# ADVANCING PRACTICE: CLINICAL CASE STUDIES IN REPRODUCTIVE MEDICINE FOR APPS AND RNS


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# DISCLOSURES:

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  - Consulting Fee (e.g., Advisory Board)
    - EMD Serono
- Hayley Rapp, DNP, WHNP-BC, CPPS
  - Nothing to disclose
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  - Nothing to disclose
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# LEARNING OBJECTIVES

**Analyze and Diagnose Complex Reproductive Health Cases**

**Develop Evidence-Based Management Strategies**

**Integrate Current Data into Clinical Practice**

# CASE STUDY #1

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Angela presents to your office as a 33yo G0 who has been attempting conception with appropriately timed UPIC x 13 months. Menses are regular, q30d lasting 4d. She reports a remote history of uncomplicated gonorrhea treated as an outpatient. Her medical and family history are otherwise unremarkable.

Her partner, Fred, is a 40-year-old male with no prior paternity. He is in good health with no significant medical or surgical history.

# Infertility: Prevalence & Definition

**Vital Stats**

- 15% of all couples
- 85% will conceive within 12 months

**Criteria for Diagnosis**

- <35yo with 12mos of UPIC
- >35yo with 6 mos of UPIC
- Earlier if known risk factors

**Fecundability**

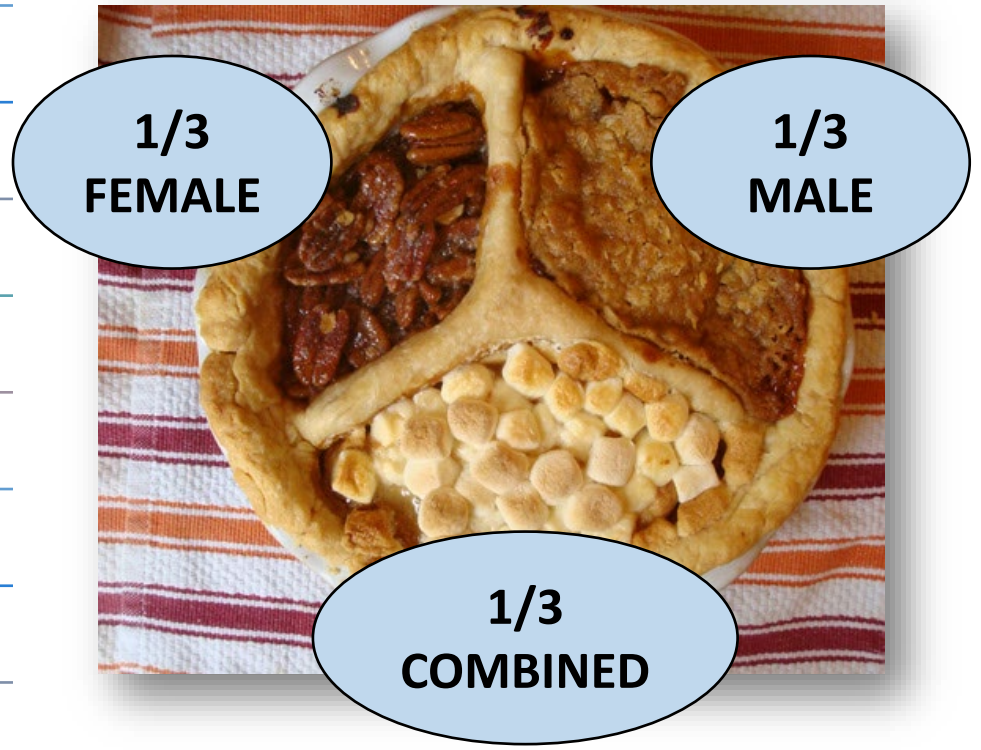
- ~20-25% per month in healthy couples
- Peak 2d prior to ovulation

UpToDate. Overview of infertility. Kuohung, Hornstein. (Jan 2019).
UpToDate. Optimizing natural fertility in couples planning pregnancy. Hornstein, Gibbons, Schenken. (Jan 2019).

# Etiology

- Ovulatory dysfunction
- Tubal disease
- Uterine pathology
- Peritoneal factors
- Genetics
- Immune factors
- Male factor
- Unexplained

## Rule of the Thirds



# DIAGNOSTIC EVALUATION: THE BASICS

- Ovarian reserve testing
- Ovulatory assessment
- Tubal evaluation
- Semen Analysis

# FEMALE FERTILITY OVERVIEW

**History**

- Infertility Duration
- Menstrual characteristics
  - Menarche
  - Duration
  - Interval
- Prior pregnancy
- Coital frequency and timing
- History of STI/PID
- Social History
  - Drugs (prescribed and lifestyle)
  - Alcohol
- Family History
  - Endometriosis
  - POI

**Physical**

- General Appearance
  - Stature
  - Weight
  - Androgen excess
- Pelvic Exam
- Labs
  - AMH
  - CD3: E2, LH, FSH
  - CD21: p4
- Imaging
  - TVUS
  - SIS
  - HSG

# Goals of the Diagnostic Evaluation

- ✓Cost-effective
- ✓Expeditious
- ✓Parallel male & female evaluations
- ✓Limit emotional, financial, physical burden

Photo credit: https://resolve.org/

# Ovarian Reserve

## Follicle Stimulating Hormone (FSH)

- Day 3, 4, or 5 levels
- Interpret with concurrent $E_2$
- Cycle-to-cycle variation
- Peak value = greatest predictor
- PPV higher in older women

## Anti-Müllerian Hormone (AMH)

- Produced by granulosa cells of small follicles
- Measure of quantitative ovarian reserve
- Does not predict pregnancy
- No intracycle variability

ASRM. (2015). Scott et al.
Riggs, R., et al. (2011).

# Methods to Detect Ovulation

- BBT
- Luteal Progesterone
- OPK
- Menstrual cycle history
- Cervical mucus
- Ultrasound
- Mittelschmerz

# WHO Classes of Anovulation

**Hypo/Hypo (5-10%)**

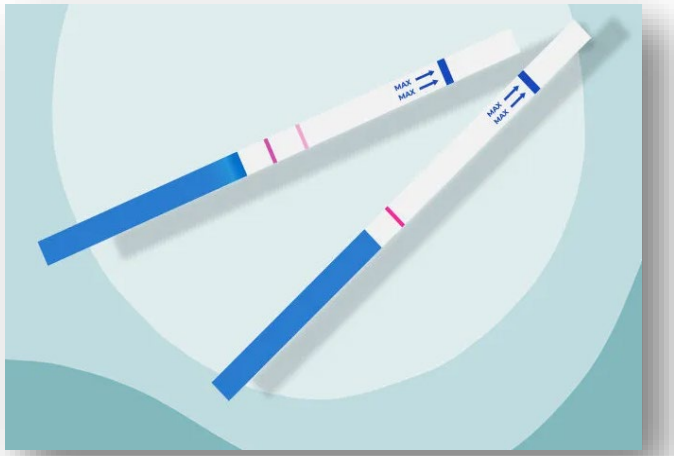
- ↓ gonadotropin pulses
- ↓ FSH, ↓ LH, ↓ $E_2$
  - Congenital & secondary causes

**Normo/Normo (75-85%)**

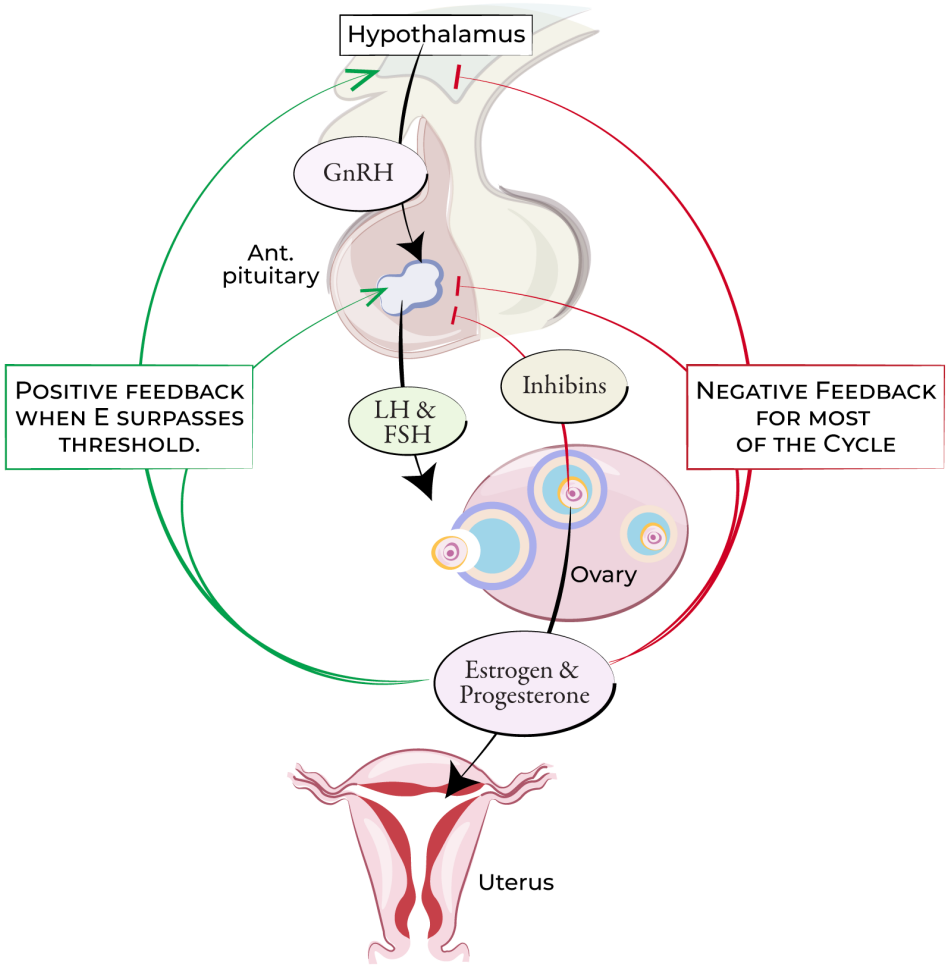
- Oligo/anovulation
- Normal FSH, Normal $E_2$, Normal or ↑ LH

**Hyper/Hypo (10-20%)**

- Gonadal failure
- ↑ FSH, ↓ $E_2$
  - Genetic, idiopathic, autoimmune causes

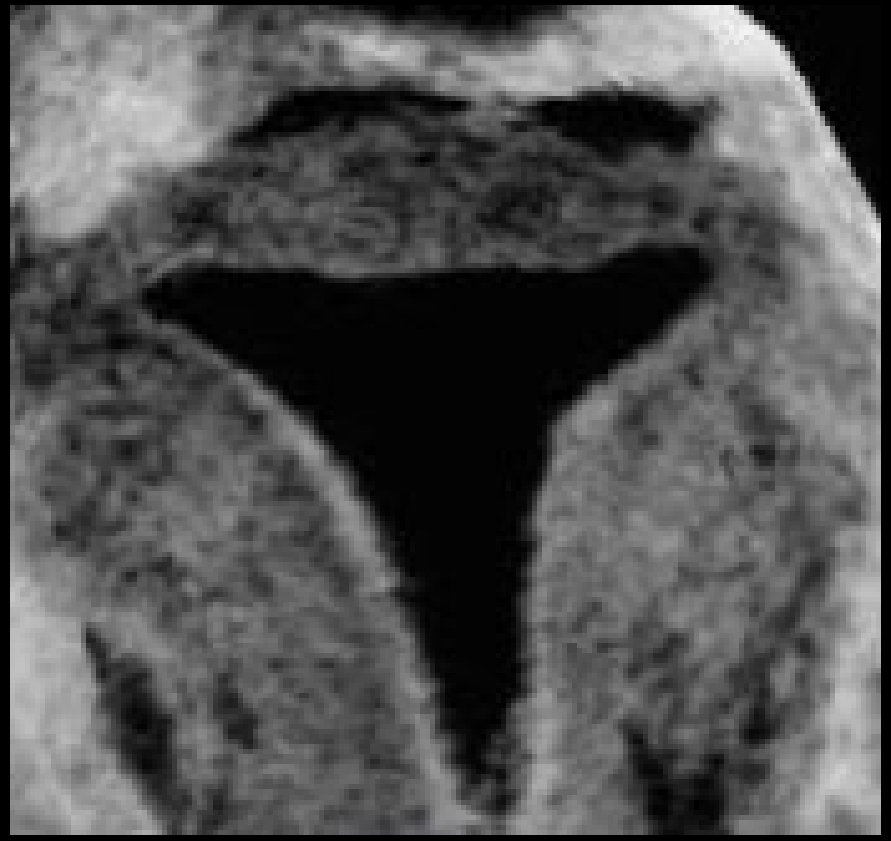


# Menstrual Cycle



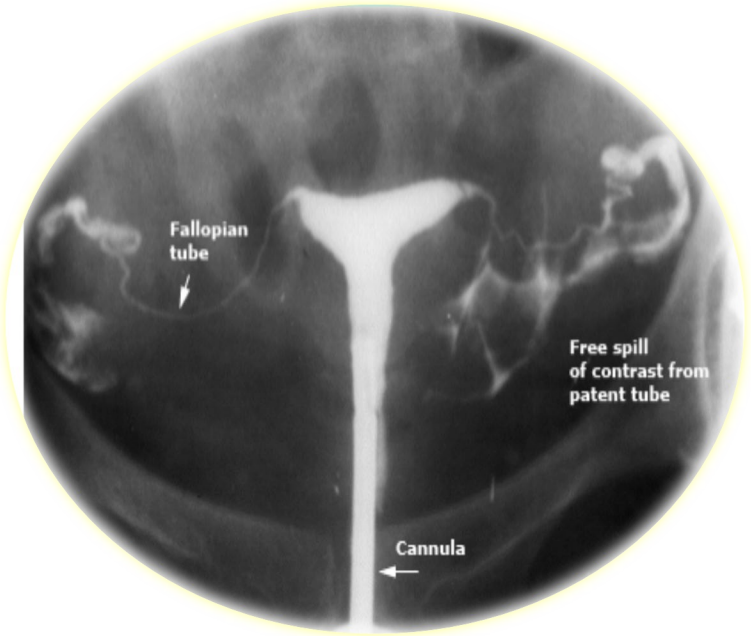
# Tubal and Cavity Tests

- HSG
- Laparoscopy with chromotubation
- 3D ultrasound
- Saline sonohysterogram
- Hysteroscopy
- Pelvic MRI



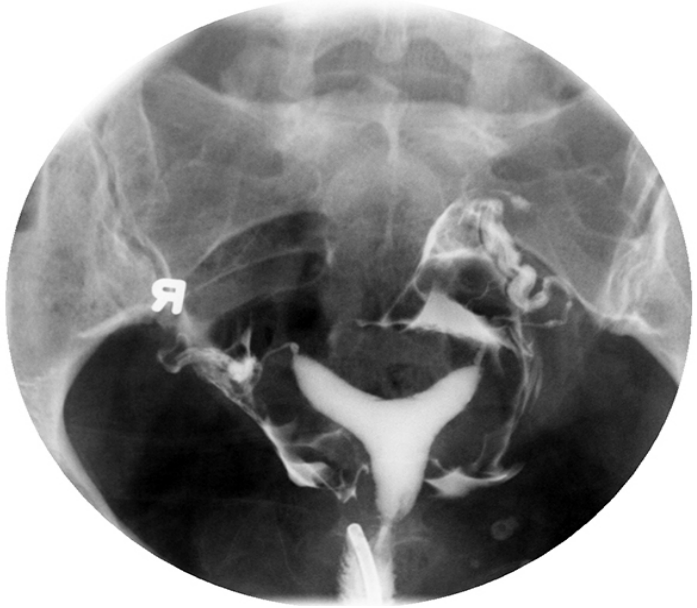
# Tubal Evaluation - HSG

## Normal HSG




UpToDate. Normal hysterosalpingogram with a Jarcho cannula. Graphic 81961 Version 7.0

## Normal/Arcuate Uterus




UpToDate. Hysterosalpingogram of arcuate uterus. Graphic 79328 Version 3.0

# Other factors

**Peritoneal**

- Endometriosis
- Pelvic adhesions

**Autoimmune**

- Sjögren's, Celiac, SLE, DM, APLAS, thyroid autoimmunity

**Unexplained (15-30%)**

- Single IVF cycle in young patient = success 3x higher than cumulative PR of 4 GND/IUI cycles without HOM risk

**Genetics**

- Autosomal dominant disorders

# MALE FERTILITY OVERVIEW

**History**

- Past Paternity
- Prior Testing
- Urologic Issues
- Sexual dysfunction
- Prior surgery/trauma
- Development/puberty
- Familial History
- Occupational/"real-life" issues
- Drug (both prescribed and lifestyle)
- Female factors

**Physical**

- General Appearance
  - Androgen deficiency
  - Gynecomastia
  - Height/weight
- Focused GU exam
  - Examination of the penis
  - Palpation of the testes
    - Tumor
    - Varicocele
    - Size/consistency
  - Palpation of epididymis/VD
  - Hernia
  - Rectal/Prostate (for low volume)

# SEMEN ANALYSIS

Table 4: World Health Organization Reference Limits for Human Semen Characteristics*

| Semen Parameter | One-Sided Lower Reference Limit (Fifth Centiles With 95% Confidence Intervals [CI]) |
|---|---|
| **Semen Volume** | 1.4 mL (1.3-1.5 mL) |
| **Total Sperm Number** | 39 million per ejaculate (35-40 million per ejaculate) |
| **Sperm Concentration** | 16 million/mL (15-18 million/mL) |
| **Vitality** | 54% Live (50-56%) |
| **Progressive Motility** | 30% (29-31%) |
| **Total Motility (Progressive + Non-Progressive)** | 42% (40-43%) |
| **Morphologically Normal Forms** | 4.0% (3.9-4.0%) |

***Semen samples from 3589 males (males with proven fertility, with unknown fertility status and other males who were normozoospermic) from 12 countries and 5 continents were analyzed. Males described above were all fertile (Partners' time-to-pregnancy ≤12 months) and their parameters were selected to calculate the values.[30, 31]**

# Treatment

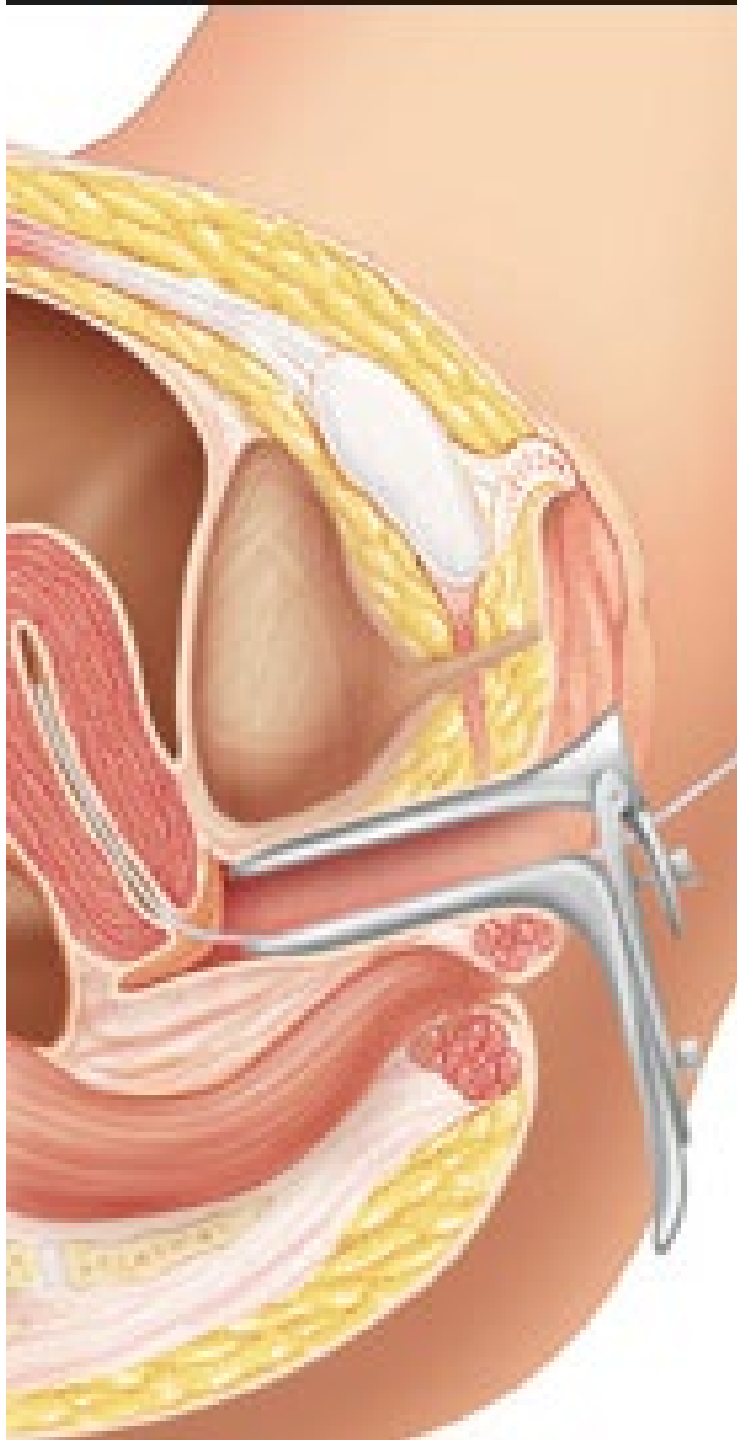
# Ovulation Induction: Letrozole

- Aromatase inhibitor
- Blocks conversion of androgens to estrogen
- Leads to negative feedback – result is ↑ gonadotropins
- Off-label use
- 2.5mg PO x5d (max 7.5mg)
- No adverse effect on endometrium
- Higher CLBR in PCOS

Legro et al., (2014)

# Ovulation Induction: Clomiphene

- Must have intact HPO axis
- Selective Estrogen Receptor Modifier
- $E_2$ agonist-antagonist that binds estrogen receptors to ↑ GND
- Anti-estrogenic effects
- 5-7% pregnancy rate <u>per cycle</u>
- 50mg PO x5d (max 150mg)
- Discontinue if visual changes occur



# Controlled Ovarian Hyperstimulation

- Injectable gonadotropins
- Goal 2-3 follicles
- hCG followed by sperm washing and IUI 36h later
- Not for severe male or tubal factor
- IUI bypasses cervix, deposits sperm closer to oocytes

# In-Vitro Fertilization

High success rates

Bypasses most causes of infertility

Cryo-all (thaw success rates 95-98%)

Advantage is selection of embryo via PGT-A

Getting your “family in the freezer”

# Case Study: Results

Angela has an AMH of 0.6ng/mL. Her HSG shows unilateral proximal tubal occlusion. Fred's semen analysis is within normal limits. The remainder of the diagnostic workup is unremarkable.

**What is the likely etiology of their infertility?**

**What are the next best steps for this couple?**

# Key Points

- Tubal assessment/semen analysis cost-effective diagnostic tools
- Careful history taking is KEY
- Treatment; oral ovulogens, injectable gonadotropins, and IVF
- IVF can bypass most causes of infertility, and is especially useful for severe male or tubal factor

# CASE STUDY #2

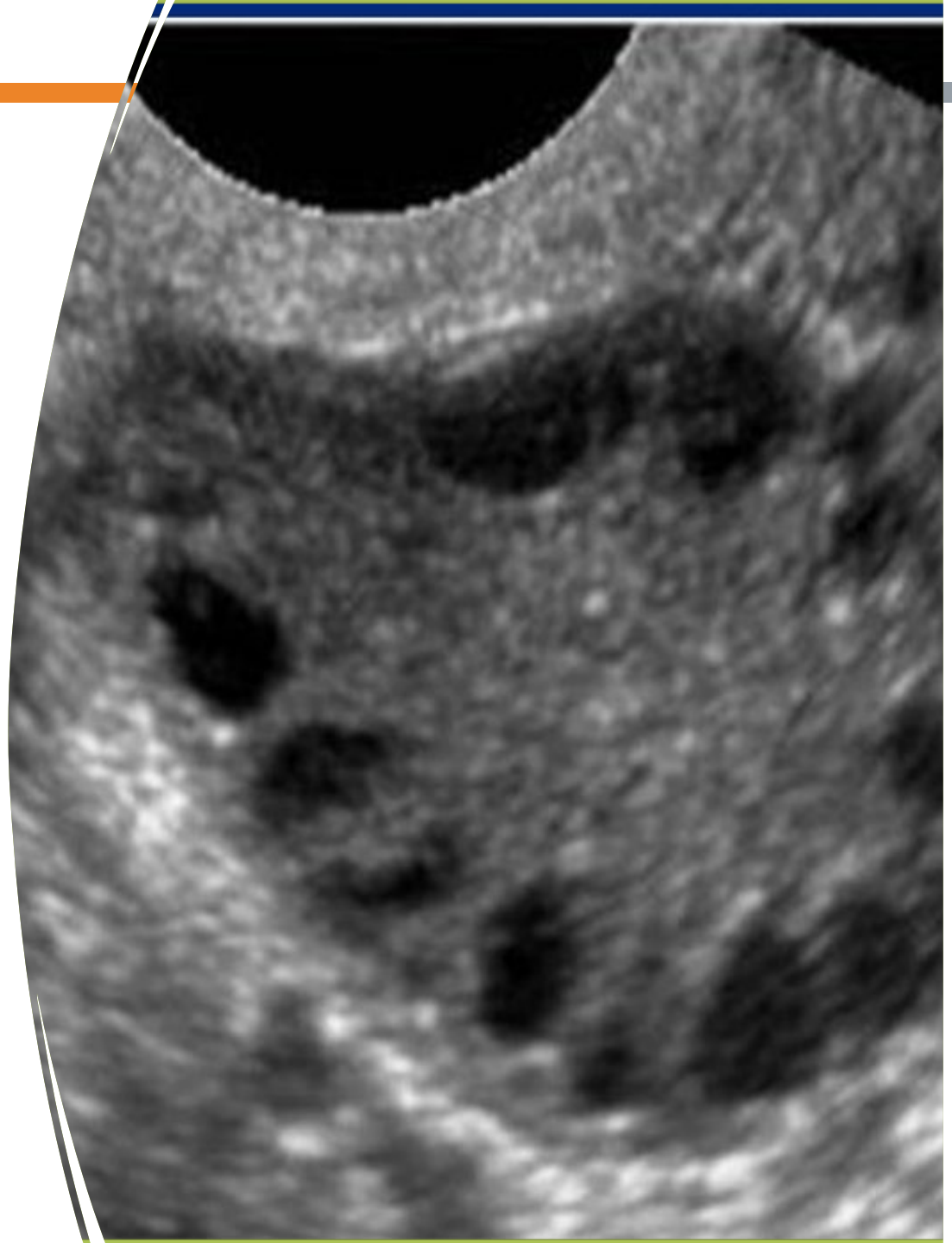
# CASE STUDY ~ SUSHMA

- 30 yr old, G0
- Married for 2 years
- Trying to conceive x 1.5 years
- Has irregular cycles ~ up to 50 days in-between cycles
- BMI 28

# DIAGNOSIS: ROTTERDAM CRITERIA

**Meet 2 out of 3:**

- Elevated androgens:
  - excess body/facial hair, acne, male-pattern baldness
- Irregular periods:
  - greater than 35 days apart or absent
- Polycystic ovaries seen on ultrasound: ≥12 follicles of 2-9 mm per ovary



# Pathophysiology

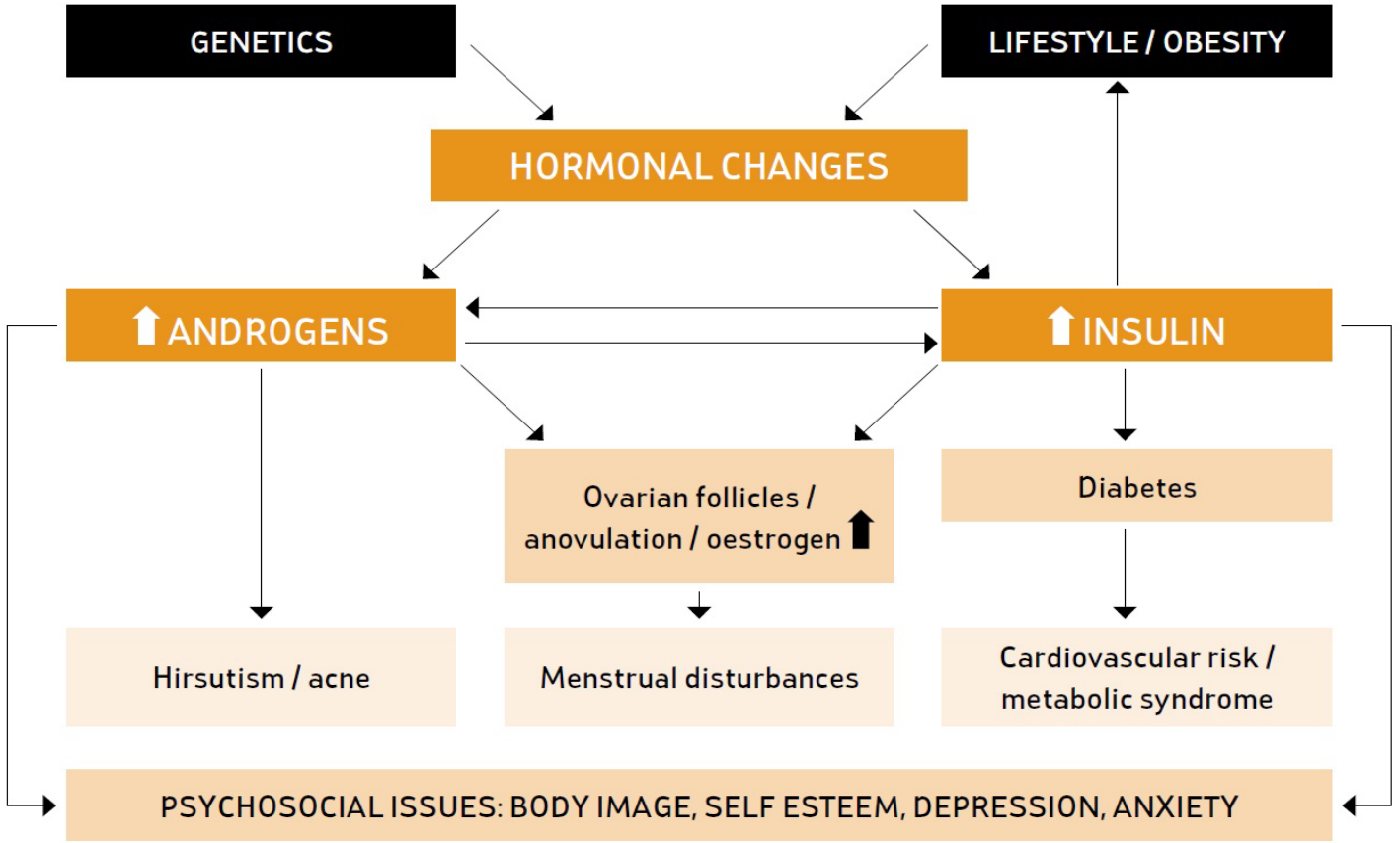
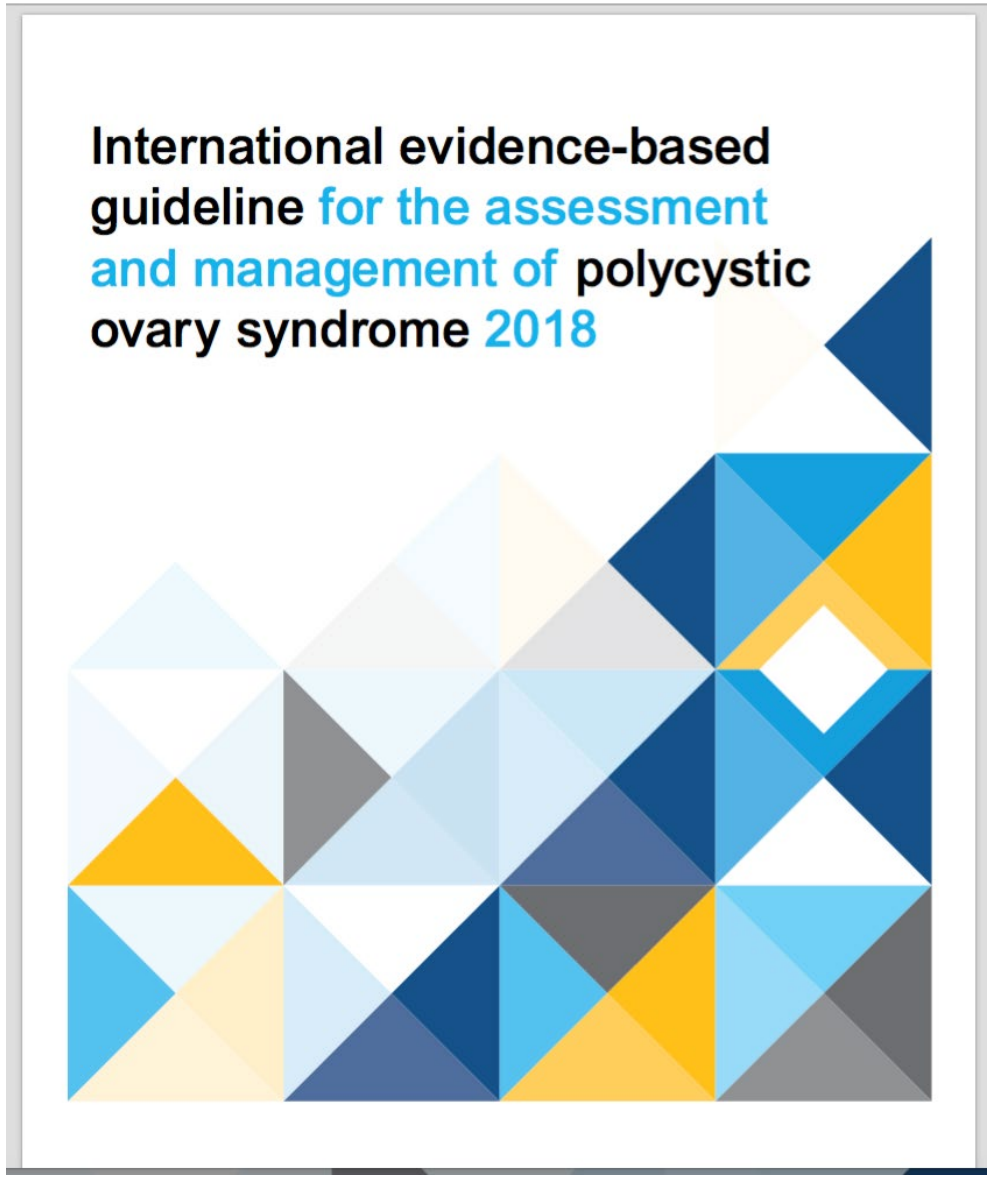



**Figure 1.** *Reproduced with permission from the Royal Australian College of General Practitioners [33].*

- 37 PCOS Professional Societies and Organizations
- 71 Countries, 3,000 Health Professionals
- 166 Recommendations
  - Increase focus on education and lifestyle modification
  - Evidence-based medical therapies
  - More cost effective and safer fertility management




https://www.monash.edu/__data/assets/pdf_file/0004/1412644/PCOS_Evidence-Based-Guidelines_20181009.pdf

# PCOS EVALUATION

- Need to exclude other causes of irregular periods and elevated androgens

## DIAGNOSTICS- BLOOD TEST

- ✓ Hormone Levels
  (Total Testosterone, DHEAS, 17-OHP)
- ✓ TSH (Thyroid function)
- ✓ Prolactin Level
- ✓ Hemoglobin A1C (diabetes screen)
- ✓ Lipid panel
- ✓ Vitamin D

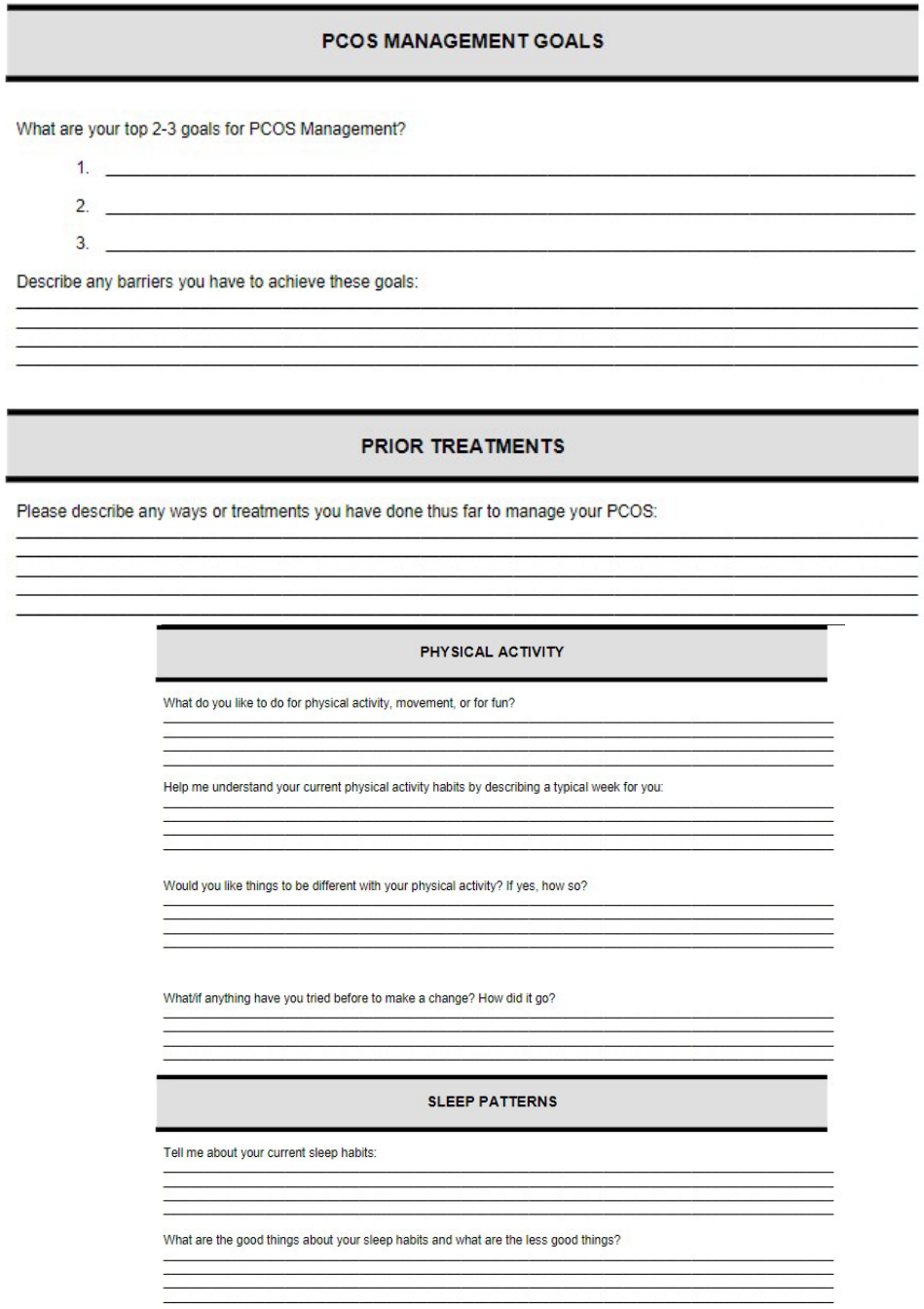
# SUSHMA'S LABS

- TSH 2.4
- AMH: 8.4, ovaries polycystic by TVUS
- Total T: 55, DHEAS: 350, PRL: 9
- 17-OHP (hydroxyprogesterone): 85
- HBA1C: 4.5%

# PCOS WELLNESS PROGRAM

## Screening questionnaires:

- Ferriman Gallway for hair growth
- Anxiety screening – GAD 7
- Depression screening – PHQ 9
- SCOFF for disordered eating
- Berlin Questionnaire for sleep apnea



**PCOS MANAGEMENT GOALS**

What are your top 2-3 goals for PCOS Management?

1. _____
2. _____
3. _____

Describe any barriers you have to achieve these goals:

_____

**PRIOR TREATMENTS**

Please describe any ways or treatments you have done thus far to manage your PCOS:

_____

**PHYSICAL ACTIVITY**

What do you like to do for physical activity, movement, or for fun?

_____

Help me understand your current physical activity habits by describing a typical week for you:

_____

Would you like things to be different with your physical activity? If yes, how so?

_____

What/if anything have you tried before to make a change? How did it go?

_____

**SLEEP PATTERNS**

Tell me about your current sleep habits:

_____

What are the good things about your sleep habits and what are the less good things?

_____

# SUSHMA~

- SCOFF:
  - Negative
- Berlin questionnaire sleep apnea
  - Negative
- Anxiety screening – GAD 7:
  - Elevated
- Depression screening – PHQ 9:
  - Elevated

# HEALTHY LIFESTYLE IS FIRST-LINE TREATMENT FOR PCOS

## Setting GOALS ~ top 3?

**What are yours?**

1. Nutrition
2. Fertility / Regulate menstrual cycles
3. Physical Activity
4. Sleep
5. Mental Health
6. Symptom Management
7. Health Risks

**Goals should be S M A R T**

**Specific-Measurable-Achievable-Realistic-Timely**

Any barriers?

# SUPPLEMENTS

## Vitamin D

- A cross-sectional comparison study examining vitamin D status in PCOS women and fertile women:
  - PCOS group had higher rates of vitamin D deficiency
  - Low vitamin D PCOS group had more insulin resistance

## Omega-3

- A systematic review and meta-analysis revealed benefits of omega-3 supplementation for women with PCOS:
  - Improved markers of inflammation and oxidative stress
  - Improved hormonal balance of LH, SHBG, TT

## Inositol

- Inositol Treatment
  - 40:1 ratio of myo-inositol to d-chiro-inositol
  - Highest efficacy for restoring ovulation, normalizing hormones and improving insulin sensitivity

- Prenatal vitamin (depending on goals)
- Vitamin B12, 250 mcg if on whole-food, plant-based diet or long-term metformin

https://www-ncbi-nlm-nih-gov.proxy.heal-wa.org/pmc/articles/PMC7140126/
https://www-ncbi-nlm-nih-gov.proxy.heal-wa.org/pmc/articles/PMC6279035/
https://apm.amegroups.com/article/view/77612/html

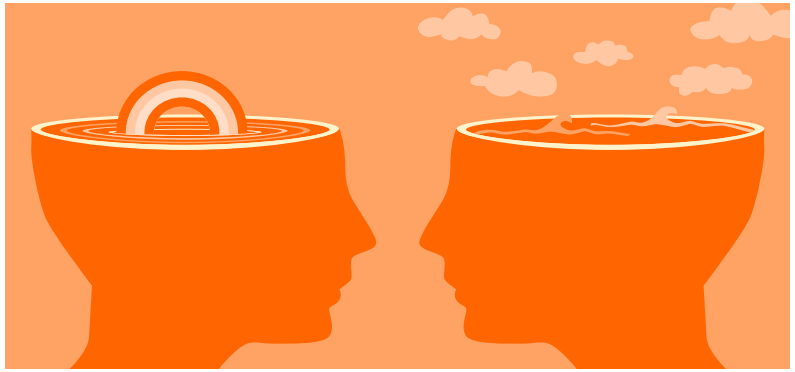
# MENTAL HEALTH

•Depression and anxiety are 3 times more common in those with PCOS

•Studies have shown links between PCOS symptoms and/or hormonal imbalances may contribute to increased rates of depression and anxiety

## Treatment is goal based

- Lifestyle changes with healthy foods, exercise, meditation, and stress management
- Medication / SSRI's
- Therapy / Counseling
- Combination Treatment



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5108561/

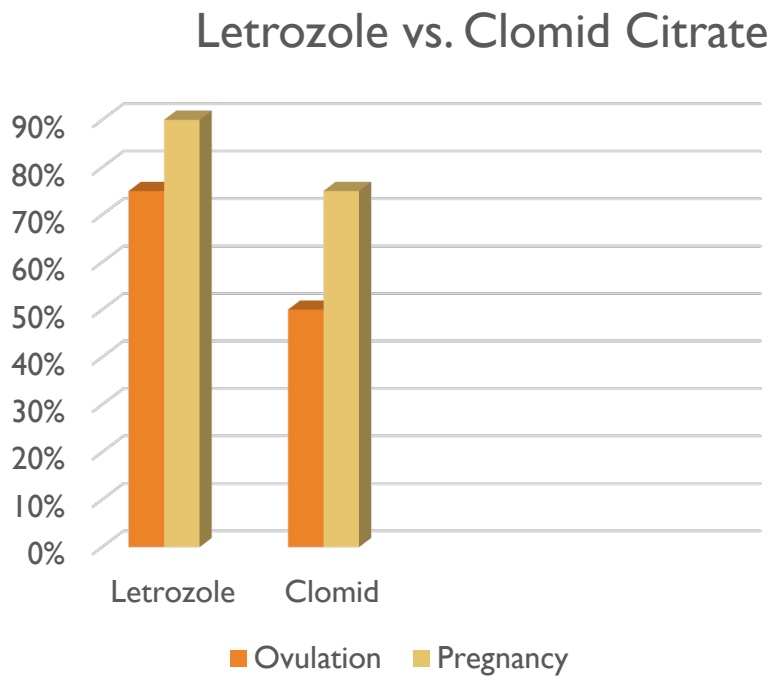
https://www-ncbi-nlm-nih-gov.proxy.heal-wa.org/pmc/articles/PMC6529622/

# FERTILITY

## PCOS is one of the most common and treatable causes of infertility

- ↑ difficulty getting pregnant due to hormonal imbalances preventing normal ovulation
- Miscarriage rates are 20-40% higher than the general OB population
- ↑ risk diabetes, high blood pressure, and pre-term delivery
- Inducing ovulation and managing lifestyle factors improve pregnancy rates and live birth rates

## Medication for Ovulation Induction




Teide H, Misso M, Costello M, Dokras A, Laven J, Moran L, Piltonen, T, Norman, R. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fert & Stert. May 2018; 0015-0282.

# SUSHMA'S PLAN

- 4 month plan, nutrition resources, regular home workout plan
- Declined counseling, gave resources
- Started Ovasitol and Vit D
- Plan to begin Letrozole 2.5mg

# WHAT IF SHE WASN'T TRYING TO CONCEIVE?

- Assess goals
  - Weight loss (will discuss this in a different case study)
  - Hirsuitism management
  - Mood and sleep
  - Cycle regulation and endometrial protection

# Focus on MOVEMENT, lifestyle and mood

Exercise Intervention to ***maintain weight***

- 2.5 hours / week of moderate intensity
  OR 1.25 hours/week of vigorous intensity
- Muscle strengthening 2 x / week

Exercise Intervention for ***modest weight loss***

- 4 hours / week of moderate intensity OR
  2.5 hours/week of vigorous intensity
- Muscle strengthening 2 x / week

# DIETARY INTERVENTIONS FOR PCOS

- The typical American diet consists of a high portion of ultra-processed foods and low amounts of vegetables and fiber

- **A plant-based, whole foods diet is best** to reduce insulin resistance, central obesity, risk of chronic disease

***Add C O L O R***

# NUTRITION

- 5-10% weight loss may restore normal ovulation
- Best tip: home cooking
- Minimize processed foods and the 5 “whites” white sugar, white bread, white rice, white pasta, and potatoes
- Increase protein to carb ratio will decrease swings in blood sugar
- Do not recommend diet drinks because of rebound appetite

# HIRSUTISM

- Hormonal contraception is the first line treatment
- Spironolactone
  - Will take 4-6 months to see improvement, hair does not disappear but will grow in finer/lighter
  - Typically add after 3-6 months on hormonal contraception if no improvement
  - Requires reliable contraception
- Laser hair removal
- Light therapy
- Electrolysis

https://www.monash.edu/__data/assets/pdf_file/0004/1412644/PCOS_Evidence-Based-Guidelines_20181009.pdf

# SLEEP AND PCOS

- Those with PCOS have ↑ risk sleep disturbances
- Inadequate sleep leads to ↑ risk diabetes and cardiovascular health
- Sleep disturbances negatively impact mood, weight, and hunger
- Berlin Questionnaire for sleep apnea

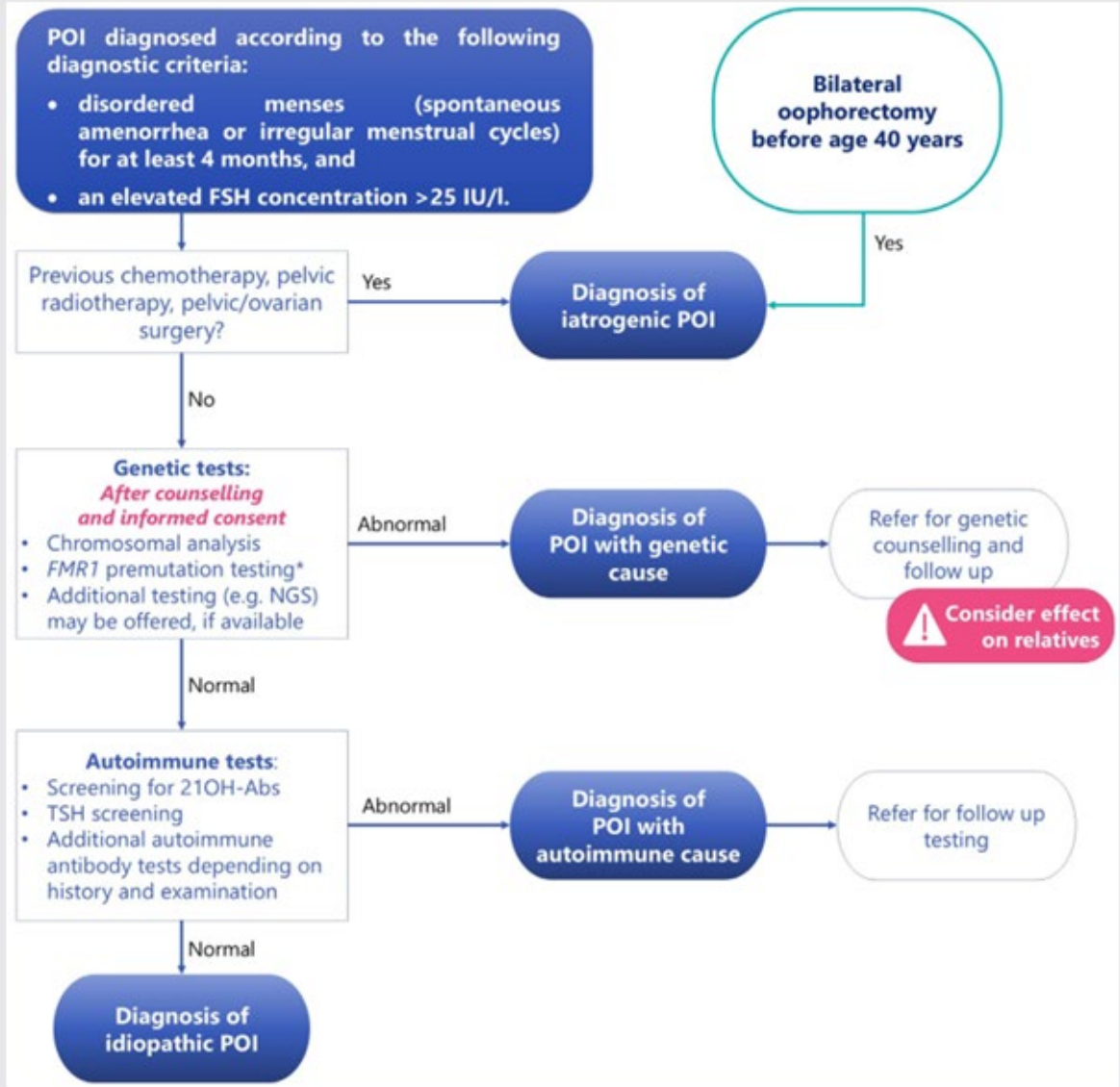
What are your sleep habits?

How much sleep do you get a night?

Treatment

- Sleep hygiene
- Melatonin
- Sleep study

## FIGURE 2

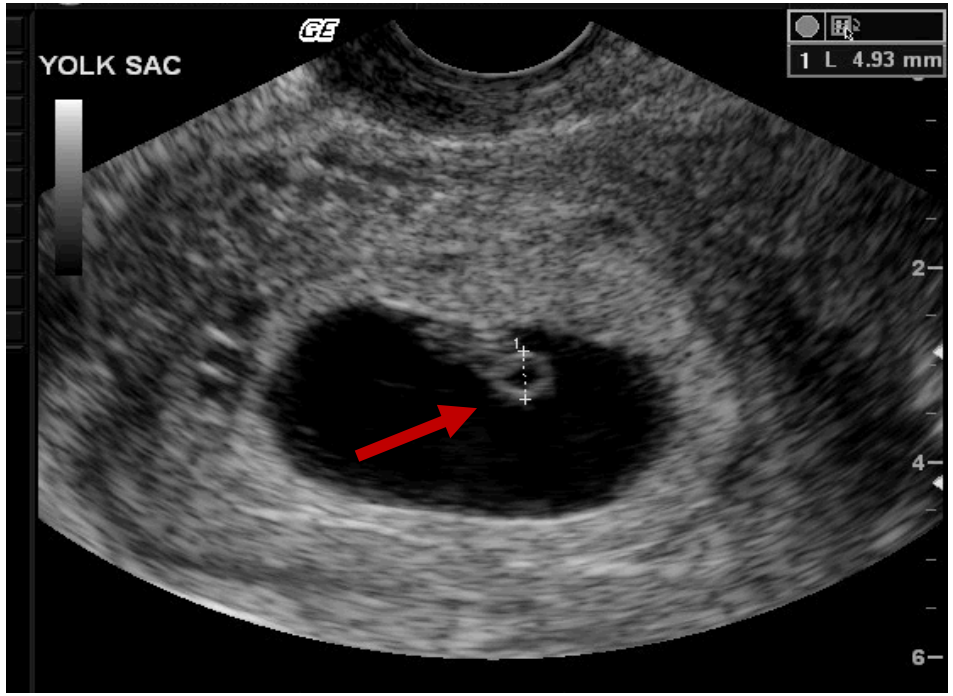



Summary of the recommendations on diagnosis of premature ovarian insufficiency (POI), as well as the recommended further testing to establish a cause for POI. *Fragile X premutation testing is indicated in all women diagnosed with POI. This needs to be performed as a specific test as multigene panels and NGS are not useful in detecting FMR1 premutation. 21OH-Abs, 21-hydroxylase autoantibodies; BSO, bilateral salpingo-oophorectomy; FSH, follicle stimulating hormone; NGS, next generation sequencing; TSH, thyroid stimulating hormone.

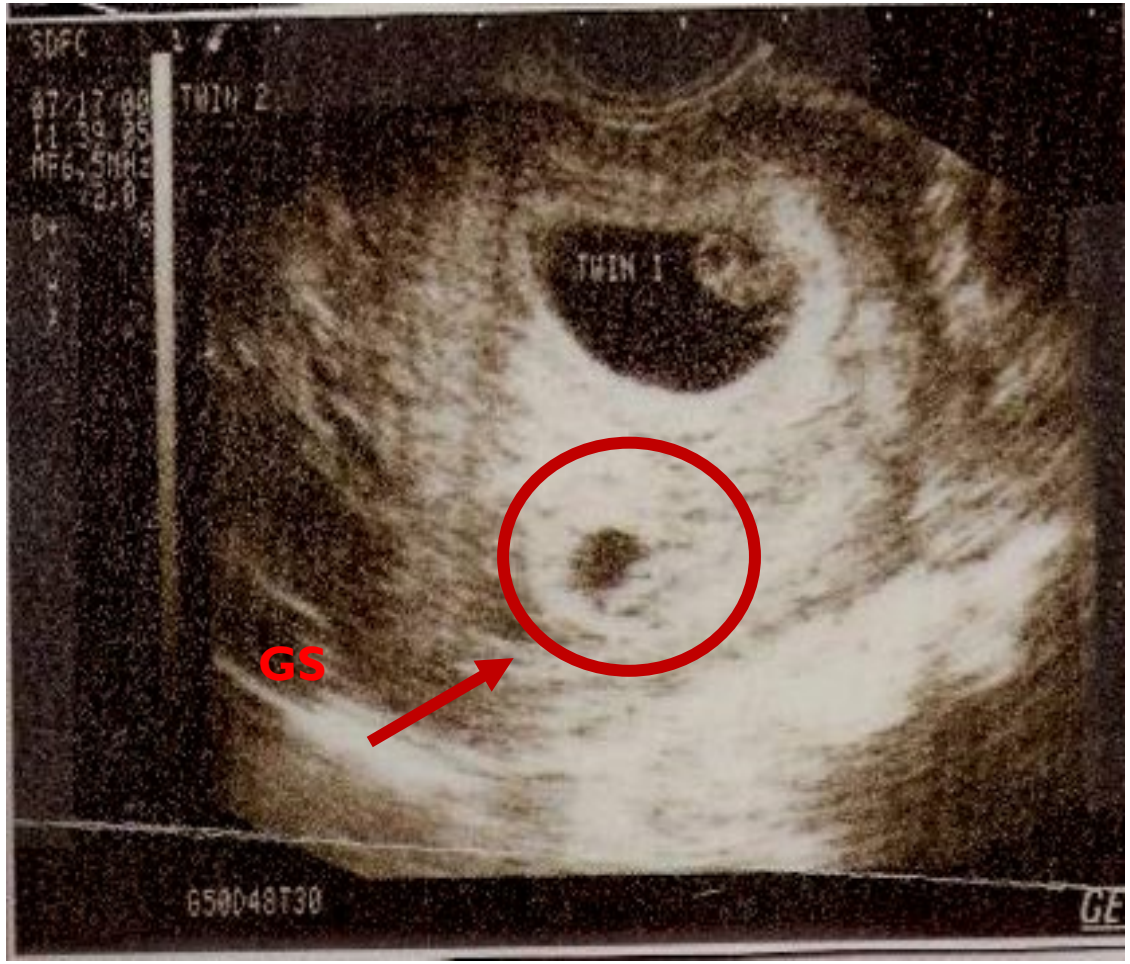
*ESHRE, ASRM, CREWHIRL and IMS Guideline Group on POI. Fertil Steril 2025.*

# YOLK SAC FEATURES

- Earliest embryonic landmark
- Should see by 6 weeks, size ≤ 6 mm
- Connected to yolk stalk until 8 weeks and then detaches, solidifies
- Indicates true gestational sac even before embryo is seen; important for r/o ectopic

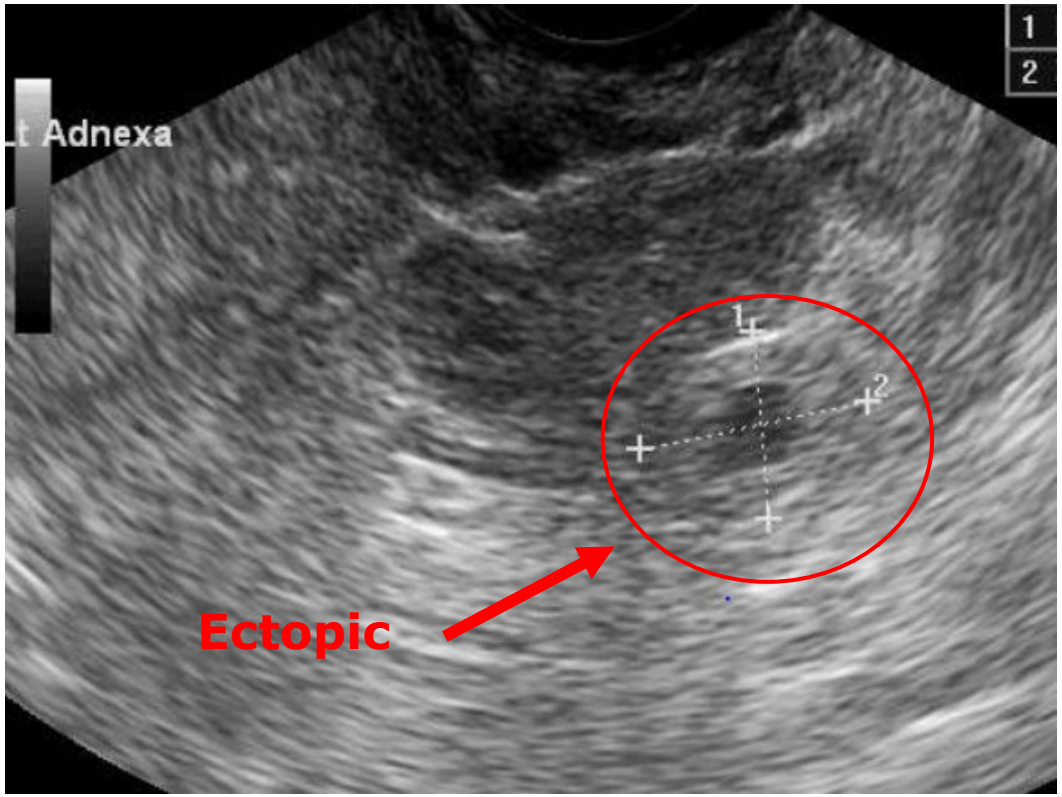



Nyberg D, Hill L, Böhm-Vélez M, Mendelson E. Transvaginal Ultrasound. 1992.

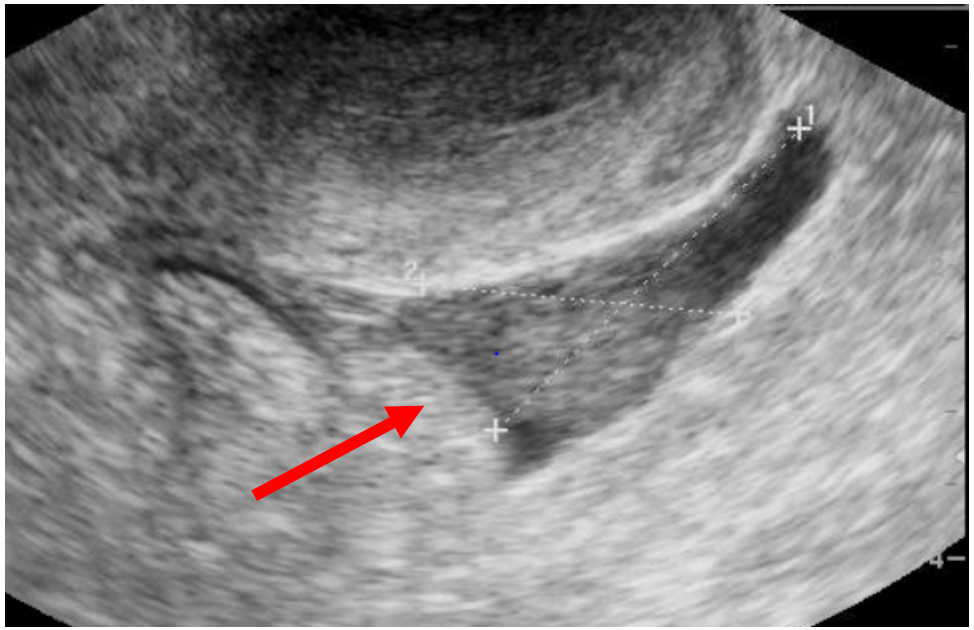



TWIN PREGNANCY WITH SMALL GS 2ND SAC

- 6 week US. No bleeding or pain but a little twinge on left side
- Uterus empty. adnexal mass 13 x 16 mm with possible yolk sac seen. no free fluid
- Gave methotrexate



- Called reporting severe left sided abdominal  pain, 8 out of 10
- Started bleeding 1 hour prior to exam
- Free fluid 29x22x31mm LLQ
- Diagnosis: rupturing/ bleeding ectopic pregnancy on left



**Free Fluid ~ Hemoperitoneum**

# CASE STUDY #7

# INTAKE – HISTORY & PHYSICAL

**History**

- Past Paternity
- Prior Testing
- Urologic Issues
- Sexual dysfunction
- Prior surgery/trauma
- Development/puberty
- Familial History
- Occupational/"real-life" issues
- Drug (both prescribed and lifestyle)
- Female factors

**Physical**

- General Appearance
  - Androgen deficiency
  - Gynecomastia
  - Height/weight
- Focused GU exam
  - Examination of the penis
  - Palpation of the testes
    - Tumor
    - Varicocele
    - Size/consistency
  - Palpation of epididymis/VD
  - Hernia
  - Rectal/Prostate (for low volume)

# ENDOMETRIAL PROTECTION

- When was her last period?
- If over 35 days, get labs and, if appropriate, start provera (medroxyprogesterone acetate)
- If pt regularly skips her period OR has gone an extended period of time without a menses, she should have an endometrial biopsy after her bleed
- Consider PCOS treatments that afford endometrial protection

Which of the following would you offer to Sushma if she was NOT trying to conceive?

- Birth Control Pills
- Metformin
- Spironolactone
- Laser Hair Removal
- Weight loss
- Myo-inositol

# CASE STUDY: KEY POINTS

- PCOS is a lifespan condition
- Concerns will vary during different stages of life
- Protect the endometrium!!
- Individualized approach with SMART goals
- Updated guidelines on PCOS management include an increased focus on education and lifestyle modification.
- There is ↑ anxiety and depression in PCOS patients and screening is recommended.
- Supplements such as Vit D, Omega-3, and Inositol may be beneficial.
- Letrozole for ovulation induction has ↑ ovulation and pregnancy rates.
- Focus on healthy lifestyle

# CASE STUDY: KEY POINTS CONTINUED

- Updated guidelines on PCOS management include increase focus on education and lifestyle modification.
- There is ↑ anxiety and depression in PCOS patients and screening is recommended.
- Supplements such as Vit D, Omega-3, and Inositol may be beneficial.
- Letrozole for ovulation induction has ↑ ovulation and pregnancy rates.

# CASE STUDY #3

# CASE STUDY #3

Kira is a 31-year-old G1P0010 female that presents with a 3y history of oligomenorrhea (q3mos) and recent onset of hot flushes. She is not currently TTC but would like to start soon. She would like to find out why she is having vasomotor symptoms and irregular periods.

# OVARIAN RESERVE

- Prognostic
- Declines with age
- Maximum 6-7 million @ 20 weeks gestation in female fetus
- Decrease to 1-2 million @ birth
- Decrease to 300k-500k @ puberty
- Decrease to 25k @ age 37
- Decrease to 1,000 @ menopause

# MEASURES OF OVARIAN RESERVE

- AMH
- FSH
- AFC

**All are quantitative markers, not qualitative**

ASRM (2020)

# OVARIAN RESERVE: AMH

**Anti-Müllerian Hormone**

- Produced by granulosa cells of small follicles
- Measure of quantitative ovarian reserve
- Does **not** predict pregnancy
- No intracycle variability

| AMH level (ng/mL) | Interpretation |
|---|---|
| >3.0 | High |
| >1.0 | Normal |
| 0.7 - 0.9 | Low Normal |
| 0.3 - 0.6 | Low |
| <0.3 | Very Low |

ASRM (2020)

# OVARIAN RESERVE: FSH

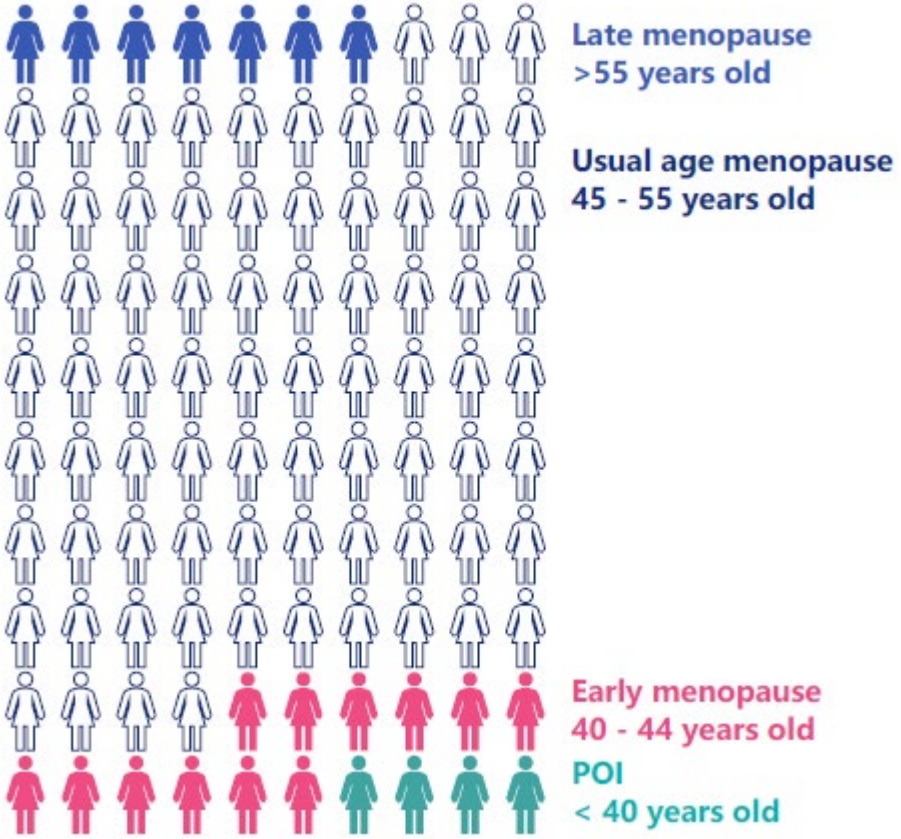
**Follicle Stimulating Hormone (FSH)**

- Early follicular phase measurement
- Interpret with concurrent $E_2$
- Cycle-to-cycle variation
- **Peak** values have greatest predictive value
- PPV for failure to conceive higher in older women

ASRM (2020)

# PREMATURE OVARIAN INSUFFICIENCY (POI)

- Loss of ovarian function before age 40 (1 - 3.5%)
- WHO Anovulation Class III: Hypergonadotropic/Hypoestrogenic
- Multifactorial, poorly understood
- Exists on a spectrum




ASRM. Evidence-based guideline: Premature Ovarian Insufficiency. (2024).

ESHRE. POI Guideline. (2024)

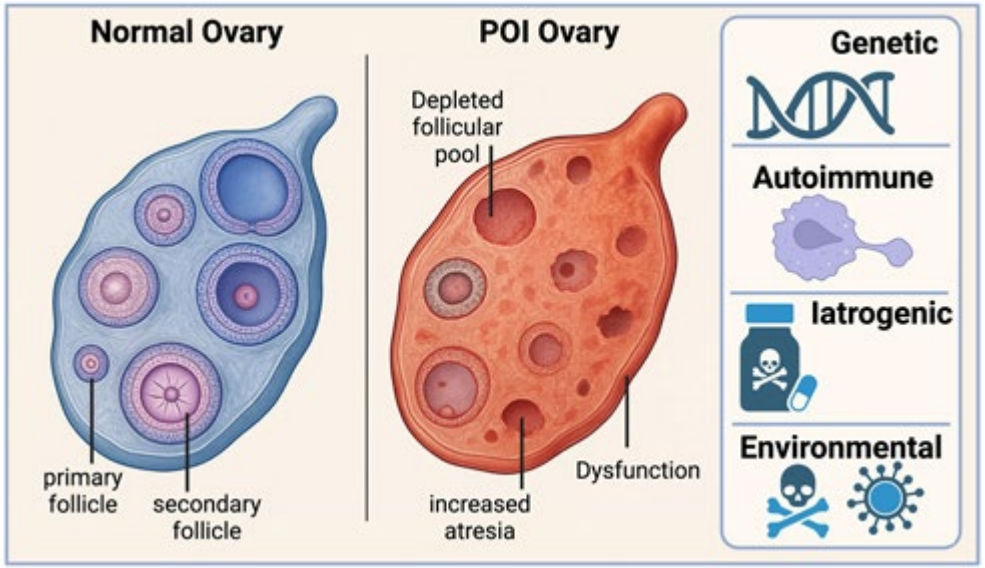
# POI: DIAGNOSIS

- **Menstrual irregularities (at least 4mos)**
- **Biochemical confirmation (FSH >25)**
- Careful history
  - Family history of POI? Unexplained intellectual delay?
  - Symptoms of estrogen deficiency?
  - Smoking? Toxins?
  - Chemo? Radiation?

Joo Chon, Umair, & Yoon (2021); Welt (2022); ASRM (2024); Hassan et al (2025)

# POI: ETIOLOGY

- Autoimmune
- Familial (10%)
- Iatrogenic
- Radiation/Chemotherapy or ovarian surgery
- Idiopathic **(75-90%)**
- Genetic mutations
- X Chromosome Disorders (Turner Syndrome)
- Fragile X Premutation Carriers




Hassan et al. Mesenchymal Stem Cells: A Therapeutic Approach in Fertility Restoration in Premature Ovarian Insufficiency (2025)

Welt (2022) & ASRM (2024)

# POI IS DIFFERENT FROM DOR

## Age-Related DOR

- Quantity ↓
  - Accelerated atresia after age 37
- Quality ↓
  - Meiotic nondisjunction

Fritz & Jindal (2018)

# POI: WORK-UP

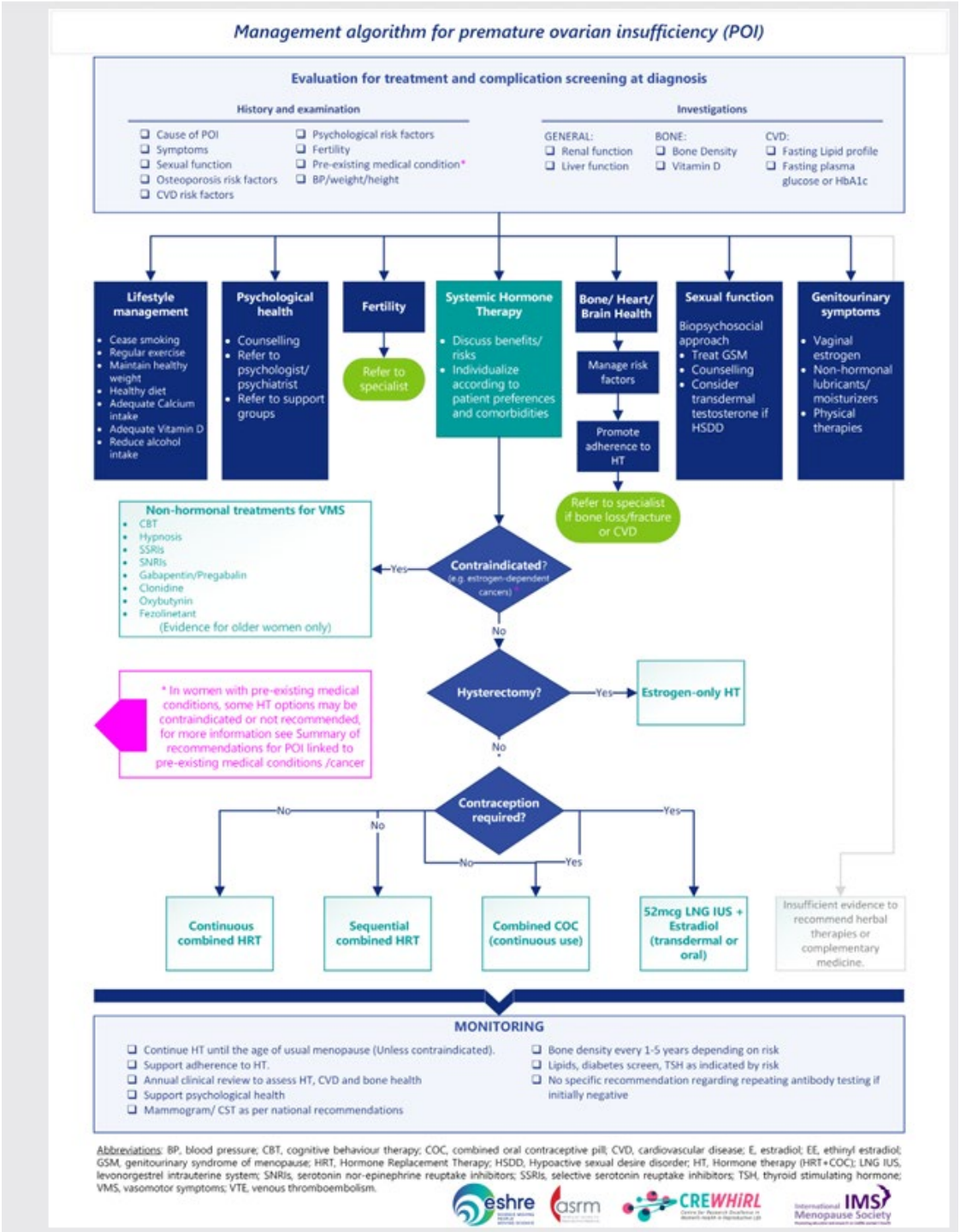
- bhCG
- ORTs
- PRL
- TSH
- Karyotype
- FMR1 premutation (20%)
  - Spontaneous conception rate ~12.6%
- Adrenal antibodies (21OH-Abs)
- DEXA

Welt (2022) & ASRM (2024)

# POI: FERTILITY TREATMENT OPTIONS

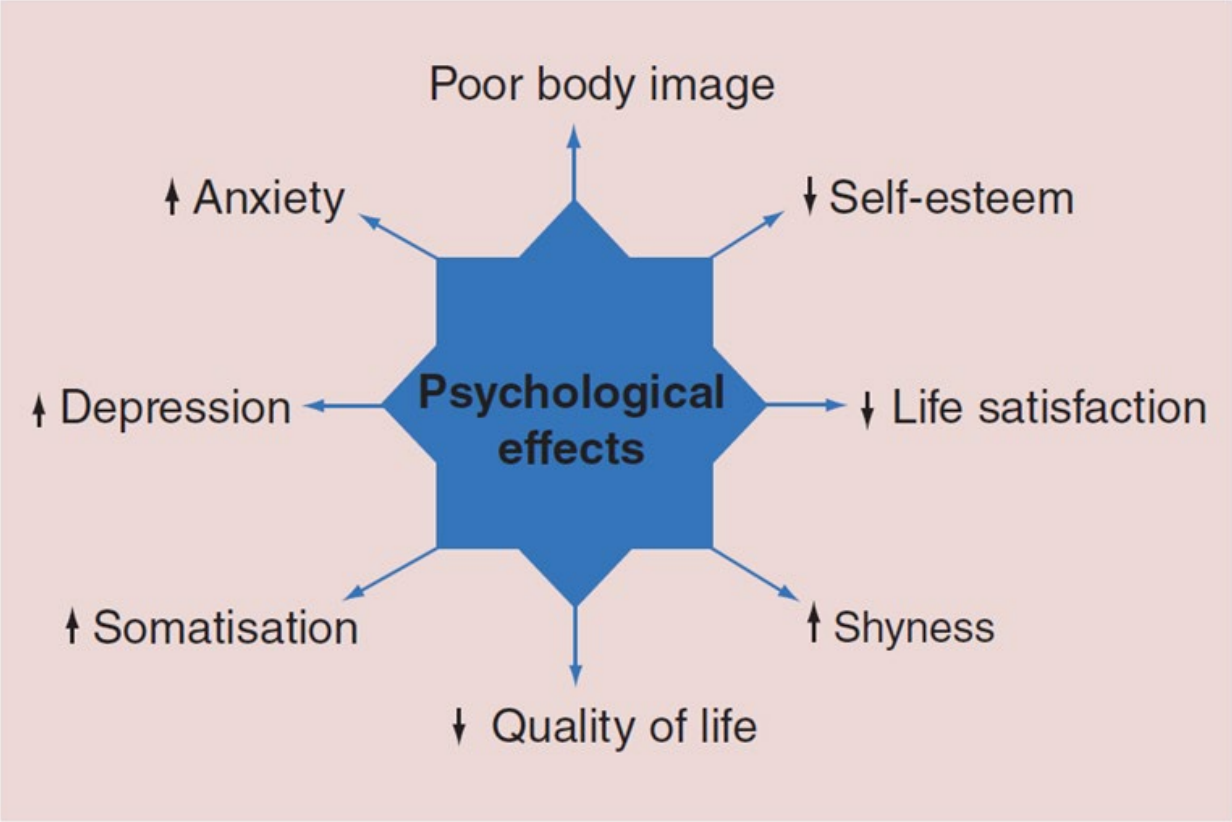
- ART
- Egg donation
- Preventative: fertility preservation prior to gonadotoxic treatments

# MANAGEMENT ALGORITHM FOR POI



# POI: OTHER CONSIDERATIONS

- Emotional support for devastating diagnosis
- Sexual wellbeing




Maclaran & Panay (2015); Welt (2022)

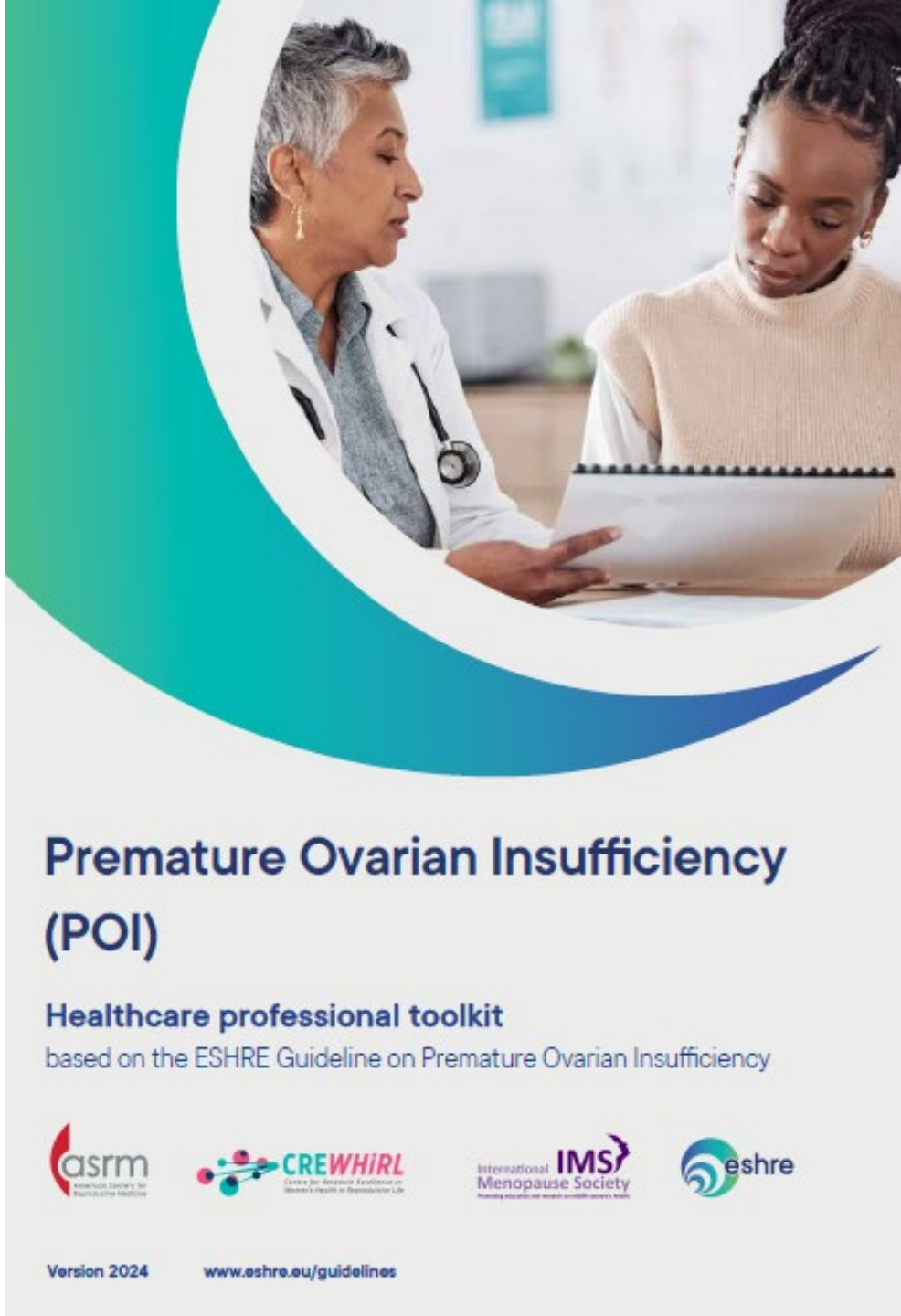
# CASE STUDY: RESULTS

Kira's AMH is undetectable and her random FSH is 78 (E2 is 15). Her TVUS shows 1 antral follicle. She has a TSH of 26 and (+) thyroid antibodies.

- **How will you communicate the diagnosis to this patient?**
- **What are the next best steps for her if she is trying to conceive?**

# CASE STUDY #3: KEY POINTS

- POI has extensive physical & emotional implications
- [Low] chance for spontaneous pregnancy
- Those wishing to conceive should undergo a full investigation prior to pregnancy, as some etiologies have important obstetric implications, & for family members
- Attention to hormone replacement, bone density, and sexual & emotional health is key



# CASE STUDY #4

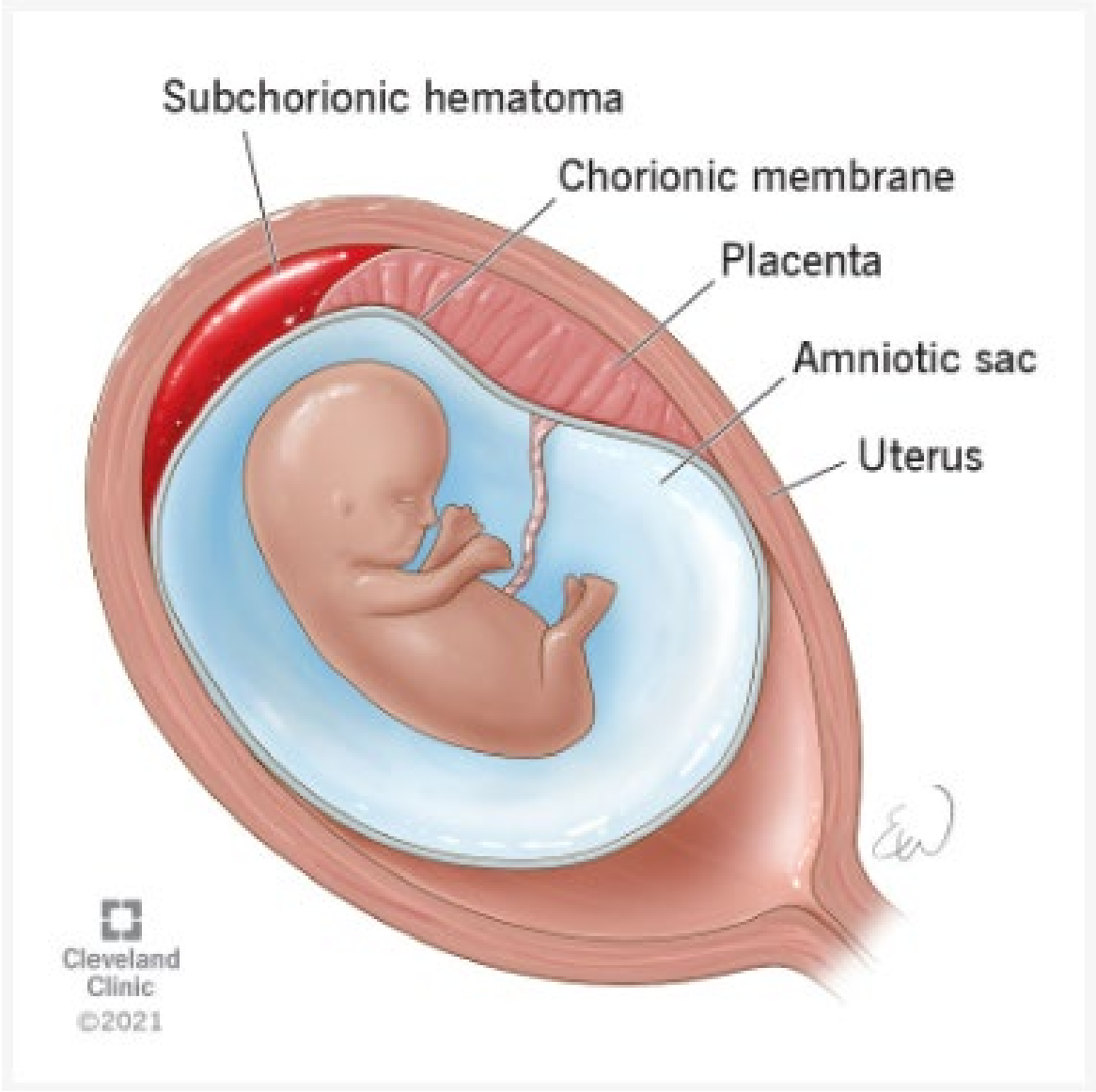
# CASE STUDY #4 (SUBCHORIONIC HEMATOMA)

Raya, a 39-year-old G1P0 patient, is finally pregnant after IVF and an embryo transfer cycle. She presents to the clinic for an urgent ultrasound due to new onset moderate vaginal bleeding. She was last seen in the office 2 days ago, where a transvaginal ultrasound showed a normally-developing 6-week IUP with cardiac activity. This morning, she is tearful and worried about the fate of the pregnancy.

# SUBCHORIONIC HEMATOMAS (SCH)

- A collection of blood between chorion and uterine wall
- Sonolucent usually crescent-shape area on ultrasound, behind or below the GS
- Incidence varies ~0.46-39.5%
- May leak through cervical canal causing vaginal bleeding, often asymptomatic

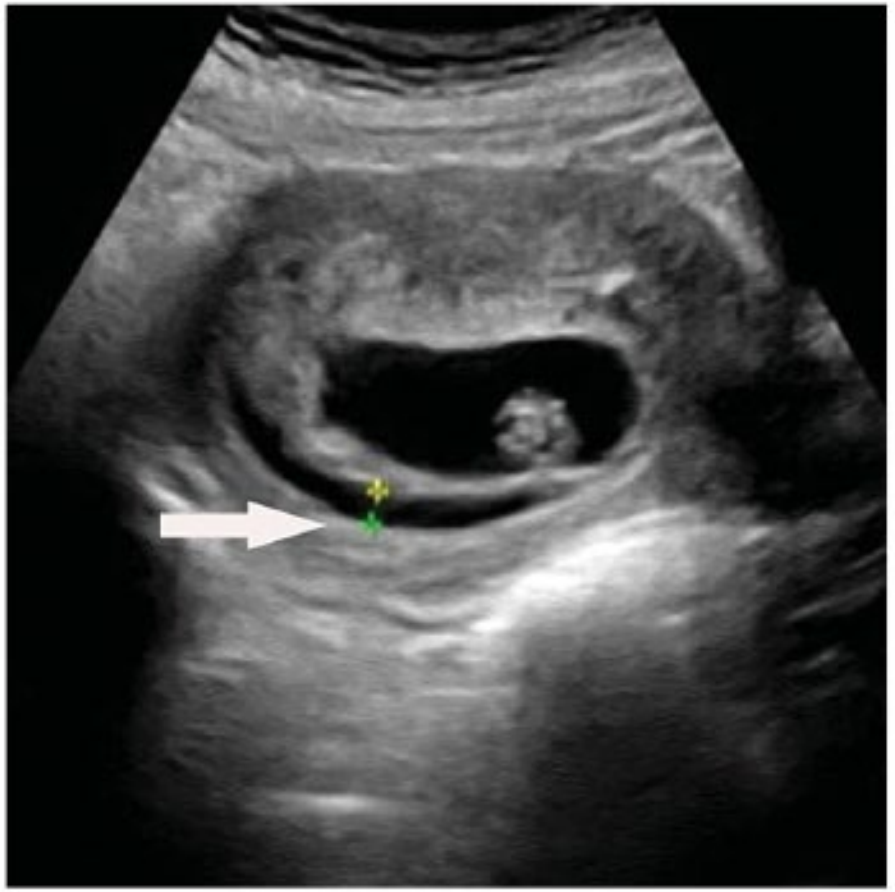
Wei et al (2025)


Subchorionic hematoma
Chorionic membrane
Placenta
Amniotic sac
Uterus
Cleveland Clinic
©2021

# SCH: ETIOLOGY & RISK FACTORS

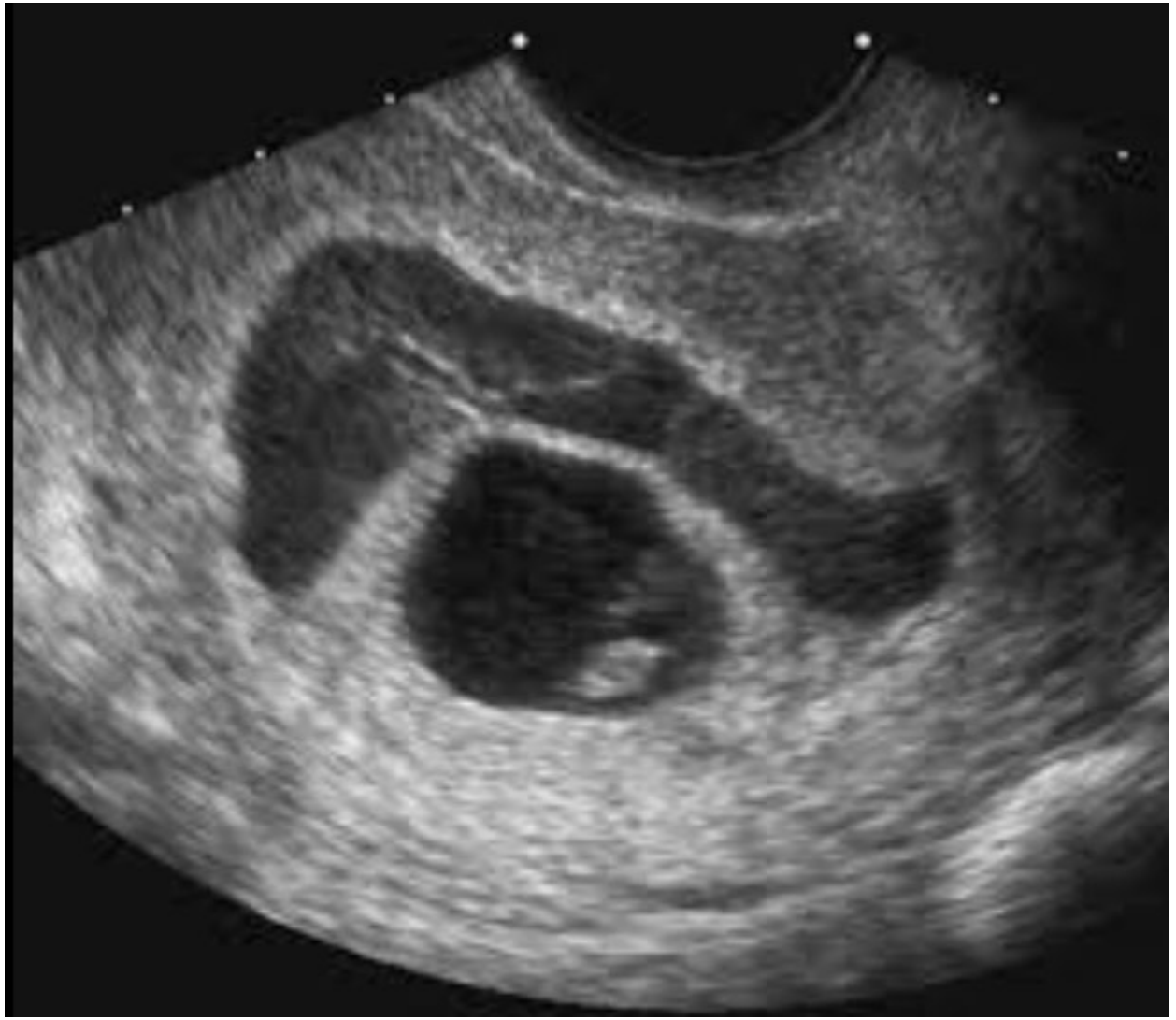
- IVF, particularly fresh ET (Wei et al 2025)
- Aspirin use
- Pathogenesis & etiology unclear
- Influence on pregnancy outcomes controversial
  - Fetal growth restriction risk factors: late (>7 weeks) GA SCH or persisting into 2nd trimester
  - Size of SCH does not correlate to outcomes in multiple studies

Wei et al (2025); Xu et al (2024); Lou et al (2025)

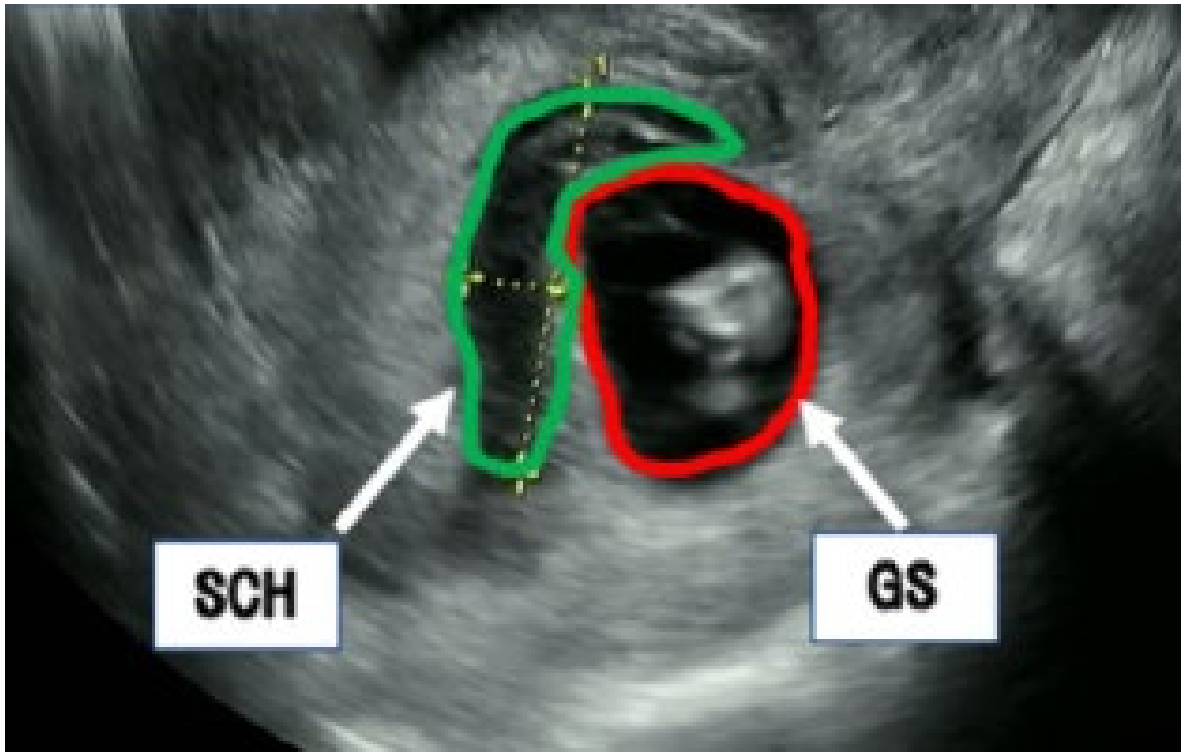


Subchorionic hematoma in the first trimester. A hypoechoic crescent-shaped area separates the uterine wall and chorion (arrow).

Li et al (2021)



Leite et al (2006)




Yoshihara et al (2024)

Findings from a retrospective cohort study at a tertiary care, university-based facility between January 2015 and March 2018 (n = 1210)

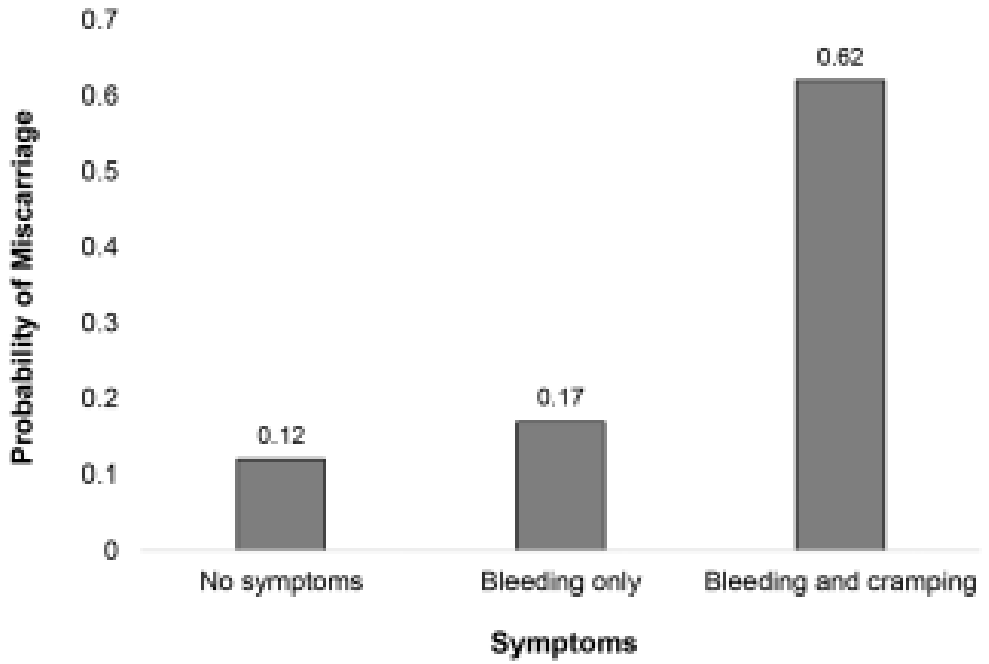



FIGURE 2 Predicted probability of miscarriage in patients with SCH by symptoms SCH, subchorionic hematoma

Inman et al (2022)

# CASE STUDY: RESULTS

- Raya's ultrasound shows a viable SIUP and a small subchorionic hematoma, which is identified as the most likely cause of the vaginal bleeding
- The clinician **acknowledges** that although bleeding in pregnancy in always scary, the majority of SCHs resolve on their own and the pregnancy typically goes on to develop normally
- **Anticipatory guidance** is provided: vaginal bleeding may continue. Precautions are provided and pelvic rest is recommended.
- The clinician **reassures** Raya that the clinic will let her OB know about the SCH once discharged

# CASE STUDY #4: KEY POINTS

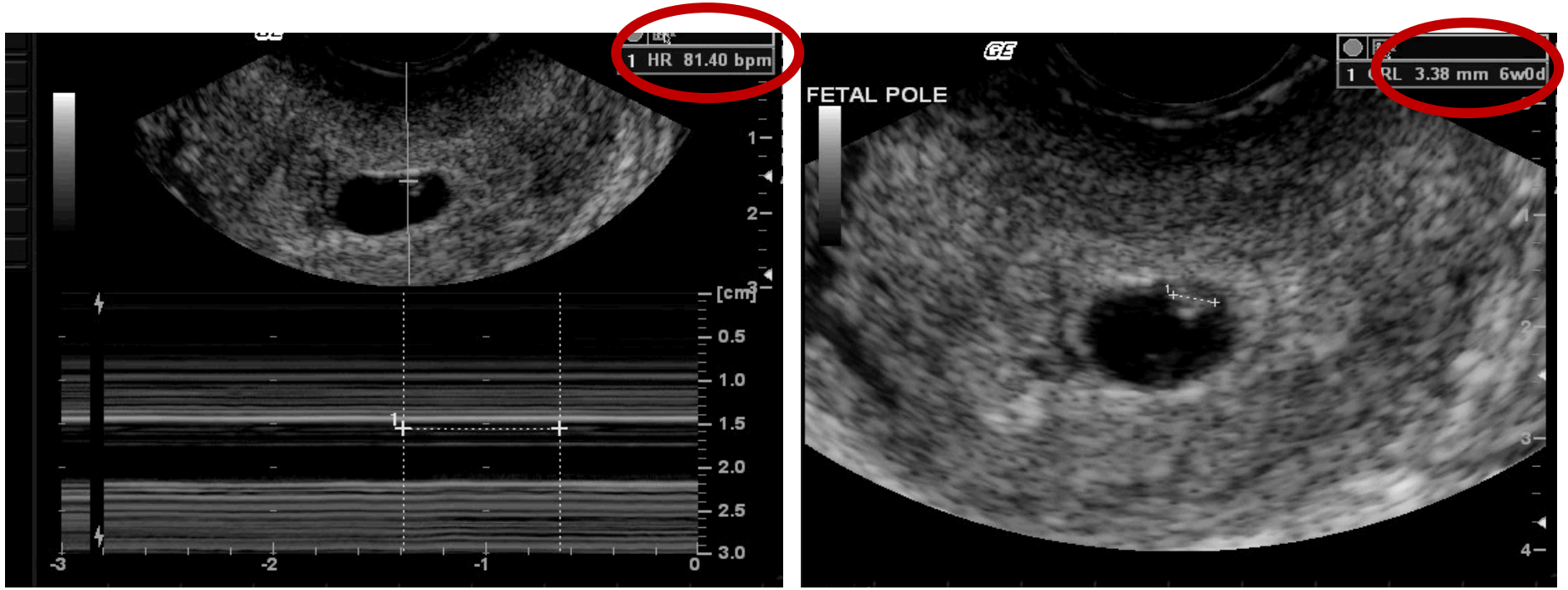
- SCH does not significantly increase the risk of adverse maternal and perinatal outcomes in those with singleton pregnancies after ART
- Empathy, support, and anticipatory guidance are critical

# CASE STUDY #5

# CASE STUDY #5 KATE

Kate presents to your office as a 37-year-old, G2 P1 SAB1 for her 1st OB US.

- Hx PCOS,  Spontaneous pregnancy
- LMP = 7W
- Initial hCG 110 with appropriate rise
- Denies any pain or bleeding



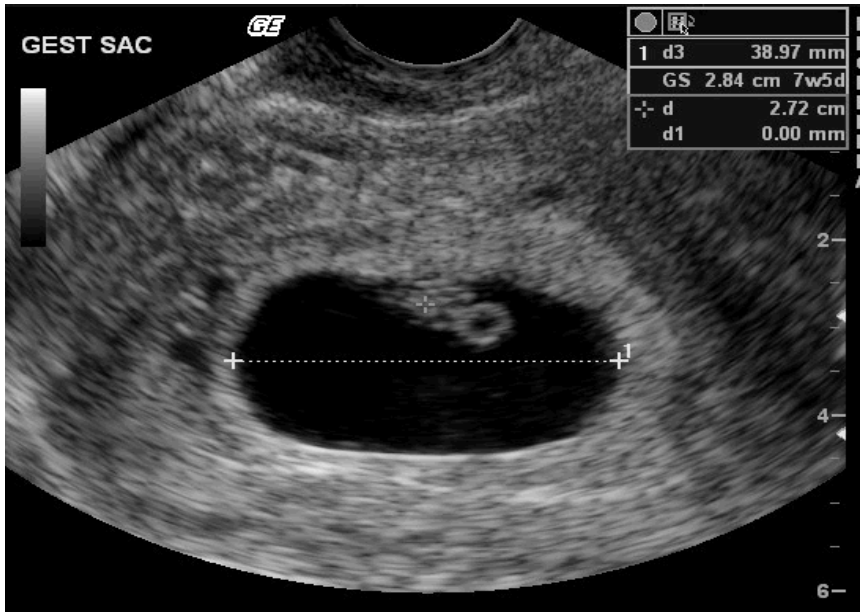

What questions would you ask?
Do you have any concerns?

# NORMAL EARLY PREGNANCY ULTRASOUND

- Gestational Sac
- Yolk Sac
- Embryo and Cardiac Activity
- Amnion

# GESTATIONAL SAC (GS) FEATURES

- First definitive sign of early pregnancy
- Earliest seen 4.5 menstrual weeks
- 5 weeks = 5 mm
- Growth 1mm/day in early pregnancy
- Location – near fundus




Nyberg D, Hill L, Böhm-Vélez M, Mendelson E. Transvaginal Ultrasound. 1992.

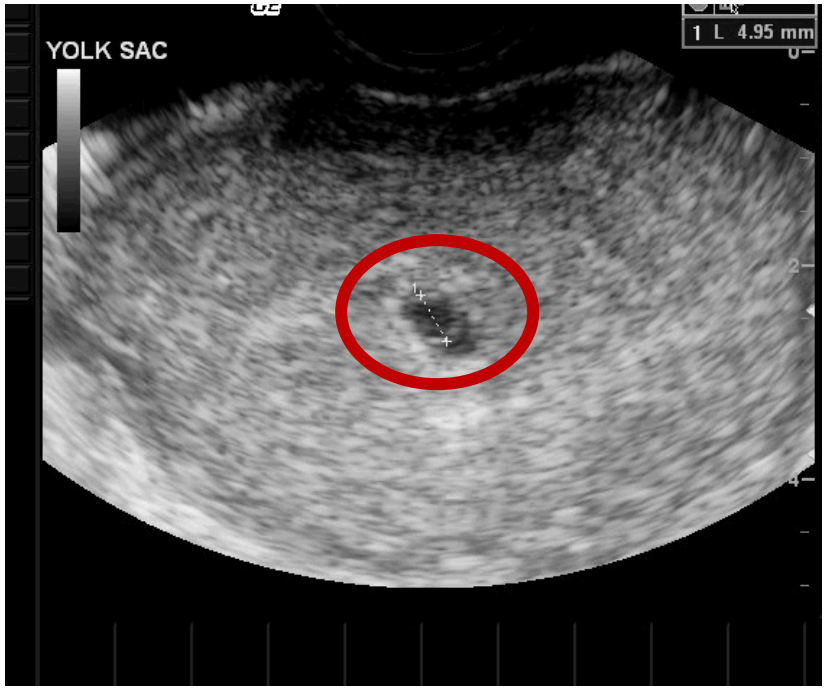
# GROWTH DELAY

Absent or small interval growth of embryo or GS demonstrated by serial ultrasounds

Small GS relative to size of embryo

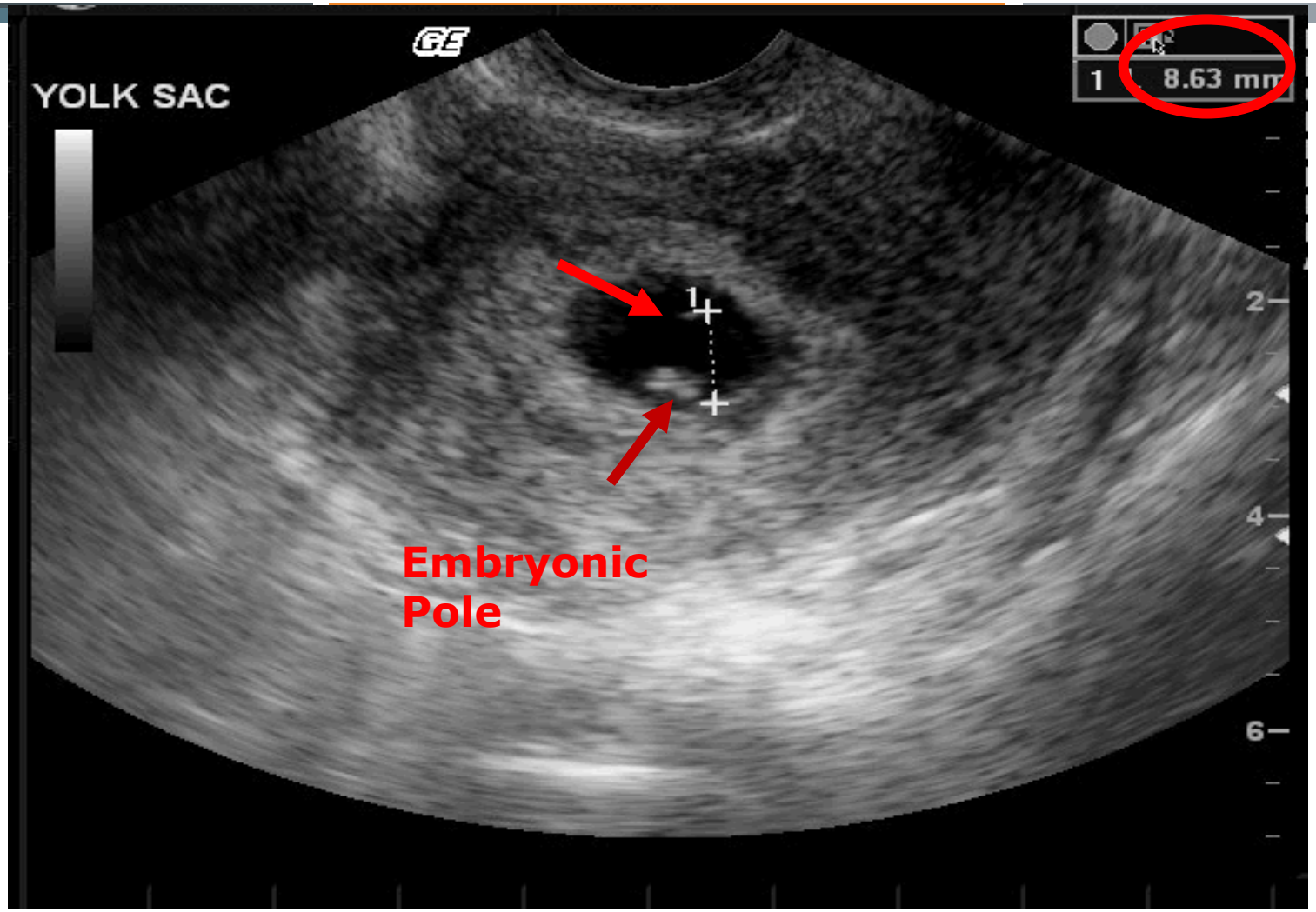
< 4mm difference = poor prognosis

Normal GS and CRL growth is 1mm/day




**ABNORMAL GS SIZE**

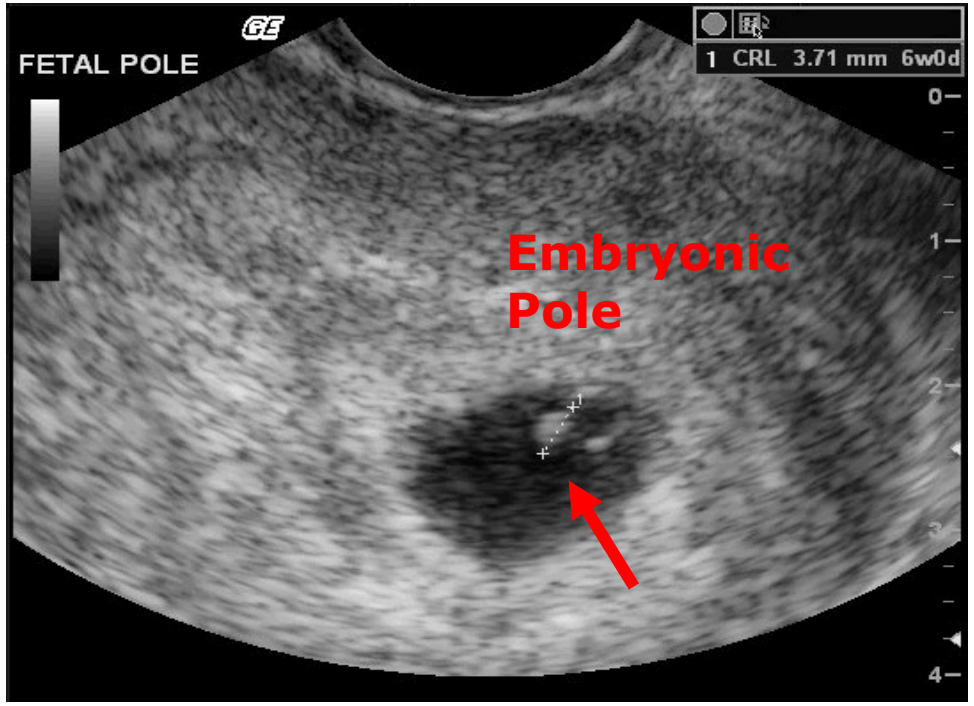
Nyberg D, Hill L, Böhm-Vélez M, Mendelson E. Transvaginal Ultrasound. 1992.




**Enlarged Yolk Sac Compared to Embryonic Pole**

# EMBRYO-CROWN RUMP LENGTH (CRL)

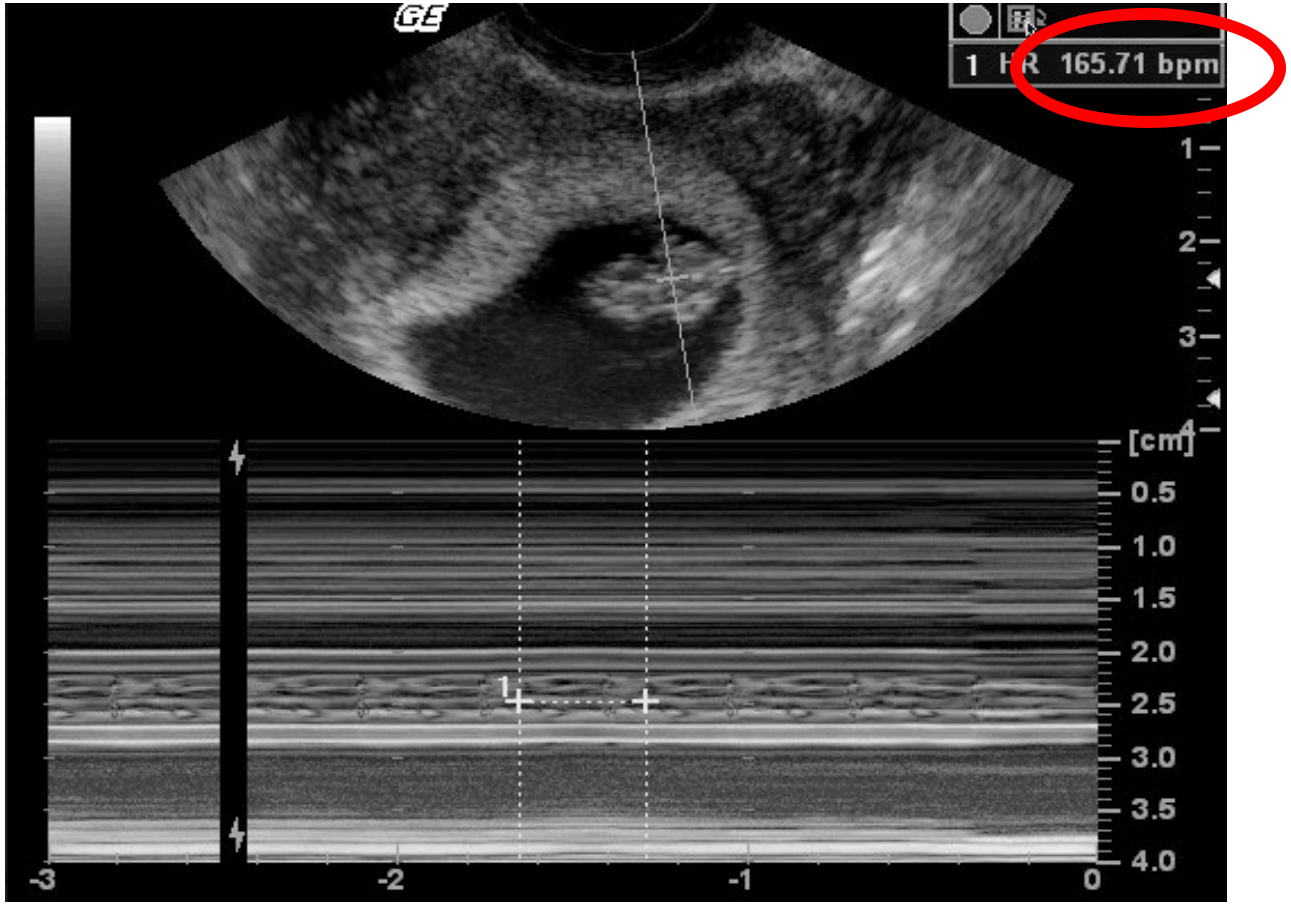
- CRL is the long axis of the embryo
- Should see embryo when gestational sac 16-20 mm
- Most accurate for dating between 6.5 – 12 weeks
- After 12 weeks, CRL less accurate because extension/flexion of fetus
- When less than 9 weeks, CRL should be measuring within +/- 5 days of EGA




ACOG, 2017

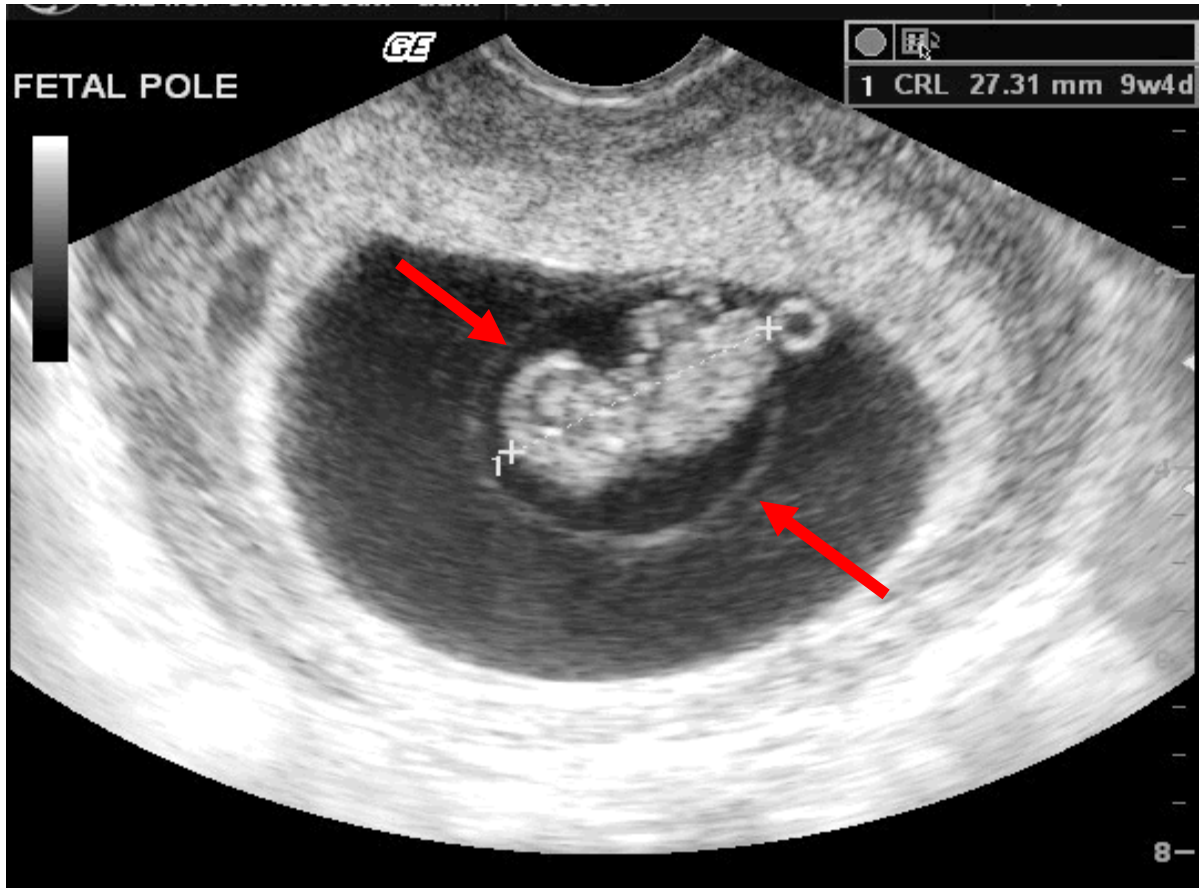
# CARDIAC ACTIVITY

- Usually, evident as soon as embryo can be seen, but may not see if CRL ≤4 mm
- Should always see by 6.5 weeks
- Slowest 80-90 bpm prior to 6 weeks = normal
- If slow < 80 bpm at 6-9 weeks = poor prognosis
- Recommend repeat ultrasound 3-5 days



# AMNION FEATURES & ULTRASOUND

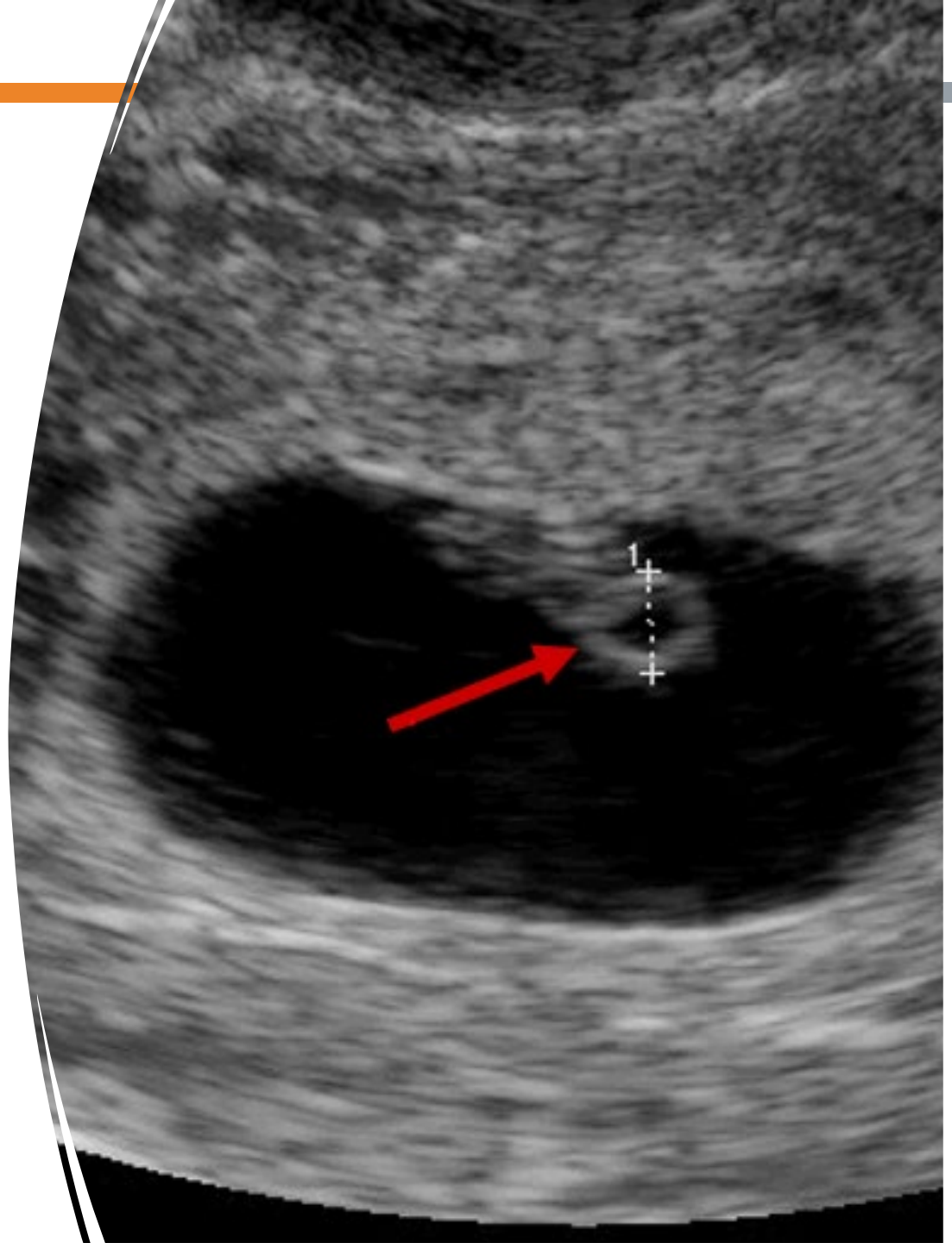
- Develops same time as yolk sac
- Grows rapidly during early pregnancy
- Very thin, may be hard to see
- Chorion-amnion fuses between 16-20 weeks
- Important for characterization of twin pregnancies



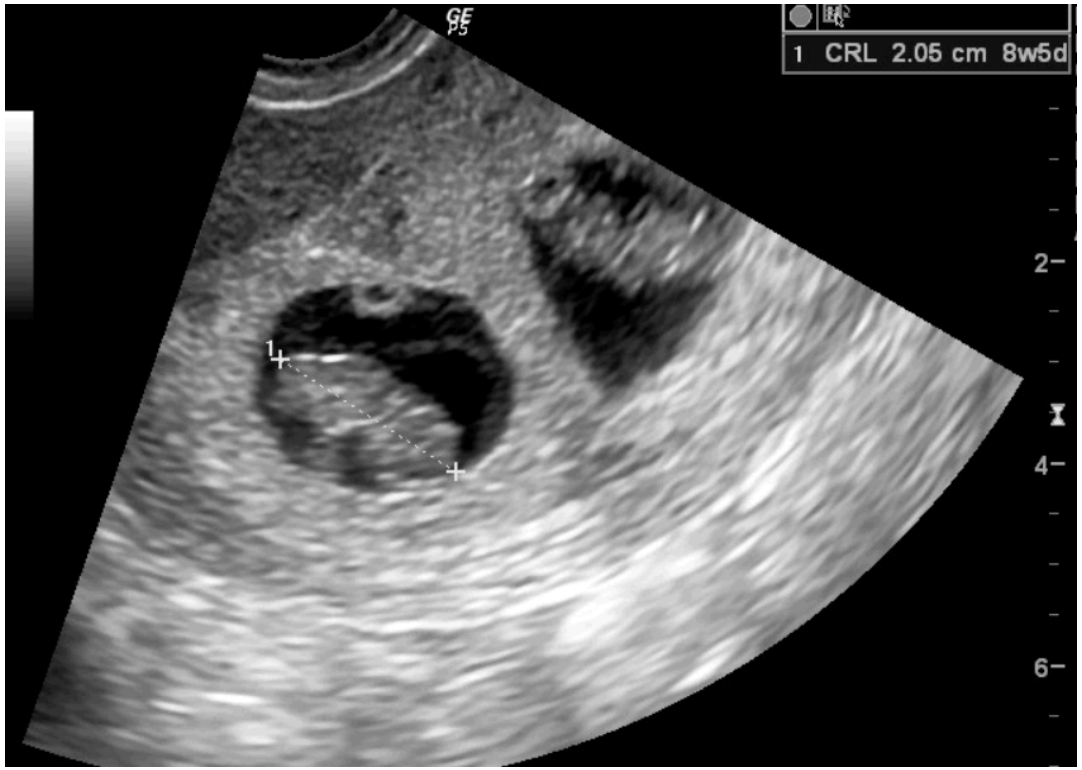

Nyberg D, Hill L, Böhm-Vélez M, Mendelson E. Transvaginal Ultrasound. 1992.

# CASE STUDY - KATE

**Normal IUP at 7 weeks**



- Molly, 36 yr old G0
- IVF for male factor infertility
  - Freeze all cycle
  - 4 embryos cryo'd
- Natural cycle FET
- 2 embryos transferred
- Initial 290 rose to 899 over 2 days



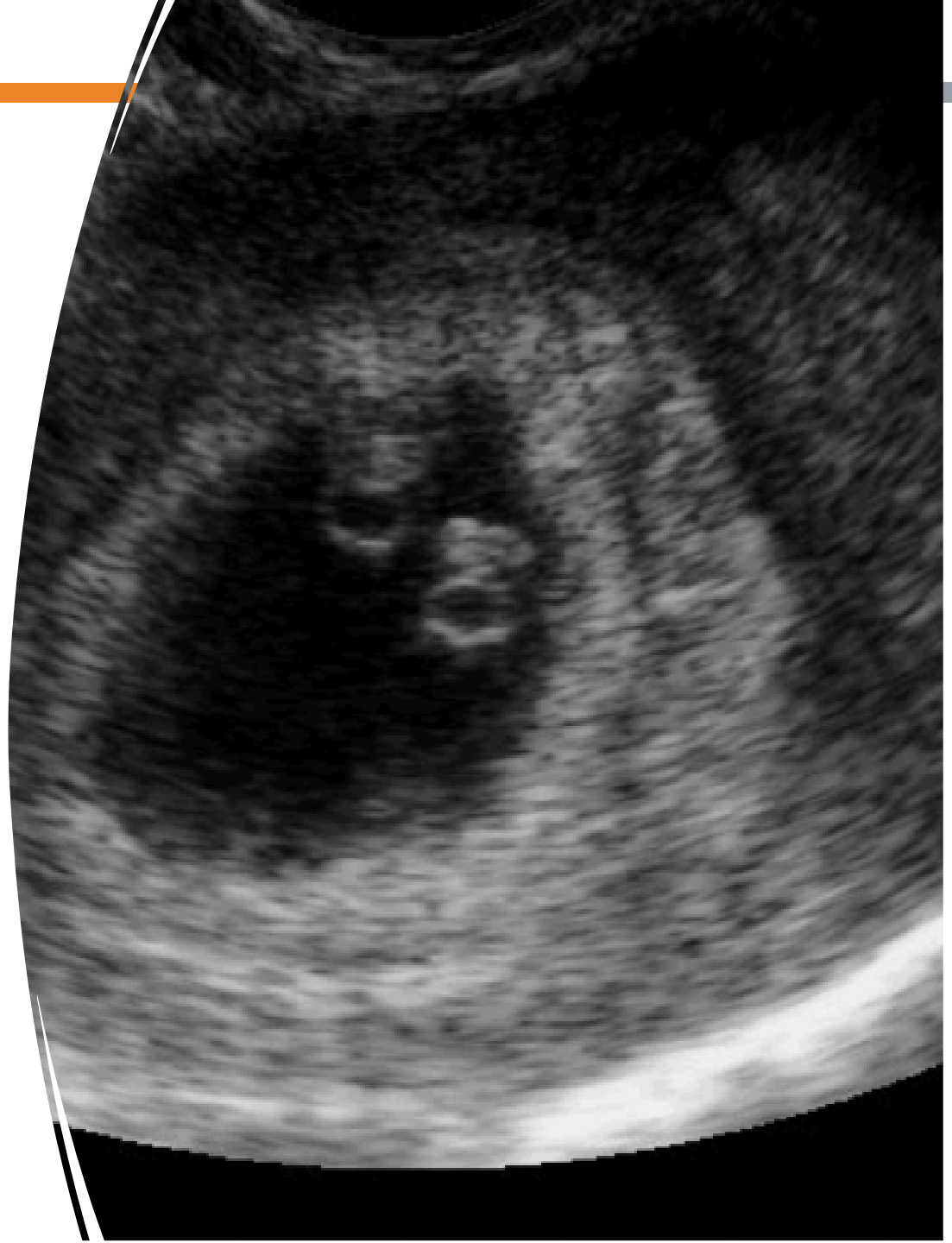

**DICHORIONIC-DIAMNIOTIC TWINS**

(Takehara et al., 2014)

- 44 yr old G0
- Donor Egg FET
- 1 embryo transferred

**Monochorionic – Diamniotic**

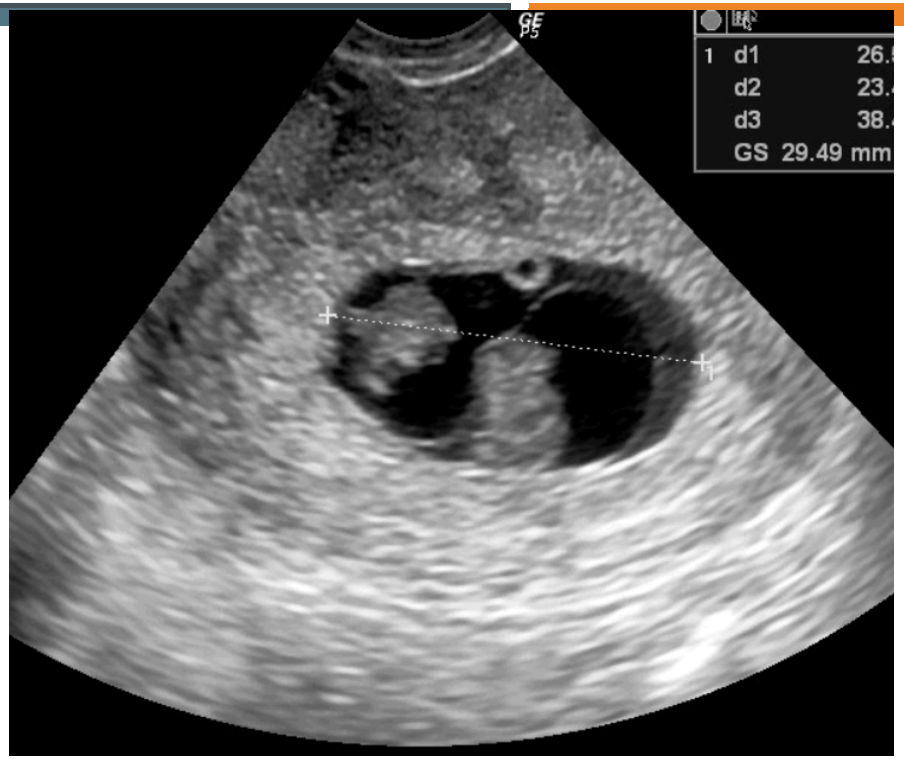
**Twins**

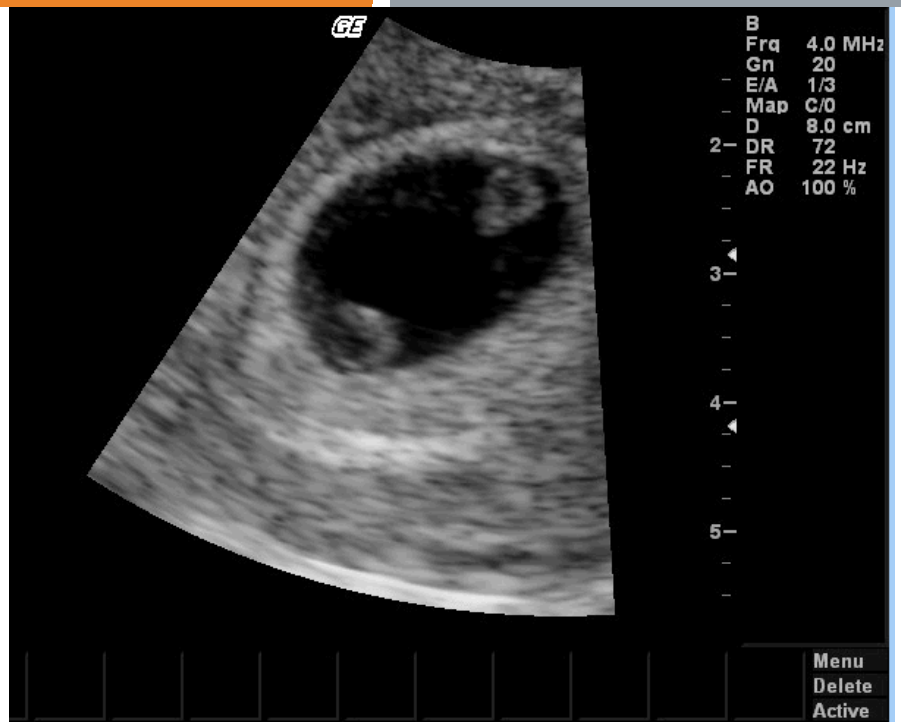


# MULTIPLE GESTATION DIFFERENTIATION ON ULTRASOUND

| Dichorionic – Diamniotic | Monochorionic - Diamniotic | Monochorionic –Monoamniotic |
|---|---|---|
| • 2 separate GS sacs with membrane between | • 1 placenta<br>• 1 GS with 2 embryos, 2 yolks sacs and 2 amnions<br>• Identical twins | • 1 chorion, 1 amnion, 1 yolk sac<br>• Very high risk and high mortality, may develop twin-to-twin transfusion syndrome |

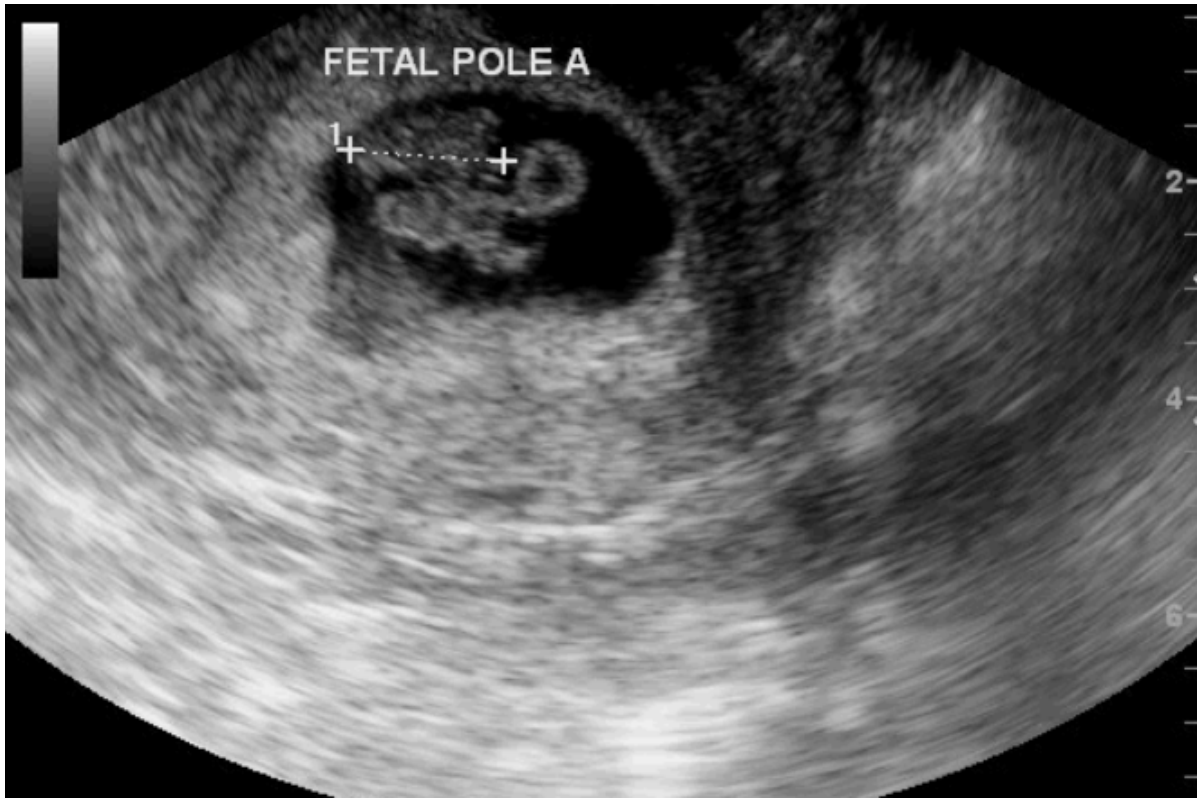
Fox, Traci B. Multiple Pregnancies: Determining Chorionicity and Amnionicity. Journal of Diagnostic Medical Sonography 2006; Vol. 22, No. 1 22:59-65.

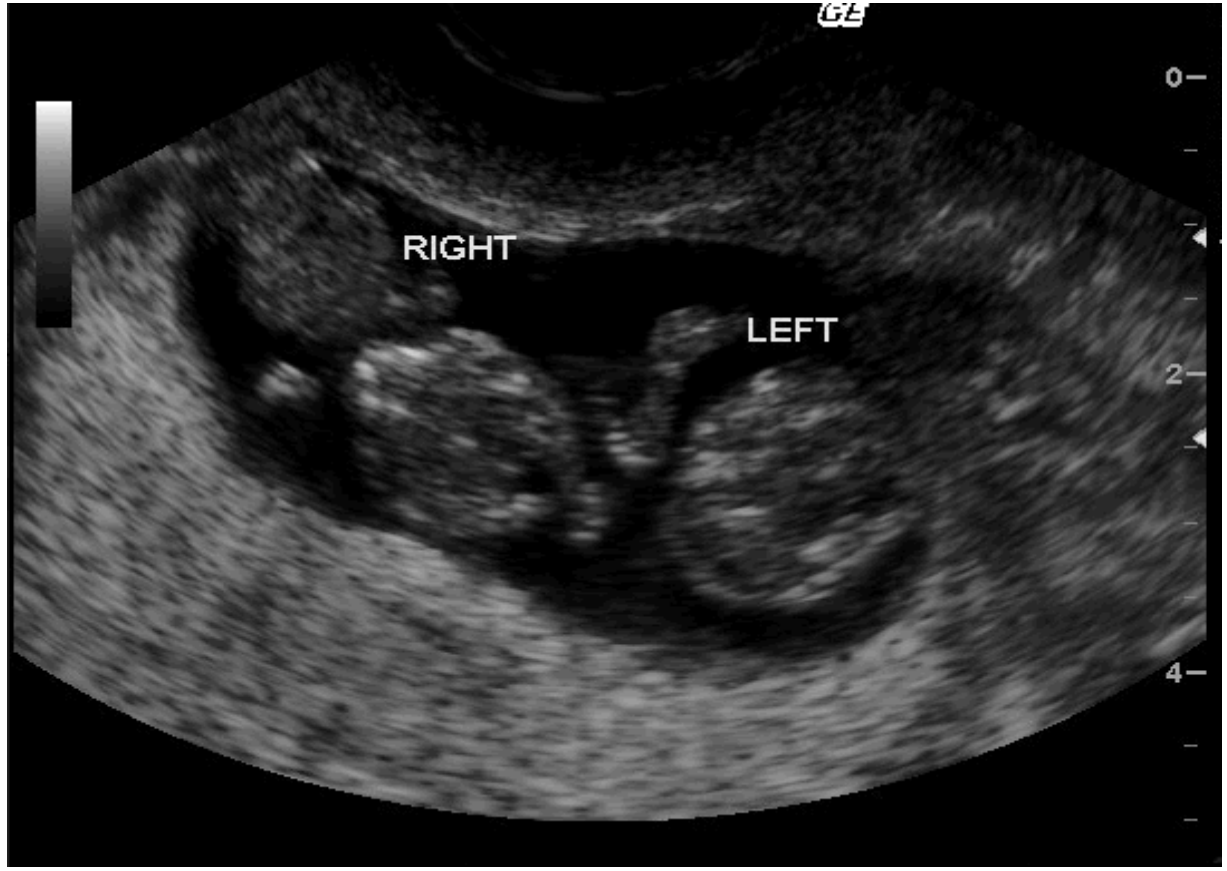



**2 Yolk Sacs; 1 GS**

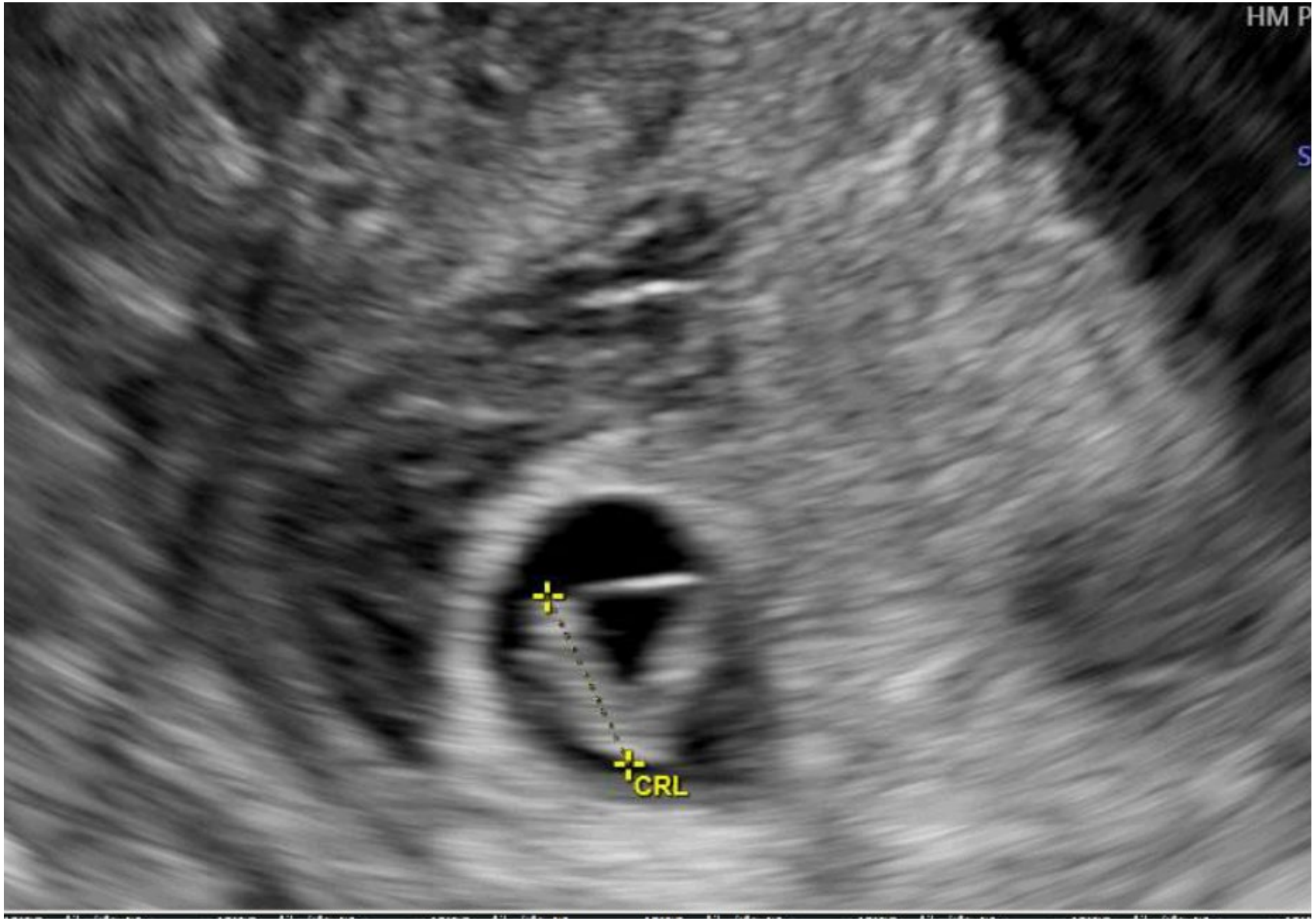
# MONOCHORIONIC – DIAMNIOTIC TWINS




**1 GS; 1 Yolk; 1 Amnion**

# Monochorionic – Monoamniotic Twins




# Conjoined Twins

# CASE STUDY: KEY POINTS

- Normal early pregnancies have distinct ultrasound landmarks.
- Understanding normal embryonic development helps to recognize abnormal findings
- Dating
  - Even when LMP is known, variation in time of ovulation and fertilization may alter visible embryonic age
- It is imperative to find the amnion for management of multiple gestations

# CASE STUDY #6

Heidi presents to your office as a 33-year-old G1 TAB 1 for her 1st OB US.

- Hx fibroids, menorrhagia affecting lifestyle
- HSG possible occlusion of the right fallopian tube
- AMH of 0.84 and AFC of 4-5
- Myomectomy 5 CM IM fibroid 5 cm and chromotubation with bilateral patent tubes
- Ovulation induction and IUI x3
- 4th IUI – pregnant, hCG rising, although not doubling

# ECTOPIC – ULTRASOUND CUL-DE-SAC

Free Fluid - most common ultrasound finding; blood is echogenic or particulate fluid

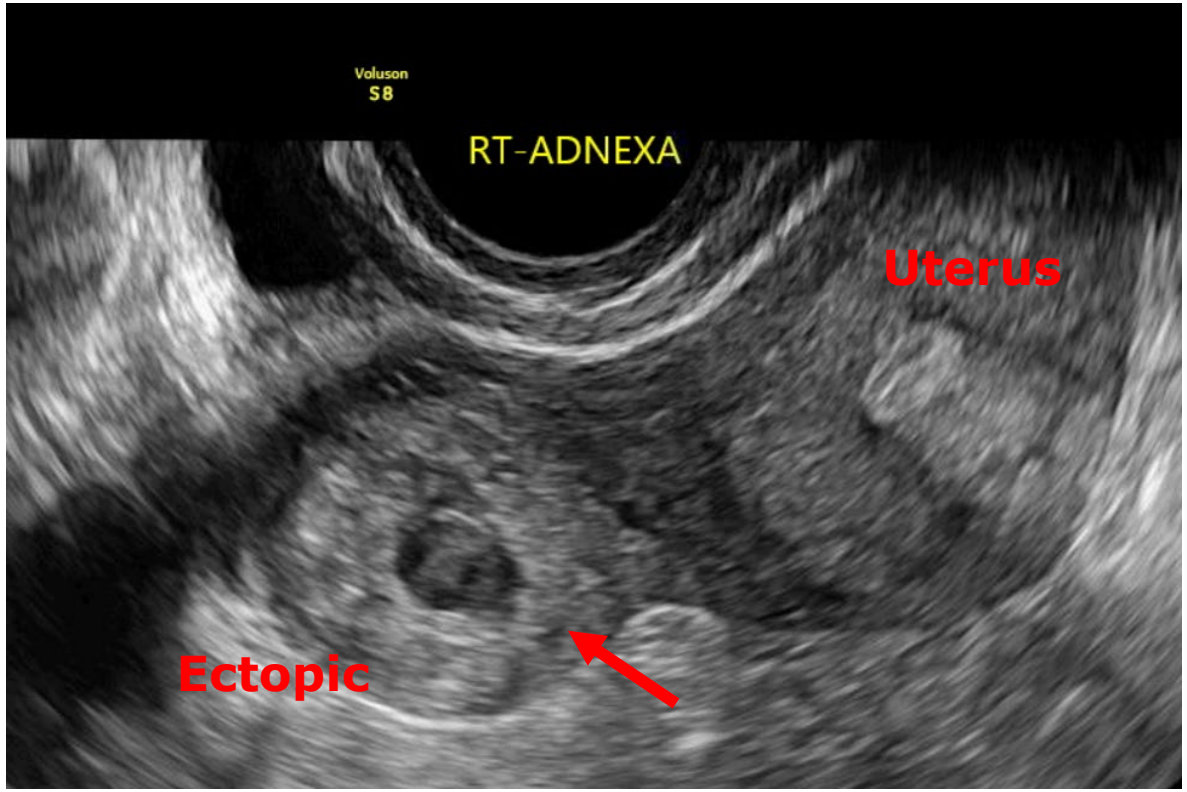
Leakage blood from end of tube

Risk of ectopic increased if moderate to large amount of free fluid associated with adnexal mass

Absence does not exclude ectopic

Braun, Daniel. Surgical Management of Ectopic Pregnancy.

- 90% tubal
- Thick, brightly echogenic, ring-like structure is located outside the uterus
- May be termed "tubal ring", "donut/bagel sign"
- Often lack yolk and embryo because suboptimal blood supply
- Complex mass represents blood clot in tube or within peritoneal cavity




(ACOG, 2018;
Nyberg D 1992)

# METHOTREXATE PATIENT EDUCATION

- ↑ hCG during initial therapy, but then drop by at least 15% days 4-7
- Vaginal bleeding or spotting
- Abdominal pain (between 3-7 days after tx begins). Resolves within 4-12 hours. If severe or persistent = evaluation

- Avoid IC until hCG undetectable
- Avoid sun (limit risk dermatitis)
- Avoid foods/supplements w/folic acid (stop PNV)
- Avoid gas-forming foods (produce pain)
- Avoid new conception until hCG undetectable (our practice uses 8 weeks at cut off)

# CASE STUDY #7

- Brian is a 42-year-old man presenting to the clinic with his female partner for fertility evaluation. He has no proven paternity and denies any issues with libido, erection, or ejaculation.
- His partner had a normal workup with her gyn. They were referred by gyn for an "abnormal SA".

# MALE FACTOR INFERTILITY CAUSES

**Endocrine & Systemic Disorders** (2-5%)

- Congenital disorders (ex. Kallman Syndrome)
- Acquired diseases (Hypothyroidism)
- Pituitary Disorders

**Defects in Spermatogenesis** (65-80%)

- Genetic (ex. YCMD)
- Congenital (ex: undescended testes)
- Acquired (ex: varicocele, torsion, radiation, infection, etc.)

**Sperm Transport Disorders** (5%)

- CBAVD, ED, retrograde ejaculation

**Idiopathic** (10-20%)

# MODIFIABLE RISK FACTORS

**Lifestyle**

- Alcohol
- Tobacco
- Marijuana
- Excessive heat
- Obesity
- Diet
- Medications – testosterone, finasteride, opioids, etc.

# SEMEN ANALYSIS

- **400% variability between specimens!**
- 2-7d abstinence prior to collection
- Collection via masturbation

# SEMEN ANALYSIS

- **Oligozoospermia:** concentration <16million/mL
  - <10million/mL – **orange flag**
  - <5million/mL – **red flag**
    - Karyotype, Y-microdel, genetic counseling
- **Asthenozoospermia:** <42% motility
- **Teratozoospermia:** <4% normal morphology
- **OAT** = Oligoasthenoteratozoospermia

# SEMEN ANALYSIS

- **Repeat if abnormal**
- TMSC is single most helpful parameter
  - Consider SA with diagnostic wash

**TABLE 1**

**Clinical pregnancy rates per intrauterine insemination cycle according to postwash total mobile sperm count.**

| Total motile sperm count (× $10^6$) | No. of insemination cycles | No. of clinical pregnancies | Clinical pregnancy per cycle |
|---|---|---|---|
| <0.25 | 263 | 11 | 4.18% |
| 0.25–0.49 | 341 | 14 | 4.11% |
| 0.50–0.99 | 627 | 23 | 3.67% |
| 1.00–1.99 | 1,611 | 120 | 7.45% |
| 2.00–3.99 | 4,561 | 462 | 10.13% |
| 4.00–4.99 | 2,845 | 331 | 11.63% |
| 5.00–5.99 | 3,109 | 400 | 12.87% |
| 6.00–6.99 | 3,474 | 484 | 13.93% |
| 7.00–8.99 | 6,810 | 976 | 14.33% |
| ≥9 | 68,830 | 11,496 | 16.70% |

*Muthigi. Postwash TMSC and IUI success. Fertil Steril 2021.*

# CASE STUDY #7

- Initial and follow-up SA demonstrate azoospermia
  - Volume: 0.4 (>/= 1.4mL)
  - Viscosity: moderate
  - PH 6.0 (>/= 7.2)
  - Concentration: 0 (>/= 16x10^6/mL) *specimen concentrated and read on low power fields. No sperm found.
  - Motility: N/A (>/= 42%)
  - Total sperm count: 0 (>/= 39x10^6)
  - Round Cells: 0.1 (<4.0x10^6/mL)
  - Morphology: N/A (>/= 4%)

# SEMEN ANALYSIS

- Abnormal Volume:
  - **Artifact:** short abstinence period, incomplete collection, etc.
  - **Psychogenic:** Anorgasmia
  - **Pathologic:** Retrograde ejaculation, ejaculatory duct obstruction, hypogonadism, seminal vesicle disease (infection, cysts, etc.)

# AZOOSPERMIA

- Absence of sperm on **2** separate specimens
- **Obstructive**
  - CBAVD
  - Vasectomy
- **Nonobstructive**
  - Impaired production
    - Hormonal
    - Genetic - chromosomal
    - Physical – varicocele, undescended testes

## TABLE 2

**Basal hormone levels in various clinical states.**

| Clinical condition | FSH | LH | T | PRL |
|---|---|---|---|---|
| Normal spermatogenesis | Normal | Normal | Normal | Normal |
| Hypogonadotropic hypogonadism | Low | Low | Low | Normal |
| Abnormal spermatogenesis[a] | High/normal | Normal | Normal | Normal |
| Complete testicular failure/hypergonadotropic hypogonadism | High | High | Normal/low | Normal |
| PRL-secreting pituitary tumor | Normal/low | Normal/low | Low | High |

[a] Many men with abnormal spermatogenesis have a normal serum FSH, but a marked elevation of serum FSH is clearly indicative of an abnormality in spermatogenesis.

*Practice Committee. Evaluation of the infertile male. Fertil Steril 2015.*

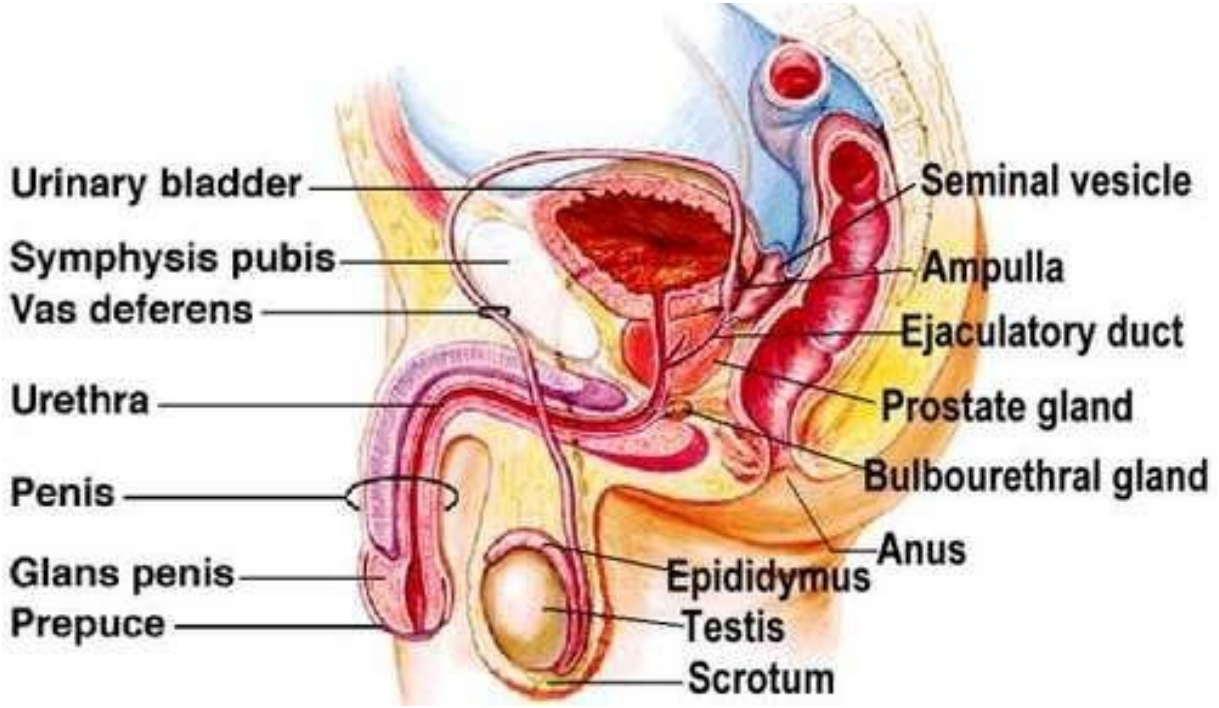
# MALE HORMONE ANALYSIS (ASRM 2015)

# CASE STUDY #7

- Bryan's Labs:
  - YCMD: No Deletion Detected
  - Chromosome Analysis: 46, XY
  - FSH 4.0 (1.4-12.0 mIU/mL)
  - LH 3.2 (1.5 - 9.3 mIU/mL)
  - Total T 374 (250-827 ng/dL)
  - Bioavailable T 119.3 (110-575 ng/dL)
  - E2 22 (</= 39 pg/mL)
  - PRL 5.7 (2-18 ng/mL)
  - TSH 2.4
  - A1C 5.2

# CASE STUDY #7

- Physical Exam:
  - Abd soft, benign, nontender, no scars
  - Testes descended bilaterally, nontender, normal size and contour, symmetric
  - *No palpable vas deferens on either side, small epididymal head remnant on each testis*
  - No Varicocele or hernia
  - Penile exam normal

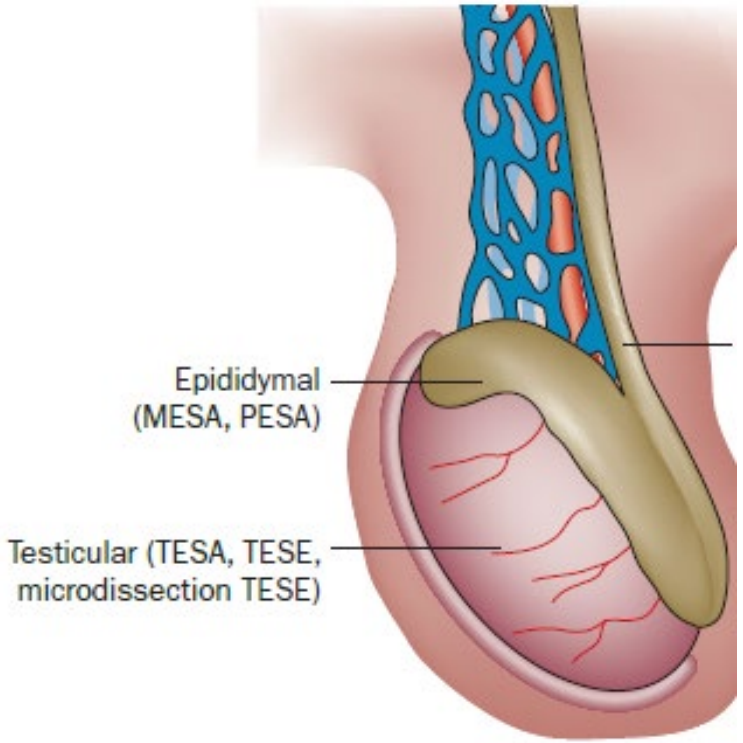


# CASE STUDY #7

- Bryan completes genetic carrier screening for CF (the most common cause of CBAVD), but his results are normal.
- Renal ultrasound reveals unilateral renal agenesis which confirms mesonephric duct anomaly (2nd most common cause of CBAVD). He is scheduled for **PESA/TESE** in order to proceed with IVF/ICSI.

# SURGICAL INTERVENTION

- PESA – percutaneous epidydimal sperm aspiration
- PESE – percutaneous epidydimal sperm extraction
- MESA – microsurgical epididymal sperm aspiration
- TESA – testicular sperm aspiration
- TESE – testicular sperm extraction
- micro-TESE – microsurgical testicular extraction of sperm



# OTHER CONSIDERATIONS

- The aging male:
  - Slow decline in male fertility after age 40
  - No cessation of sperm production
  - Advanced paternal age with increased risks
    - Autosomal dominant conditions
    - Autism spectrum disorder
    - Schizophrenia
    - Down Syndrome

# CASE STUDY #7: KEY POINTS

- Simultaneous workup of the couple is recommended
- History and physical exam provide context
- Confirm abnormal results
- Male hormone panel can provide many clues

# CASE STUDY #8

# Case Study #8

Sierra is a 38-year-old woman who presents to clinic with a BMI of 45, regular cycles, seeking IVF d/t partners previous vasectomy. AMH .8, AFC 8, A1C 5.8, TSH 2.5

# Obesity Impact:

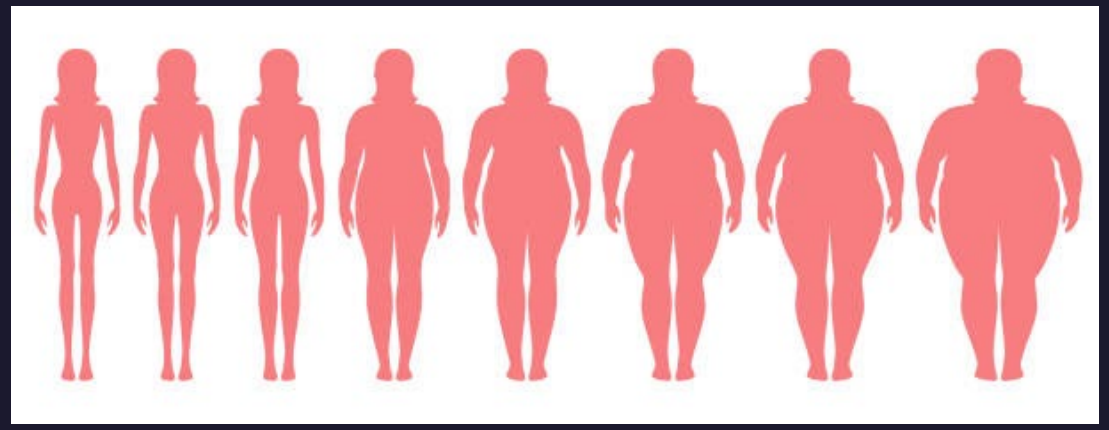
## Potential Impact on Fertility

- Poor ovarian response –higher doses of gonadotropins longer stimulation, cycle cancelation, fewer eggs retrieved
- Risk during anesthesia and greater technical difficulty retrieving eggs.
- Decreased Egg quality
- Decreased Embryo quality
- Endometrial receptivity and implantation rates
- Lower pregnancy and live birth rates

## Potential Risks during Pregnancy

- Increased miscarriage rates
- Greater anesthesia and surgical complications
- Increased risk of congenital anomalies, gestational hypertension, gestational diabetes, pre-eclampsia and stillbirth
- Increased risks of requiring caesarean section delivery
- Increased risk for large for gestational age babies, potentially leading to delivery complications

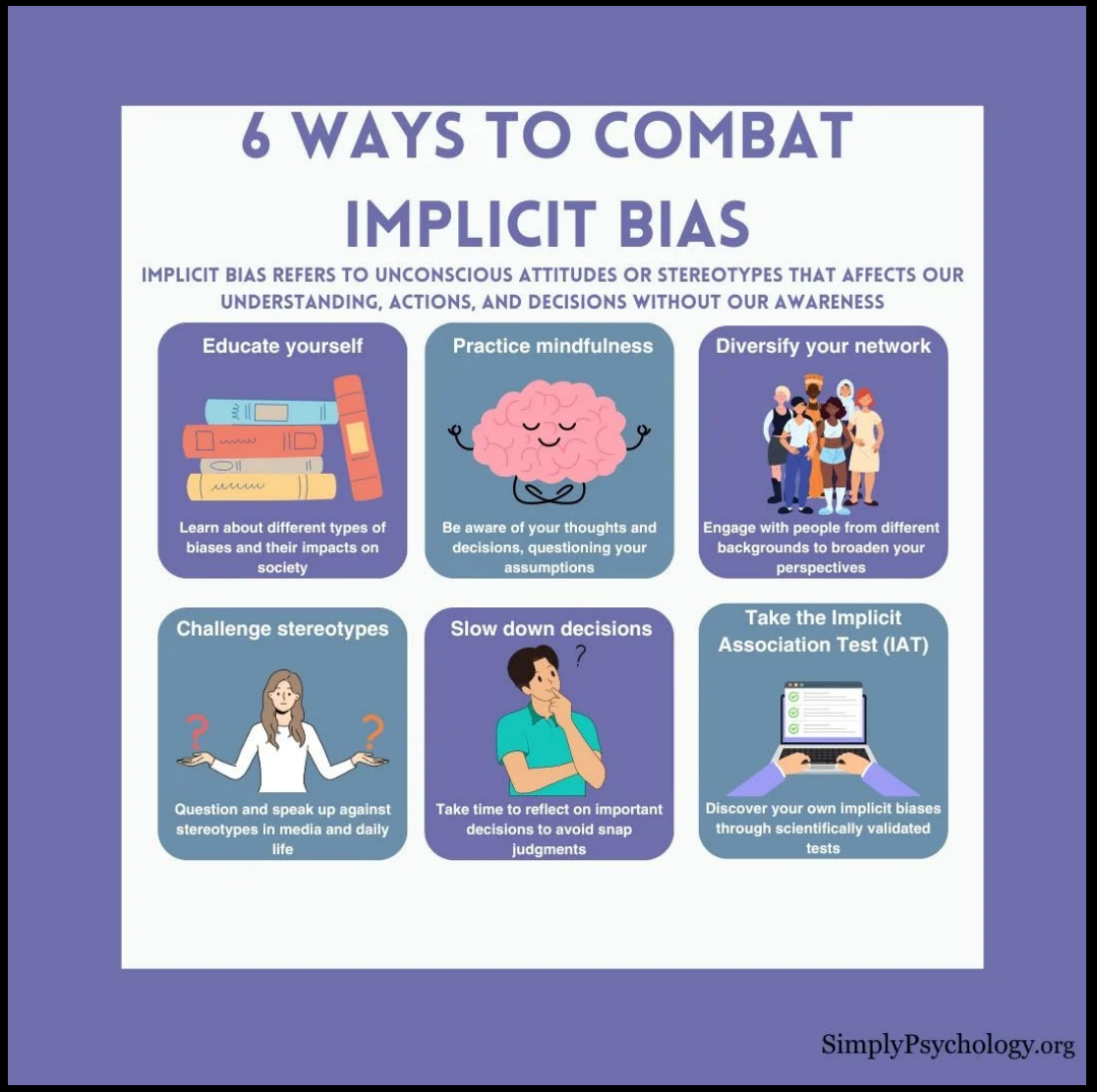
# Weight Bias:



Tendency to negatively judge an overweight or obese individual based on assumed, false character traits, or personality flaws.

- Lazy
- Unmotivated
- Not compliant
- Not doing enough
- Doesn’t care
- Doesn’t try hard enough
- No will power
- Poor diet

# Implicit Weight Bias:  What can you do?



# 5 A's Framework/Motivational Interviewing

1

**Ask:** Permission to discuss weight/non-judgmental

2

**Assess:** Pt hx, co-morbidities, barriers, pt goals, behavioral/lifestyle, nutrition, and mental health impacts

3

**Advise:** Educate on behavioral/lifestyle, nutrition, and impact on health and reproduction, treatment options

4

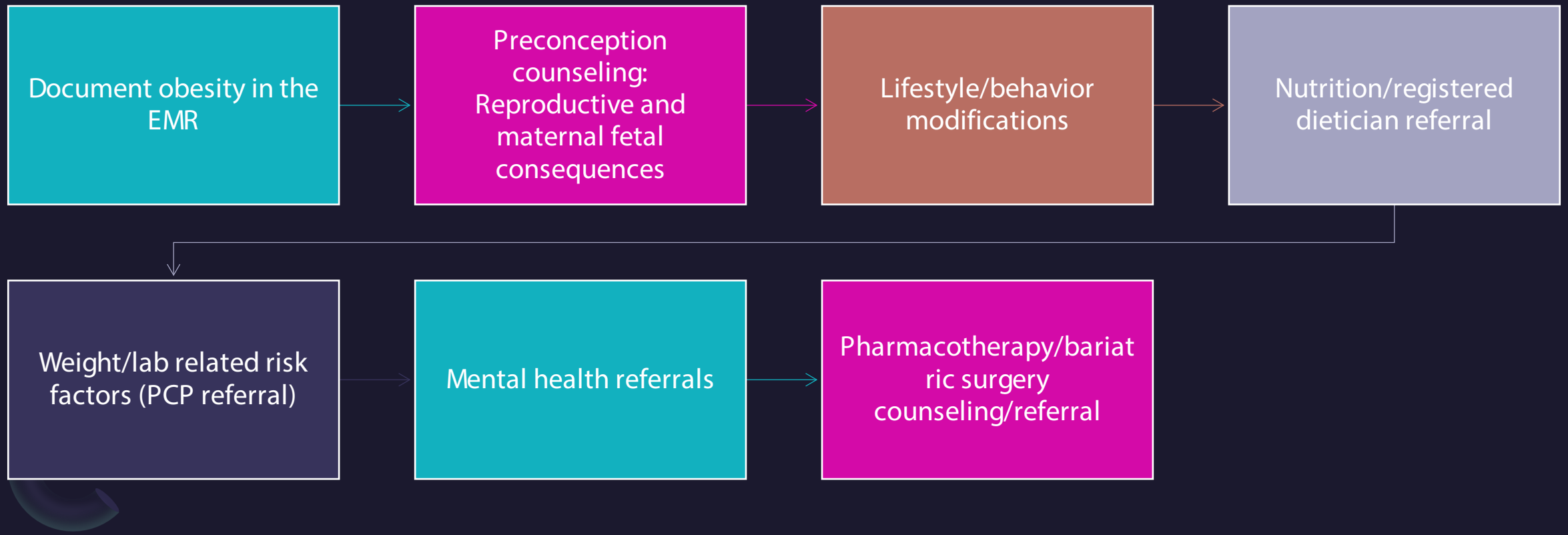
**Agree:** Collaborate with pt for a personalized plan

5

**Assist:** Verbalize your support, address barriers, make referrals

Obesity Canada. 5As of Obesity Management™. 2011.

# Personalized Treatment for Fertility Patients with Obesity



# Prescribing GLP-1

30/45 min initial appt & 15 min f/u appt

Contraindications: MTC, MEN, Pregnancy, Pancreatitis

Considerations: Surgery, Disordered Eating

Weekly SQ injection

Lowest dose for longest time producing results

Follow-up- 4weeks: Nutrition, weight loss, movement, side effects, mental health, refill

No lab monitoring needed

Side effects: GI symptoms-n/v/d/c, site reaction, fatigue, rare serious GI

## Semaglutide:

Is a selective glucagon-like peptide-1 (GLP-1) receptor agonist that increases glucose-dependent insulin secretion, decreases inappropriate glucagon secretion, slows gastric emptying; also works in areas of the brain to decrease food intake

- 5 tiered doses
- 4 weeks minimum at each dose
- Once weekly SQ injection
- Minimum dose for desired effects


*At month 5 and on, you may either stay at 1.7 mg or increase to 2.4 mg. Work with your health care provider to determine which dose is right for you.

## Tirzepatide:

Is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist that increases glucose-dependent insulin secretion, decreases inappropriate glucagon secretion, slows gastric emptying, and decreases food intake

- 6 tiered doses
- 4 weeks minimum at each dose
- Once weekly SQ injection
- Minimum dose for desired effects

| Phentermine | Semaglutide | Tirzepatide |
|---|---|---|
| 5% | 5%-15% | 15%-30% |

| Weight loss expectations | Success? | Key Components |
|---|---|---|
| 1-3lbs a week | 5% in 12 weeks | High Fiber<br>High Protein<br>Strength Training |

# WHO? HOW? WHY?

- Designed to treat medical obesity- BMI>30
- BMI<30 with at least one weight related comorbidity
- No personal or family hx of Medullary Thyroid Cancer (MTC) or Multiple Endocrine Neoplasia Syndrome Type 2 (MEN 2) (receptor tyrosine kinase (RET) mutations)
- Slows the GI system, feel full longer, less "food noise"
- Optimally a multidisciplinary approach- Nutritionist/Behavioral Therapy/PCP/Physical Activity
- Long term treatment of obesity as a medical disease- weight gain reoccurs when treatment is stopped

# PREGNANCY: CONTRAINDICATED

Semaglutide- 2 month wait prior to pregnancy

Tirzepatide- no advised wait period on US insert, Canadian insert is 4 week wait prior to pregnancy

# Case Study Results

Sierra in interested in weight loss support

**What would your recommendations/treatment plan include for her?**

**What time frame would you council her with in order to reach a BMI of 40 to start IVF treatment cycle?**

# Key Points

Obesity is a chronic health condition

Recognize weight bias

Multi-factorial

GLP-1 consideration