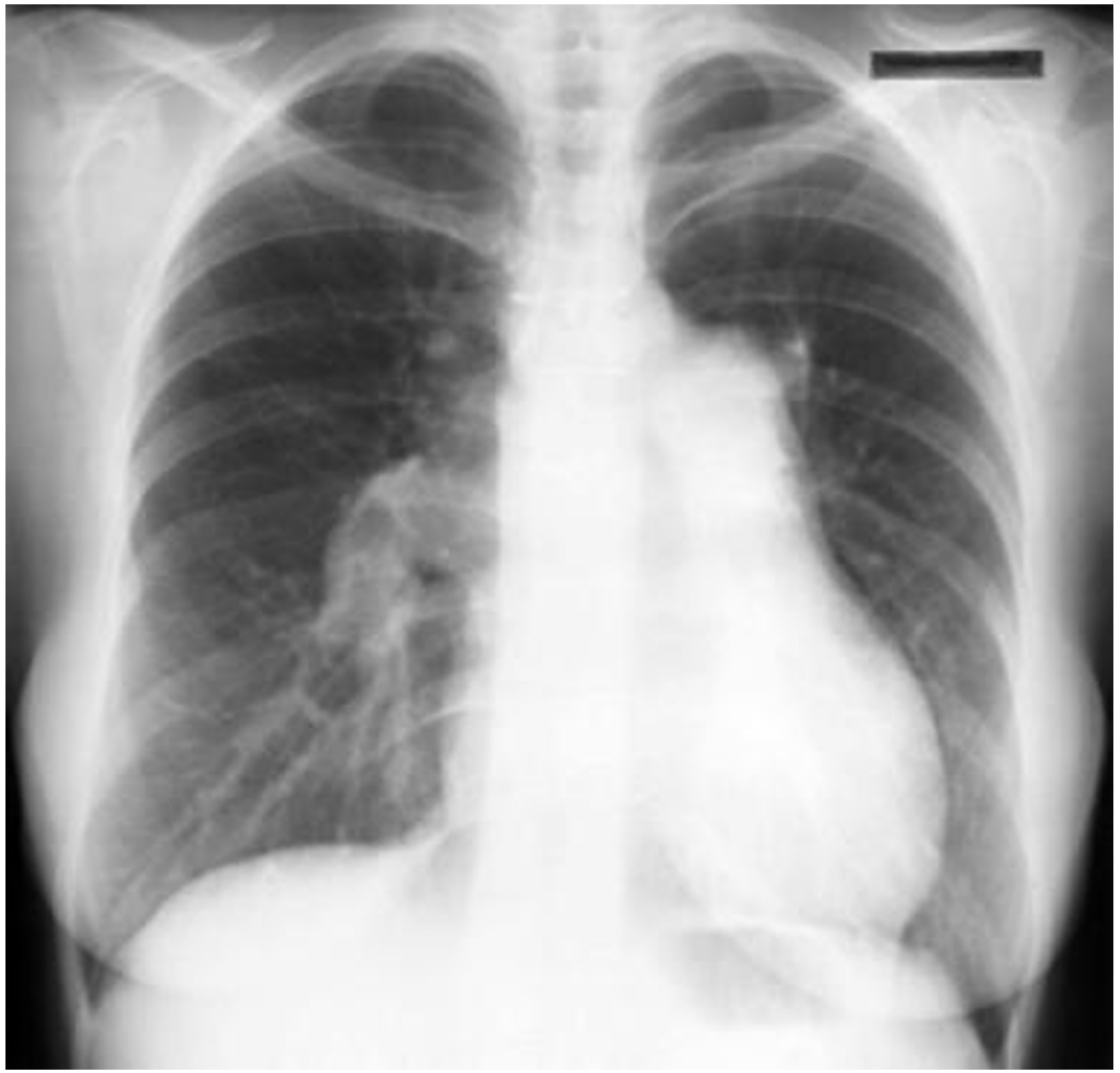
University of Colorado
Anschutz Medical Campus

AFE treatment

- Supportive care
  - ACLS
  - ECMO
- A-OK protocol
  - Atropine
  - Ondansetron
  - ketorolac



Pulmonary Hypertension



Pulmonary Hypertension

- Heterogenous group of diseases (Hemnes, 2015)
  - Characterized by mPAP ≥25 mmHg
  - May be accompanied by increase of pulmonary vascular resistance
  - WHO classification

Pulmonary Hypertension

Table 1.

Table 1. Updated clinical classification of pulmonary hypertension (PH)

View table image

Group	Definition	Selected etiologies
Group 1	Pulmonary arterial hypertension (PAH)	Idiopathic PAH, connective tissue disease–associated PAH, congenital heart disease–associated PAH, heritable PAH, schistosomiasis-associated PAH, persistent PH of the newborn
Group 2	PH due to left heart disease	Left ventricular systolic dysfunction, left ventricular diastolic dysfunction, aortic or mitral valvular heart disease
Group 3	PH due to lung diseases and/or hypoxia	Chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, developmental lung disease
Group 4	Chronic thromboembolic PH	
Group 5	PH with unclear multifactorial mechanisms	Sarcoidosis, chronic hemolytic anemia

Note Adapted from Simonneau et al.[1]

Pulmonary Hypertension

- Improved outcomes in modern era, but mortality remains high (Hemnes, 2015)
  - 30-56% in older studies
  - 16-22% in recent studies
    - Subject to publication bias, availability of termination
  - Rapid deterioration occurs 20-24 weeks GA
  - Usually due to RV failure

Pulmonary Hypertension

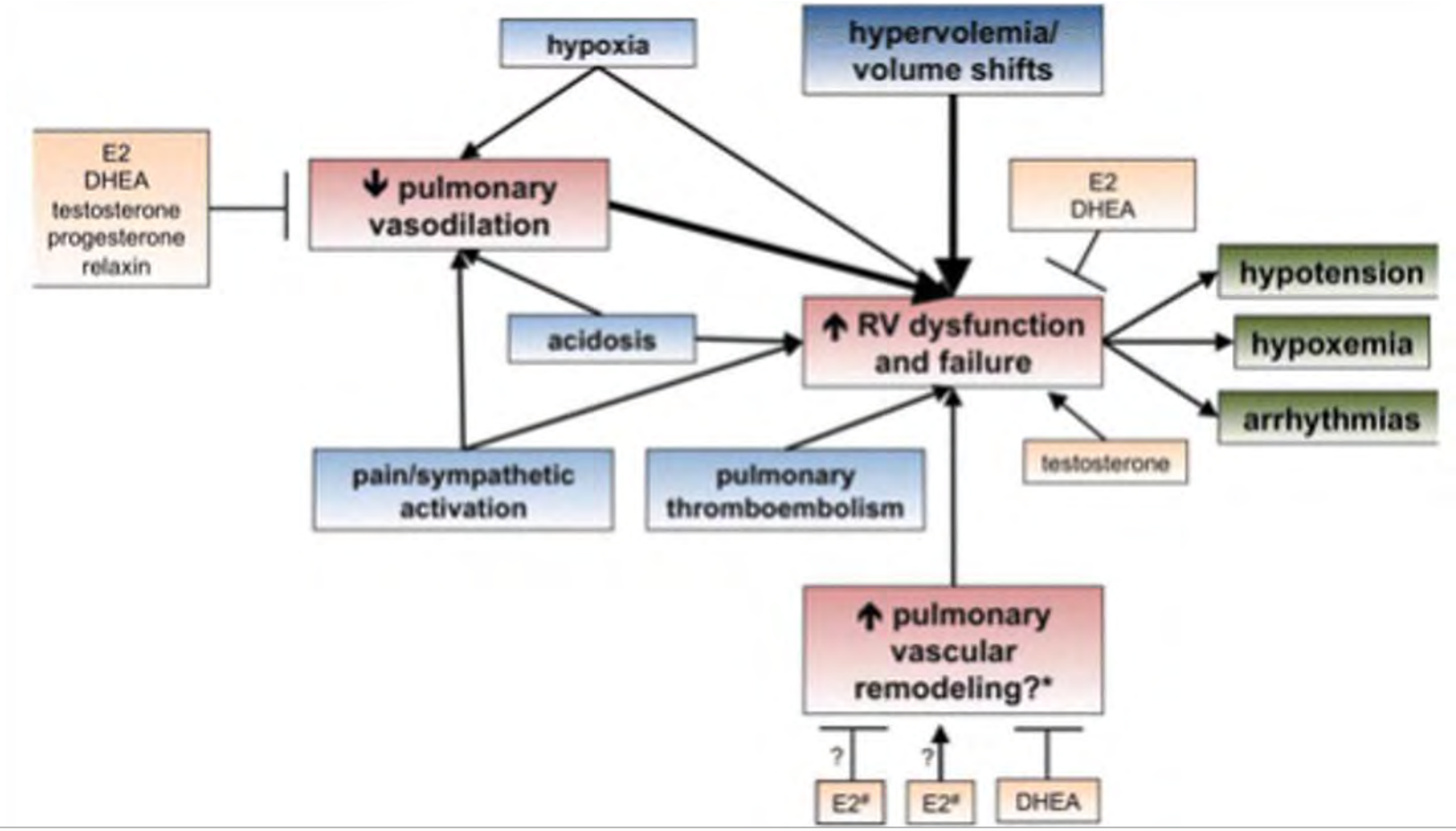


Figure 3. Pathophysiology of pulmonary hypertension (PH) and right ventricular (RV) dysfunction in pregnancy. Items in red represent the underlying preexisting alterations in PH; items in blue represent pregnancy-related modifiers that may aggravate these alterations. Potential contributions of sex hormones are shown in yellow (derived from studies in normal animals as well as PH models). Decreased pulmonary

Pulmonary Hypertension

Figure 2. Adaptation of the pulmonary vascular system and the right ventricle (RV) to increased pulmonary blood flow during pregnancy in a healthy patient and in pulmonary vascular disease. Note that the diseased pulmonary vasculature in pulmonary arterial hypertension (PAH; characterized by vasoconstriction, pulmonary vascular remodeling with lumen obliteration, and in situ thrombosis) is unable to accommodate the increased cardiac output, thus leading to RV strain, dilation, and eventually decompensation. PE: pulmonary embolism.

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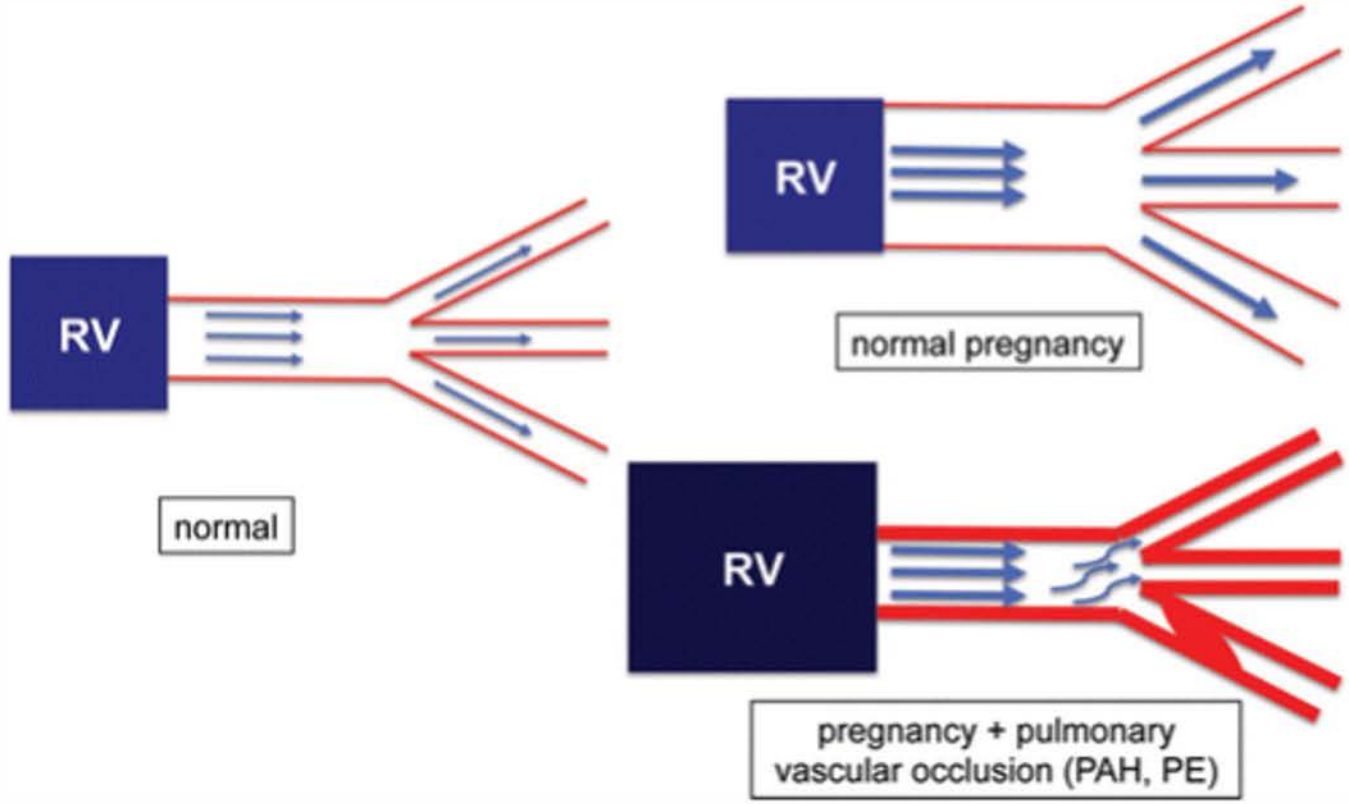

Pulmonary Hypertension

- All patients should be counseled to avoid pregnancy (Hemnes, 2015)
  - Especially with pulmonary arterial hypertension
- Permanent contraception should be strongly considered in pregnancy
  - Hysteroscopic sterilization or laparoscopic BTL
  - Progestin-only is second-line
  - Estrogen contraindicated

Pulmonary Hypertension

- Well, she's pregnant.

Pulmonary Hypertension

- Well, she's pregnant.
- Now what?

Pulmonary Hypertension

- Genetic counseling (Hemnes, 2015)
  - Should be offered to all patients with idiopathic or hereditary PH
  - BMPR2 mutations in 80% of families
    - Other mutations also known (CAV1, KCNK3, EIF2AK4)
  - Dominant gene with weak penetrance
    - Only 20% will develop clinical PH

Pulmonary Hypertension

- Pregnancy management (Hemnes, 2015)
  - Counsel and offer termination
  - Multidisciplinary Team
    - MFM, pulmonary hypertension specialist, cardiologist, anesthesiologist, neonatologist
  - Highest risk period is peripartum and up to 2 months postpartum
  - Cesarean section recommended over VD
  - Epidrual or spinal recommended over general
  - Avoid vasalvagal triggers

Pulmonary Hypertension

- Medications (Hemnes, 2015)
  - Prostaglandins are potent pulmonary vasodilators and recommended in RV impairment
    - Epoprostenol, treprostinil, and iloprost
  - Phosphodiesterase 5 inhibitors
    - Experience with sildenafil + prostaglandin in pregnancy
    - Monotherapy reserved for normal RV function
  - Calcium channel blockers
    - Improved prognosis if used in patients who respond to inhaled vasodilator
  - Endothelin receptor antagonists
    - Ambrisentan, bosentan, macitentan, and sitaxentan
    - Category X

Pulmonary Hypertension

Figure 4. Recommended evaluation of and follow-up for a pregnant patient with pulmonary arterial hype
natriuretic peptide; ETRA: endothelin receptor antagonist; FC: World Health Organization function class; I
low-molecular-weight heparin; PH: pulmonary hypertension; RV: right ventricular; 6MWT: 6-minute walk

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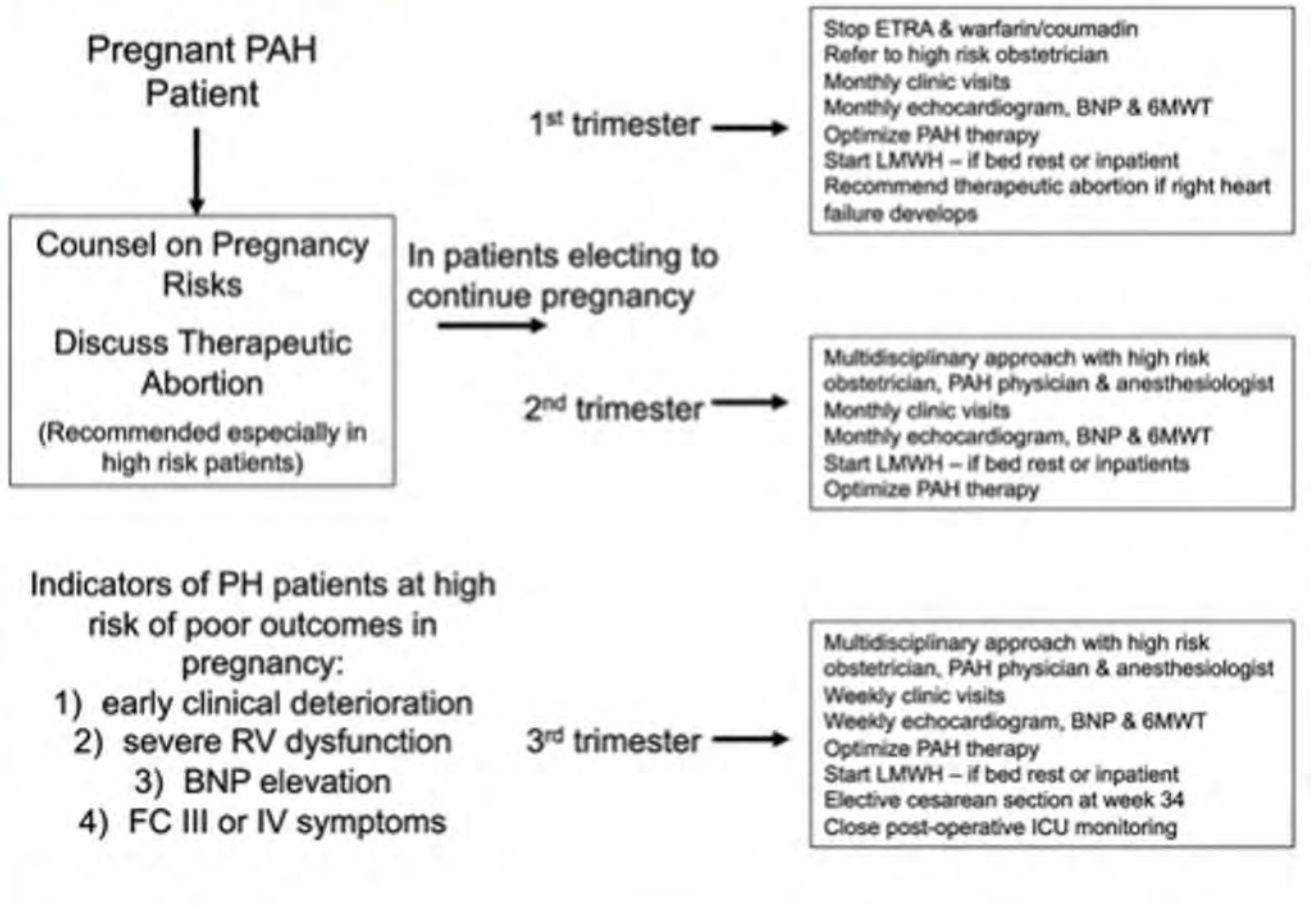
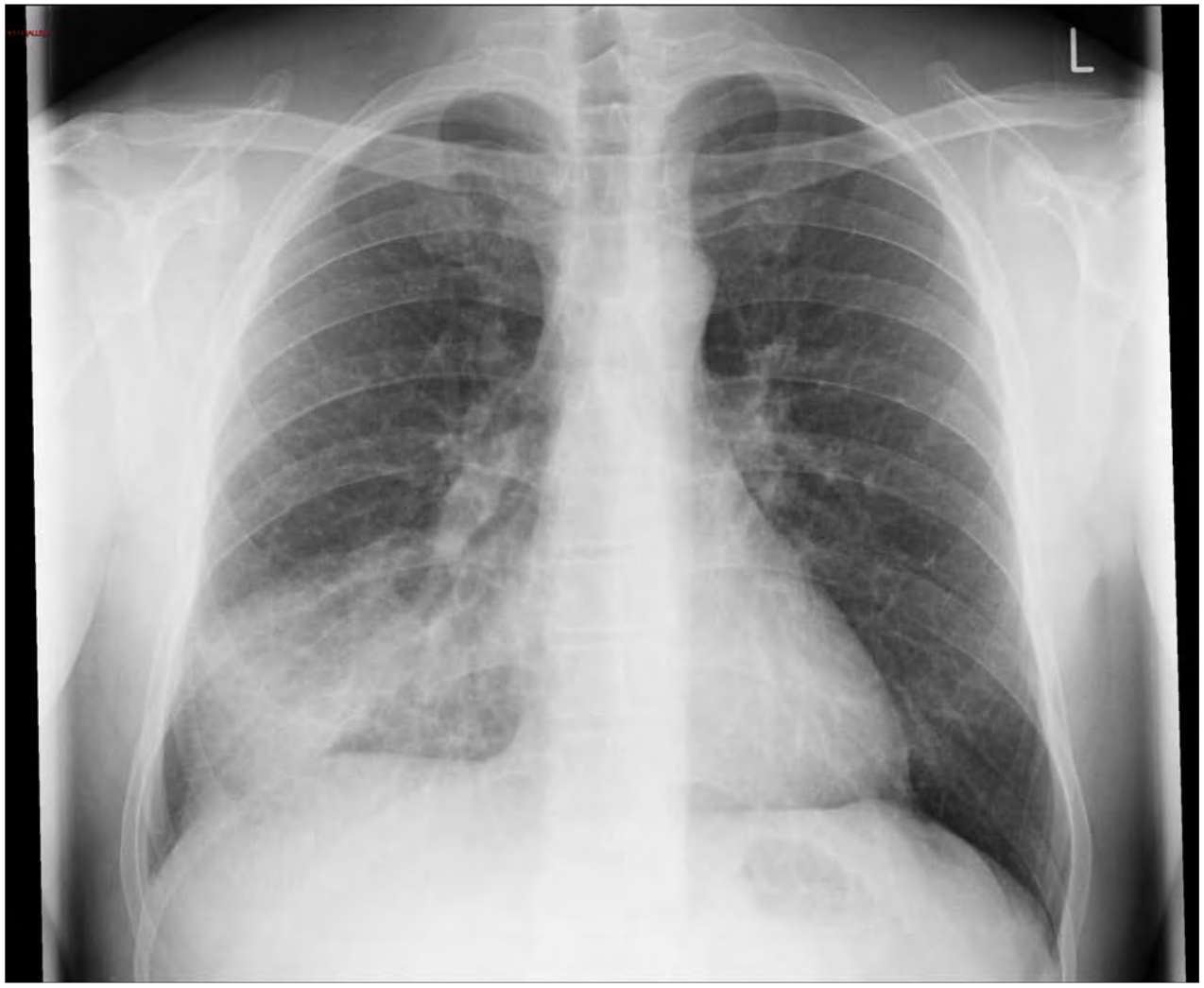


Pulmonary Hypertension

- Delivery management (Hemnes, 2015)
  - Consider IV prostaglandins
  - Central venous catheter, arterial line
  - Swan-Ganz catheterization not recommended
  - Prophylactic heparin recommended

Pneumonia



Pneumonia

- 1.2-2.7 per 1,000 deliveries, 0-4% mortality (Lim 2001)
  - Not significantly different from nonpregnant
- Associated with:
  - Preterm <34 week delivery (34%)
  - LBW (16%)
- No clear evidence on perinatal mortality

Pneumonia

- Risk factors (Lim 2001)
  - Asthma
  - Tocolysis
  - Smoking
  - ?Steroids for fetal lung maturity
  - Underlying lung disease
- Misdiagnosis common in pregnancy
    - Up to 20%
    - Leading misdiagnosis: pyelenephritis, appendicitis, PTL
- Diagnosis by CXR

Pneumonia

- Pathogens (Lim 2010)
  - Bacterial
    - –S. pneuomoniae and H. influenzae
    - –Legionella and mycoplasma rare
      - »Publication bias?
    - –Coxiella burnetti (Q fever)
      - »Contact with newborn animals
      - »Poor fetal outcome
        - 15 case series: 10 SABs, 3 PTD, 2 normal

Pneumonia

- Pathogens
  - Influenza virus (Jamieson 2009)
    - H1N1 epidemic in 2009
    - Pregnant women not more susceptible, but more severely affected
      - 1% general population mortality, 5% in pregnancy
      - Severe morbidity in 3T and 4 weeks postpartum
    - Fetal anomalies associated with fever in 1T
      - Cleft lip, ONTD, hydrocephlay, cardiac anomalies
      - Attenuated with use of anti-pyretic
    - Also associated with poor obstetrical outcome
      - SAB, PTD, IUGR, IUFD

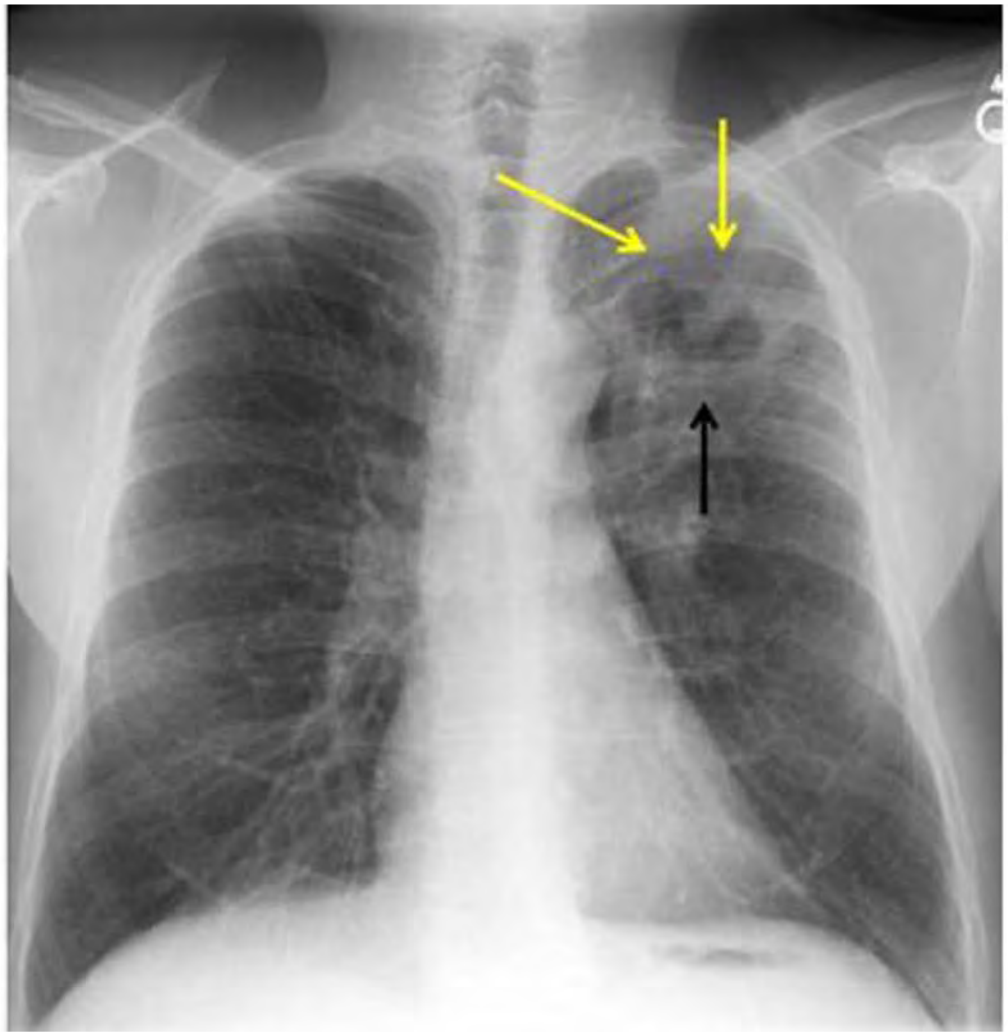
Pneumonia

- Pathogens
  - Varicella virus (Lim 2010)
    - 5-10 per 10,000 pregnancies
    - Pneumonia occurs in 15-20% of pregnant women
    - Mortality as high as 35%
    - Most severe in 3T
    - 2% risk of fetal infection prior to 20 weeks
      - » LBW, scarring of legs/arms/CNS/eyes

Pneumonia

- Pathogens (Lim 2010)
  - Fungal
    - Rare in pregnancy
    - Coccidioidomycosis
      - 10 cases over 6 years
      - Greater risk for dissemination
      - High mortality if aquired in 3T
    - Cryptococcas
      - Rare in immunocompetent individuals
      - 5 cases reported
        - » Cough/dyspnea to severe pleuritic chest pain
        - » No reported deats
      - Blastomycosis
        - » Rare, unclear impact by or on pregnancy

Tuberculosis



Tuberculosis

- Background (Sugarman 2014)
  - More than 200,000 cases of TB in pregnancy worldwide in 2011
  - Pathogenesis similar to nonpregnant popluation
  - Morbidity reflection of general incidence

Tuberculosis

- Diagnosis (Laibl 2005)
  - Routine testing in pregnant women not indicated!
  - Only if indication for treatment
    - Active disease
    - Immunocompromised and at risk for latent TB
  - In absence of this, targeted testing and treatment should be delayed to 3 months postpartum

Tuberculosis

- Testing (Worjohloh 2011)
  - Skin test
  - Interferon gamma release assays
  - Both are safe in and not influenced by pregnancy
- If positive, screen for active disease
  - History
  - Physical
  - CXR

Tuberculosis

Treatment (American Thoracic Society, 2003)

- Latent TB
  - Only if high risk for progression to active disease
  - Daily Isoniazid x 9 months
  - 6-month duration and/or twice weekly directly observed therapy
- Active TB
  - Isoniazid, rifampin, and ethambutol administered x 2 months, AND
  - Isoniazid and rifampin for 7 months
  - Pyrazinamide not absolutely necessary
    - Limited safety data
    - Standard in pregnancy by WHO regimen
    - Consider in complicated cases
  - Streptomycin, kanamycin, amikacin, capreomycin contraindicated
    - Interferes with CN VIII development congenital deafness, renal toxicity

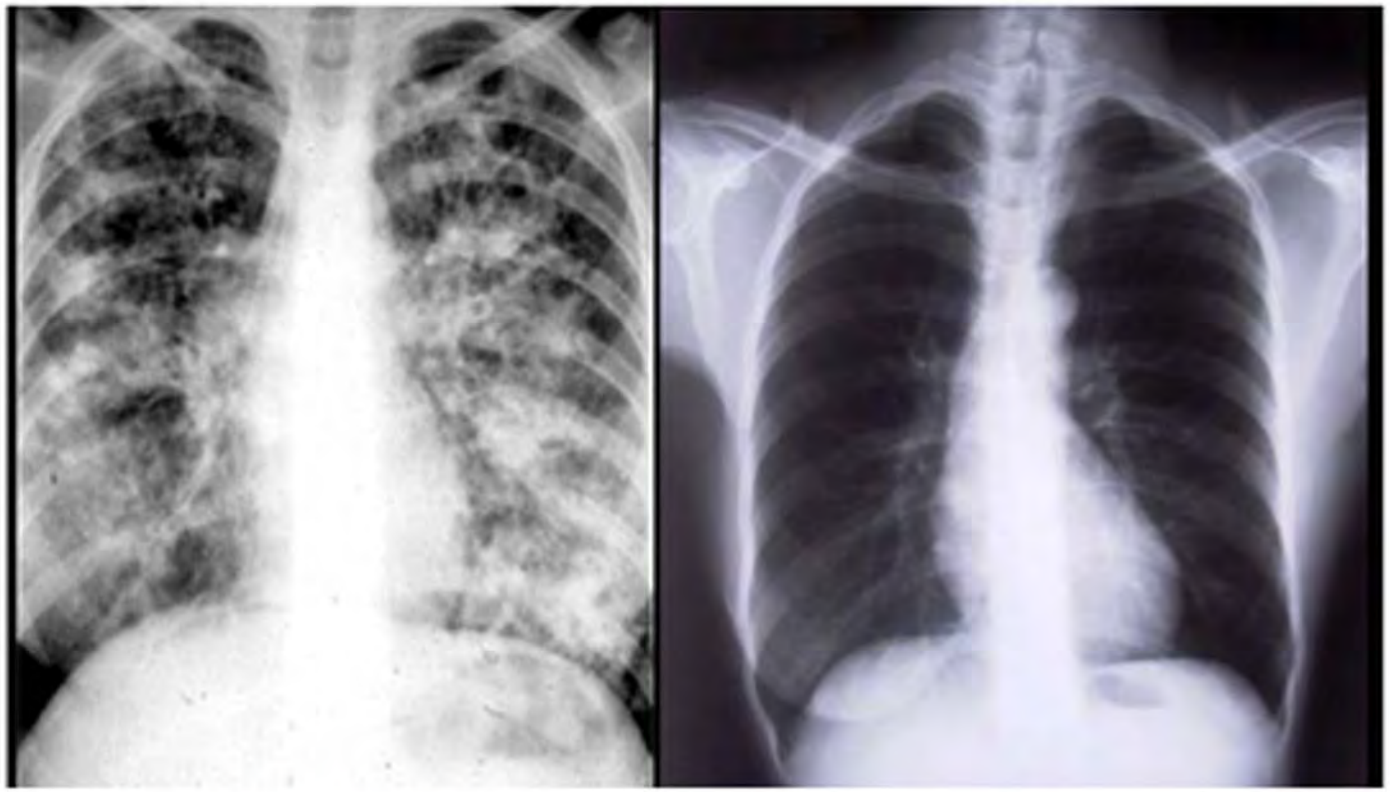
Tuberculosis

- Congenital TB is very rare (Manji 2001)
  - Associated with maternal HIV infection, miliary or uterine TB
  - In regions with high maternal HIV and TB rates
  - Hematogenous spread or fetal aspiration of AF
  - Respiratory distress, fever, hepatosplenomegaly, lethargy, LBW, low Apgars
  - Evaluate with neonatal CSF, placenta AFB stain/cx
  - Mortality of untreated congenital/neonatal TB is 50%

Tuberculosis

- Maternal-Infant separation (Manji 2001)
  - ONLY if mom has suspected active disease
  - Separation until mom is not infectious ONLY if mom has confirmed drug-resistance and newborn has no evidence of infection
  - Will always treat infant if mom has active disease
- Breastfeeding
  - Not contraindicated by disease or treatment
  - Supplemental pyridoxine for mother and infant

Cystic Fibrosis



Cystic Fibrosis Lung Healthy Lung

Cystic Fibrosis

- Background (Patel, 2015)
  - Autosomal recessive disorder affecting 1 in 3,500 births
  - 2000 genes identified
  - 1/25 carrier rate in Caucasions
  - Disorder of cystic fibrosis transmembrane conductance regulator protein
    - Abnormal transport of chloride and sodium ions
    - Impaired clearance in respiratory, GI, and GU tracts
  - Respiratory failure, chronic infection, malabsorption, pancreatic insufficiency
    - Biliary tract cirrhosis, diabetes, male factor infertility
    - 20% develop diabetes by age 20

Cystic Fibrosis

- Background (Patel, 2015)
  - Median predicted survival 36.8 in women in 2011
  - Recent literature suggest normal female fertility
  - Pregnancy tolerated well with good-moderate lung function
    - FEV1 50-70%
    - However, treatments for CF increased during pregnancy

Cystic Fibrosis

- Increasing rates of delivery in women with CF (Patel, 2015)
  - 2.99 to 9.85 per 100,000 women from 2000-2010
  - 257 pregnancies reported in 2013 in the Cystic Fibrosis Foundation Registry 4 live births per 100 women

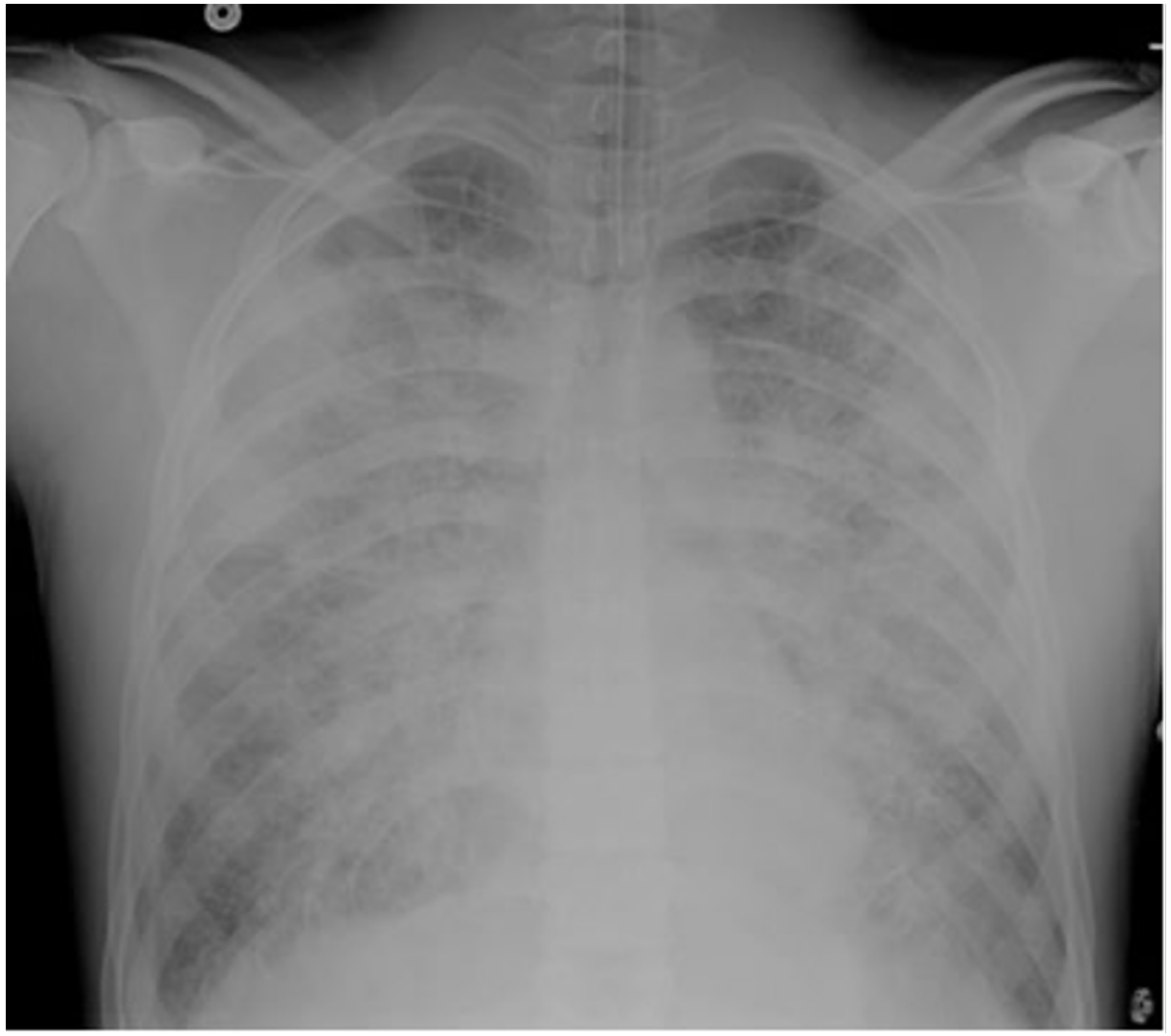
Cystic Fibrosis

- Higher risks of: (Patel, 2015)
  - Pneumonia (OR 69)
  - Mechanical ventilation (OR 32)
  - Death (OR 125)
  - Preterm labor (OR 2.5)
  - GDM (OR 2.5)
- Comparable risks of:
  - Cesarean, PIH, abruption, IUGR, PPH, chorioamnionitis
- Overall mortality: 1 percent
  - Worse with severe lung disease (pulmonary hypertension)

Cystic Fibrosis

- General guidelines: (Patel, 2015)
  - Achieving optimal pulmonary function prior to conception
  - Carefully monitoring during pregnancy
  - Providing genetic counseling
    - Carrier testing of the father
    - Options for prenatal diagnosis
  - Close monitoring of maternal nutrition, weight gain
  - Early screening for gestational diabetes

ARDS



ARDS

- Acute, diffuse inflammatory lung injury (Cole 2005)
- 16-70 per 100,000 in pregnancy
- Pathologic and Clinical hallmark:
  - Hypoxemia and bilateral opacities on CXR
  - Diffuse alveolar damage
- 30-50% mortality in obstetrical population
  - Long term morbidity
  - Similar to nonobstetrical population
  - 23-50% perinatal mortality and high rate of morbidity
    - Preterm labor, NRFHT

ARDS

- Berlin definition
  - Bilateral opacities without collapse or nodules
  - Respiratory collapse not explained by cardiac failure or pulmonary edema
  - Moderate to severe oxygenation impairment
    - Mild ARDS:
      - » PaO_2/FiO_2 >200 mmHg, but ≤300 mmHg, PEEP/CPAP ≥5 cm H_2O
    - Moderate ARDS:
      - » PaO_2/FiO_2 >100 mmHg, but ≤200 mmHg, PEEP ≥5 cm H_2O.
    - Severe ARDS:
      - » PaO_2/FiO_2 ≤100 , PEEP ≥5 cm H_2O

ARDS

- ARDS from obstetric and nonobstetric conditions (Cole 2005)
  - Amniotic fluid embolism
  - Chorioamnionitis
  - Trophoblastic embolism
  - Placental abruption
  - Aspiration
  - Pneumonia
  - Air embolism
  - Massive hemorrhage
  - Pyelonephritis

ARDS

- Risks of the obstetrical population: (Cole 2005)
  - Fluid administration and tocolytic therapy
  - Reduced albumin level and plasma oncotic pressure
    - Pulmonary edema develops at much lower pressures compared to nonpregnant patients

ARDS

- Adequate maternal oxygen saturation essential
  (Cole 2005)
  - General population: PaO2 55 mmHg, SaO2 88%
  - Pregnancy: PaO2 of 70 mm Hgm SaO2 95%

- Fetal CO2 clearance requires 10 mmHg gradient
  - PaCO2 of 45 mm Hg, maternal pH of 7.30 “seems reasonable”

ARDS

- Fetal assessment (Cole 2005)
  - EFM limited in critically ill patients
  - BPP potentially better modality
  - Soft recommendation of twice weekly testing at 26 wks or with change in maternal status

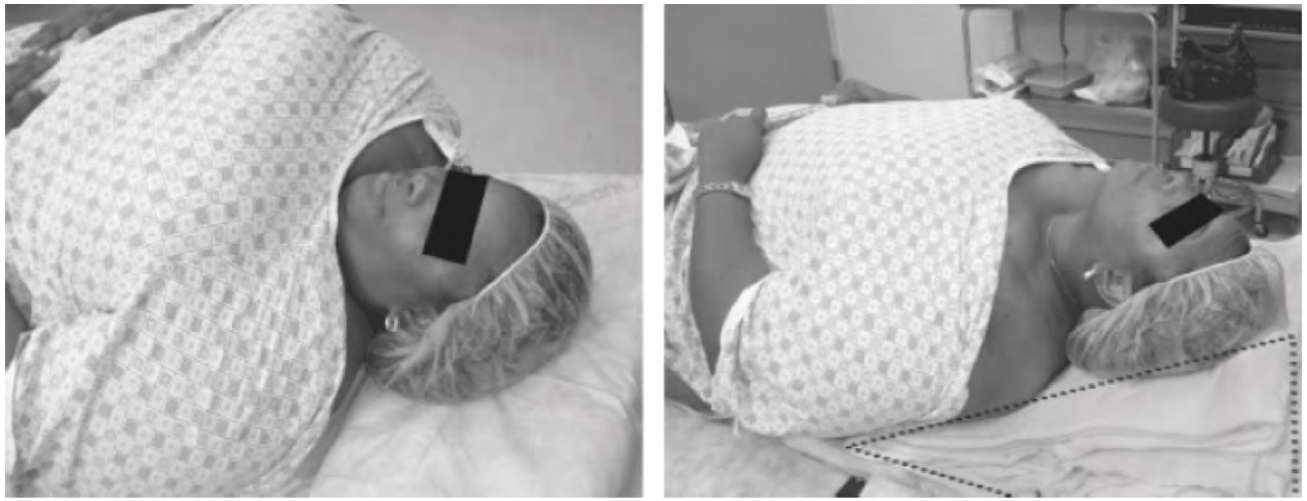
- No other major differences exist in the management
- Survival similar to ARDS in the general population
- Perimortem cesarean
  - Within 4 minutes for maternal and fetal benefit

Acute respiratory failure

- The increased respiratory demands and decreased respiratory reserve
- Pregnancy related
  - Pulmonary edema
  - AFE
- Pregnancy associated
  - Viral ARDS
  - Asthma
  - Embolism

Indications for intubation	Indications for ventilation
• Need to secure airway • Depressed sensorium • Imperfect airway reflexes • Upper airway instability after trauma • Decreased airway patency • Need for sedation in a situation of poor airway control • Imaging (CT, MRT) and transportation of the patient	• Hypoxia: acute hypoxemic respiratory failure • Hypoventilation • Unacceptably high work of breathing • Hemodynamic compromise • Cardiorespiratory arrest • Refractory shock • Raised intracranial pressure • Flail chest

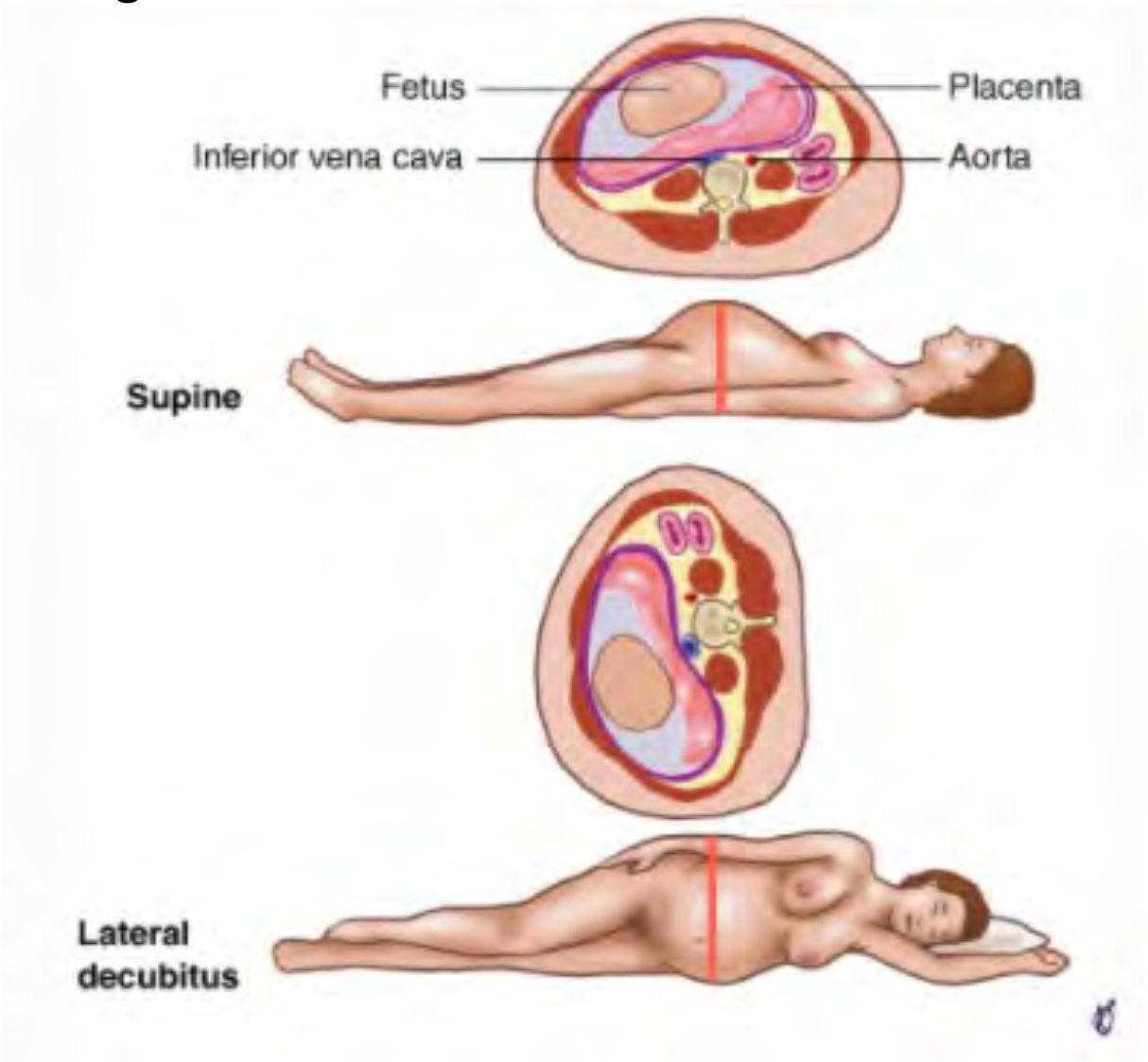
Intubation in Pregnancy



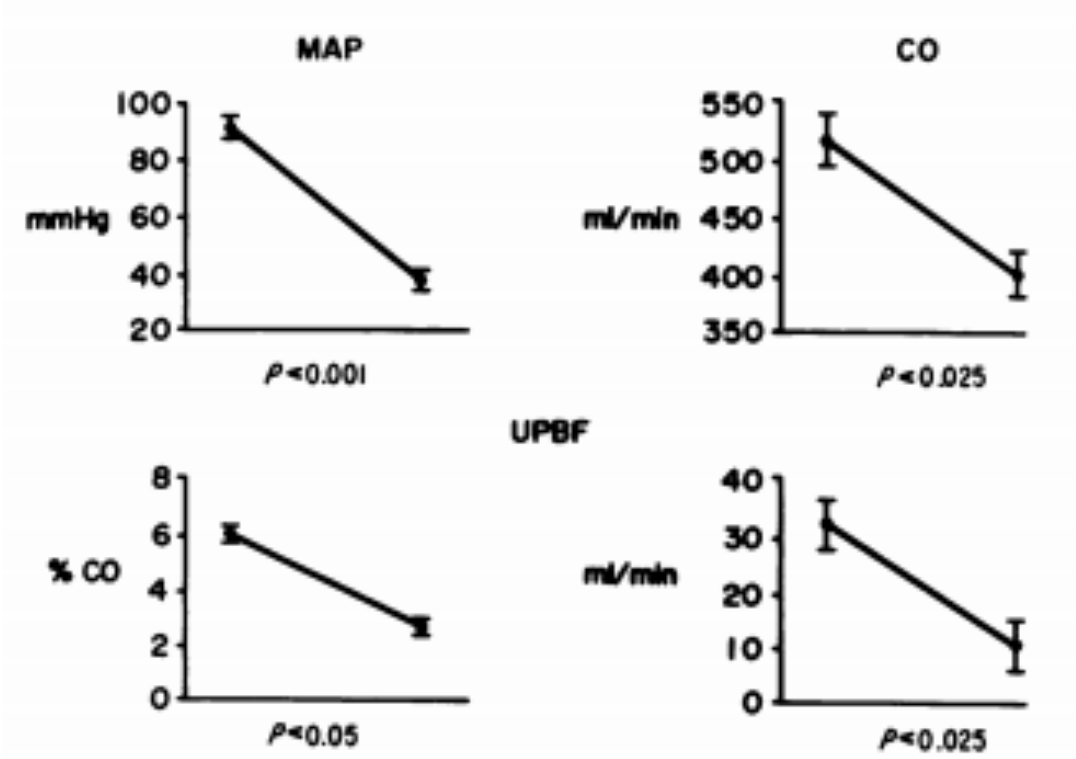
Intubation

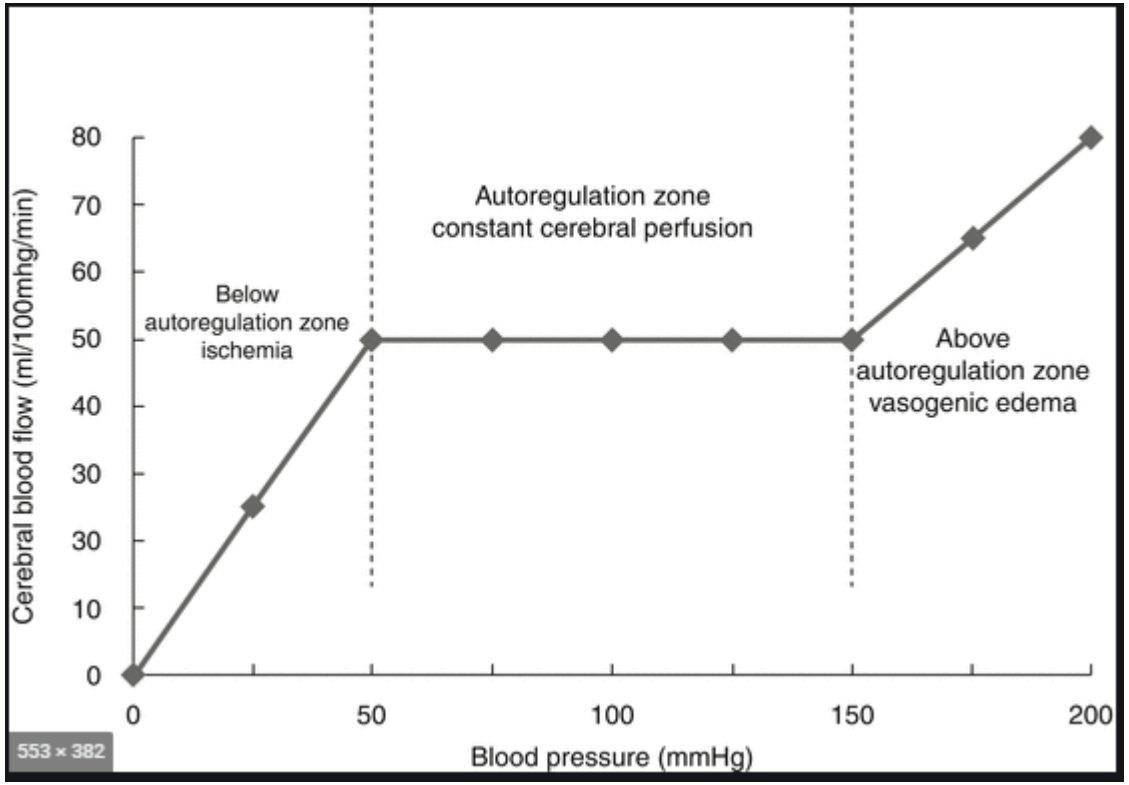
- Bipap is a safe ventilatory option
- Demand is high and reserve is low
- Rapid hypoxia-Preoxygenate
- Difficult airway-anterior and narrow, edema, aspiration
- Avoid nasal intubation-nasopharengyl congestion
- No autoregulation of uterine blood flow-maintain perfusing BP
- Have OB/peds at the bedside

Patient positioning



Autoregulation of placental perfusion



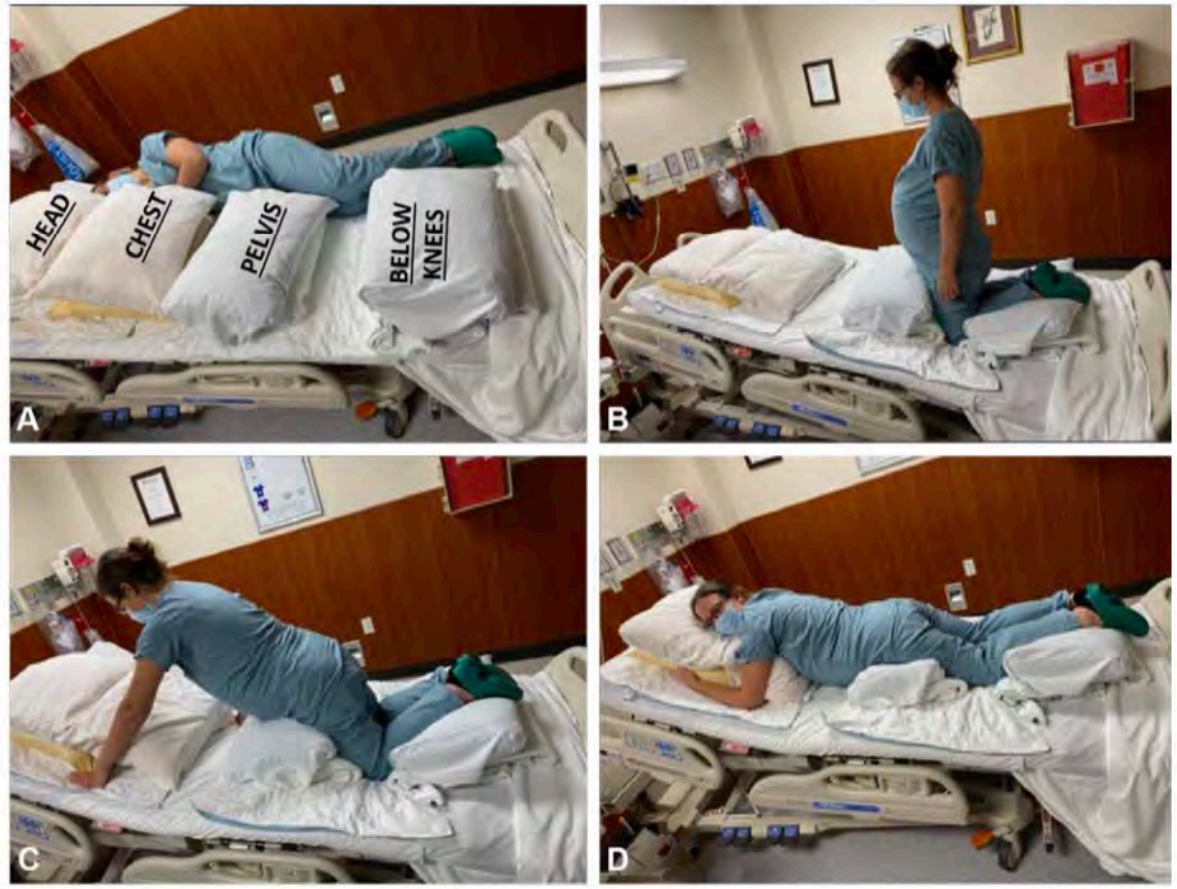


Ventilation in Pregnancy

What is different?

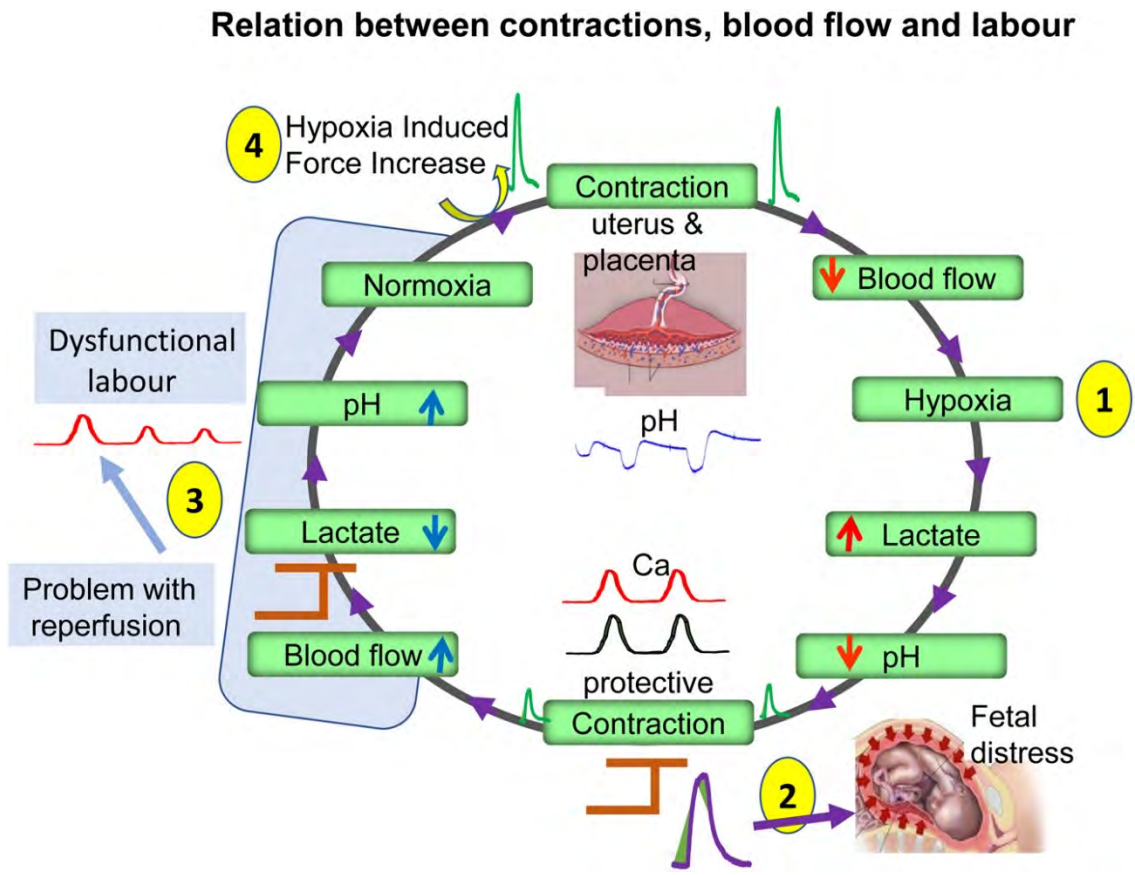
- Minute ventilation and CO2 goals
- SpO2 goals
- Offload the IVC
- Prone positioning is safe in pregnancy
  - Adequate bolstering is required to avoid abdominal compression
- Pulmonary vasodilator therapy can be used in pregnancy
  - Nitric oxide, sildenafil, and epoprostenol (IV and inhaled) are safe in pregnancy
  - Bonsentan is contraindicated
- Neuromuscular blockade is safe in pregnancy

Appendix 2. Prone positioning in awake pregnant patient. A. Patient lies on side facing towards the oxygen source. Adjust bed to reverse Trendelenburg (~10°). Place three pillows at head, two above gravid uterus, two at level of the pelvis (line up with symphysis pubis), and two under knees. B. Help patient kneel between two lower sets of pillows (lower leg pillows may be placed once she is prone). Ensure pelvic pillows are touching her thighs. Raise head of the bed. C. Help patient lie forward onto the pillows. D. Lower head of the bed (maintain reverse Trendelenburg). Adjust padding for patient comfort. Check gravid abdomen and ensure no pressure. Replace maternal and fetal monitors.



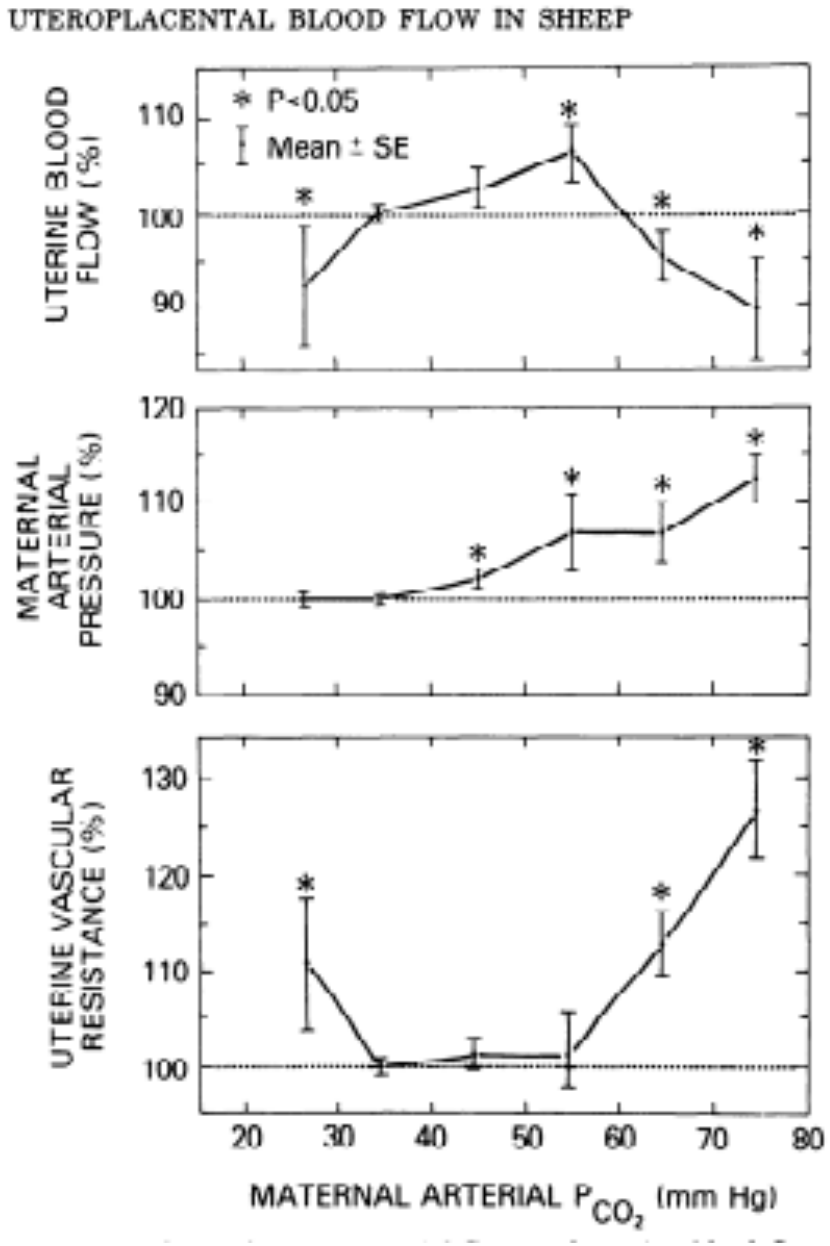
Hypoxia in pregnancy

- Short term effects:
  - HIE
  - Uterine contractions
  - Acidosis
- Long term
  - Fetal growth restriction
  - Oxidative damage
  - Placenta stress response pathways



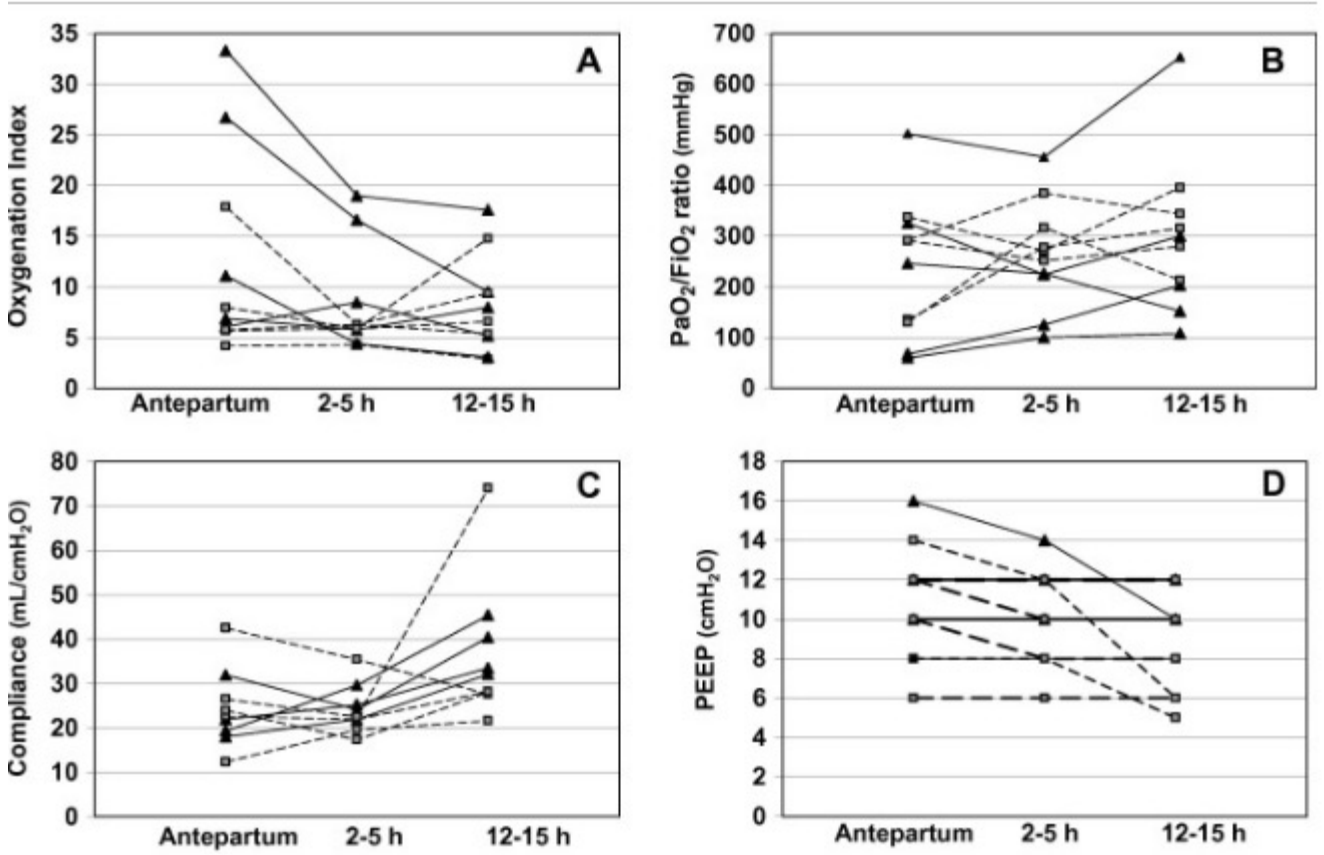
Permissive hypercapnia

- Fetal acidemia and hypoxic ischemic encephalopathy are closely associated
  Shifts O2 dissociation curve
- The fetus has a very limited buffer system
- Co2 must be offloaded across a concentration gradient
- Hypercarbia increases uterine artery resistance and decreases uterine artery blood flow



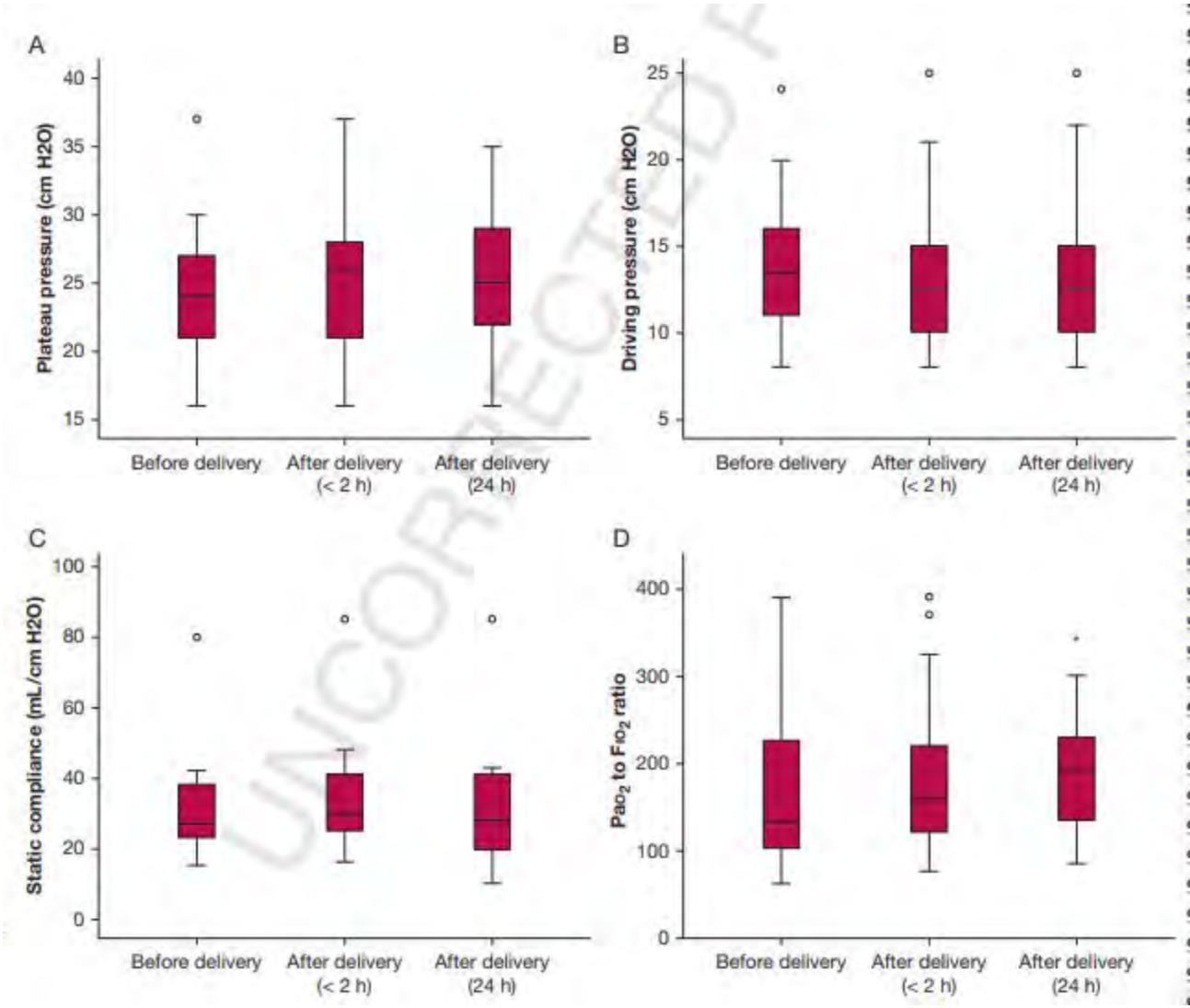
Does delivery improve Ventilation/oxygenation?

- Case series 10 patients requiring mech vent
- Pre COVID
- Mean GA 25 weeks

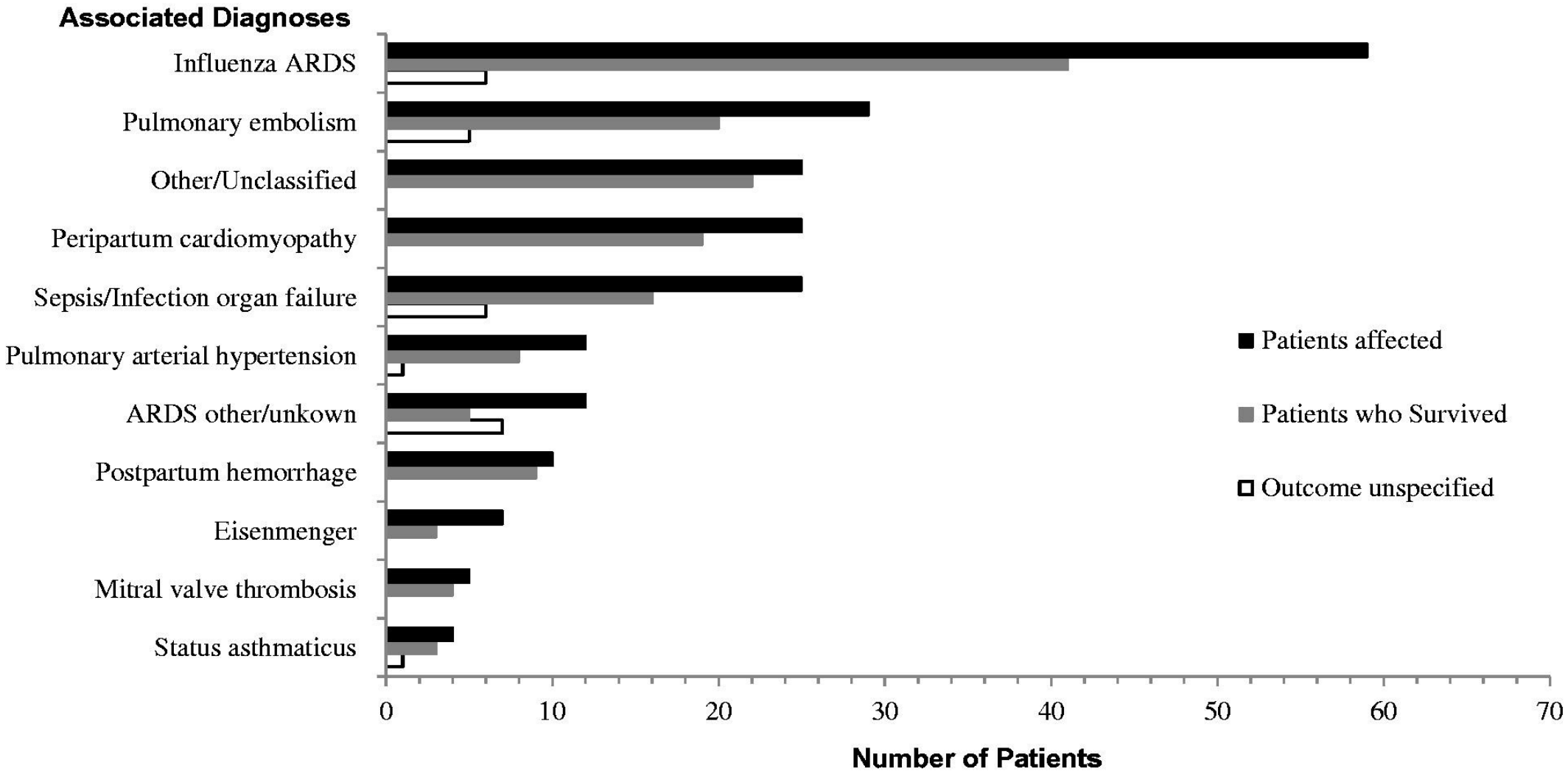


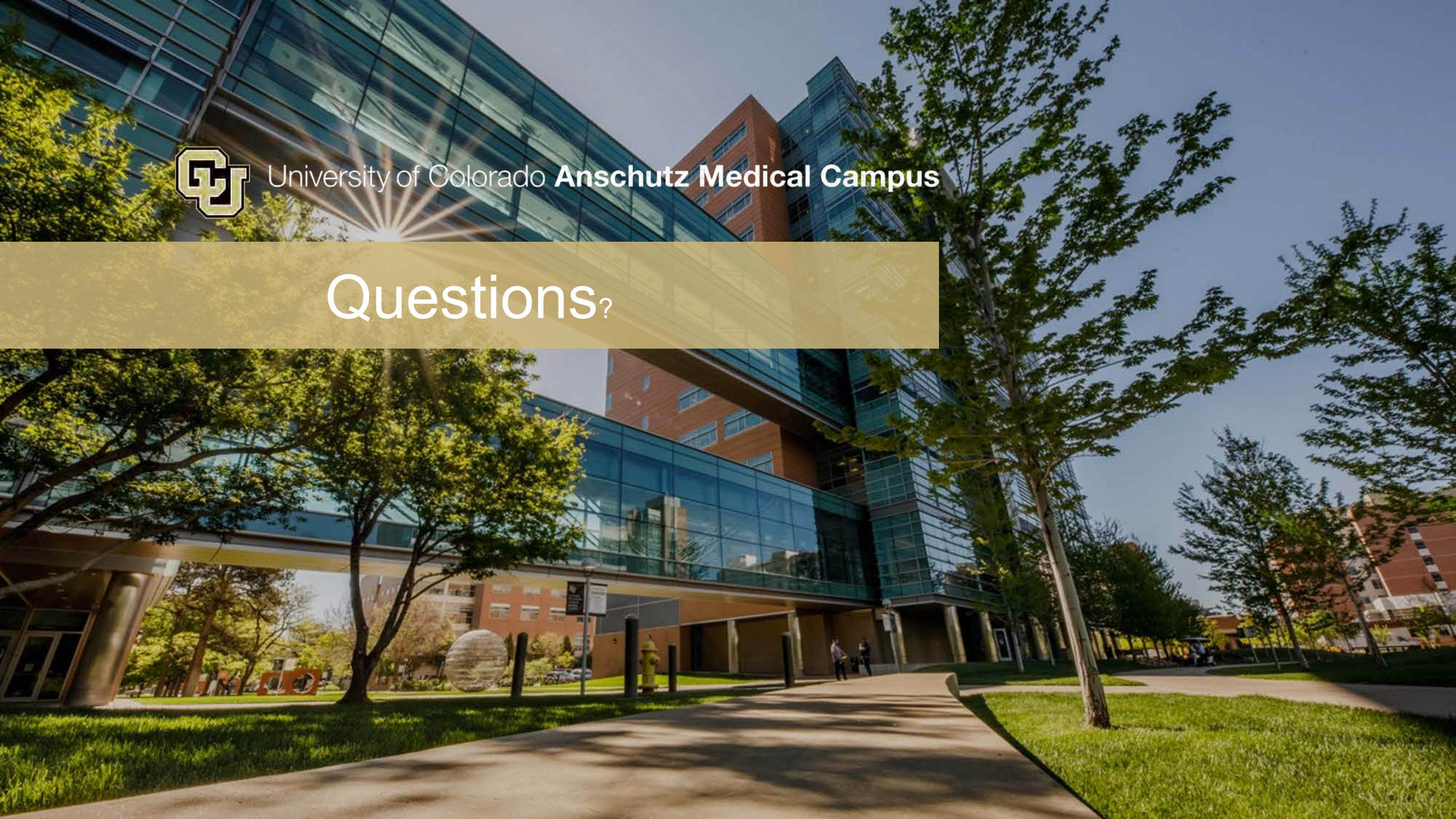
Does delivery improve ARDS?

- Data from COVID ARDS
- P:F improves 2 and 24 hrs after delivery
- Trend towards increased compliance
- No changes in driving pressure, PEEP, or plateau pressure



ECMO in Pregnancy





Questions?

Hot Articles: Practice Changing (and Sometimes Controversial) Publications in OB Research

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HEALTH
UNIVERSITY OF UTAH

Disclosures

- No relevant conflicts of interest
- Investigator for CHAP and ALPS
- University of Utah site for PRAECIS

Objectives

- Describe practice-changing publications in obstetrics
- Understand study populations and limitations of available evidence
- Describe how to incorporate trial findings into practice

CHAP

- Treatment for Mild Chronic Hypertension in Pregnancy (CHAP)
- Multicenter RCT of individuals with CHTN < 23 weeks
- Randomized to
  - Active management (BP <140/90)
  - Standard treatment (BP <160/105)
- Pragmatic medication choice – labetalol or nifedipine XL

Tita et al NEJM 2022

CHAP

- Primary outcome
  - Superimposed preeclampsia with severe features
  - Medically indicated PTB < 35 weeks
  - Placental abruption
  - Fetal or neonatal death
- Secondary safety outcome
  - Fetal weight <10%ile for GA and sex at birth

Tita et al NEJM 2022

CHAP

- 2,408 participants
- Primary outcome less frequent in active management
  - 30.2% vs 37.0%, aRR 0.82 (95% CI 0.74-0.92)
- Secondary safety outcome not different between groups
  - 11.2% vs 10.4%, aRR 1.04 (95% CI 0.82-1.31)
- Treatment <140/90 improved maternal outcomes and did not increase SGA

Tita et al NEJM 2022

Should it be <130/80?

- Secondary analysis of CHAP trial
- Compared participants with mean clinic BP 130-139/80-89 vs those with BP <130/80
- Those mean clinic BP <130/80 more likely to be in active treatment arm
- <130/80 associated with lower risk of maternal composite
  - PreE with severe fxs, MIPTB < 35 wks, abruption, perinatal death
  - 16% vs 36%, aRR 0.45, 95% CI 0.38-0.54
- No difference in SGA

Bailey et al Obstet Gynecol 2023

Timing of Delivery

- Planned secondary analysis CHAP trial
  - RCT of CHTN treatment to different BP goals
  - Participants who remained pregnant at start of each gestational week were classified as planned delivery or expectant management
  - Primary maternal composite- death, serious morbidity, preE with severe fxs, blood transfusion, abruption
  - Secondary- cesarean and neonatal outcomes

Timing of Delivery- Maternal Primary Outcome

Outcome	37w0d-39w6d n=1417 aOR (95% CI)	38w0d-39w6d n=961 aOR (95% CI)	39w0d-39w6d n=460 aOR (95% CI)
Primary maternal composite outcome	1.11 (0.71-1.75)	0.90 (0.53-1.52)	1.22 (0.63-2.35)
Preeclampsia severe features	0.91 (0.54-1.53)	0.88 (0.50-1.57)	0.88 (0.43-1.80)
Hemorrhage with transfusion	1.38 (0.64-3.00)	0.87 (0.35-2.19)	---

Serious maternal morbidity and abruption could not be modeled due to low event counts

Timing of Delivery- Secondary Outcomes

Outcome	37w0d-39w6d n=1417 aOR (95% CI)	38w0d-39w6d n=961 aOR (95% CI)	39w0d-39w6d n=460 aOR (95% CI)
Primary neonatal composite	1.43 (0.96-2.14)	1.02 (0.64-1.63)	1.15 (0.66-2.01)
Cesarean birth	2.07 (1.48-2.91) **	1.25 (0.89-1.76)	1.37 (0.91-2.06)
RDS	2.58 (1.34-4.98) **	2.35 (0.86-6.42)	---
Hypoglycemia	1.87 (1.20-2.91) **	1.73 (1.02-2.92) **	0.44 (0.18-1.06)

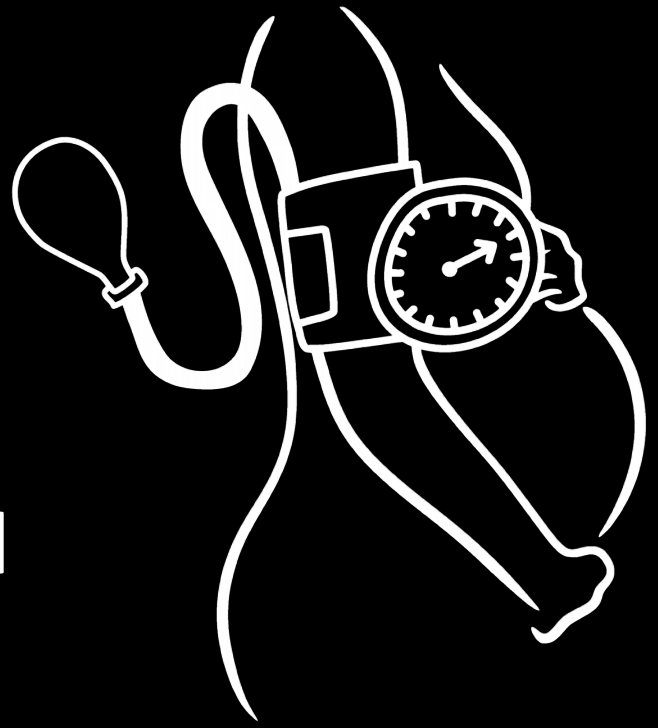
Timing of Delivery- Summary

- No association between planned delivery and primary maternal outcome
- Planned delivery in week 37 associated with cesarean
- Planned delivery in week 37 associated with RDS
- Planned delivery in week 37 and 38 associated with hypoglycemia
- No association with neonatal LOS or NICU

Integration into Practice- CHAP

- Goal BP for individuals with CHTN <140/90
  - Likely requires some home BP monitoring
  - Likely OK to dip to <130/80
- Treat with labetalol or nifedipine XL
- If well controlled, consider delivery at 39 weeks
- Cannot extrapolate to gHTN or preeclampsia

PRAECIS



- Multicenter cohort
- Evaluated predictive value of serum soluble fms-like tyrosine kinase 1 (sFlt-1) to placental growth factor (PlGF)
- Enrolled pregnant people hospitalized between 23 and 35 weeks with hypertensive disorders of pregnancy
- Primary outcome progression to severe fxs < 2 weeks
- Other adverse outcomes were secondary outcomes

Thadhani et al NEJM Evidence 2022

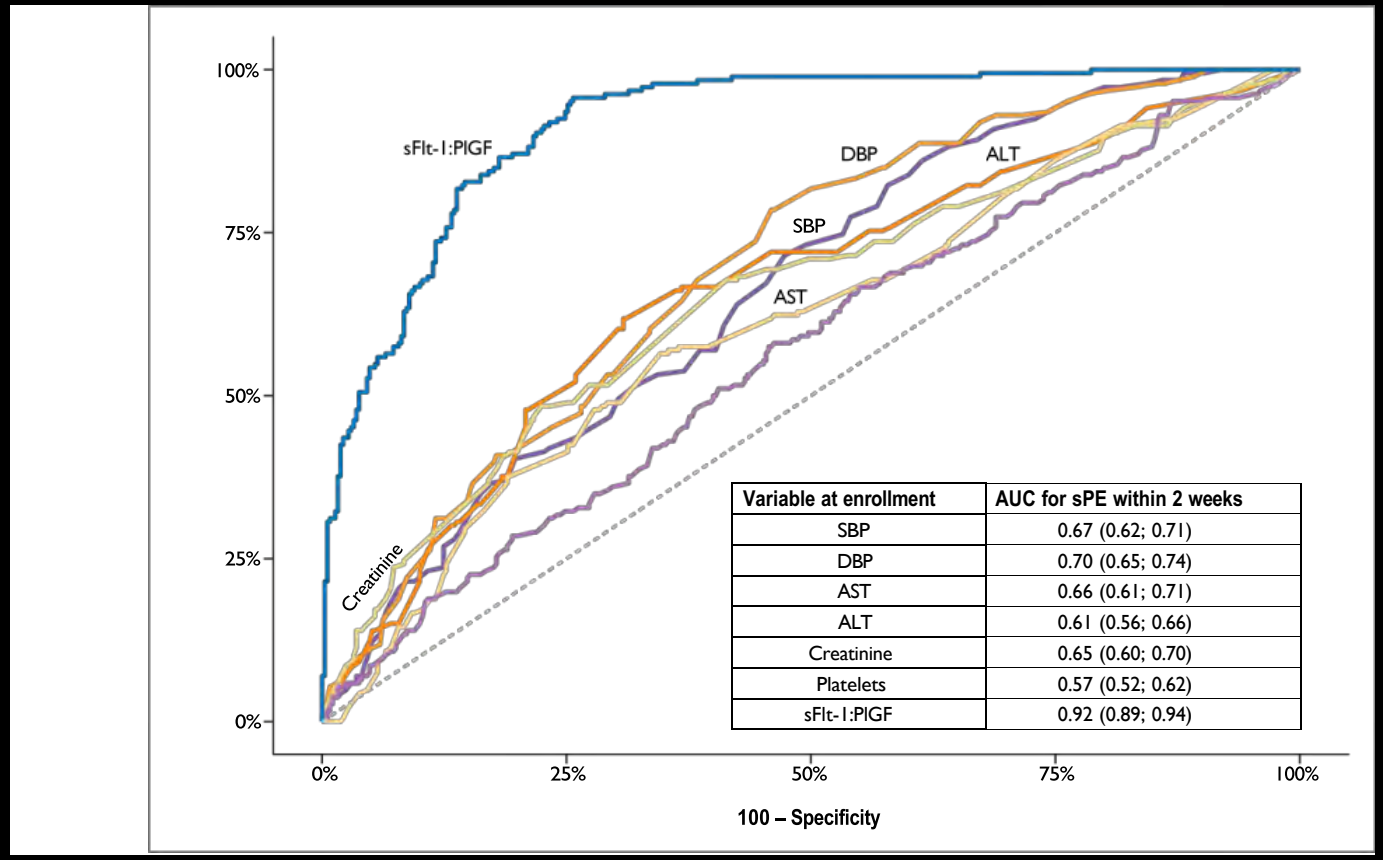
PRAECIS

- Preeclampsia Risk Assessment: Evaluation of Cut-Offs to Improve Stratification (PRAECIS)
- 1014 enrolled
  - 299 derivation cohort
  - 715 validation cohort
- Derivation cohort median sFlt-1:PlGF 200 among those who developed severe features
  - sFlt-1:PlGF 6 among those who did not develop severe fxs
- Based on AUC, used ratio ≥ 40 as potentially predictive of progression to severe features within 2 weeks

Thadhani et al NEJM Evidence 2022

PRAECIS- Validation Cohort

- Using ratio ≥ 40
- NPV 96%
- PPV 65%
- AUC 0.92
- Risk adverse maternal outcomes (16% vs 3%, RR 5.8)



Variable at enrollment	AUC for sPE within 2 weeks
SBP	0.67 (0.62; 0.71)
DBP	0.70 (0.65; 0.74)
AST	0.66 (0.61; 0.71)
ALT	0.61 (0.56; 0.66)
Creatinine	0.65 (0.60; 0.70)
Platelets	0.57 (0.52; 0.62)
sFlt-1:PlGF	0.92 (0.89; 0.94)

Thadhani et al NEJM Evidence 2022

History of Assays

- sFlt-1:PlGF assay approved in Europe 2009
- NICE recommends assay used in conjunction with standard clinical assessment for preE
- Used widely in Canada, Asia, Australia, New Zealand
- Approved by FDA (KRYPTOR Test System)

  May 18, 2023

Burwick et al Obstet Gynecol 2024

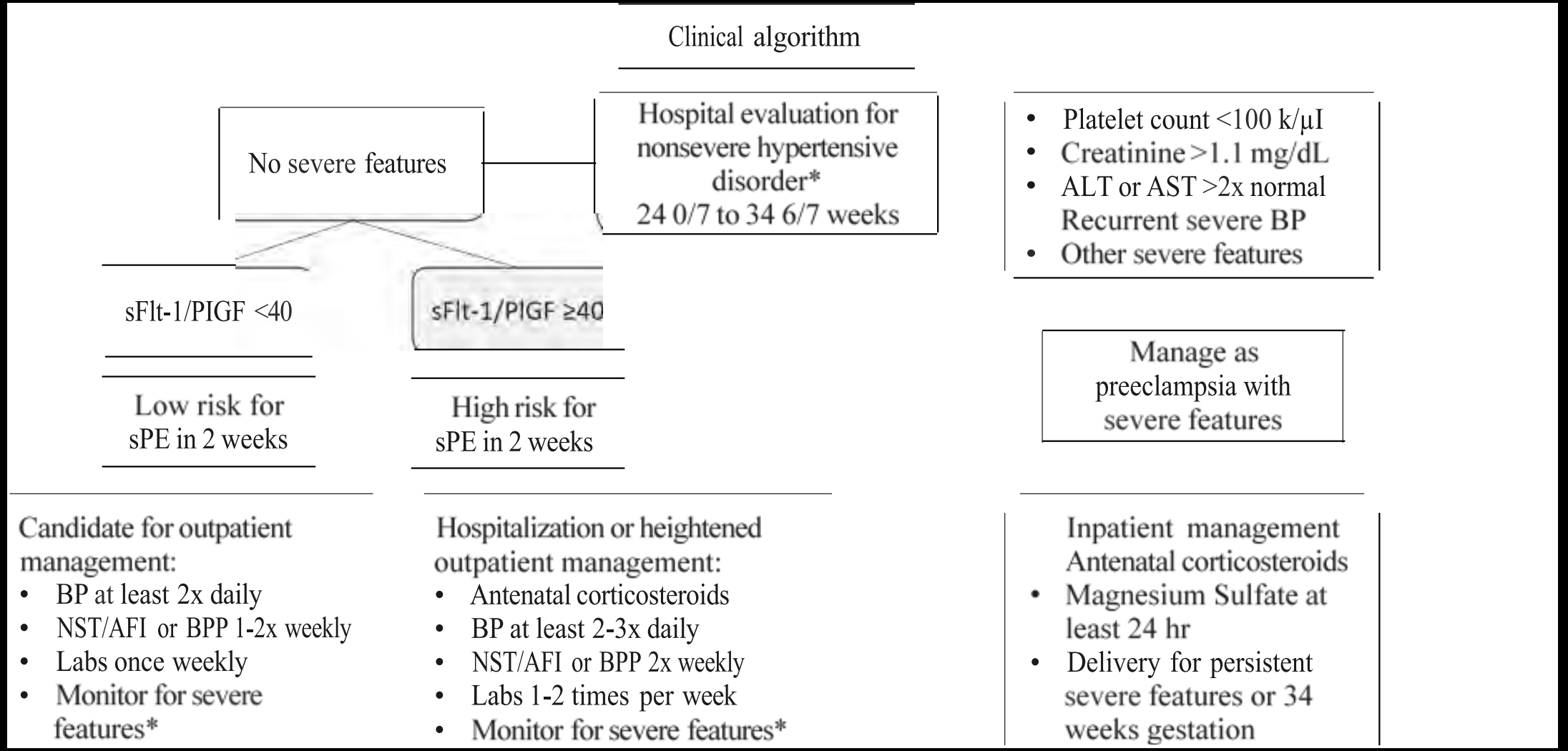
Other sFlt-1/PlGF Studies

Table 1. Clinical Studies Evaluating the Soluble fms-Like Tyrosine Kinase 1/Placental Growth Factor Ratio for Prediction of Preeclampsia

Study	Study Location, Type	Study Group	n	Primary Outcome	sFlt-1/PlGF Ratio Threshold*		NPV (%)	PPV (%)
					Low Risk	High Risk		
PROGNOSIS[14]	Multicentert	Suspected PE 24 0/7-36 6/7 wk	1,050	PE within 1 wk	38 or less	Greater than 38	99	17
		Suspected PE 24 0/7-36 6/7 wk	1,050	PE within 4 wk'	38 or less	Greater than 38	95	39
PROGNOSIS[21]	Asia, multicenter§	Suspected PE 20 0/7-36 6/7 wk	700	PE within 1 wk'	38 or less	Greater than 38	99	18
		Suspected PE 20 0/7-36 6/7 wk	700	PE within 4 wk'	38 or less	Greater than 38	95	30
ROPE Study[40]	Boston, Massachusetts, single-center	Suspected PE before 34 wk	199	sPE within 2 wk	38 or less	Greater than 38	98	65
		Suspected PE before 34 wk	199	sPE within 2 wk	85 or less	Greater than 85	91	74
PRAECIS[10]	United States, multicenter	GHTN, PE, CHTN±PE at 23 0/7-34 6/7 wk	715	sPE within 2 wk	Less than 40	40 or greater	96	65
ROPE Study[15,7,7,4]o	Boston, Massachusetts, single-center	Confirmed PE 20 0/7-34 6/7 wk	459	sPE within 2 wk	38 or less	Greater than 38	94	66
		Confirmed PE 20 0/7-34 6/7 wk	459	sPE within 2 wk	85 or less	Greater than 85	85	77

Burwick et al Obstet Gynecol 2024

Proposed algorithm if integrated into care



Burwick et al Obstet Gynecol 2024

Integration into Clinical Practice

- FDA approved (KRYPTOR Test System)
- Can be considered for use as risk stratification tool
- CANNOT replace standard clinical management and decision making
- May add to our tools when risk stratifying patients for need for hospitalization and BMZ administration

ALPS

- Multicenter RCT enrolled individuals between 34w0d and 36w5d at risk for preterm delivery
- Received 2 doses betamethasone 24 hrs apart or placebo
- Primary outcome neonatal composite within 72 hrs of birth
  - Use of CPAP or HFNC for ≥ 2 hours
  - Supplemental oxygen with FiO2 ≥ 0.30 for ≥4 hours
  - ECMO or mechanical ventilation
  - Stillbirth or neonatal death

Gyamfi-Bannerman et al NEJM 2016

ALPS

- Primary outcome less frequent in BMZ group

Outcome	Betamethasone	Placebo	RR (95% CI)
Primary Outcome	11.6%	14.4%	0.80 (0.66-0.97)
CPAP for ≥ 2 hrs	10.2%	13.1%	0.77 (0.63-0.95)
FiO2 ≥ 0.30 for ≥ 4 hrs	3.4%	4.4%	0.77 (0.53-1.12)
Mechanical ventilation	2.4%	3.1%	0.78 (0.50-1.21)
ECMO	0	0	N/A
Stillbirth or NND	0	0	N/A

Gyamfi-Bannerman et al NEJM 2016

ALPS

- Neonatal hypoglycemia more frequent BMZ group
  - 24.0% vs 15.0%, RR 1.60 (95% CI 1.37-1.87)
  - Individuals with diabetes excluded from trial

ALPS Implementation

- Cross sectional study U.S. births
- Liveborn singleton gestation born 34 to 36 weeks without pre-existing maternal diabetes
- Adjusted rate of steroid use increased from 5% to 12%
- Assisted ventilation use decreased after dissemination period
  - 8.9% vs 8.2% (adjusted incidence rate ratio 0.91, 95% CI 0.85-0.98)
- No change assisted ventilation > 6 hours

Clapp et al JAMA Network Open 2022

ALPS and Neurodevelopment

- Some animal data suggest adverse effects on fetal brain
- Rhesus macaques decreased number of pyramidal neurons in hippocampus and degeneration of axodendritic synaptic terminals
  - Effect was dose dependent
- Rat models demonstrate changes in transcription factors involved in cell differentiation with dexamethasone exposure
- Repetitive doses of BMZ had adverse effects in humans

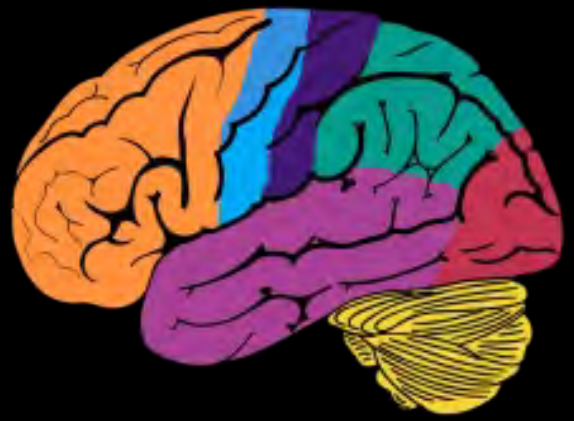
Uno Brain Res Dev Brain Res 1990; Slotkin Brain Res Dev Brain Res 1998; Wapner NEJM 2007

Finnish Data

- Population-based retrospective cohort using nationwide registries in Finland
- 674,877 children included
  - 14,868 steroid-exposed
- Increased frequency of mental and behavioral disorder with exposure
  - 12% vs 6%, aHR 1.33 (95% CI 1.26-1.41)
- Among preterm born children, no statistically significant difference when comparing exposed vs unexposed
- No data on indication, deaths or GA at administration

Raikkonnen et al JAMA 2020

ALPS and Neurodevelopment



- China National Birth Cohort study
- 1759 participants
  - 710 exposed to antenatal corticosteroids (dex or prednisone at any gestational age)
- Increased risk of being “non-competent” cognitive development of Bayley scales at 1 year of age
- Exposure to dexamethasone aRR 1.62 (95% CI 1.10-2.38) of non-competent neurodevo compared with unexposed

Tao et al Am J Obstet Gynecol 2022

JAMA Peds Systematic Review and Meta-Analysis

- Included 30 cohort studies
  - 26 focused on neurodevo and/or psych outcomes
- Duration of participant follow-up 1-3 years
- Examined exposure to corticosteroids during pregnancy
- Primary outcome any adverse neurologic or psychologic disorder
- Assessed both overall and by timing of exposure

Ninan et al JAMA Peds 2022

JAMA Peds Systematic Review and Meta-Analysis

- Single course among extremely preterm birth significant reduction in risk of neurodevelopmental impairment
  - aOR 0.69, 95% CI 0.57-0.84
- Children with late preterm birth exposure associated with higher risk of neuro disorder
  - aHR 1.12, 95% CI 1.05-1.20
- Children with term birth exposure associated with higher risk of psychiatric or behavioral disorder
  - aHR 1.47, 95% CI 1.36-1.60

Ninan et al JAMA Peds 2022

RCT Follow-Up Studies

- Follow-up study of RCT of BMZ vs placebo
- Initially enrolled 24w0d to 36w6d
  - Majority in late preterm period
- No differences in measures of cognitive testing at 6 years of age
- No differences in cognitive functioning, working memory and attention, psychiatric morbidity, handedness, or health-related quality of life at 30 yrs

MacArthur et al Pediatrics 1982

SMFM 2023 ALPS Neurodevelopment

- Prospective follow-up study of participants MFMU ALPS trial
- Of 2,831 in parent trial, 1026 enrolled
- Children ≥ 6 years of age completed Differential Ability Scales, 2nd Edition (DAS-II)
- Primary outcome general conceptual ability score (GCA) <85 or 1 SD less than mean
- No difference 17% BMZ group and 19% placebo group
  - aRR 0.94 (95% CI 0.73-1.22)

Gyamfi-Bannerman AJOG SMFM abstracts 2023

Integrating into Clinical Practice

- ALPS offered between 34w0d and 36w5d
- Restrict to those anticipated to deliver preterm but more than 12 hours from first dose
- Withhold from those with pre-existing diabetes
- Discuss evolving long term safety data
- Shared decision-making

Thank you!

- Questions and Discussion

FRIDAY

Lactation Suppression After Delivery or Termination

Shannon Leigh Son, MD, MSCI

Assistant Professor

Maternal-Fetal Medicine

Disclosures

- None

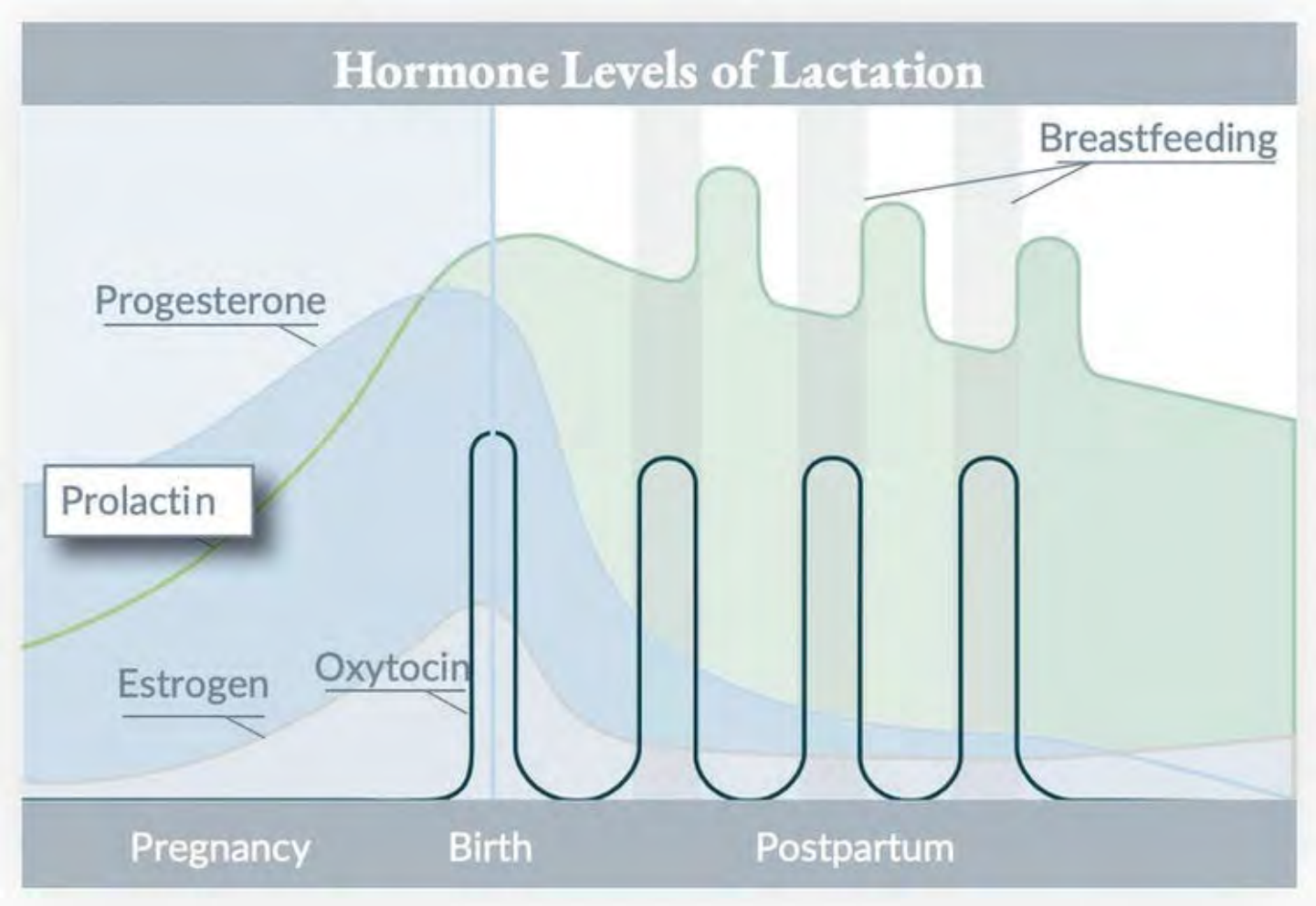
Objectives

- Discuss the incidence of breast concerns after pregnancy loss/interruption
- Discuss evidence-based strategies for mitigating breast concerns
- Propose a “protocol” for optimizing care in this population

What is the issue?

- A large majority (97%) of people who experience loss or pregnancy interruption experience undesired breast symptoms
- In addition to pregnancy loss/interruption, patients may choose not to lactate due to a need to initiate medications that are not compatible with lactation, adoption, or personal preference, among other reasons
- These breast symptoms can be distressing and a trigger for further grief
- Some strategies exist to minimize breast symptoms, which may, in part, improve the patient experience.

Lactogenesis



Background

- After a 14-20 week pregnancy loss/interruption, breast symptoms are common:
  - Breast tenderness in 50%
  - Breast engorgement in 45%
  - Breast leaking 20%
- This is often unexpected and has been demonstrated to exacerbate physical pain as well as emotional distress

Anecdotal strategies

- Cochrane review 2020
- 21 studies (2170 patients randomized) evaluating interventions such as:
  - Cabbage leaves
  - Herbal compresses (ginger, cactus, aloe, hollyhock)
  - Massage (manual, electromechanical, Oketani)
  - Acupuncture
  - Ultrasound
  - Acupressure
  - Scraping therapy
  - Cold packs
  - Medical treatment (serrapeptase, protease, oxytocin)

Anecdotal strategies

- Cochrane review 2020
- Certainty of evidence is LOW
- Cabbage leaves, cold gel packs, herbal compresses and massage “may be promising” but quality of evidence is LOW to VERY LOW
- Many studies were comparing items to one another (ie cabbage leaves to ice packs)

Cabbage leaves

- Might help slightly with pain, breast ”hardness,” and patient satisfaction compared to routine care

- VERY LOW level of certainty

Compresses

- No studies comparing this to ”routine care” only to one another (ie herbal compress vs hot compress)
- Herbal compresses were better than hot compresses for pain
- Cactus and aloe cold compresses were better than massage for hardness

- LOW to VERY LOW level of confidence

Medical treatments

- Protease may help pain and swelling compared to placebo
- Serrapeptase may reduce engorgement compared to placebo

- LOW level of confidence

Cold gel packs

- May be more effective than routine care for breast hardness
- VERY LOW level of confidence

Medication Comparisons

- Cochrane review 2012
- Reviewed RCTs that evaluated the effectiveness of treatments used for suppression of postpartum lactation
- 62 trials (6428 study participants)
- Outcome was persistence of one of the following: milk secretion, breast engorgement, or breast pain)
- Data were generally “small” and of “limited” quality. Many trials were excluded based on study design/flaws

Medication Comparisons

- Cochrane review 2012
- Bromocriptine vs placebo/no treatment
- Estrogen containing medications/derivatives vs placebo/no treatment
- Bromocriptine vs other medications

Medication Comparisons

- Cochrane review 2012

- Three trials (107 participants total) demonstrated bromocriptine was efficacious in reducing lactation compared to placebo/no treatment (RR 0.36, 95% CI 0.24-0.54).

- Seven trials demonstrated effectiveness of estrogen containing compounds (diethylstilbestrol, quinestrol, chlorotrianisene, hexestrol) compared to placebo/no treatment RR 0.40, 95% CI 0.29-0.56)

Medication Comparisons

- Cochrane review 2012
- Bromocriptine vs other medications (methergoline, prostaglandins, pyridoxine, cabergolein, diethylstilbestrol, cyclofenil) = similar effect

- NOTE: side effects and complications were poorly reported in the included trials

- Overall conclusion by authors: weak evidence supports bromocriptine use but does not seem to be better than other anents and side effect data is insufficient

Cabergoline

- Dopamine agonist → antagonizes prolactin release
- Approved for treatment of hyperprolactinemic disorders (idiopathic or related to prolactinoma)
- Has been studied in both term and 2nd trimester pregnancy loss/termination
- Also is recommended for use in patients with HIV for lactation suppression (2020 US Department of Health and Human Services Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission)

Cabergoline at term

- 1988 Double blind RCT (Melis et al, Obstet Gynecol) comparing cabergoline in varying dose sizes to placebo
  - 32 patients, 4 treatment groups (placebo, 400, 600, or 800 mcg of cabergoline) with doses at <24h after delivery
  - Lactation was suppressed in 50% of patients on 400mcg and all of patients on 600 or 800mcg.
    - 12.5% of those on placebo were suppressed
  - Prolactin levels were lower in the cabergoline group but not different among different doses

Cabergoline at term

- 1991 Multicenter RCT (European Mulitcenter Study Group or Cabergoline in Lactation Inhibition BMJ)
  - Compared bromocriptine (0.25mg BID x14d) to cabergoline (1mg once, day of delivery) in term deliveries
  - Complete suppression in 78% cabergoline and 69% of bromocriptine
  - AT LEAST partial suppression in 93% with either group
  - Cabergoline group had lower rebound breast symptoms (3.7% vs 17.0%), adverse events (16% vs 26%), and was less complicated administration (1 dose vs 14 days)

TABLE III—*No of adverse events in women treated with cabergoline or bromocriptine*

Sign/symptom	No of adverse events	
	Women receiving cabergoline (n=136)	Women receiving bromocriptine (n=136)
Dizziness	8	17
Vertigo	1	2
Symptomatic hypotension		1
Palpitation	1	
Headache	7	6
Nausea	2	10
Vomiting		3
Abdominal pain	2	
Epigastric pain	1	1
Drowsiness	1	
Other	2	4
Total	25*	44†

*Occurring in 22 women. †Occurring in 36 women.

Cabergoline at term

- Author conclusions: Cabergoline should be the agent of choice at term for suppression of lactation

Cabergoline in the 2nd trimester

- Double blind RCT (Henkel, et al, 2023)-Stanford, 4/2021-6/2022
  - Cabergoline vs Placebo in 2nd trimester uterine evacuation for suppression of breast symptoms
  - Primary outcome:
    - Composite of ANY breast symptom (engorgement, milk leakage, tenderness, or need for pain relief) on DAY 4
    - Assessed through surveys at baseline and multiple time points after procedure (up to 2 weeks after)
- Inclusion: 2nd trimester uterine evacuation (18-28w)-interruption or demise
- Exclusions: <18y, prior mastectomy, currently breastfeeding, those on dopamine agonist/antagonist already, contraindications to cabergoline, non-English/Spanish speaking

Cabergoline in the 2nd trimester

- RCT (Henkel, et al, 2023)-Stanford
  - Randomized to either:
    - 1mg cabergoline OR placebo within 4 hours of procedure or fetal expulsion
  - All participants also received mifepristone 200mg PO and had either D&E or IOL
    - If >22w had feticidal digoxin injection
    - If undergoing IOL or if demise >24w → serial misoprostol
  - Block randomization: alternating blocks of 4 and 8
  - Electronic surveys administered at various time points: baseline, days 2, 3, 4, 7, and 14

- RCT (Henkel, et al, 2023)-Stanford
  - 73 participants (36 treatment, 37 placebo)
  - Median EGA 21 weeks
  - Grand majority were pregnancy interruptions
  - Baseline breast symptoms similar between groups

Table 1. Demographic and Clinical Characteristics of Participants Randomized to Cabergoline or Placebo to Prevent Breast Pain After Second-Trimester Abortion or Pregnancy Loss

Characteristic	Cabergoline (n=36)	Placebo (n=37)
Age (y)	30.5±5.4	31.6±5.7
Parity	1 (0–4)	0 (0–4)
Nulliparous	16 (44.4)	25 (67.6)
Gestational age (d)	148.9±13.4	147.7±12.8
Gestational age (wk)		
18 0/7–19 6/7	10 (27.8)	9 (24.3)
20 0/7–21 6/7	11 (30.6)	12 (32.4)
22 0/7–23 6/7	15 (41.7)	15 (40.5)
24 0/7–28 0/7	0 (0)	1 (2.7)
Indication		
Undesired pregnancy	14 (38.9)	8 (21.6)
Fetal anomaly	20 (55.6)	27 (73.0)
Maternal comorbidity	0 (0)	1 (2.7)
Fetal death	2 (5.6)	1 (2.7)
Abortion method		
Procedural	31 (86.1)	32 (86.5)
Medication	5 (13.9)	5 (13.5)
Insurance		
Private	22 (61.1)	24 (64.9)
Medicaid	14 (38.9)	13 (35.1)
Gender*		
Female	35 (97.2)	37 (100)
Nonbinary	1 (2.8)	0 (0)
Race*		
American Indian	0 (0)	1 (2.7)
Asian or Pacific Islander	14 (38.9)	15 (40.5)
Black	1 (2.8)	1 (2.7)
White	11 (30.6)	15 (40.5)
None of the above	3 (8.3)	0 (0)
No response	7 (19.4)	5 (13.5)
Ethnicity*		
Non-Hispanic	24 (66.7)	24 (64.9)
Hispanic	12 (33.3)	13 (35.1)
Prior breast surgery	2 (5.8)	2 (5.4)
Prior breastfeeding	17 (47.2)	13 (35.1)
Length of breastfeeding (mo)		
Less than 6	8 (47.1)	5 (38.5)
More than 6	9 (52.9)	8 (61.5)

Data are mean±SD, median (range), or n (%).
* Self-identified.

Cabergoline in the 2nd trimester

- RCT (Henkel, et al, 2023)-Stanford
  - Surveys-Bristol Breast Symptoms Inventory-assesses engorgement, leaking, tenderness, pain med need
    - Validated in postpartum but not this population
    - Considered “positive” for the outcome if anything but “absent” on a symptom
    - Side effects from medications also assessed through utilization of the medication package insert (FDA)

Cabergoline in the 2nd trimester

- RCT (Henkel, et al, 2023)-Stanford
  - Subset of patients recruited for serum prolactin levels on days 0, 4, 7, 14
    - This was also appropriately powered

Cabergoline in the 2nd trimester

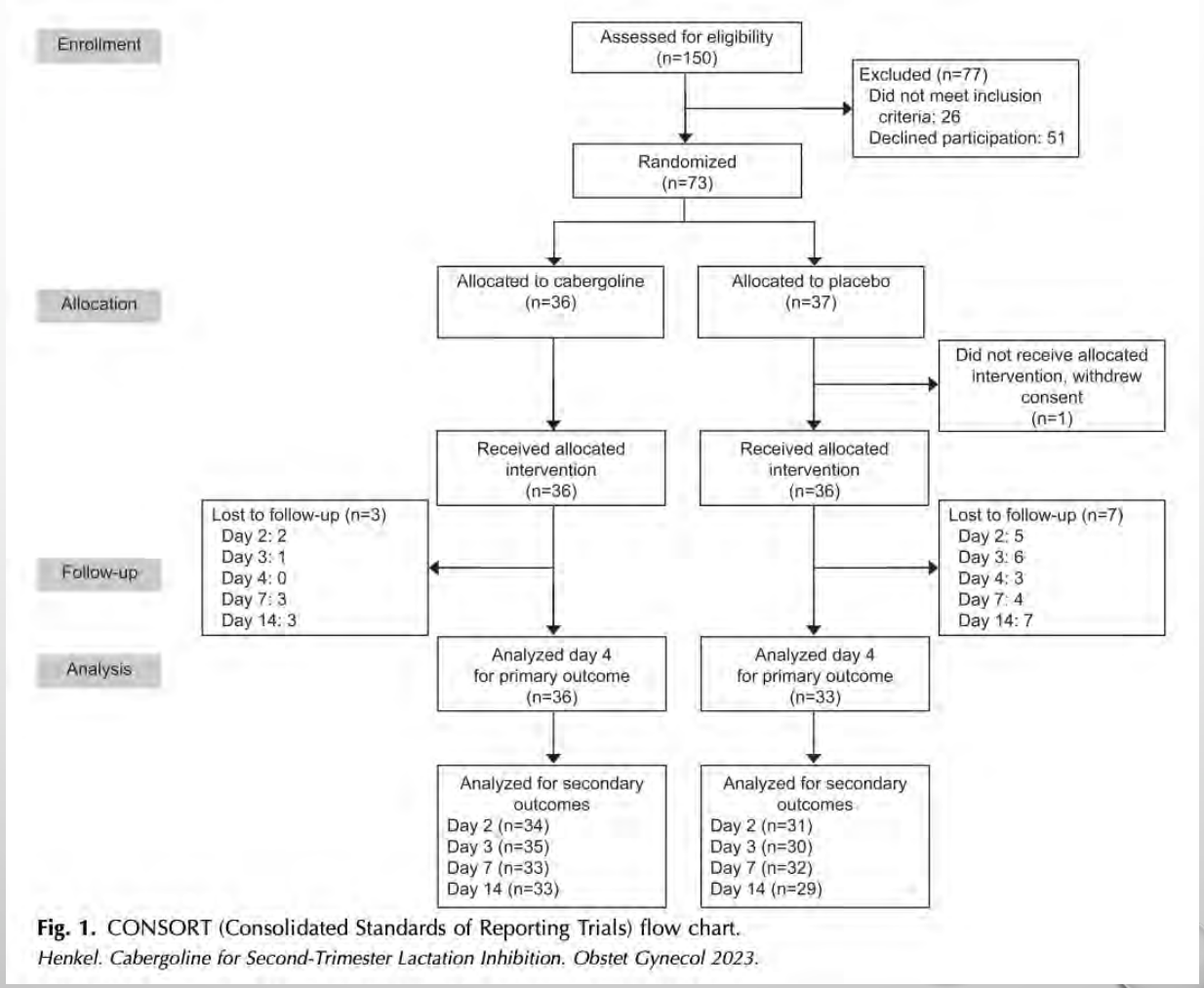
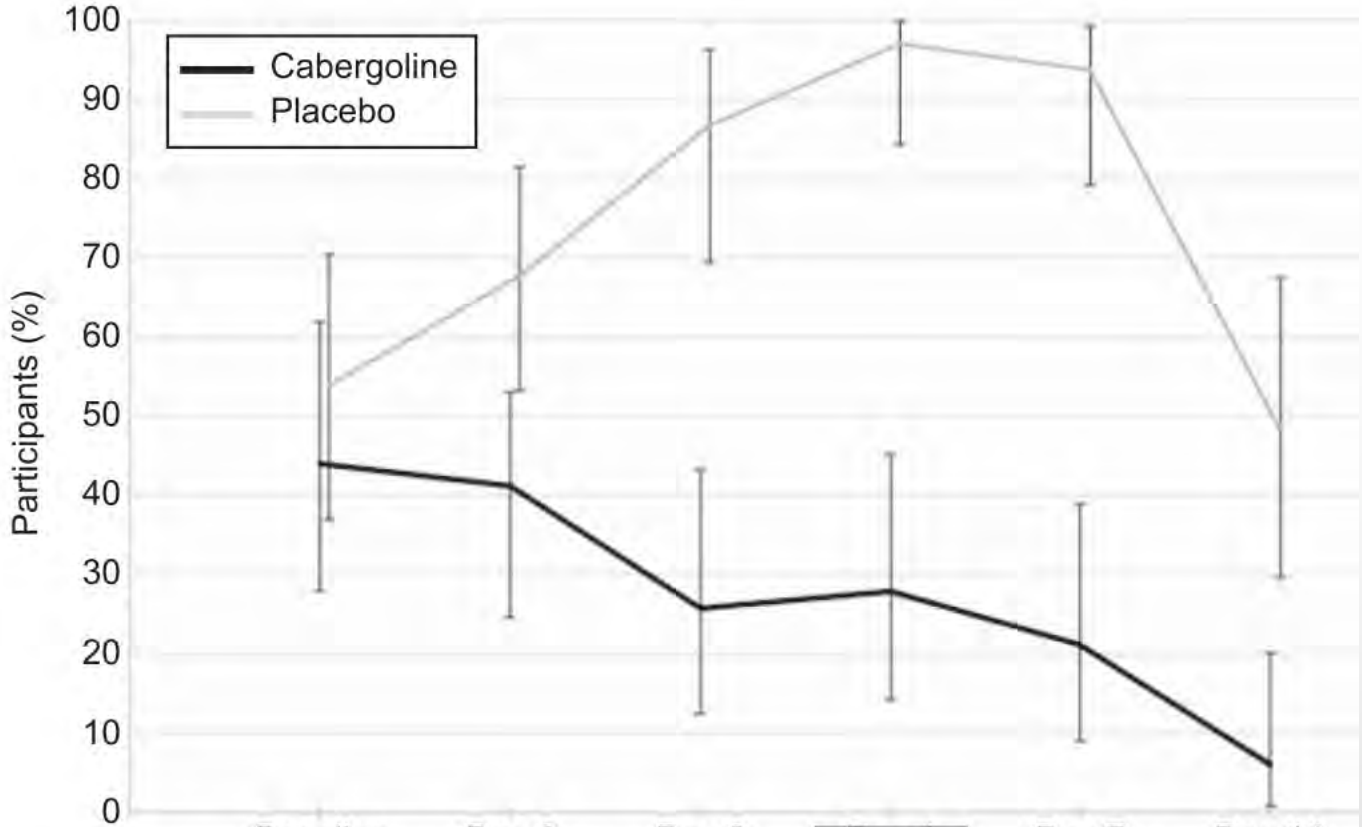


Fig. 1. CONSORT (Consolidated Standards of Reporting Trials) flow chart.

Henkel. Cabergoline for Second-Trimester Lactation Inhibition. Obstet Gynecol 2023.

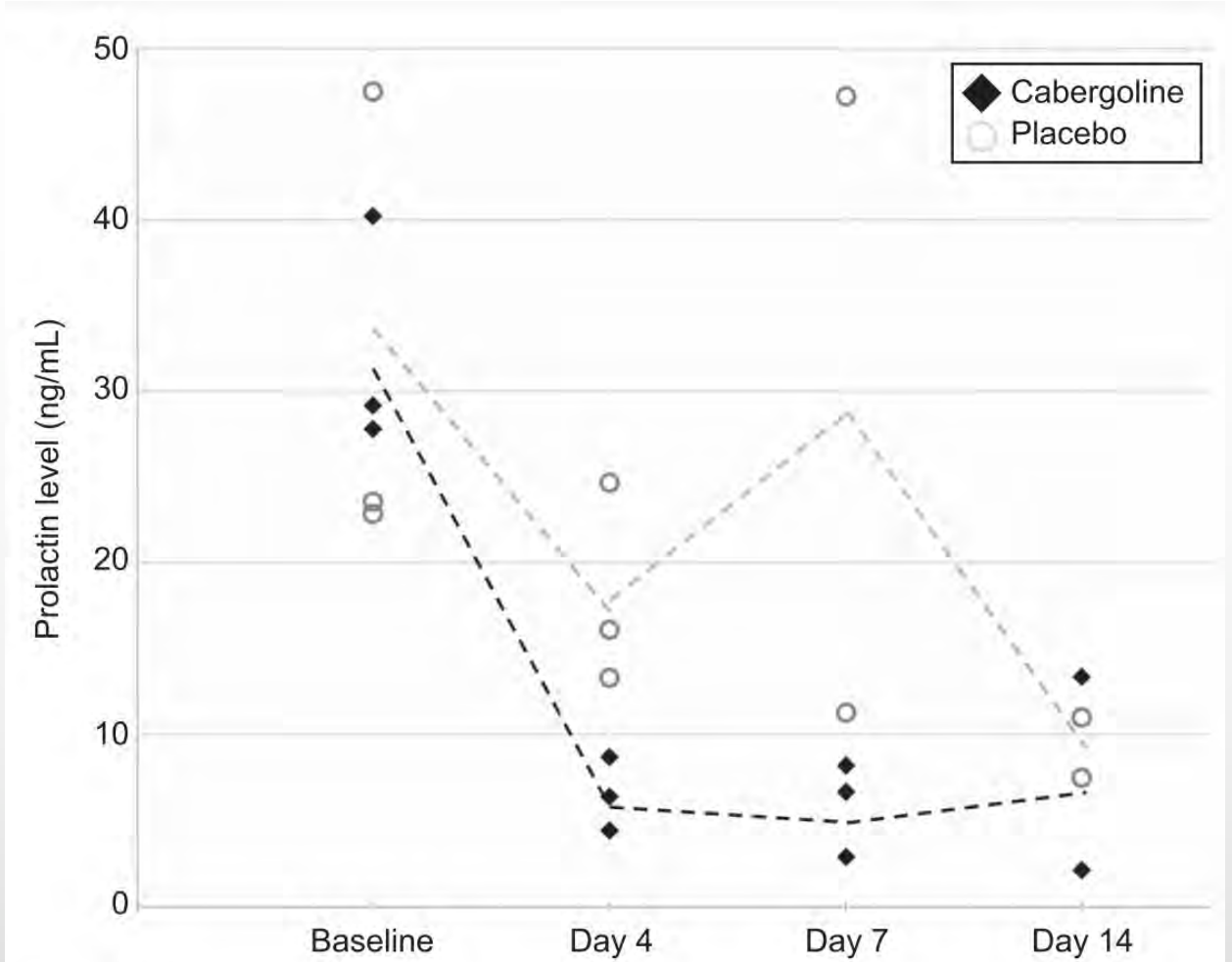


	Baseline	Day 2	Day 3	Day 4	Day 7	Day 14
Cabergoline	16/36	14/34	9/35	10/36	7/33	2/33
Placebo	20/37	21/31	26/30	32/33	30/32	14/29
P value	.41	.032	<.001	<.001	<.001	<.001

Table 2. Bother* Associated With Breast Symptoms of Participants Randomized to Cabergoline or Placebo After Second-Trimester Abortion or Pregnancy Loss

	Cabergoline	Placebo	*P*
Baseline	n=36	n=37	
Bother rating	0 (0–4)	0 (0–4)	.464
Significant bother	1 (2.8)	1 (2.7)	>.99
Day 2	n=34	n=31	
Bother rating	0 (0–3)	1 (0–4)	.040
Significant bother	0 (0)	1 (3.2)	>.99
Day 3	n=35	n=30	
Bother rating	0 (0–4)	2 (0–6)	<.001
Significant bother	1 (2.8)	1 (3.3)	>.99
Day 4	n=36	n=33	
Bother rating	0 (0–4)	3 (0–6)	<.001
Significant bother	1 (2.8)	11 (33.3)	.001
Day 7	n=33	n=32	
Bother rating	0 (0–3)	1.5 (0–5)	<.001
Significant bother	0 (0)	4 (12.5)	.11
Day 14	n=33	n=29	
Bother rating	0 (0–3)	0 (0–3)	.001
Significant bother	0 (0)	0 (0)	>.99

Data are median (range) or n (%) unless otherwise specified.
* Bother on facial pain score (0=none, 6=extremely); significant bother 4 or higher.



	Baseline	Day 4	Day 7	Day 14
Cabergoline	n=3 32.4+6.8	n=3 6.5+2.2	n=3 5.9+2.7	n=2 7.7+8.0
Placebo	n=3 31.3+14.0	n=3 18.0+5.9	n=2 29.3+25.4	n=2 9.3+2.5
P value	.513	.049	.083	.999

Table 3. Side Effects Reported by Participants Randomized to Cabergoline or Placebo After Second-Trimester Abortion or Pregnancy Loss

Side Effect	No. of Participants With Side Effects		*P*
	Cabergoline (n=36)	Placebo (n=37)	
Nausea or vomiting	5 (13.9)	2 (5.4)	.261
Headache	12 (33.3)	9 (24.3)	.395
Dizziness or lightheadedness	7 (19.4)	7 (18.9)	.955
Constipation	14 (38.9)	18 (48.6)	.401
Acid reflux	3 (8.3)	2 (5.4)	.674
Fatigue	12 (33.3)	11 (29.7)	.704
Lower extremity edema	4 (11.1)	4 (10.8)	>.99
Hot flushes	2 (5.6)	9 (24.3)	.025
Palpitations	1 (2.8)	1 (2.7)	>.99
Anxiety	4 (11.1)	3 (8.1)	.711
Insomnia	8 (22.2)	11 (29.7)	.465
Visual disturbance	1 (2.8)	2 (5.4)	>.99
Total reporting side effects	29 (80.6)	26 (70.3)	.308

Data are n (%) unless otherwise specified.

**not powered to detect differences in side effects

Author Conclusions

- *We found cabergoline to be an effective, well tolerated pharmacologic intervention to prevent bothersome breast symptoms after second-trimester abortion or pregnancy loss.*
- *Given the current lack of evidence-based interventions to prevent breast symptoms in this population, these findings support routine use of cabergoline after second trimester-abortion or pregnancy loss*
- *Limitations: underpowered to detect small differences in side effects, low trial acceptance (66%), lack of GA stratification at randomization*

Cabergoline side effects (not obstetric specific)

The following adverse drug reactions and incidences are derived from product labeling unless otherwise specified. Adverse reactions reported in adults.

>10%:

Gastrointestinal: Nausea (27% to 29%)

Nervous system: Dizziness (15% to 17%), headache (26%)

1% to 10%:

Cardiovascular: Dependent edema (1%), hypotension (≤1%), orthostatic hypotension (4%), palpitations (≤1%), peripheral edema (1%), syncope (≤1%)

Dermatologic: Acne vulgaris (≤1%), pruritus (≤1%)

Endocrine & metabolic: Hot flash (3%)

Gastrointestinal: Abdominal pain (5%), anorexia (≤1%), constipation (7% to 10%), diarrhea (≤2%), dyspepsia (2% to 5%), flatulence (≤2%), toothache (1%), vomiting (2% to 4%), xerostomia (≤2%)

Genitourinary: Dysmenorrhea (≤1%), mastalgia (1% to 2%)

Nervous system: Anxiety (≤1%), asthenia (6%), depression (3%), drowsiness (≤2%), fatigue (5% to 7%), insomnia (≤1%), lack of concentration (1%), malaise (≤1%), nervousness (≤2%), pain (2%), paresthesia (≤2%), vertigo (1% to 4%)

Neuromuscular & skeletal: Arthralgia (1%)

Ophthalmic: Periorbital edema (1%), visual disturbance (≤1%)

Respiratory: Flu-like symptoms (≤1%), rhinitis (1%), throat irritation (1%)

Contraindications to cabergoline (uptodate)

- "Uncontrolled" hypertension
- Known hypersensitivity to cabergoline, ergot derivatives, or any component of the formulation
- History of cardiovascular valvular disorders (valvulopathy of any valve, thickened leaflets, valve restriction, or mixed valve restriction/stenosis)-only demonstrated increased risk at >2mg/day
- History of pulmonary, pericardial, or retroperitoneal fibrotic disorders
- Possibly history of psychotic illness (low level of evidence)

These are for general cabergoline use that would be long term, presumably less risk in a single dose

Availability of Cabergoline

- Immediately available in the inpatient and outpatient pharmacies
- Cost: approximately 10$ for one tablet

Key Points and Action Items

- Conservative measures (cabbage leaves, ice packs, pressure) may or may not work but have limited downsides
- Cabergoline for lactation suppression is still considered off label use (as are many medications)
- >50% of patients at 18-28w did not anticipate breast symptoms
  - Opportunity for counseling on expectations
- Consider offering, for those interested and >18w, the following:
  - 1mg cabergoline within 4 hours of D&E or fetal expulsion

Suggestion for counseling/documentation

- Lactation discussion: We discussed that the majority (up to 97%) of patients at this gestational age (>18 weeks) will experience some level of breast symptoms after delivery/procedure including tenderness, engorgement, pain, and/or leakage. These symptoms can impact both physical and emotional recovery. Patients may choose to pursue lactation suppression for various reasons including pregnancy loss, pregnancy interruption, the need to initiate medications that are not compatible with lactation, adoption, or personal preference (among other reasons). Additionally, some patients going through loss may choose to initiate and continue lactation. For those hoping to suppress lactation, symptoms may be improved with ice packs, compresses, and possibly cabbage leaves although the data are limited on this. Cabergoline is a medication that can be used "off label" for lactation suppression. While cabergoline is not FDA approved for lactation suppression, data in pregnant women have been reassuring and the medication has been demonstrated to be effective in reducing and eliminating symptoms in the majority of patients between at >18 weeks gestational age. Side effects were similar among patients who did and did not receive the medication and included nausea, dizziness, and headache. This medication should not be used in those patients with uncontrolled hypertension or fibrotic disorders. In patients with a history of cardiovascular disease or psychotic illness, the care should be individualized. After a thorough discussion about risks and benefits, the patient expressed a desire to suppress/continue lactation with the following plan:
- *If suppressing lactation*
- -Ice packs, tight fitting bras, and cabbage leaves as able
- -Ibuprofen and acetaminophen for breast discomfort/pain
- -Cabergoline 1mg oral to be given within 4 hours after delivery/procedure
- -Resources provided: https://perinatalgrief.Com/lactation
-
- *If continuing lactation*
- -Lactation consultation
- -Resources provided: https://perinatalgrief.Com/lactation

Options For Milk Banking

- Human milk banking association of North America (www.Hmbana.Org)
- Mother's milk bank (www.Mothersmilk.Org)

Sample summary notes for your teams: Lactation suppression with cabergoline

- The deficit: The majority of people experiencing loss or undergoing termination of pregnancy at 18w+ have bothersome breast symptoms and many do not realize this will occur. This has been demonstrated to have significant physical and emotional impacts.
- The data:
  - In a recent double blind RCT, 1mg dose of cabergoline (single dose) has been demonstrated to decrease breast symptoms from 97% to 27% compared to placebo in patients 18-28w.
  - Additionally, studies in term patients have shown similar reductions.
  - Data on strategies like ice/compresses, wraps, cabbage leaves, etc are limited.
- The medication: Cabergoline is considered safe with few contraindications and few major side effects (that were generally not different between treatment and placebo groups). Few contraindications exist.
- The plan: Patients will be counseled on the likelihood of breast symptoms with a discussion about goals (suppression vs lactation) and provision of resources. For those interested in suppression, a single dose of cabergoline 1mg will be given in the immediate post-delivery/post-procedure period (<4h). If on L&D, dose will be given there.
  - Additional strategies will also be offered-compresses, ice, ibuprofen, etc.

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What's new in anesthetic management for OB-GYN patients

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Disclosures

I have no commercial interests or other financial disclosures

Learning Objectives

- Evaluate the benefits and drawbacks of labor epidurals
- Understand various pain management techniques for cesarean delivery
- Analyze current perioperative pregnancy testing and breastfeeding recommendations after anesthesia exposure
- Review recent anesthetic management recommendations for second trimester abortions

Epidural Analgesia for Labor: Benefits and Drawbacks

decrease in PGF2

7.8 hours

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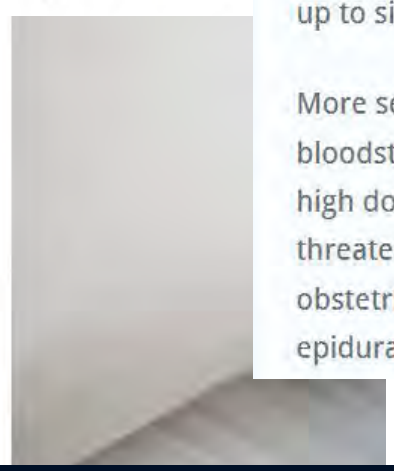

Opiate drugs, especially administered as spinals, can sometimes cause unexpected breathing difficulties for the mother, which may come on hours after birth and may progress to have serious effects. One author comments, "Respiratory depression remains one of the most feared and least predictable complications of . . . intrathecal [spinal] opioids."[47]

Many observational studies have found an association between epidural use and bleeding after birth (postpartum hemorrhage).[48–53] For example, a large UK study found that women were twice as likely to experience postpartum hemorrhaging when they used an epidural in labor.[54] This may be related to the increase in instrumental births and perineal trauma (causing bleeding), or may reflect some of the hormonal disruptions mentioned above, including increased risks of exposure to synthetic oxytocin.

An epidural gives inadequate pain relief for 10 to 15 percent of women,[55] and the epidural catheter needs to be reinserted in about 5 percent.[56] For around 1 percent of women, the epidural needle punctures the dura (dural tap); this usually causes a severe headache that can last up to six weeks, but can usually be treated by an injection into the epidural space.[57, 58]

More serious side effects are rare. If the epidural drugs are inadvertently injected into the bloodstream, local anesthetics can cause toxic effects such as slurred speech, drowsiness, and, at high doses, convulsions. This occurs in around one in 2,800 epidural insertions.[59] Overall, life-threatening reactions occur for around one in 4,000 women.[60–63] Death associated with an obstetric epidural is very rare,[64] but can be caused by cardiac or respiratory arrest, or by an epidural abscess that develops days or weeks afterward.

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place. This is significant because instrumental deliveries can increase the short-term risks of bruising, facial injuries, displacement of skull bones and

And TikTok?

POPSUGAR 7/17/23: What exactly is an epidural?

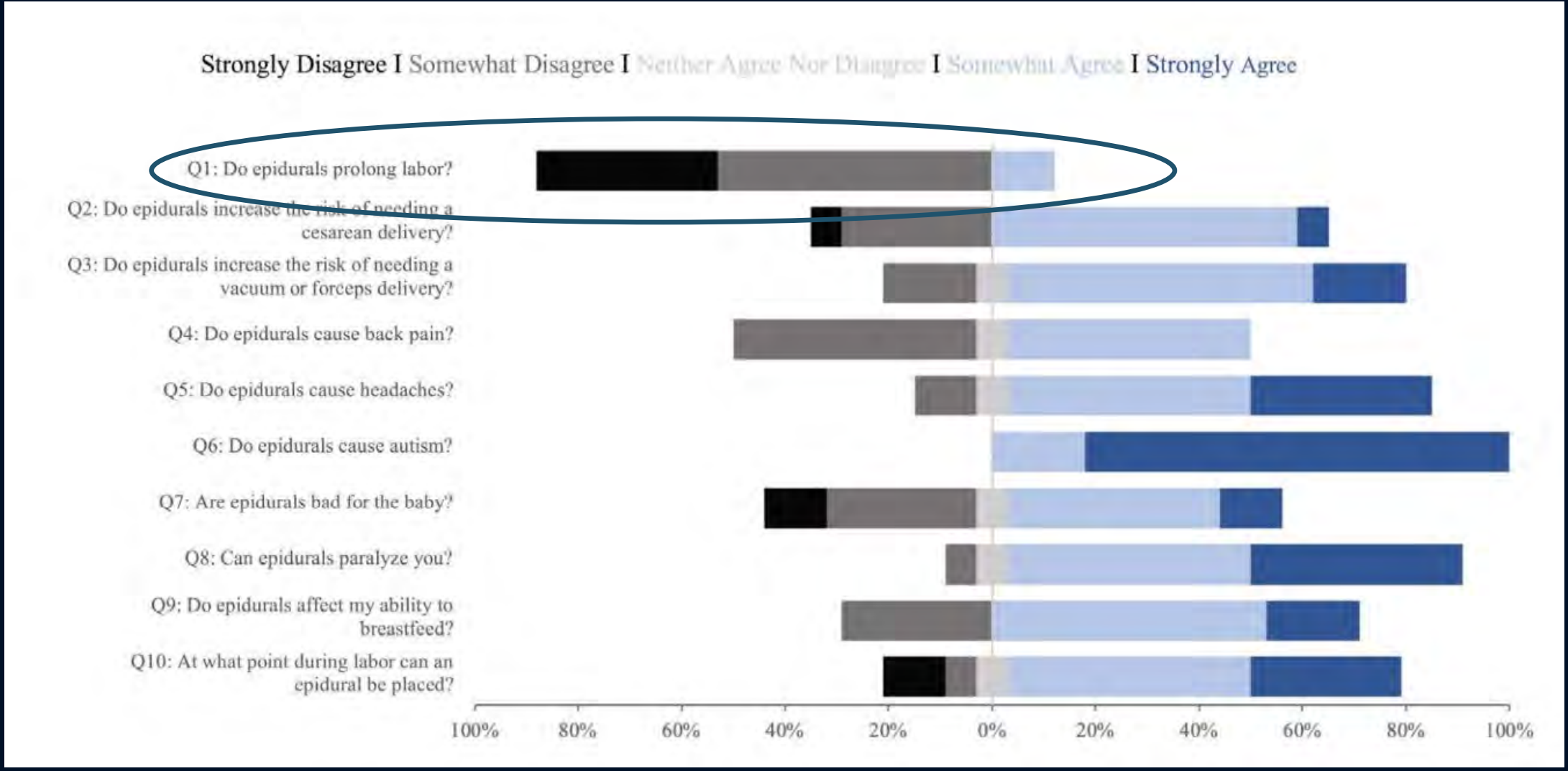
TikTok recently went viral for a post in which she expresses her shock at learning what's actually involved in an epidural.

'Finding out that the epidural isn't a shot, it's a tube that stays in your back for your entire labor' she wrote over video of her mouth hanging open. 'I have no words'….

"They really don't tell us anything on purpose" one person wrote.

"Wait, I thought it was a pill" someone else said.

What does ChatGPT say?



Mootz A Survey-Based Study. Anesth Analg. 2024 Jan 5.

Received: 30 September 2022 | Accepted: 15 March 2023
DOI: 10.1111/jog.15640

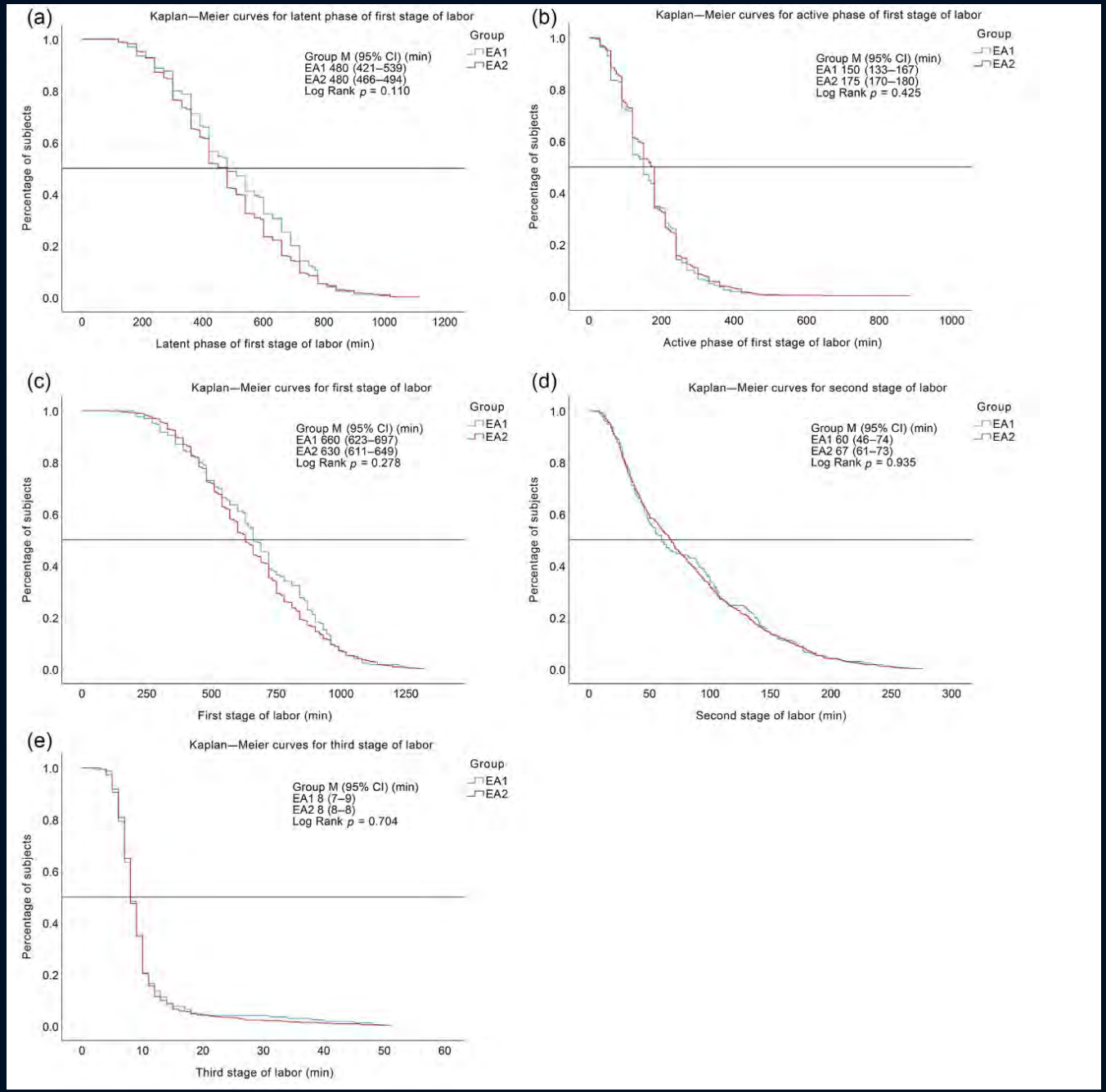
ORIGINAL ARTICLE

Effects of epidural analgesia at 1 cm cervical dilatation on labor interventions in full-term primigravida: A retrospective cohort study

Shunbin Chen | Siping Ye | Chenhua Wu | Xiufeng Jia | Sangsang Li | Xiaomei Zeng

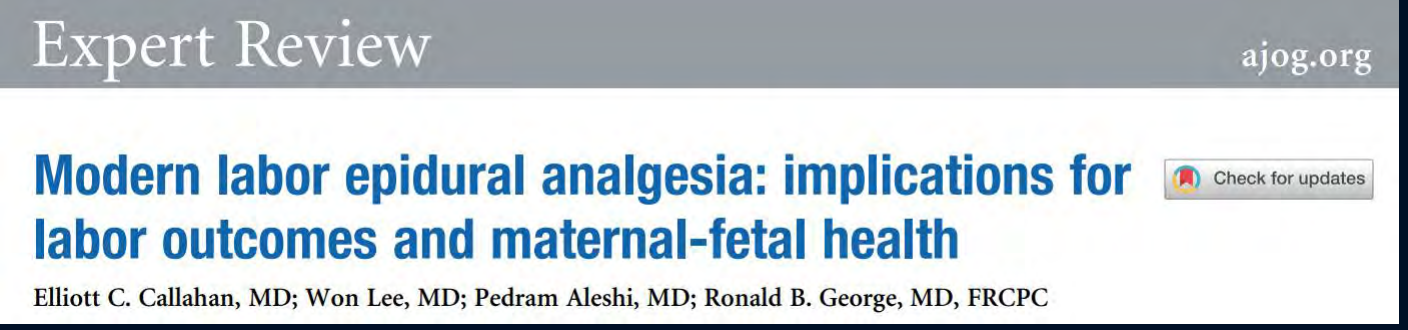
1000 term Nulliparous patients:

- Divided into early (1cm) or late (greater than 1cm).
- There were no significant differences in the median time to latent phase of labor, active phase of labor, second, and third stages of labor (p> 0.05).
- There were no significant differences in maternal and neonatal outcomes.



- 2015-2016: 51,000 patients, multicenter
- Neuraxial analgesia resulted in:
  - Reduced cesarean deliveries: OR 0.68
    - Maternal request for intrapartum cesarean without medical indication decreased from 11.6% to 3.3% with the use of neuraxial analgesia ($p < .0001$)
  - $3^{rd}/4^{th}$ degree lacerations: OR 0.36
  - 5-minute Apgar: OR 0.15

Xi Meng, Anesth Analg 2023



MAY 2023 American Journal of Obstetrics & Gynecology

- Clinically negligible prolongation of labor
- No increased risk of assisted vaginal or cesarean delivery.
- Transient hypotension on initiation is not associated with adverse outcomes if treated with fluids and/or pressors.
- Infants have a better acid-base status at delivery compared with systemic opioid analgesia.
- There is ↑ incidence of non-infectious fever that has not been shown to affect neonates; its cause is unknown.

Epidural-related maternal fever: incidence, pathophysiology, outcomes, and management

Selina Patel, BMBS, FRCA; Sarah Ciechanowicz, BMBCh, MRes, FRCA; Yair J. Blumenfeld, MD; Pervez Sultan, MBChB, FRCA, MD (Res)

- 20% of OB patients who receive neuraxial analgesia will have fever regardless of the medication concentration or rate.
- Etiology is unknown but it is non-infectious.
- It may be caused by:
  - Sterile inflammation involving reduced activation of caspase-1.
  - Thermoregulatory mechanisms due to neuraxial local anesthetic may contribute.

FIGURE 1
Proposed mechanisms of sterile inflammation resulting in epidural-related maternal fever

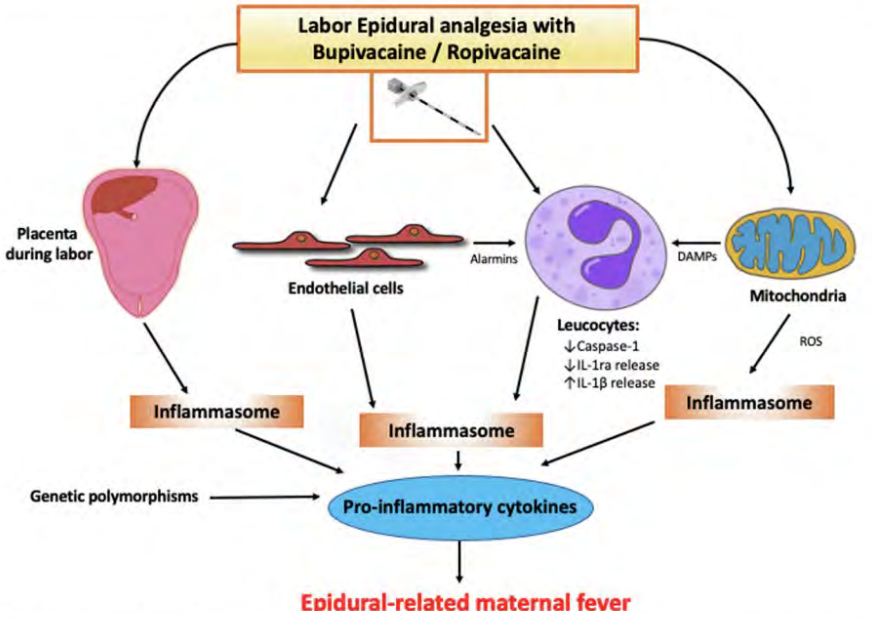
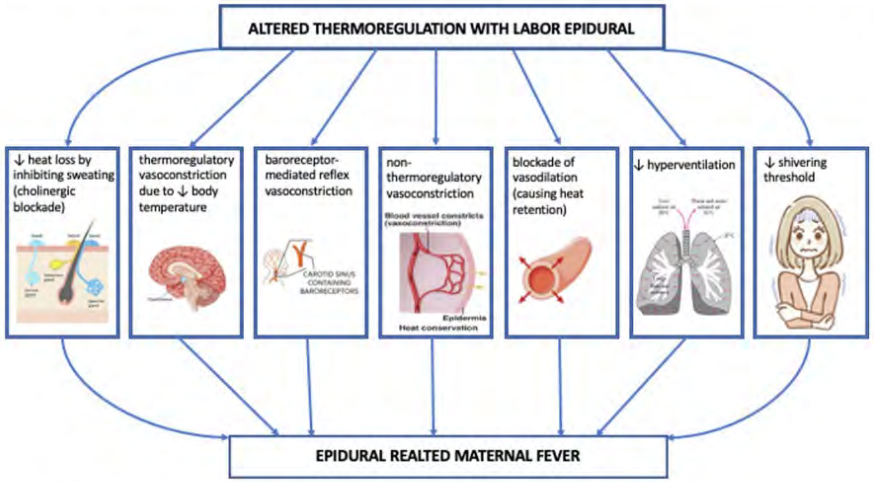


FIGURE 2
Proposed mechanisms of epidural-related maternal fever secondary to altered thermoregulation



Patel. Epidural-related maternal fever narrative review. Am J Obstet Gynecol 2023.

ANESTHESIOLOGY

Association of Labor Neuraxial Analgesia with Maternal Blood Transfusion

Jean Guglielminotti, M.D., Ph.D., Ruth Landau, M.D., Jamie Daw, Ph.D., Alexander M. Friedman, M.D., M.P.H., Guohua Li, M.D., Dr.P.H.

ANESTHESIOLOGY 2023; 139:734–45

https://www.blood.ca/sites

- 12,503,042 U.S. deliveries from 2015-2018
  - 9,479,291 (75.82%) were with neuraxial analgesia
  - 42,485 (0.34%) involved maternal blood transfusion
  - Propensity matching with 2,589,493 patients in each group
- All deliveries: OR 0.87
- Cesarean deliveries: OR 0.55
- Vaginal deliveries: OR 0.93

TO EAT or NOT TO EAT…

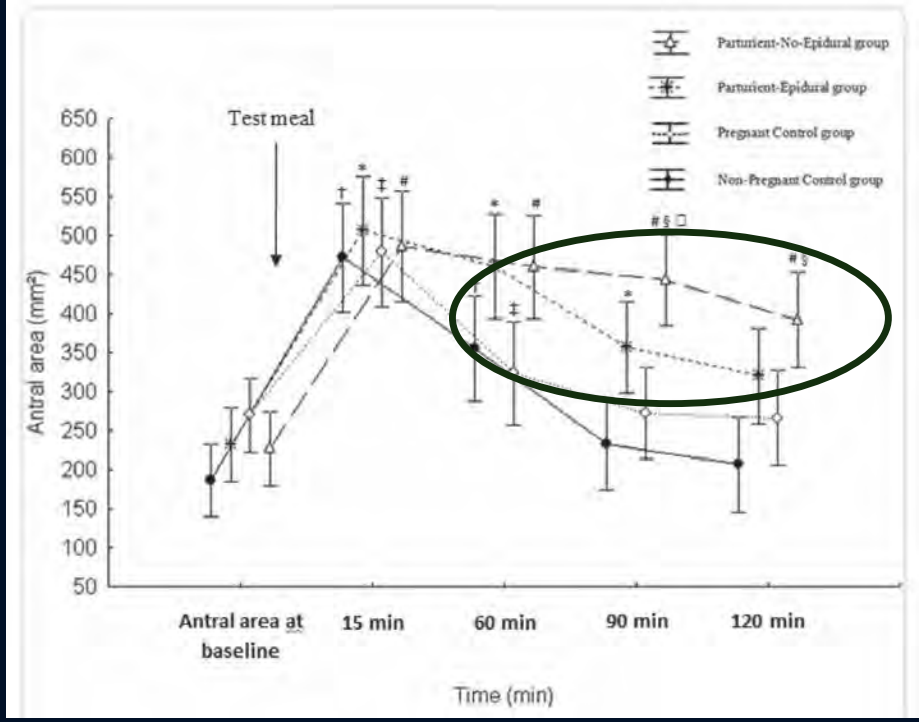
ANESTHESIOLOGY

Pregnancy and Labor Epidural Effects on Gastric Emptying: A Prospective Comparative Study

Lionel Bouvet, M.D., Ph.D., Thomas Schulz, M.D., Federica Piana, M.D., François-Pierrick Desgranges, M.D., Ph.D., Dominique Chassard, M.D., Ph.D.

ANESTHESIOLOGY 2022; 136:542–50

"Gastric emptying in parturients after a light meal was delayed, and labor epidural analgesia seems not to worsen but facilitates gastric emptying."



Ultrasound evaluation of gastric emptying of high-energy semifluid solid beverage in parturients during labor at term: a randomized controlled trial

Xiu Ni[1] · Jiang Li[1] · Qi-Wei Wu[1] · Shuang-qiong Zhou[1] · Zhen-Dong Xu[1] · Zhi-Qiang Liu[1]

Received: 29 September 2022 / Accepted: 29 September 2023 / Published online: 26 October 2023

- *40 parturients*
- *Semi-solid carbohydrate drink*
- *Clears*
- *No difference in gastric emptying at 2 hours*

OBSTETRICS

Labor epidural analgesia and subsequent risk of offspring autism spectrum disorder and attention-deficit/hyperactivity disorder: a cross-national cohort study of 4.5 million individuals and their siblings

- 24% were exposed to epidural analgesia during labor, 1.2% were diagnosed with ASD and 4% with ADHD.
- On a population level there was a significant association with epidural, but when controlling for maternal anxiety or depression & using siblings not exposed to epidural as the control group, there was no significant association.
- Conclusion:

"In this large cross-national study, we found no support for the hypothesis that exposure to labor epidural analgesia causes either offspring autism spectrum disorder or attention-deficit/hyperactivity disorder."

Am J Obstet Gynecol 2023;228:233

OBSTETRICS

Fentanyl in the labor epidural impacts the results of intrapartum and postpartum maternal and neonatal toxicology tests

- Prospective cohort study used urine samples before and after initiation of neuraxial analgesia plus at intervals during labor and up to 4 times postpartum + a neonatal urine sample.
- 33 maternal-infant dyads yielded a total of 178 urine specimens.
- No specimens were + before neuraxial.
- Intrapartum 77% had + mass spec and 40% had + immunoassay.
- Postpartum 91% had + mass spec and 62% had + immunoassay.
- Neonatal samples were + in 77%.

Am J Obstet Gynecol 2023;228:741

Multimodal analgesic approach for cesarean delivery

Anaesthesia
Peri-operative medicine, critical care and pain
Association of Anaesthetists

Correspondence | Free Access

PROSPECT guideline for elective caesarean section: an update

E. Roofthooft, G. P. Joshi, N. Rawal, M. Van de Velde, on behalf of
the PROSPECT Working Group of the European Society of Regional Anaesthesia and Pain Therapy

CURRENT OPINION

Analgesia after cesarean section – what is new?

Heidrun Lewald[a,b,c] and Thierry Girard[d]

Multi-modal regimens are underused and should be standard.

- Neuraxial morphine should be utilized if possible (150mcg spinal or 3mg epidural).
- NSAIDs and acetaminophen should be scheduled and given together.
- Intravenous dexamethasone 8-10 mg is opioid-sparing.
- Truncal blocks or local infiltration helpful if neuraxial morphine not utilized.

ORIGINAL CLINICAL RESEARCH REPORT

Outpatient Treatment With Gabapentin in Women With Severe Acute Pain After Cesarean Delivery Is Ineffective: A Randomized, Double-Blind, Placebo-Controlled Trial

Cedar Fowler, MD, PhD, Amy W. Chu, MD, Nan Guo, PhD, Jessica R. Ansari, MD, Steven L. Shafer, MD, and Pamela D. Flood, MD

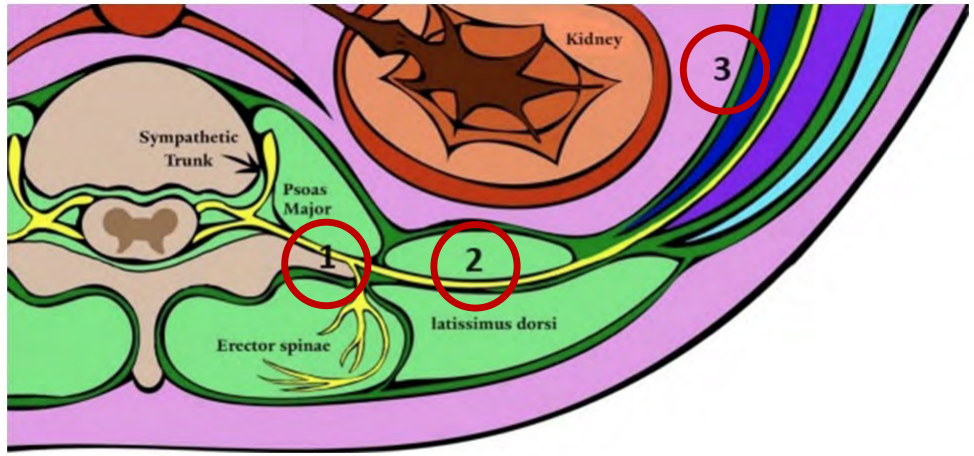
- Avoid gabapentin; limited analgesia and excess side effects.

Open Access Full Text Article

REVIEW

Regional Analgesia for Cesarean Delivery: A Narrative Review Toward Enhancing Outcomes in Parturients

Matthew Silverman[1], Nicholas Zwolinski[1], Ethan Wang[2], Nishita Lockwood[1], Michael Ancuta[1], Evan Jin[1], Jinlei Li[1]



1. Erector Spinae Plane block (ESP)
2. Quadratus Lumborum block (QL)
3. Transversus abdominal plane block (TAP)

- Neuraxial morphine continues to be the gold standard.
- If neuraxial morphine cannot/is not provided: overwhelming evidence that regional anesthetic techniques improve post-cesarean section analgesia and decrease post-operative opioid use.
- All provide analgesic benefit.
- More data is accumulating that QL and ESP blocks may provide improved analgesia.

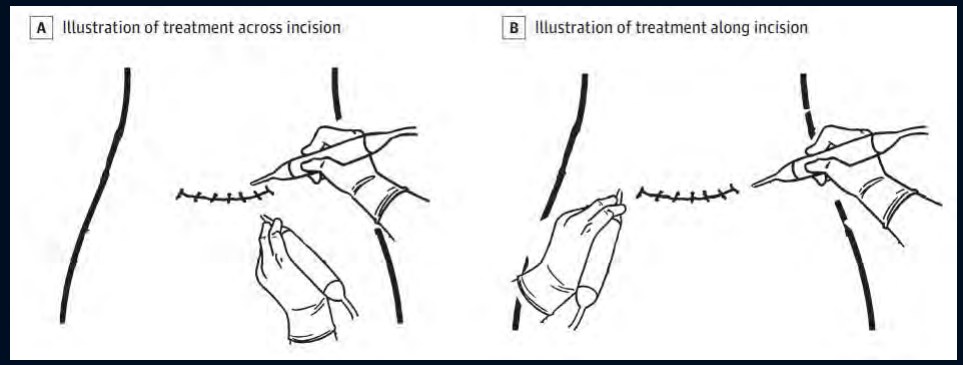
JAMA Network | Open

Original Investigation | Obstetrics and Gynecology

Noninvasive Bioelectronic Treatment of Postcesarean Pain
A Randomized Clinical Trial

Jennifer L. Grasch, MD; Maged M. Costantine, MD; Devra D. Doan Mast, BSN; Baylee Klopfenstein, BSN; Jessica R. Russo, RDMS; Taryn L. Summerfield, MS; Kara M. Rood, MD

- Blinded comparison of a functional or sham TENS device
- Each group received 3 treatments (real or sham) at the incision site:
  - Within 2 hours postop
  - 12 hours after first application
  - 12 hours after second application
- 47% less opioid while inpatient



- Prescribed less at discharge (MME 82.5mg v 90mg, p<0.001)
- No opiates at discharge (10% v 25%, p=0.03)

Research article

Effect of chamomile aromatherapy with and without oxygen on pain of women in post cesarean section with spinal anesthesia: A randomized clinical trial

Hajar Zamani Habibabad [a], Ardashir Afrasiabifar [b], Afshin Mansourian [c], Mahboubeh Mansourian [d], Nazafarin Hosseini [e,*]

- Decrease in pain scores at 6h (9 vs 8), not clinically significant
- Decrease in pain scores at 12 h (8.5 vs 6) and 18h (7.5 vs. 4.5) postoperatively ($p < 0.001$)

Chamomile Essential Oil Benefits & Uses in Treatment | Seema

Perioperative pregnancy testing and breastfeeding after anesthesia

Ethical Principles Do Not Support Mandatory Preanesthesia Pregnancy Screening Tests: A Narrative Review

Stephen Jackson, MD,* James Hunter, MD,† and Gail A. Van Norman, MD‡

- Mandatory routine non-consented preop pregnancy testing does not respect patient autonomy.
- It can be coercive, e.g. if canceling surgery is the option.
- It can cause harm socially, medically (by delaying needed treatments), and financially (insurance implications).
- Not performing a test does not have medicolegal issues for anesthesiologists.

Anesth Analg 2023

American Society of Anesthesiologists

Pregnancy Testing Prior to Anesthesia and Surgery

Developed By: Committee on Quality Management and Departmental Administration
Last Amended: October 13, 2021 (original approval: October 26, 2016)

- Informed consent or assent of the risks, benefits, and alternatives related to preoperative pregnancy testing.
- Shared decision-making between patients and providers.
- Preanesthetic educational materials should include information about false positives and negatives of pregnancy testing and effects of anesthesia.
- Pregnancy testing may be offered to female sex patients of childbearing age and for whom the result would alter the patient's management, **but testing should not be mandatory.**

INTERIM UPDATE

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

American Society of Anesthesiologists™

ACOG COMMITTEE OPINION SUMMARY

Number 775

(Replaces Committee Opinion No. 696, April 2017)

For a comprehensive overview of these recommendations, the full-text version of this Committee Opinion is available at http://dx.doi.org/10.1097/AOG.0000000000003174.

Scan this QR code with your smartphone to view the full-text version of this Committee Opinion.

Committee on Obstetric Practice
American Society of Anesthesiologists

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice and the American Society of Anesthesiologists.

INTERIM UPDATE: The content on nonobstetric surgery in this Committee Opinion has been updated to reflect a limited, focused change in the language regarding sedative drugs, medically necessary surgery, antenatal corticosteroids, and venous thromboembolism. For complete details on these updates, please see the full-text version.

Nonobstetric Surgery During Pregnancy

"No currently used anesthetic agents have been shown to have any teratogenic effects in humans when using standard concentrations at any gestational age."

Anaesthesia 2023, 78, 159–169 doi:10.1111/anae.15884

Original Article

Neurodevelopmental outcomes after prenatal exposure to anaesthesia for maternal surgery: a propensity-score weighted bidirectional cohort study

T. Bleeser,[1] S. Devroe,[2] N. Lucas,[3] T. Debels,[4] M. Van de Velde,[5] J. Lemiere,[6] J. Deprest[7] and S. Rex[5]

A cohort study of children who had received prenatal anesthesia during maternal surgery (N=129) vs unexposed.

- Single exposure, short duration
- Excluded fetal surgery
- No difference in the global executive composite of the behavior rating inventory of executive function score.
- No difference in problems from the child behavior checklist, psychiatric diagnoses or learning disorders.

Breastfeeding after Anesthesia

- Relative infant dose (RID)
- Accounts for maternal and infant weight + concentration of drug in breastmilk
- RID levels less than 10% are generally considered safe
- Codeine or tramadol
  - CYP2D6 metabolism
  - “ultra-metabolizer” patient breastfeeds a “slow metabolizer” neonate

Relative Infant Dose for Common Anesthesia Medications

Table. Relative Infant Dose (RID) of Anesthesia Medications and Recommendations

Medication Class (Drug)	Mean RID (%)*
Anticholinergics (atropine, glycopyrrolate)	Unknown: generally considered safe with single systemic or ophthalmic dosing
Anticholinesterases (neostigmine, pyridostigmine)	0.1
Antiemetics (metoclopramide, ondansetron)	Unknown: considered safe due to lack of sedating side effects
Benzodiazepines (diazepam, lorazepam, midazolam)	0.3
Intravenous Anesthetics	
Etomidate	0.1
Ketamine	Unknown: recommended only if medically necessary
Propofol	0.1
Local Anesthetics (bupivacaine, lidocaine, ropivacaine)	0.1
Narcotics	
Fentanyl	1
Hydrocodone	3
Hydromorphone	3
Morphine	9
Oxycodone	3 (maximum daily dose 30mg§)
Remifentanil	Unknown: considered safe secondary to short half-life
Codeine/Tramadol	Avoid: FDA warning against use in women with a CYP2D6 mutation
Non-narcotic Analgesics	
Acetaminophen	4 (maximum daily dose < 3gm¥)
Ibuprofen	0.5
Ketorolac	0.3
Miscellaneous	
Gabapentin	3
Dexamethasone	Unknown: considered safe (may cause temporary loss of milk secondary to ↓ prolactin levels)
Diphenhydramine	Unknown: generally considered safe
Volatile Gases	Unknown: considered safe secondary to rapid excretion, poor bioavailability and OR scavenging of gases

* Mean RID is an estimated average from multiple sources reviewed.

§ LactMed. Toxicology Data Network. US National Library of Medicine. NIH. HMS. Bethesda, MD. Accessed at: https://toxnet.nlm.nih.gov/cgi-bin/sis/search2.

American Society of Anesthesiologists

Statement on Resuming Breastfeeding after Anesthesia

Developed by: Committee on Obstetric Anesthesia

Approved: October 23, 2019

- Patients should resume breastfeeding as soon as possible after surgery because anesthetic drugs appear in such low levels in breastmilk.
- Because pain interferes with successful breastfeeding, pregnant patients should not avoid pain medicines after surgery.
- Pain meds such as oxycodone can and should be given in PACU as needed and should not delay breast-feeding.
- **It is not recommended that patients "pump and dump."**

Anesthesia for Second Trimester Abortions

Anesthetic Considerations for Second-Trimester Surgical Abortions

Elizabeth Ozery, MD,* Jessica Ansari, MD,* Simranvir Kaur, MD,† Kate A. Shaw, MD, MS,† and Andrea Henkel, MD, MS†

- Abortion is safer than carrying a pregnancy to term: the estimated fatality rate is 0.41 deaths per 100,0003vs 17.4 per 100,000 in term birth resulting in a 42-fold increase in risk of death for pregnancy compared to abortion. (Obstet Gynecol. 2021;137:763–771)
- 5579 pregnant people receiving abortion care in an outpatient setting (31% in second trimester) with IV moderate or deep sedation without endotracheal intubation.
  - There were no incidents of pulmonary complications or anesthesia-related adverse events with BMI up to 40.
- Deep sedation or monitored anesthesia care should routinely be considered as the default anesthetic modality for patients undergoing D&E.

Anesth Analg. 2023 Aug 1;137(2):345-353.

Summary

- Many misconceptions about labor epidurals
- Labor epidurals
  - Do NOT slow down labor progression
  - Reduce patient requested cesarean
  - Reduce 3rd and 4th degree lacerations
  - Reduce blood transfusions, esp in CD
  - Improve gastric emptying
  - Increase incidence of noninfectious fevers
  - Neuraxial opiates found in maternal urine and neonatal meconium
- Cesarean analgesia
  - ERAC protocols
  - Truncal blocks if no neuraxial morphine
  - Consider non-pharmacologic options (TENS, aromatherapy)
- Perioperative Pregnancy Testing: Offered but not mandatory
- Breastfeeding After Anesthesia: No Pump and Dump
- Anesthesia for Second Trimester Abortions: Sedation is a safe option

Thank you!


University of Colorado
Anschutz Medical Campus


Colorado Fetal
Care Center

Venous Thromboembolism Prevention in Obstetric Practice

Torri Metz, MD, MS

Division Chief, Maternal-Fetal Medicine

Vice-Chair for Research, Department Ob/Gyn

University of Utah Health

Feb 23, 2024

HEALTH

UNIVERSITY OF UTAH

No relevant disclosures

Objectives

- Describe current prevalence of VTE in obstetric patients
- Identify patients at increased risk for VTE requiring thromboprophylaxis
- Describe available literature surrounding VTE prophylaxis postpartum

Maternal Morbidity & Mortality

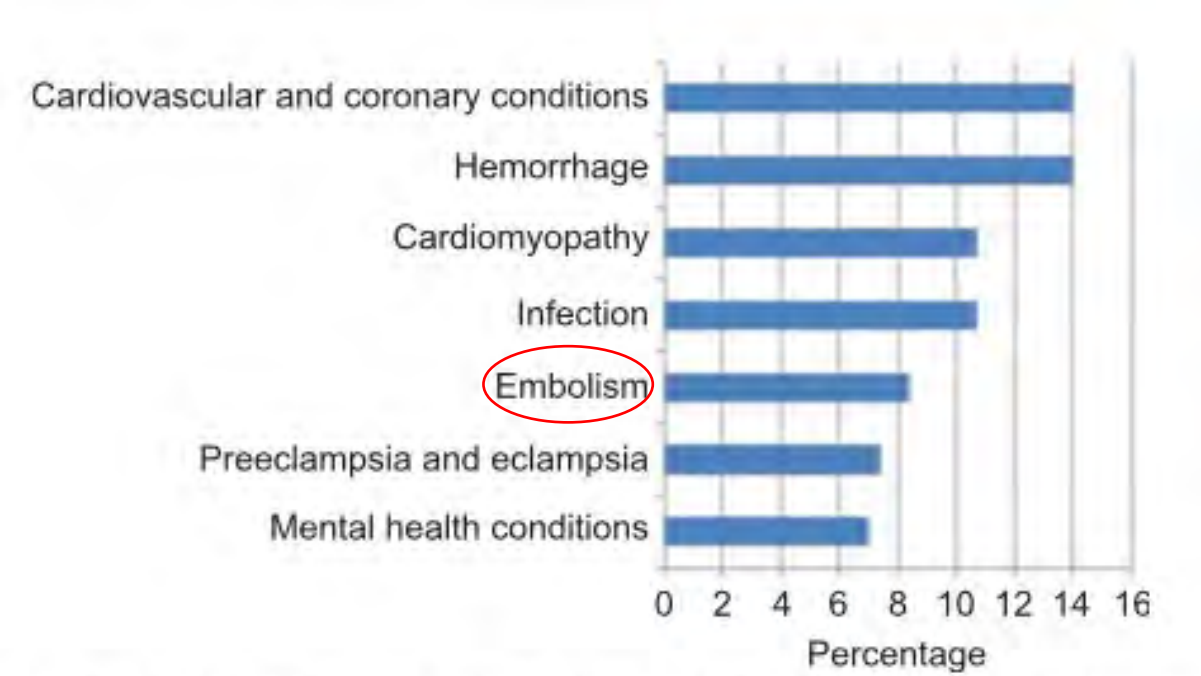


Fig. 1. Graphic representation of the leading underlying causes for the 237 pregnancy-related deaths from nine states analyzed for the "Report from Nine Maternal Mortality Review Committees." Adapted from: Building U.S. Capacity to Review and Prevent Maternal Deaths (2018). Report from nine maternal mortality review committees.

- Venous thromboembolism (VTE)
  - Includes deep vein thrombosis (DVT) & pulmonary embolism (PE)
  - Contributes to 9.3% of maternal deaths
- Significant morbidity
  - Post-thrombotic syndrome
  - Pulmonary hypertension
  - Anticoagulation

Clark et al. Obstet Gynecol 2017; 130(1): 198-202.
Metz et al. Obstet Gynecol 2018; 132(4): 1040-1045
ACOG. Obstet Gynecol 2018; 132(1): e1-e17.

The first two weeks postpartum are “peak” risk period for VTE in obstetric population

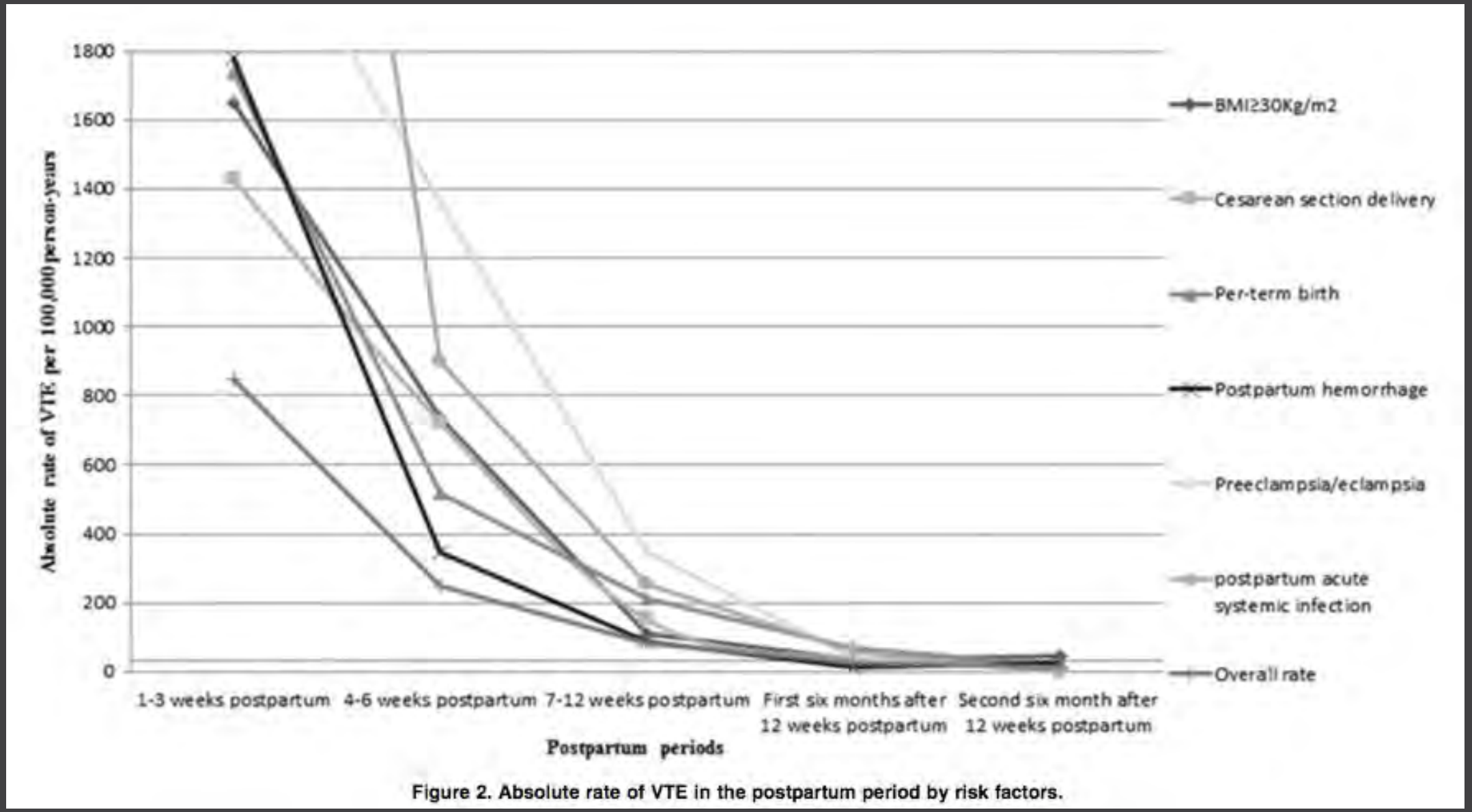


Figure 2. Absolute rate of VTE in the postpartum period by risk factors.

Sultan et al. Br J Haematol 2011; 156:366
Sultan et al. Blood 2014; 124(18): 2877

37 year old G1 at 39w0d presents for induction of labor. After 28 hours, undergoes primary cesarean delivery for arrest of dilation at 6 cm.

Pregnancy history:

- Conception by IVF
- Antepartum admission for non-obstetric surgery (cholecystectomy)

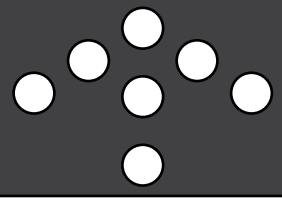
Medical history includes:

- Crohn's Disease (well-controlled, no recent flares)
- Obesity (body mass index 39 kg/m^2)

What's her risk of venous thromboembolism?
Should we place her on prophylaxis?
What are the risks and benefits?

Current Intervention Model in Obstetrics

Hypercoagulable + Risk Factors → Venous Thromboembolism → Maternal Morbidity & Mortality



Interventions

- Mechanical prophylaxis
- Chemical prophylaxis

Interventions

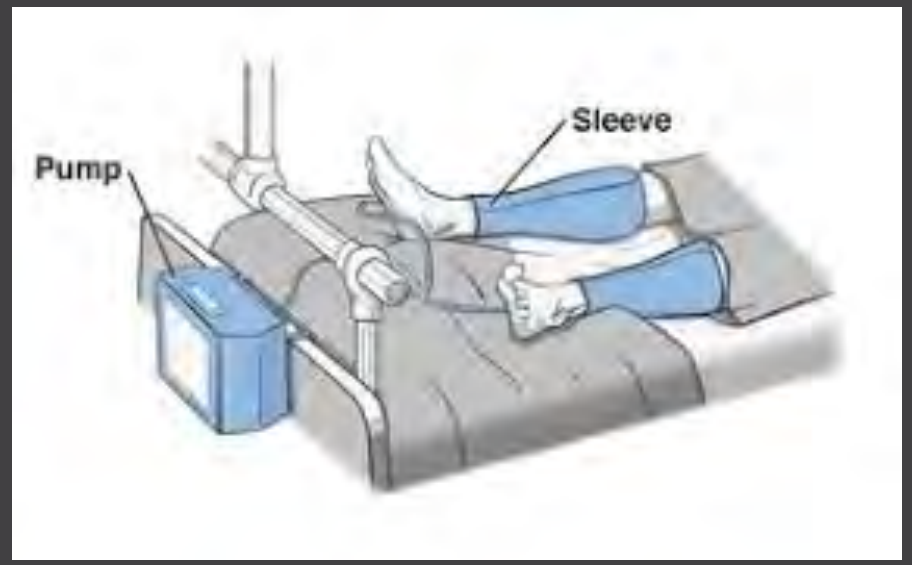
Low-molecular weight heparin

- Enoxaparin preferred
  - Bioavailability
  - Safety profile
  - Cost & availability (in United States)

LOVENOX®
(enoxaparin sodium injection)®

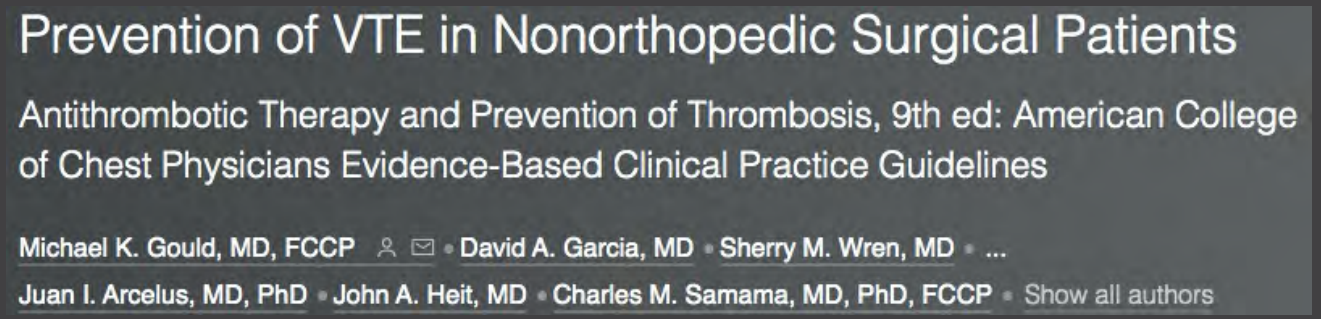
Sequential compression devices

- Non-invasive
- Low risk
- During cesarean & postpartum



Evidence for thromboprophylaxis

- Efficacious in reducing post-operative VTE in non-obstetric surgical fields
  - Orthopedic surgery → general surgery



Bates et al. Chest 2012 ; 141(2 Suppl):e691S-e736S.
Bates et al. J Thromb Thrombolysis 2016;41(1):92-128.
Felder et al. Cochrane Database Syst Rev. 2019; 26;8(8):CD004318.

Sequential Compression Devices

- Retrospective observational cohort
- Hospital Corporation of America (~6% deliveries in U.S.)
- Evaluated maternal death pre- and post-implementation of pneumatic compression device protocol for individuals undergoing cesarean
- Significant decrease in post-cesarean fatal pulmonary embolism

Category of Death	**2000-2006 (Pre) n = 1,461,270**	**2007-2012 (Post) n = 1,256,020**	**p**
Post-cesarean pulmonary embolism	7	1	0.038

Clark et al. AJOG 2014; 211(1):32.e1-9

Low molecular weight heparin prophylaxis

- Confidential Enquiries – UK tracking of maternal deaths
- Decline in thromboembolic deaths following 2004 introduction of RCOG thromboprophylaxis guidelines

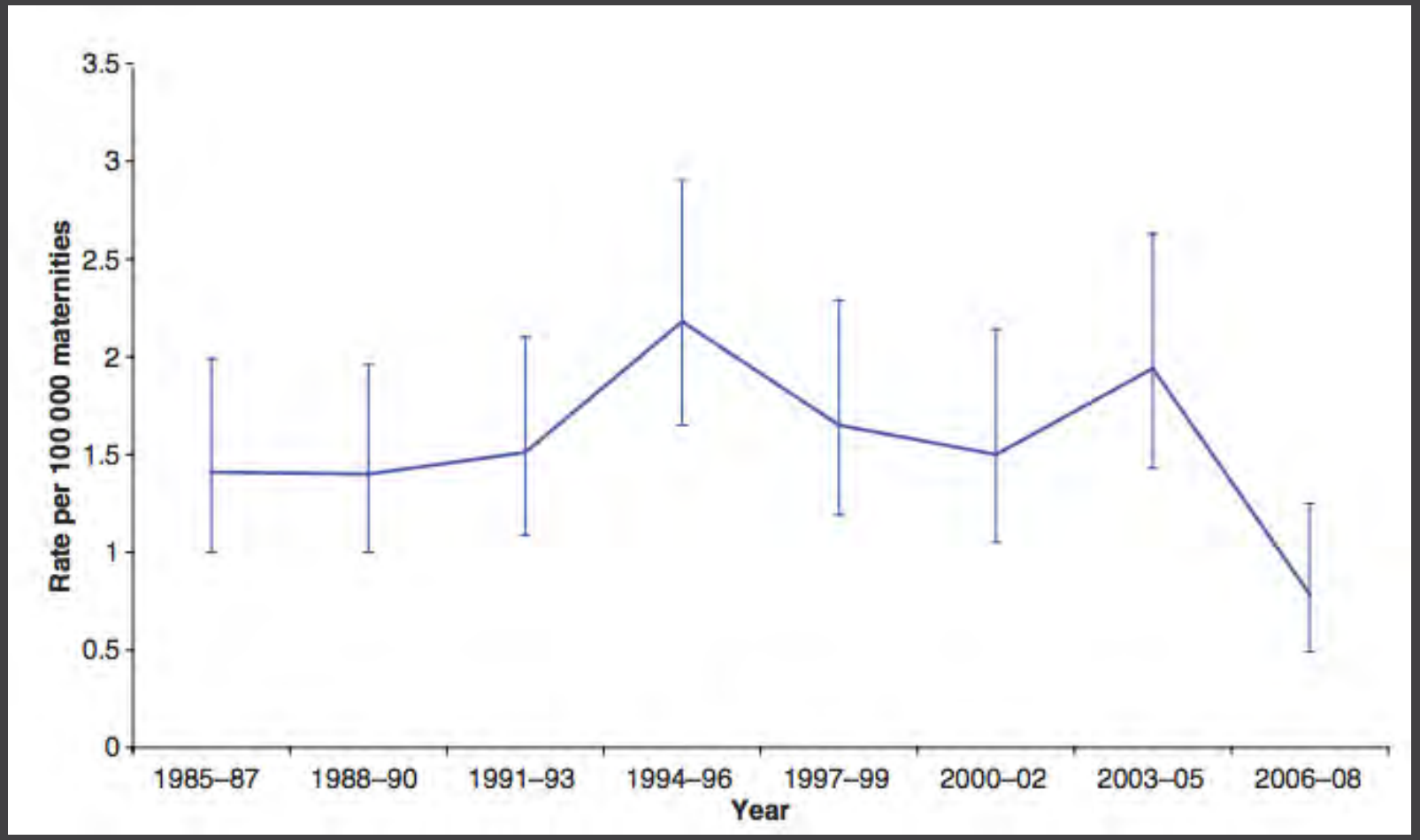
Table 2.1. *Direct* deaths from thrombosis and thromboembolism and rates per 100 000 maternities; UK: 1985–2008

	Pulmonary embolism			Cerebral vein thrombosis			Thrombosis and thromboembolism		
	n	Rate	95% CI	*n*	Rate	95% CI	*n*	Rate	95% CI
1985–87	30	1.32	0.83–1.89	2	0.09	0.02–0.32	32	1.41	1.00–1.99
1988–90	24	1.02	0.68–1.51	9	0.38	0.20–0.72	33	1.40	1.00–1.96
1991–93	30	1.30	0.91–1.85	5	0.22	0.09–0.51	35	1.51	1.09–2.10
1994–96	46	2.09	1.57–2.79	2	0.09	0.02–0.33	48	2.18	1.65–2.90
1997–99	31	1.46	1.03–2.07	4	0.19	0.07–0.48	35	1.65	1.19–2.29
2000–02	25	1.25	0.85–1.85	5	0.25	0.11–0.59	30	1.50	1.05–2.14
2003–05	33	1.56	1.11–2.19	8	0.38	0.19–0.75	41	1.94	1.43–2.63
2006–08	16	0.70	0.43–1.14	2	0.09	0.02–0.35	18	0.79	0.49–1.25

8th Report of the confidential enquiries into maternal deaths in the United Kingdom. BJOG 2011; 118:S1

UK epidemiologic data – basis for widespread LMWH use for prophylaxis in obstetrics

Rates of death from thromboembolism per 100 000 maternities; UK: 1985–2008



8th Report of the confidential enquiries into maternal deaths in the United Kingdom. BJOG 2011; 118:S1

Guidelines Abound

Table. Society guidelines for postpartum risk stratification and recommendations for thromboprophylaxis

Guideline	Population & Recommendations
Royal College of Obstetricians and Gynaecologists (RCOG)	In individuals undergoing any mode of delivery: ▪ Recommend LMWH prophylaxis for 10 days in those with 1 major or 2 (or more) minor risk factors. ▪ Recommend LMWH prophylaxis for 6 weeks in those with high risk conditions including: previous VTE, requiring antenatal LMWH, high-risk thrombophilia, or low-risk thrombophilia with family history
American College of Obstetricians and Gynecologists (ACOG)	In individuals undergoing cesarean delivery: ▪ Recommend mechanical prophylaxis at delivery and postpartum until ambulatory. ▪ If additional risk factors present, may consider chemical prophylaxis. ▪ Each institution should review and select a protocol for implementation.
American College of Chest Physicians (CHEST)	In individuals undergoing cesarean delivery: ▪ Recommend LMWH prophylaxis in the hospital in those with 1 major or 2 (or more) minor risk factors. ▪ If 'very high risk' use combination LMWH and mechanical prophylaxis. ▪ If significant risk factors persist after delivery, consider LMWH for up to 6 weeks.

Society for Maternal·Fetal Medicine

Royal College of Obstetricians and Gynaecologists

CHEST AMERICAN COLLEGE of CHEST PHYSICIANS

ACOG

SOAP Society for Obstetric Anesthesia and Perinatology

American Society of Hematology

University of Utah Postpartum Prophylaxis Guidelines

HEALTH
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- SCDs recommended for all undergoing cesarean
- LMWH prophylaxis for 14 days postpartum with 1 major or ≥ 2 moderate risk factors
- Enoxaparin dosing
  - BMI <40: 40mg SQ every 24 hours
  - BMI ≥ 40: 40mg SQ every 12 hours

Major Risk Factors	Moderate Risk Factors
History of VTE	BMI ≥ 30 kg/m^2
BMI ≥ 40 kg/m^2	Multi-fetal gestation
High-risk thrombophilia: • Antiphospholipid Syndrome • Antithrombin deficiency • Factor V Leiden homozygote • Prothrombin gene mutation homozygote • Compound heterozygote for Factor V Leiden and Prothrombin gene mutation	PPH (>1L or blood transfusion) Tobacco use Elective cesarean Preeclampsia Infection Preterm delivery <37 weeks Age > 35 years Family history of VTE Varicose veins Stillbirth Prolonged labor (>24 hours) Low-risk thrombophilia: • Factor V Leiden heterozygote • Prothrombin gene mutation heterozygote • Protein C deficiency • Protein S deficiency
Medical comorbidities • Heart disease • Cancer • Systemic Lupus Erythematosus (SLE) • Inflammatory Bowel Disease (IBD) or inflammatory polyarthropathy • Sickle cell disease (SCD) • Intravenous drug use	
Nephrotic range proteinuria	
Cesarean hysterectomy	
Cesarean section in labor	

37 year old G1 at 39w0d presents for induction of labor. After 28 hours, undergoes primary cesarean delivery for arrest of dilation at 6 cm.

Pregnancy history:

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- Crohn's Disease (well-controlled, no recent flares)
- Obesity (body mass index 39 kg/m^2)

What's her risk of venous thromboembolism?
Should we place her on prophylaxis?
What are the risks and benefits?

Cochrane Systematic Review, 2014

- From 10 postpartum trials: prophylaxis vs no prophylaxis
  - Included < 1000 individuals
  - Only 1 trial reported on maternal deaths (none)
  - No differences in symptomatic VTE
  - One trial with increased bleeding complications (unfractionated heparin)
  - Low quality studies

"There is ***insufficient evidence …***Large scale, high-quality randomised trials …are warranted."

Bain et al. Cochrane Database Syst Rev 2014; 11;(2):CD001689.

Risk of Harm

- Single center retrospective cohort study
  - Implemented institutional prophylaxis protocol in 2016
  - Compared VTE & wound hematomas pre-protocol (2013-2015) to post-protocol (2016-2018)
  - Unchanged VTE rates & increased wound complications post-protocol

Outcome	Preprotocol (n=11,799)	Postprotocol (n=12,430)	OR (95% CI)*	aOR (95% CI)*
Efficacy outcomes				
Diagnosis of VTE	15 (0.1)	16 (0.1)	1.01 (0.50–2.05)	—
DVT	8/15 (53.3)	5/16 (31.3)	0.40 (0.09–1.72)	0.50 (0.11–2.37)
PTE	5/15 (33.3)	8/16 (50.0)	2.00 (0.47–8.56)	1.25 (0.22–7.23)
Other	2/15 (13.3)	3/16 (18.8)	1.50 (0.21–10.52)	3.68 (0.23–58.98)
Safety outcomes				
Any wound hematoma	50 (0.4)	90 (0.7)	2.61 (1.74–3.90)	2.34 (1.54–3.57)
Superficial wound hematoma	36 (0.3)	76 (0.6)	2.98 (1.91–4.64)	2.55 (1.61–4.02)
Deep wound hematoma	15 (0.1)	18 (0.1)	1.37 (0.67–2.78)	—

Lu et al. Obstetrics & Gynecology 2021;138:530–8

No shortage of dissent

Editorial Headlines:

Postpartum Heparin Thromboprophylaxis
More Harm Than Good

Postpartum venous thromboembolism prophylaxis may cause more harm than benefit: a critical analysis of international guidelines through an evidence-based lens

Pharmacologic Thromboprophylaxis in Obstetrics
Broader Use Demands Better Data

Warn against widespread pharmacologic prophylaxis implementation given unproven efficacy & risk of harm

Kotaska A. BJOG 2018; 125(9):1109-1116
Sibai & Rouse. Obstetrics & Gynecology 2016; 128(4):681-4.
Kotaska A. Obstetrics & Gynecology 2021; 138(4): 527-29.

But also calls for more widespread use

Editorial Headlines:

Maternal risk from thromboembolism needs to be reduced

Pregnancy-related venous thromboembolism: Progress but questions remain

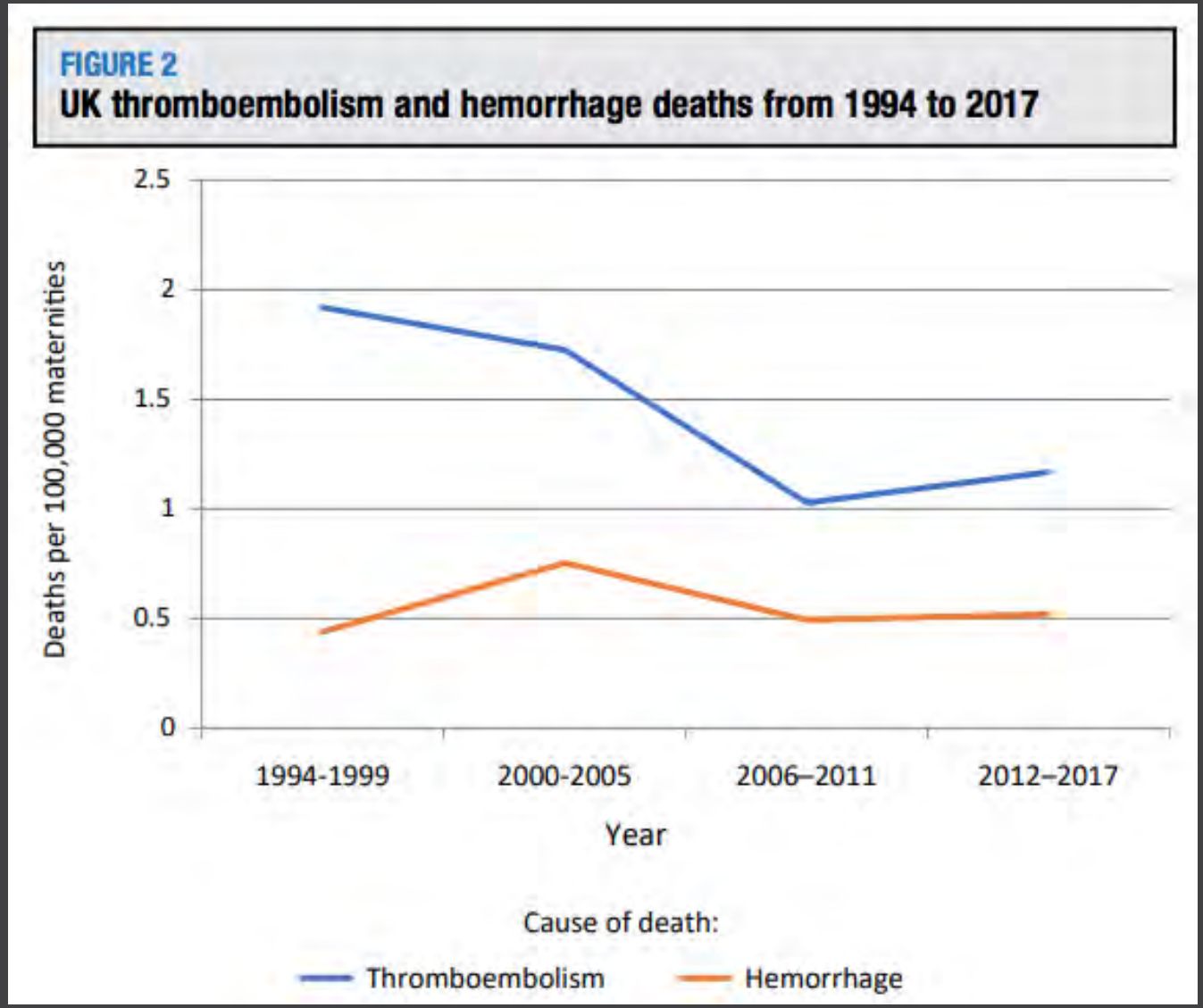
Call for more widespread implementation of prophylaxis protocols & additional research

Friedman & D'Alton. AJOG 2020;223(6):794-795.
Bates. Eur J Intern Med. 2022;97:32-33.

But continued population level decrease in UK…

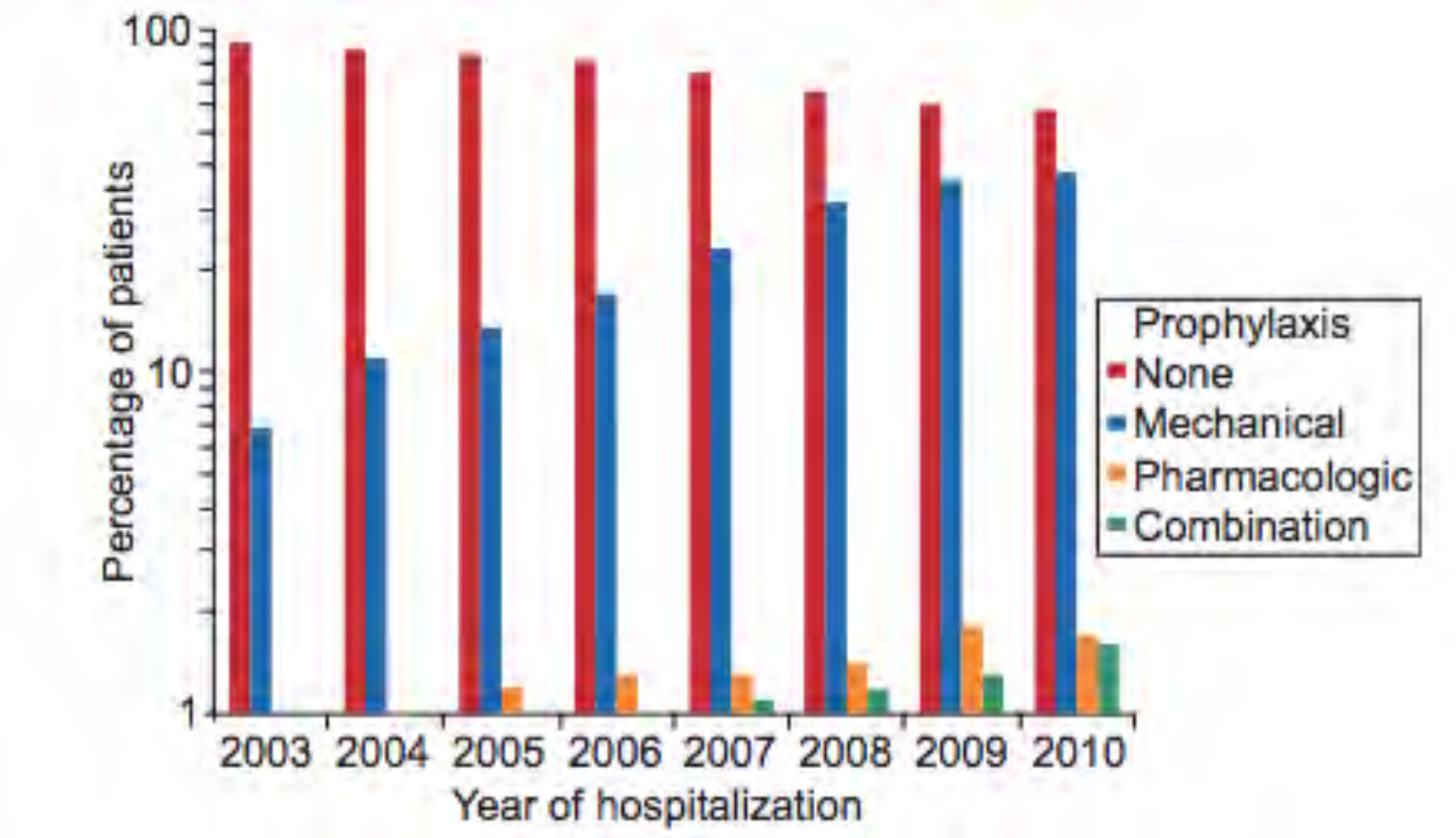
UK population level data continue to demonstrate decline in VTE (1994-2017)

Decrease maternal mortality due to VTE without increase in hemorrhage-attributed deaths



Friedman & D'Alton. AJOG 2021; 225(3):228-236.

Institutional/Population Level Implementation



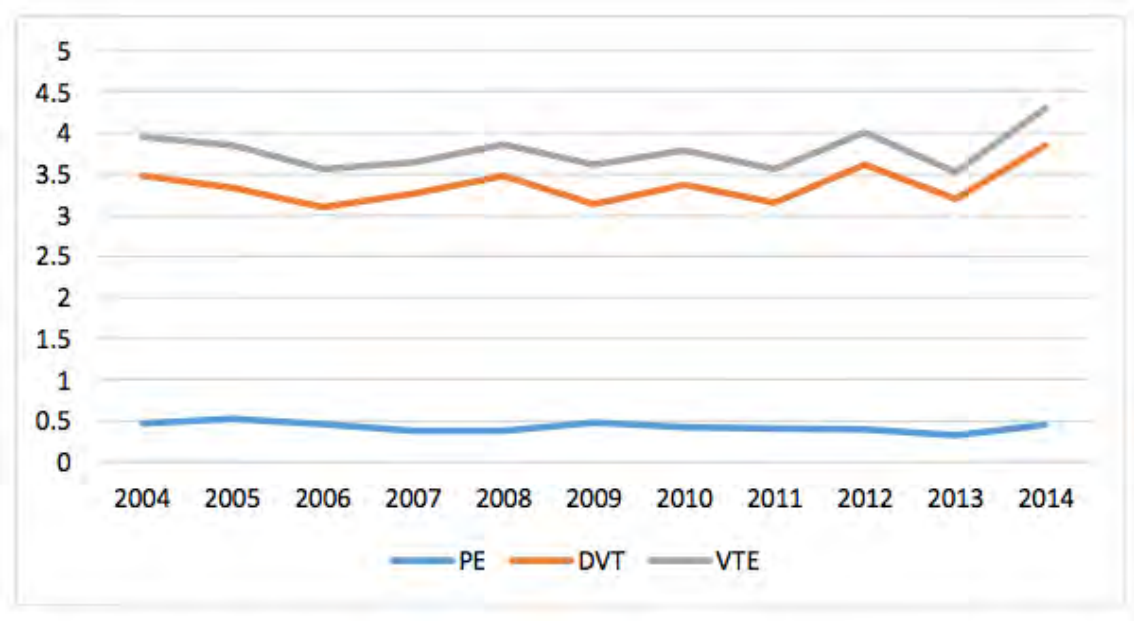
- US data, 2003-2010
- Post-cesarean
- Over 1 million deliveries
- 22.1% receiving mechanical prophylaxis
- 1.3% receiving LMWH prophylaxis

Friedman et al. Obstet & Gynecol 2013; 122(6): 1197-1204

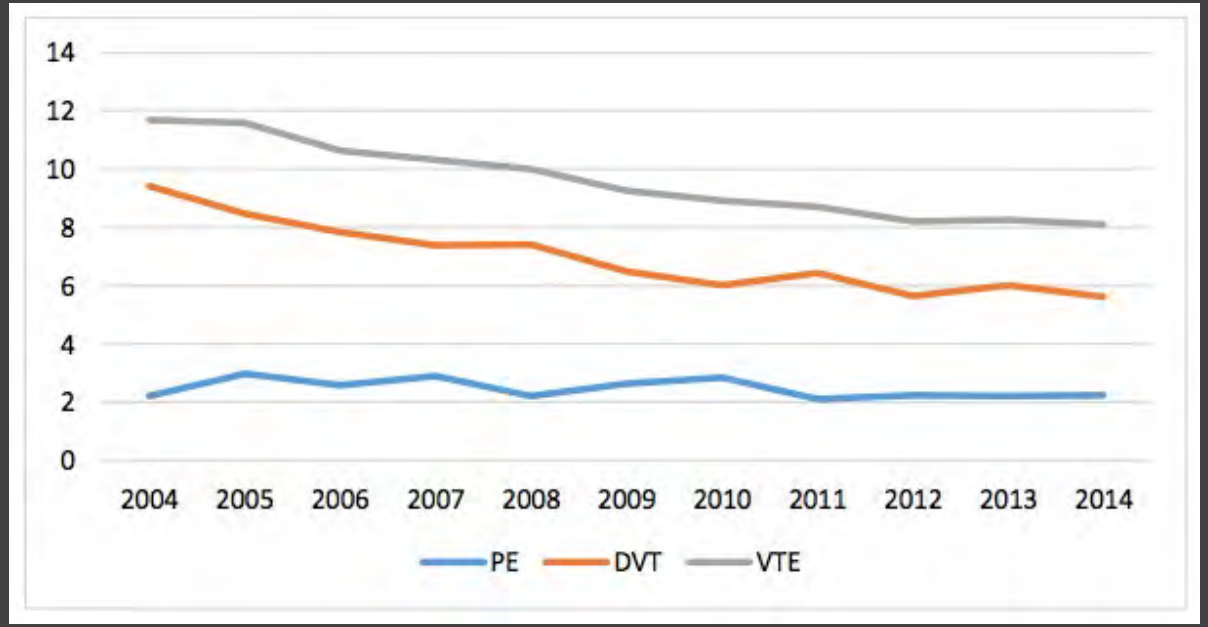
Similar U.S. Population level data?

Rates of venous thromboembolism per 10,000 delivery hospitalizations from the Nationwide Inpatient Sample, 2004-2014.

Vaginal Delivery



Cesarean Delivery



Abe et al. Semin Perinatology 2019; 43(4):200-204.

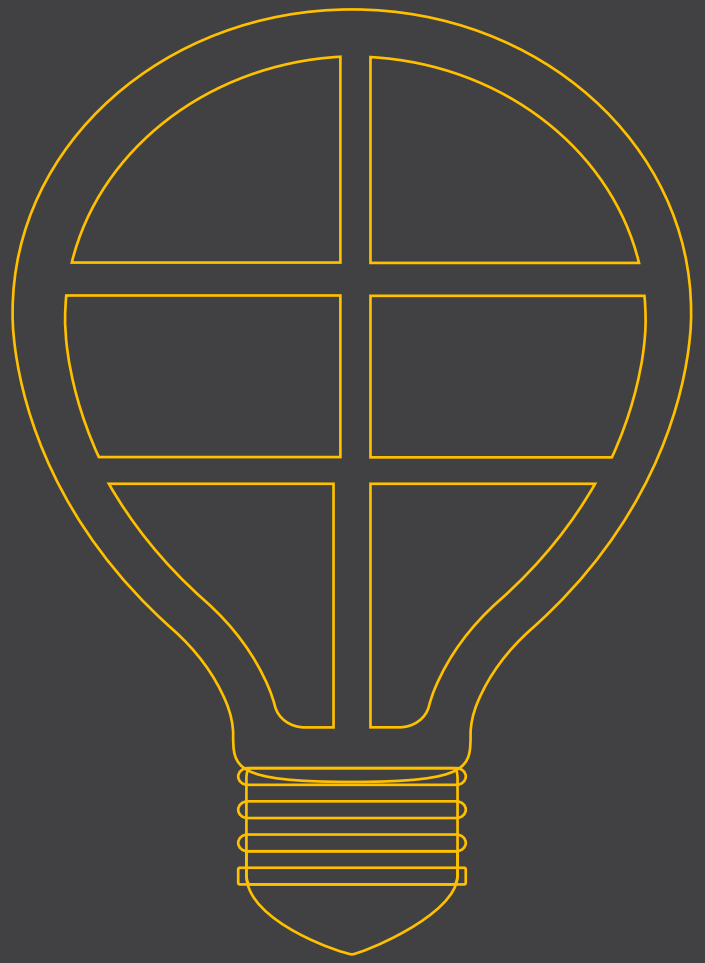
Current Intervention Model in Obstetrics

Hypercoagulable + Risk Factors → Venous Thromboembolism → Maternal Morbidity & Mortality

Interventions

- Mechanical prophylaxis
- Chemical prophylaxis

Why not conduct a large RCT?



- LARGE sample size
- Multiple unanswered questions
  - Target population – who is ‘at risk’?
  - Enoxaparin dose
  - Enoxaparin length of therapy
  - Surrogate outcome
  - Compliance/Willingness to use

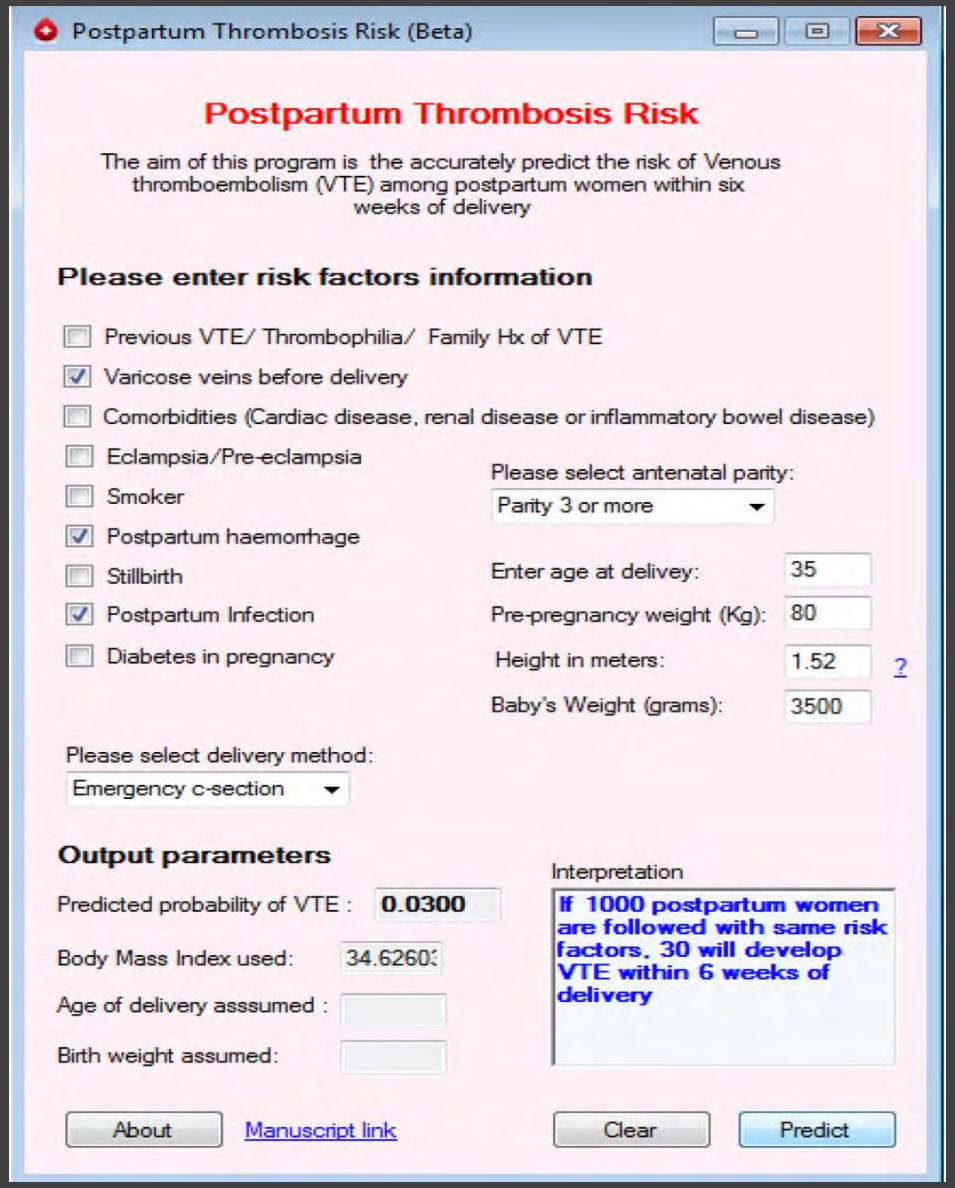
Variable uptake across U.S.

- Use of VTE prophylaxis continues to vary widely across the U.S.
  - Cross sectional study at single tertiary hospital
  - Assessment of patient risk factors and rates of chemical (LMWH) prophylaxis by varying guidelines post-cesarean:
    - RCOG – 85% (95% CI 80.5-88.6%)
    - ACOG – 1% (95% CI 0.3-3.0%)
    - CHEST – 34.8% (95% CI 29.6-40.4%)

Palmerola et al. BJOG 2016;123(13):2157-2162.

Defining ‘at risk’

- No validated prediction model in clinical practice
- CHEST/RCOG use risk algorithm
  - Additive? Multiplicative?
- What risk threshold should we use?



Sultan et al. BMJ 2016; 355: i6253

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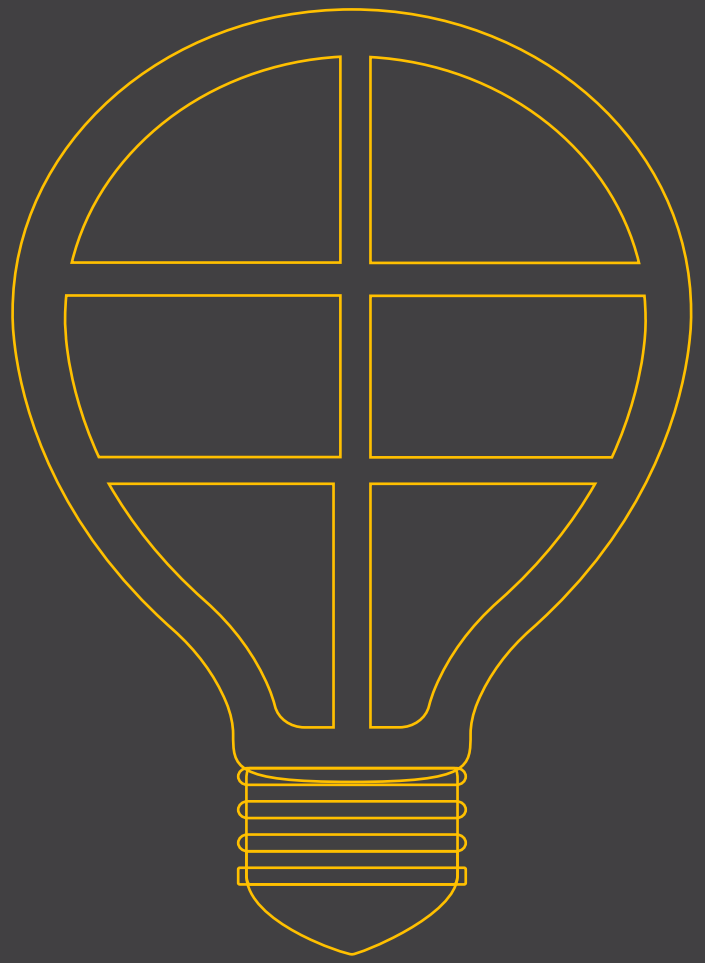

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Enoxaparin Dosing

- Current guidelines – ‘fixed’ dosing
  - Society for Maternal-Fetal Medicine (SMFM) / American College of Obstetricians & Gynecologists (ACOG)
    - BMI <40 kg/m^2: Enoxaparin 40 mg once daily
    - BMI ≥ 40 kg/m^2: Enoxaparin 40 mg every 12 hours

- Expert opinion & extrapolation from non-obstetric surgical fields

ACOG. Obstet Gynecol 2018;132(1):e1-e17.
Pacheco et al. SMFM. Am J Obstet Gynecol 2020;223(2):B11-17.

Enoxaparin Dosing

- Weight-based enoxaparin dosing superior to fixed dosing in non-pregnant individuals with obesity

Table. Prior Studies of LMWH Dosing in Postpartum Women

Author	Study Type and N	Findings
Hiscock et al	Prospective cohort, N=80	Weight-based dosing* achieved prophylactic anti-Xa levels in 72% of participants, no comparison (POD #1 and #3)
Overcash et al	Prospective cohort BMI ≥ 40 kg/m^2, N=85	Weight-based dosing* achieved prophylactic anti-Xa levels in 85% compared to 26% fixed dose LMWH (POD #2)
Stephenson et al	Randomized controlled trial BMI ≥ 35 kg/m^2, N=84	Weight-based dosing* achieved prophylactic anti-Xa levels in 88% compared to 14% fixed dose LMWH (POD #2)

*Weight-based dosing strategy differed by trial. For Hiscock, weight-based dosing was stratified by 40kg weight increments as in the RCOG guidelines. Overcash and Stephenson utilized 0.5 mg/kg twice daily.

- No change in national guidelines based on results

Hiscock et al. Int J Obstet Anesth 2013; 22(4): 280-8
Overcash et al. Obstet Gynecol 2015; 125(6): 1371-6.
Stephenson et al. J Perinatol 2016; 36(2): 95-9.

Enoxaparin Dosing – RCT @ UUH

- **Objective**: To evaluate fixed versus weight-based enoxaparin dosing to achieve prophylaxis in individuals following cesarean delivery across all body mass index (BMI) categories.

- Included: Age 18+, cesarean delivery, met institutional criteria for postpartum enoxaparin prophylaxis

- Excluded: contraindication to prophylaxis, plan for postpartum therapeutic anticoagulation, known renal dysfunction

Bruno et al Obstet Gynecol 2023

Enoxaparin Dosing – RCT @ UUH

- Randomization arms
  - Weight-based enoxaparin
    - 0.5 mg/kg every 12 hours
  - Fixed enoxaparin
    - BMI <40 kg/m^2 – 40 mg daily
    - BMI ≥40 kg/m^2 – 40 mg every 12 hours

- LMWH inpatient & through 14 days post-discharge
- Followed through 6 weeks postpartum

Bruno et al Obstet Gynecol 2023

Enoxaparin Dosing – RCT @ UUH

- Primary outcome – prophylactic peak anti-Xa level
  - At steady state – after at least third dose enoxaparin
  - Peak – 4-6 hours after enoxaparin dose
  - Prophylactic range – 0.2-0.6 units/mL

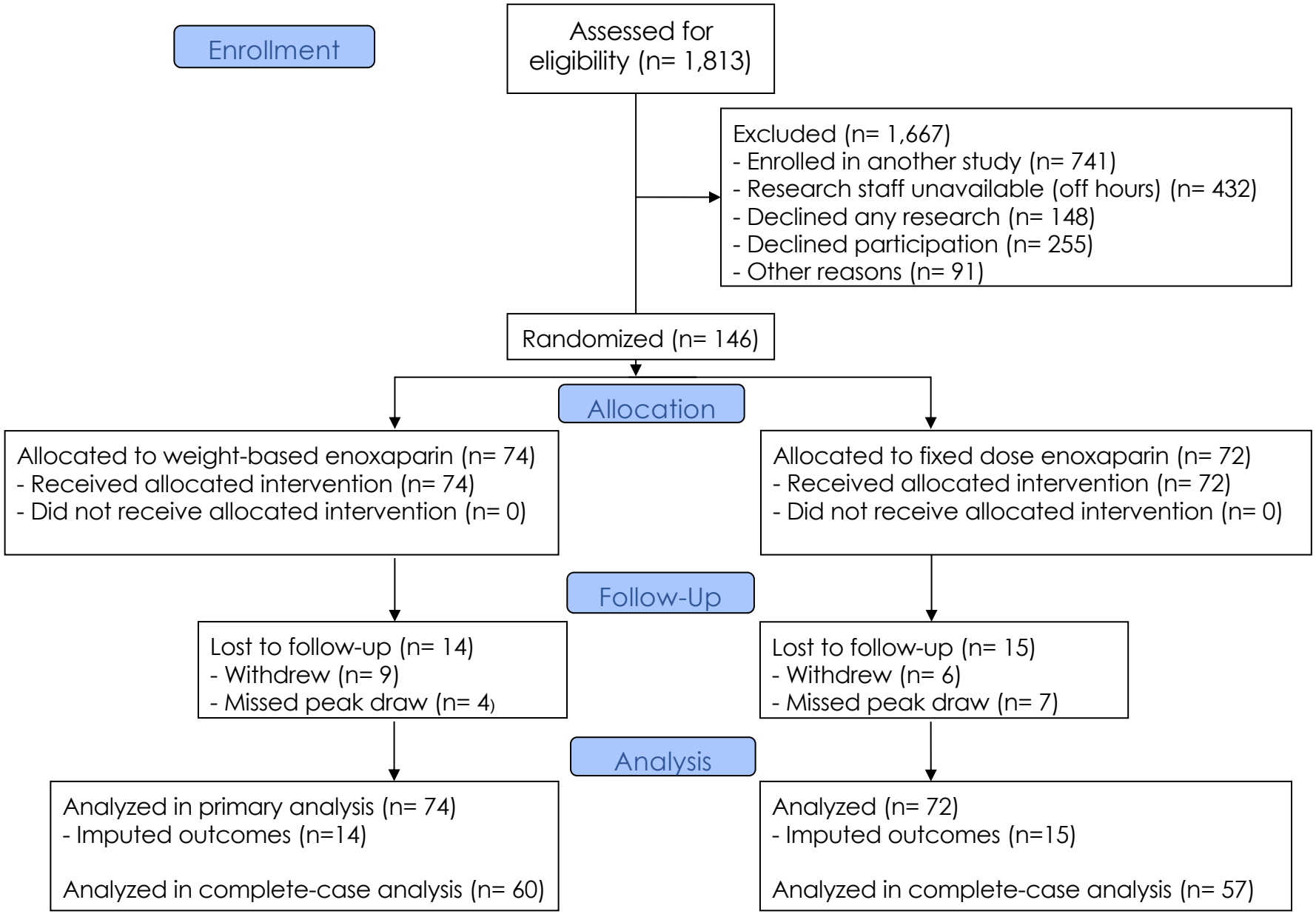
- Secondary outcomes
  - Sub-prophylactic peak level (<0.2 units/mL)
  - Supra-prophylactic peak level (>0.6 units/mL)
  - Outpatient peak anti-Xa level (Between postoperative day 10-18)
  - VTE within 6 wks postpartum
  - Wound complications within 6 wks postpartum

Bruno et al Obstet Gynecol 2023

Enoxaparin Dosing – Work @ UUH

- Methods
  - Enrolled from June 19, 2020 – November 18, 2021
  - Data & Safety Monitoring Board (DSMB) – monitored adverse events & progress
  - Single interim analysis at 50% enrollment
    - Pre-specified ‘stopping criteria’
    - Stopped enrollment early for efficacy
  - Modified intention-to-treat (ITT) analysis

Bruno et al Obstet Gynecol 2023


Enrollment
Assessed for eligibility (n= 1,813)
Excluded (n= 1,667)
- Enrolled in another study (n= 741)
- Research staff unavailable (off hours) (n= 432)
- Declined any research (n= 148)
- Declined participation (n= 255)
- Other reasons (n= 91)
Randomized (n= 146)
Allocation
Allocated to weight-based enoxaparin (n= 74)
- Received allocated intervention (n= 74)
- Did not receive allocated intervention (n= 0)
Allocated to fixed dose enoxaparin (n= 72)
- Received allocated intervention (n= 72)
- Did not receive allocated intervention (n= 0)
Follow-Up
Lost to follow-up (n= 14)
- Withdrew (n= 9)
- Missed peak draw (n= 4)
Lost to follow-up (n= 15)
- Withdrew (n= 6)
- Missed peak draw (n= 7)
Analysis
Analyzed in primary analysis (n= 74)
- Imputed outcomes (n=14)
Analyzed in complete-case analysis (n= 60)
Analyzed (n= 72)
- Imputed outcomes (n=15)
Analyzed in complete-case analysis (n= 57)

Modified intention-to-treat analysis

Outcome	Weight-based (N=74)	Fixed (N=72)	Relative Risk (95% CI)	p
Prophylactic peak anti-Xa*	49 (66)	32 (44)	1.49 (1.10-2.02)	0.008
Sub-prophylactic peak*	24 (32)	40 (56)	0.58 (0.40-0.86)	0.005
Supra-prophylactic peak*	15 (20)	15 (21)	0.97 (0.51-1.84)	0.933
Prophylactic outpatient peak*	15 (20)	5 (7)	2.92 (1.12-7.61)	0.019
Venous thromboembolism	0 (0)	0 (0)	–	–
Any wound complication	5 (7)	1 (1)	4.86 (0.58-40.63)	0.102
Hematoma	3 (4)	0 (0)	–	0.084
Surgical site infection	2 (3)	0 (0)	–	0.160
Other	0 (0)	1 (1)	–	0.309

Data as n(%)
*Worst-case imputation for missing data

Key Findings

- Weight-based LMWH dosing more effective than fixed dosing to achieve prophylactic peak anti-Xa levels
- Weight-based dosing remained more effective than fixed at achieving prophylactic anti-Xa level at 2-wk postpartum visit
- No postpartum VTEs in the study
- Wound complications did not differ by dosing regimen

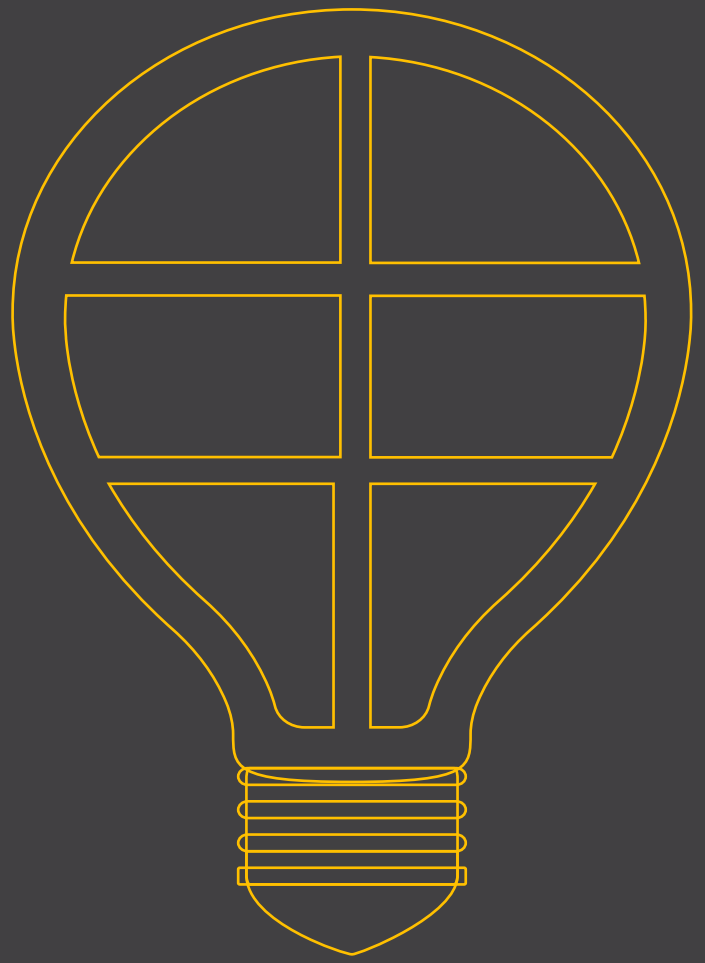
In Context

- Together with 3 other studies, growing pool of data supporting weight-based enoxaparin dosing

- National guidelines and institutional protocols should consider a weight-based approach to post-cesarean thromboprophylaxis dosing

Hiscock et al. Int J Obstet Anesth 2013; 22(4): 280-8
Overcash et al. Obstet Gynecol 2015; 125(6): 1371-6.
Stephenson et al. J Perinatol 2016; 36(2): 95-9.

Why not conduct a large RCT?



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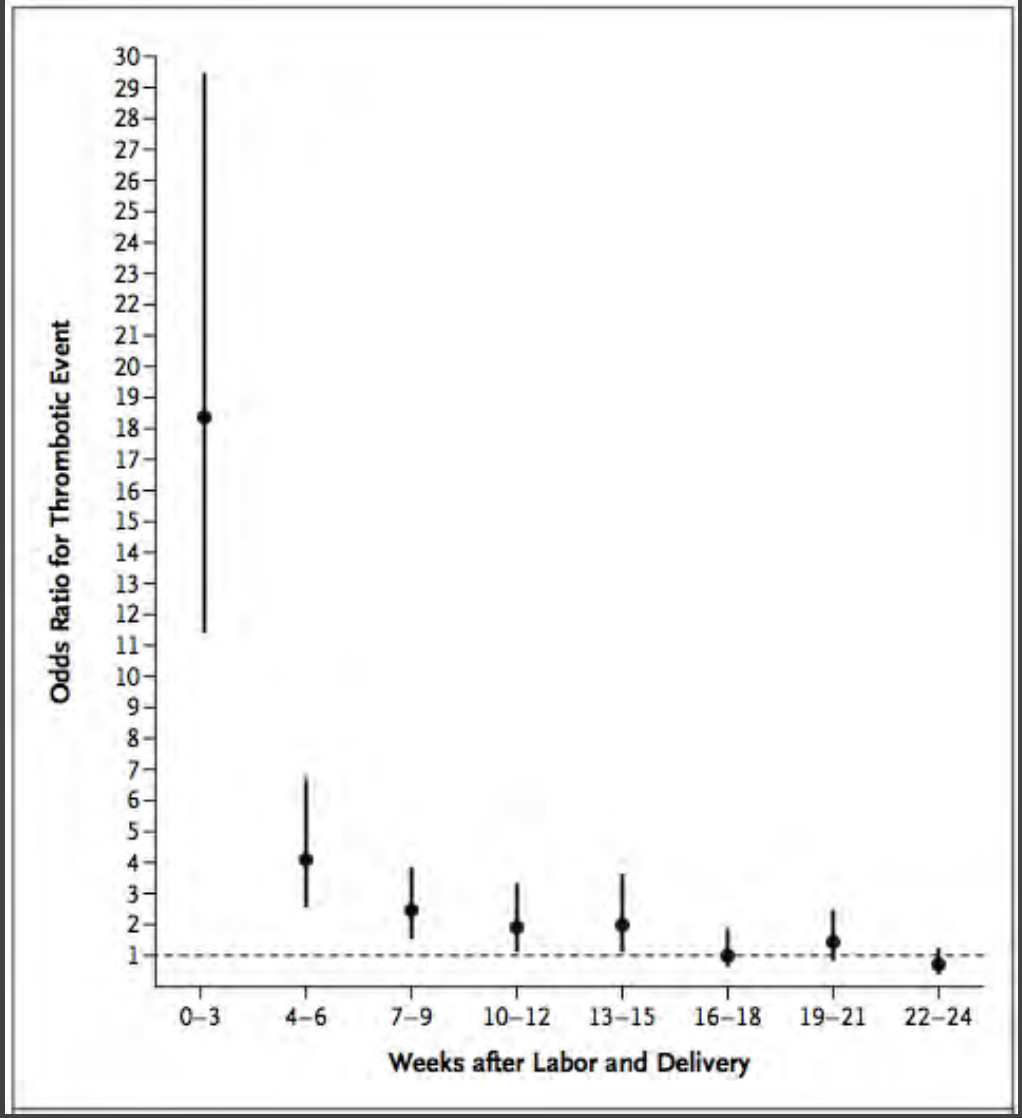
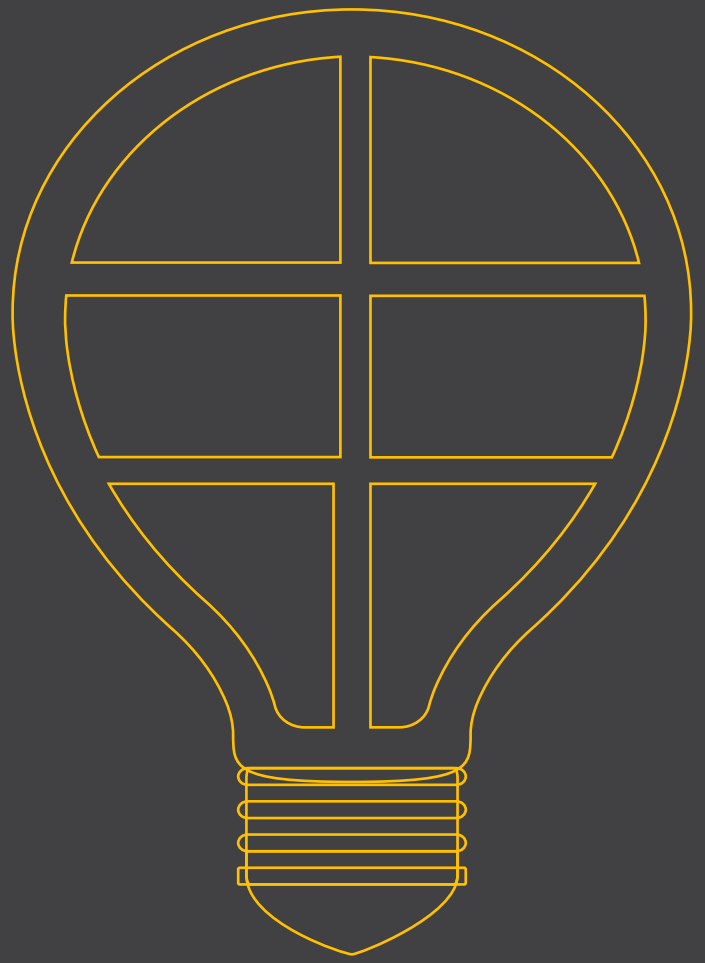
Length of Therapy



- Length of LMWH prophylaxis varies by guideline
- Risk not eliminated post-discharge
- QI/QA review – UUH (2017-19)
  - 18 VTE – range from PPD# 0-34
- 1-2 doses of enoxaparin inpatient only likely not useful

Kamel et al. NEJM 2014; 370(14): 1312

Why not conduct a large RCT?



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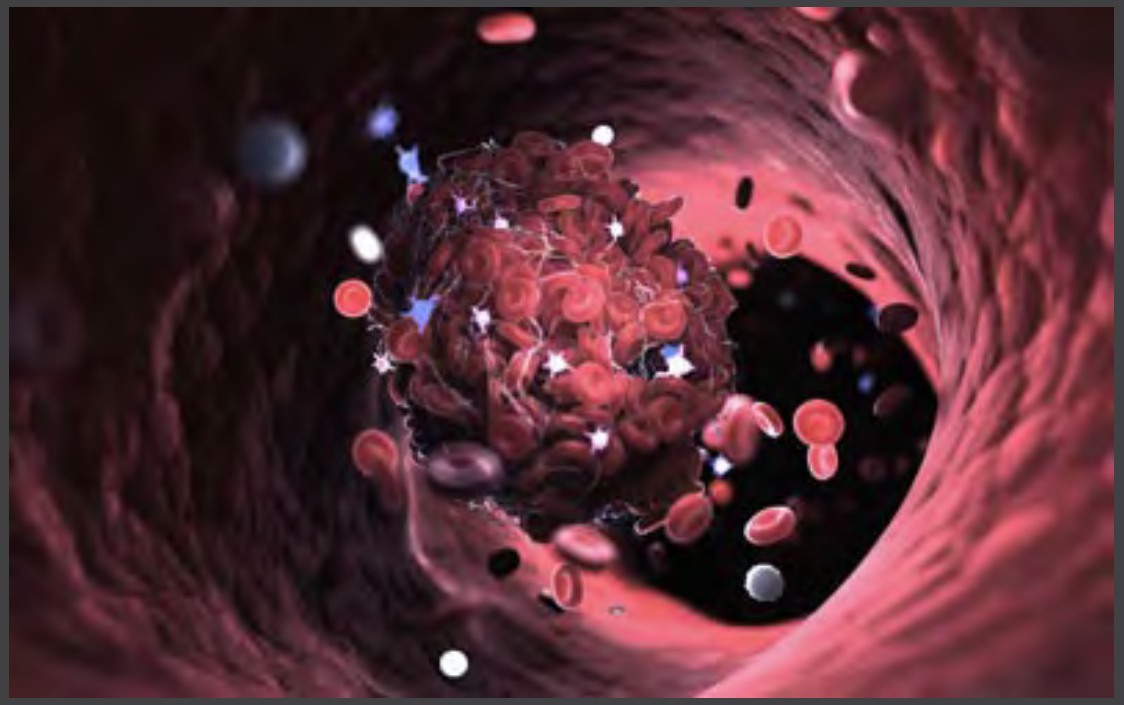
Surrogate Outcome

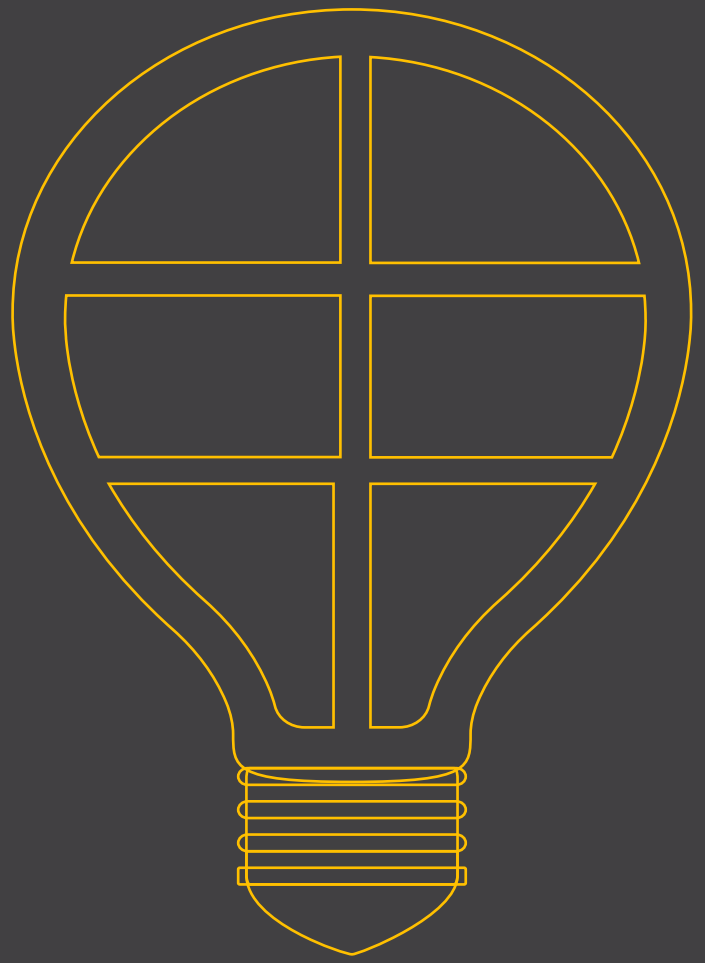
- Symptomatic VTE relatively rare event
- More prevalent marker of VTE ideal for trial feasibility
- Potential:
  - Lower extremity Doppler
  - Biomarker (D-dimer, other thrombosis markers)



Surrogate Outcome

- Lower Extremity (LE) Doppler Study
  - Prospective cohort study of individuals undergoing cesarean and with obesity (defined as BMI >/= 30 kg/m^2)
  - Receive **NO** LMWH prophylaxis but otherwise standard of care
  - Primary outcome: asymptomatic deep vein thrombosis (DVT)
    - LE Doppler between postoperative day #10-18

Why not conduct a large RCT?



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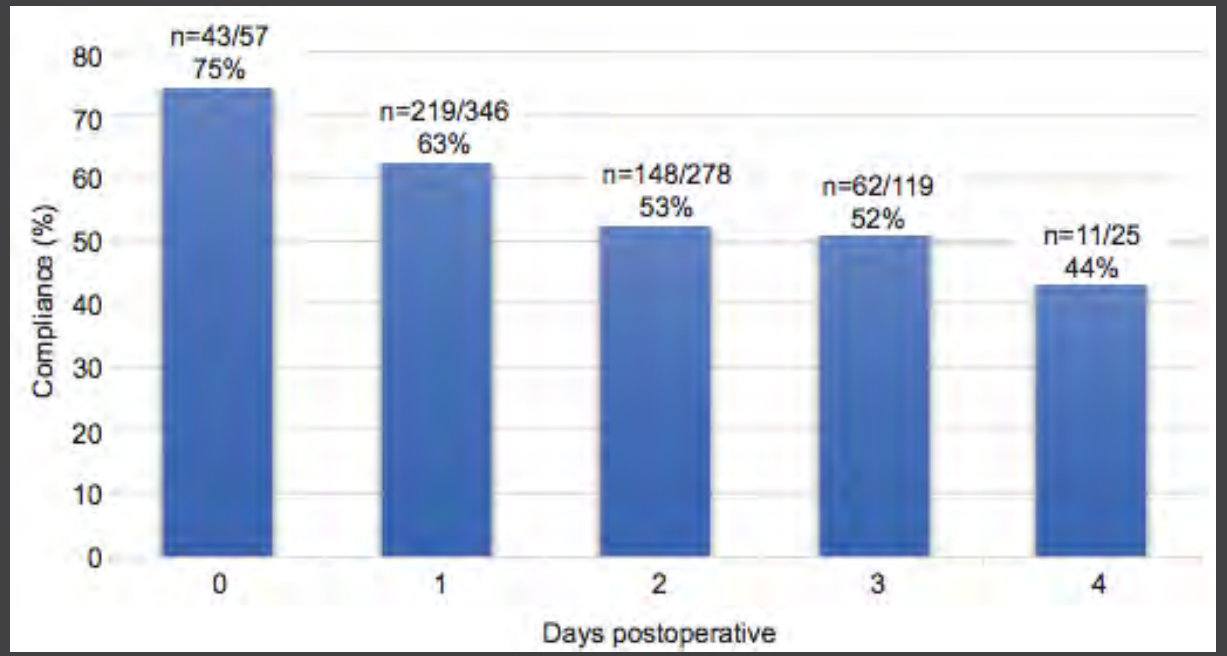
SCD Compliance

- Single center prospective study (gyn & OB)
- 4 month window with educational interventions
- 859 observations in 228 patients
- No difference in compliance over time
  - 61.3% first month
  - 60.1% last month
- Compliance decreased over course of hospitalization by day



Brady et al. Obstet Gynecol 2015; 125: 19–25.
Palmerola et al. J Matern Fetal Neonatal Med 2016; 29(19): 3072–3075

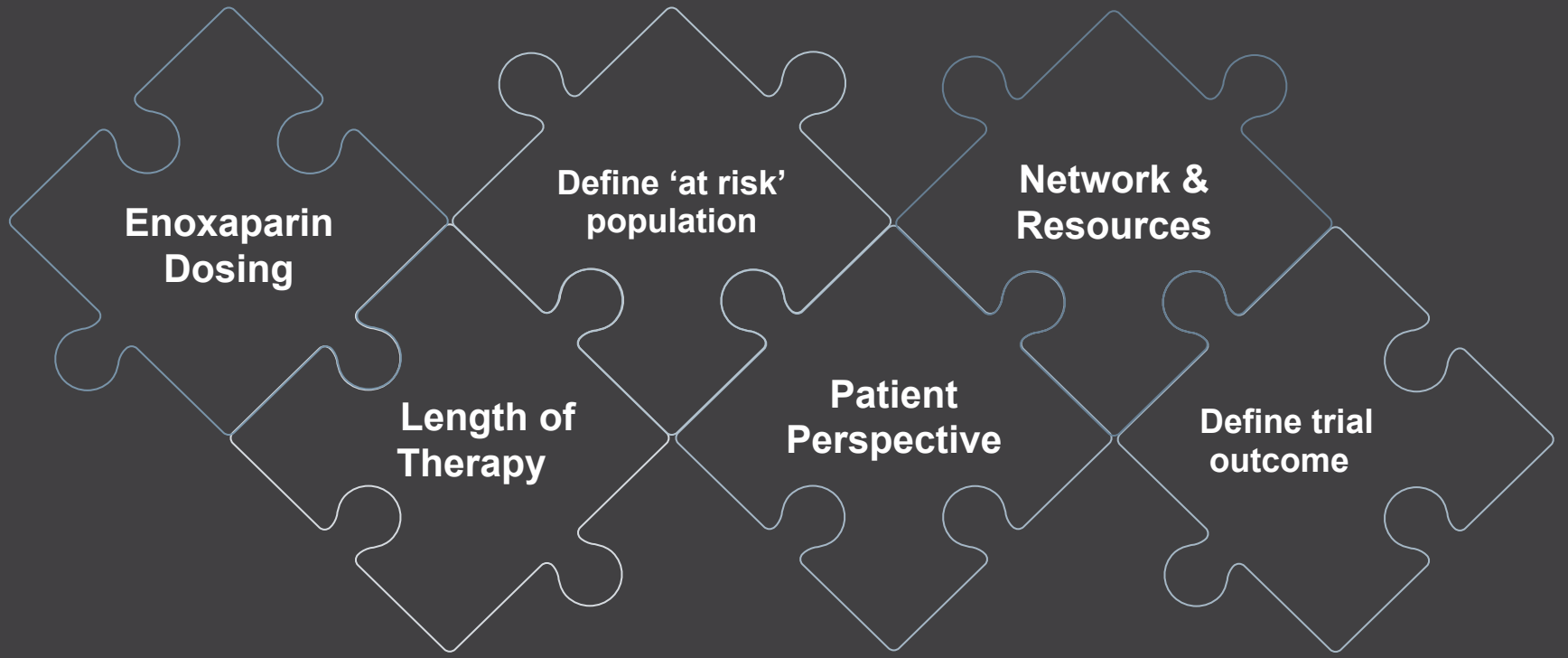
LMWH Compliance

- Few studies
- Single center observational study of individuals receiving postpartum thromboprophylaxis, in 67 individuals:
    - 82.4% reported no missed doses of LMWH
    - Survey data – ‘Good’ understanding of risks of VTE
- U of U Institutional LMWH RCT –
    - Participant report of outpatient compliance with LMWH therapy
    - Reported compliance – 79% (fixed) vs 88% (weight)

Guimicheva et al. Thrombosis Research 2019; 173:85-90.

More work to do…

Hypercoagulable + Risk Factors → Venous Thromboembolism → Maternal Morbidity & Mortality



Connect the Dots

- VTE significant contributor to maternal morbidity & mortality
  - Deserves our time & resources

- More work to be done to address postpartum VTE reduction
  - Better defining ‘at risk’ population
  - Consider implementation of weight-based enoxaparin dosing
  - Understanding of willingness to use enoxaparin & patient adherence
  - Surrogate outcomes as VTE rare event

- Need an efficacy trial: enoxaparin vs placebo

Until then… what do we?

37 year old G1 at 39w0d presents for induction of labor. After 28 hours, undergoes primary cesarean delivery for arrest of dilation at 6 cm.

Pregnancy history:

- Conception by IVF
- Antepartum admission for non-obstetric surgery (cholecystectomy)

Medical history includes:

- Crohn's Disease (well-controlled, no recent flares)
- Obesity (body mass index 39 kg/m^2)

What's her risk of venous thromboembolism?
Should we place her on prophylaxis?
What are the risks and benefits?

Key Takeaways

- Use a standardized protocol at institutional level
    - Existing protocols focus on ‘at risk’ population
    - Consider use of therapy through 2 weeks postpartum – especially in higher risk

- Ongoing patient education & engagement in research

Thank you!

Ann Bruno, MD
Associate Professor
University of Utah Health

Questions?

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