Fertility Evaluation for the Generalist

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Fertility Evaluation for the Generalist

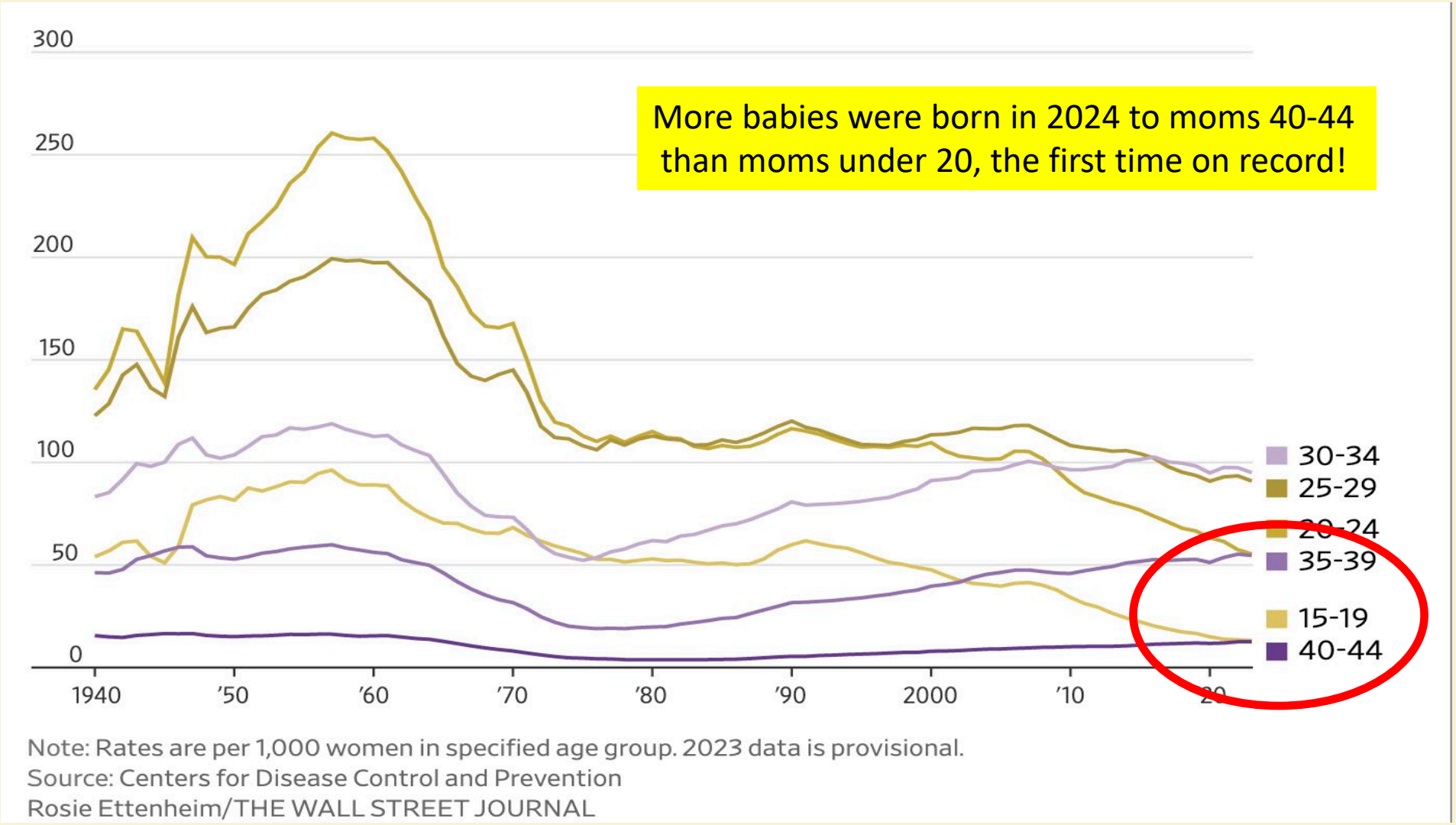
DISCLOSURES: None

LEARNING OBJECTIVES: At the conclusion of this presentation, participants should be able to:

1. Discuss the basic infertility evaluation
2. Initiate age-based testing and when to refer
3. Understand initial treatment plans
4. Counsel patients about assisted reproduction

Birthrates by Age Group in the US

(20- to 29-year-old women are postponing childbearing until age 30-39



Normal Pregnancy Rates in Newly Married Couples

(85% are pregnant after the first year, 90% are pregnant after two years)

http://www.uptodate.com/contents/overview-of-infertility

ASRM 2023 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 I 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.

Nothing in this definition shall be used to deny or delay treatment to any individual, regardless of relationship status or sexual orientation.

ASRM Practice Committee Definition of Infertility: A practice Committee Opinion. Oct . 2023.

When to Initiate the Evaluation of Infertility Patients

Unprotected intercourse, no contraception, and without conception

AGE OF FEMALE	WHEN TO START EVALUATION
< 35 years	After one year of trying
35 to < 40 years	After 6 months of trying
40 or more years	Immediately

Most people diagnosed with infertility are in reality “Subfertile”

Primary Management of Infertility

- Identify risk factors

  (Age, menstrual history, STD, prior surgery, Tobacco, alcohol, obesity, radiation, toxins, sexual function, prior pregnancies)

- Perform essential investigations

  (HSG, Semen analysis, documented ovulation)

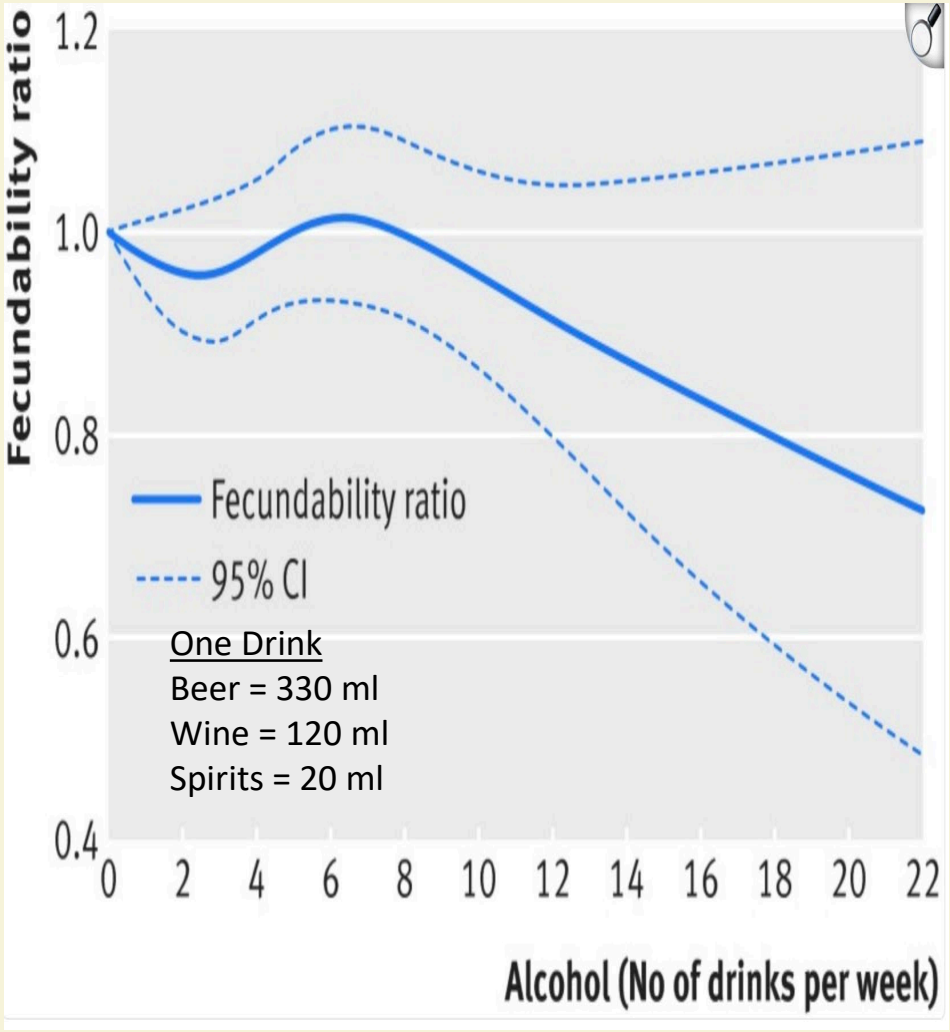
- Counsel couple

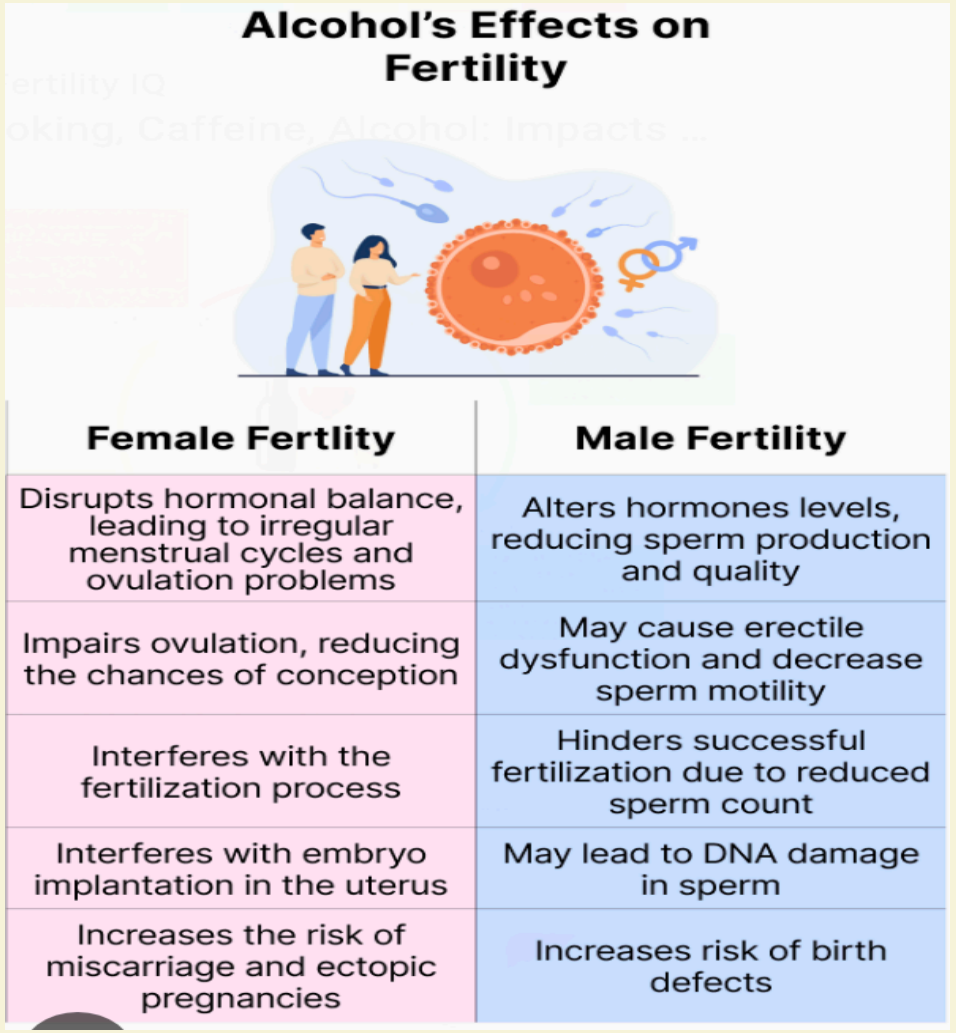
  (age, years of trying, prior treatments)

- Initiate treatment or refer

ASRM Practice Committee. Fertil Steril 116:1255-1265 , 2021.

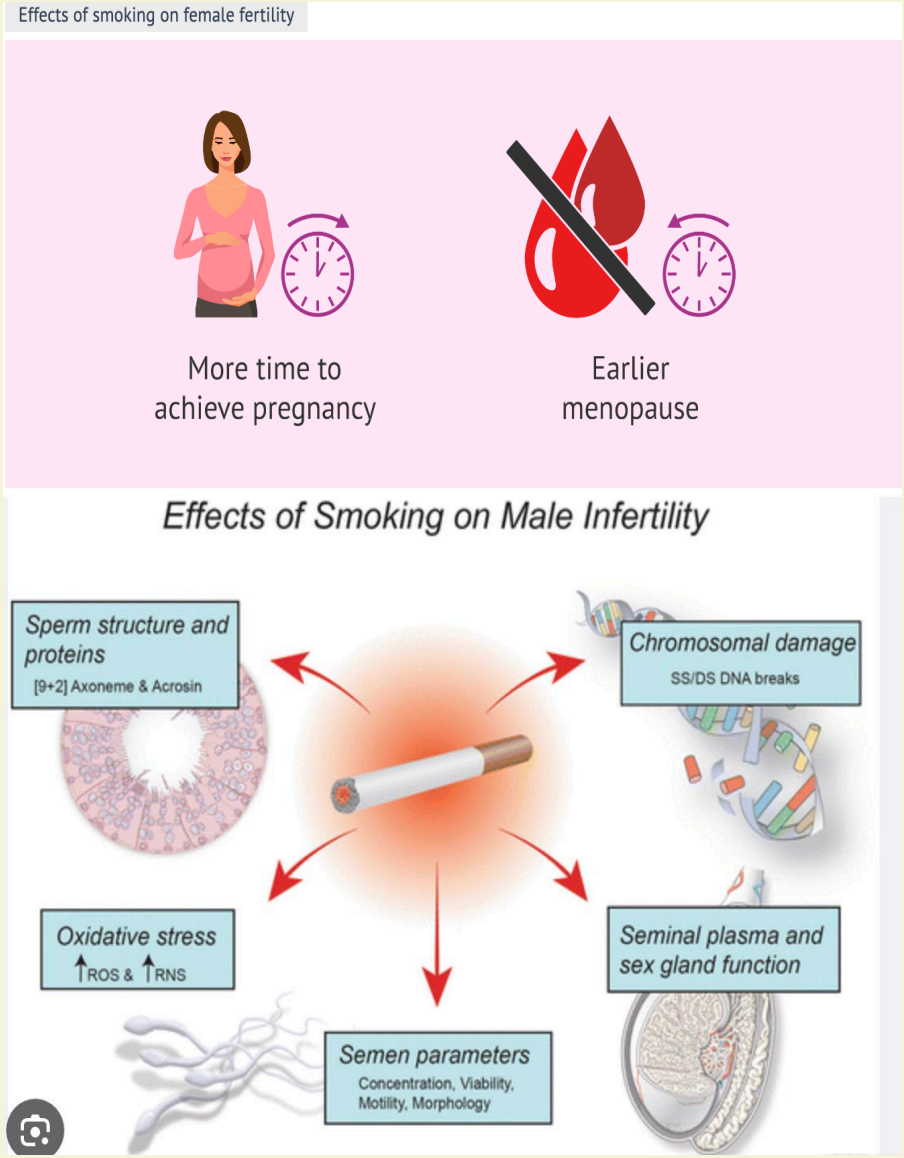
Relation between amounts of pre-pregnancy alcohol consumed per week and fecundability (n=6120)

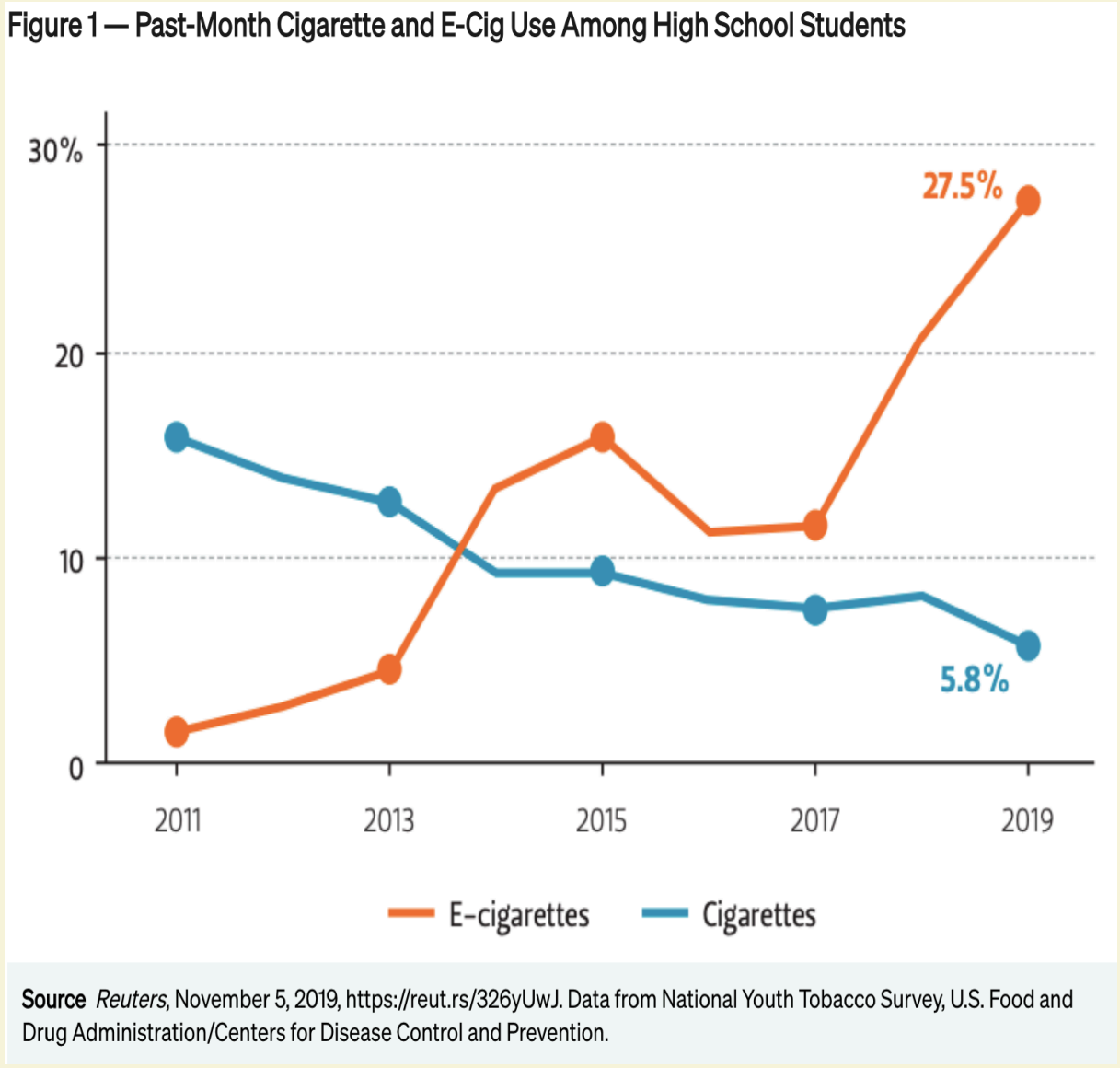




Mikkelslen EM et al. Brit Med J. 2016 Aug 31, 354::i4262. doi: 10.1136/bmj.i4262

Believe It or Not, 1 Vape has 20- 40 Cigarettes Worth of Nicotine



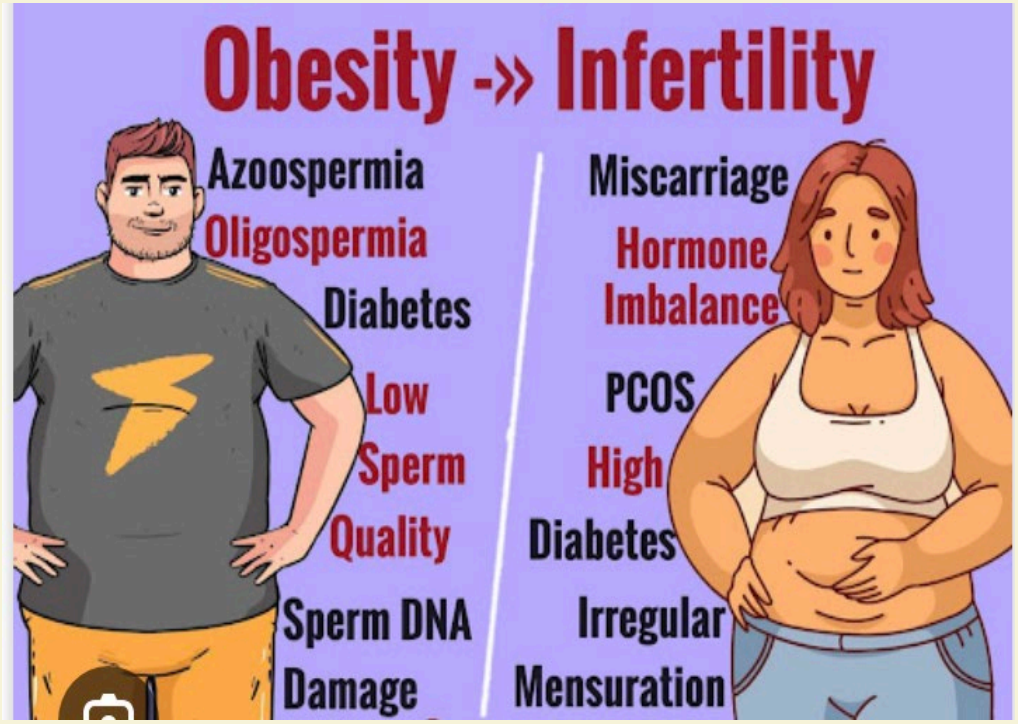


Source *Reuters*, November 5, 2019, https://reut.rs/326yUwJ. Data from National Youth Tobacco Survey, U.S. Food and Drug Administration/Centers for Disease Control and Prevention.

Obesity Negatively Impacts Fertility

MALE FACTOR

Decreased count
Decreased Motility
Altered hormones
Erective dysfunction
Sperm DNA Damage



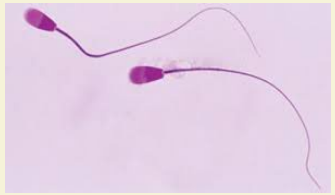
FEMALE FACTOR

Impaired ovulation
Altered hormones
Disrupted cycles
Reduced egg quality
Increased miscarriage
Lower IVF success
(Down 40% if BMI >40)

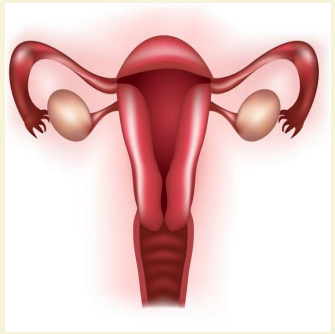
OVERALL: Increased time to conceive and Increased risk of miscarriage

ASRM Practice Committee. Fertil Steril 117: 53-63, 2022.

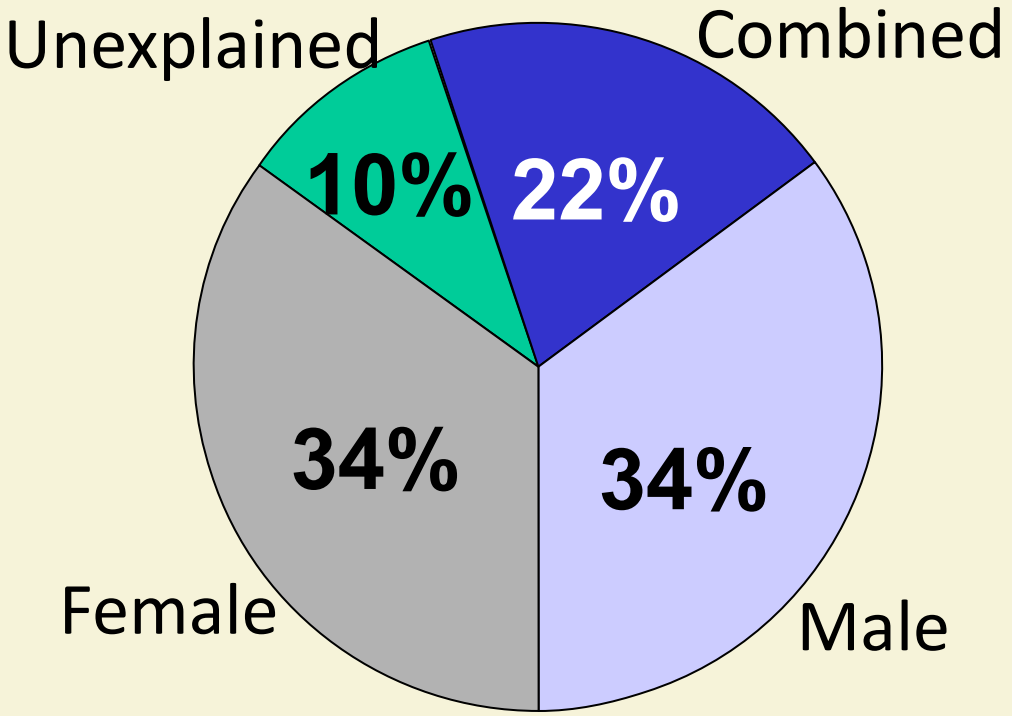
Etiologies of Infertility



- Male Factors (1/3)
  - Poorly functioning and/or few sperm



- Female Factors (1/3)
  - Ovulatory problems
  - Tubal Problems
  - Uterine Problems
  - “Hostile” Peritoneal Environment



- Combined or Unknown Factors (1/3)

ASRM. Fertility evaluation of infertile women. Fertil Steril 116: 1255-1265,2021

Causes of Female Infertility: Ovulation Disorders

Ovulatory Dysfunction

- Polycystic Ovaries (PCOS)
  "obese, amenorrhea, hirsute"
- Hyperprolactinemia
- Hypothyroidism
- Idiopathic Hypothalamic (IHH)
- Premature ovarian failure (POF)

Decreased Ovarian Reserve

-Advanced age of the female
- Prior chemo and/or radiation therapy
- Prior surgery on the ovary
- Turner mosaic, Fragile X premutation
- Smith-Lemli-Opitz syndrome
- FSH > 10 miu/ml, AMH < 1 ng/ml
-Antral (2-9 mm)follicles < 8

ACOG. Infertility work up for the women's health specialist. 2019
ASRM. Fertility evaluation of infertile women. Fertil Steril 116: 1255-1265,2021

Tests to aid in the Evaluation of Ovulatory Disorders

- Normal Ovulatory Function

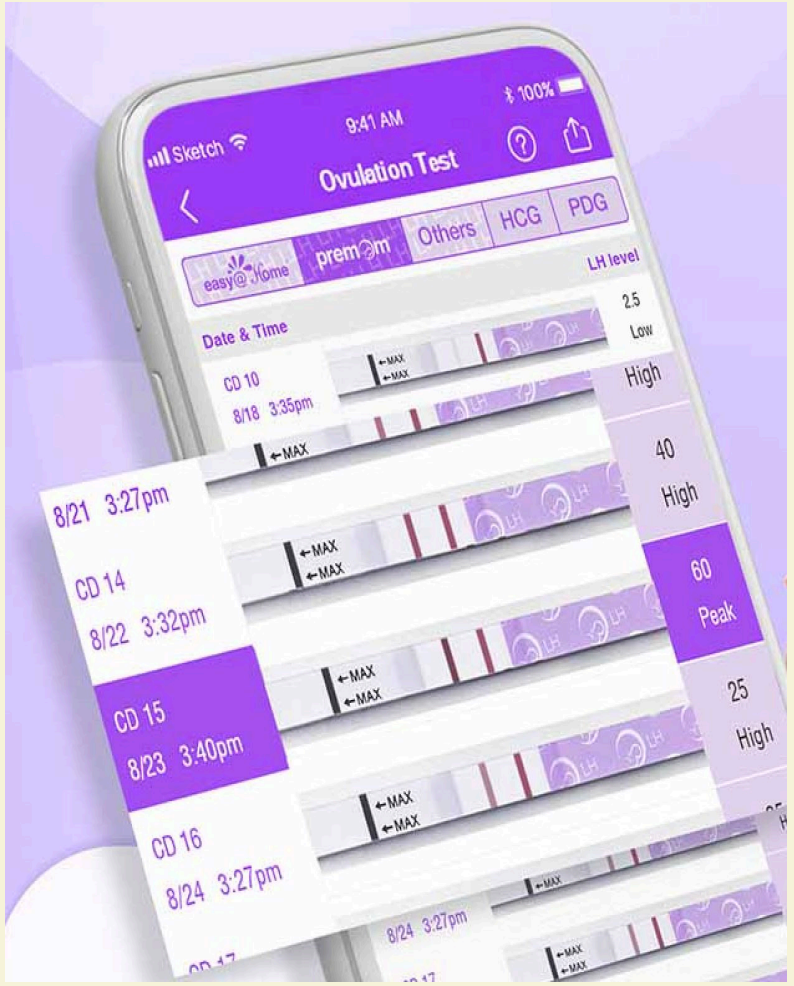
  --Normal menstrual cycle (26-34 days)

  --Positive urinary LH surge at midcycle

  (Premom LH kits-25 strips for $10)

  – Cycle day 21 Progesterone: > 10 ng/ml

  – Midcycle ultrasound of follicles



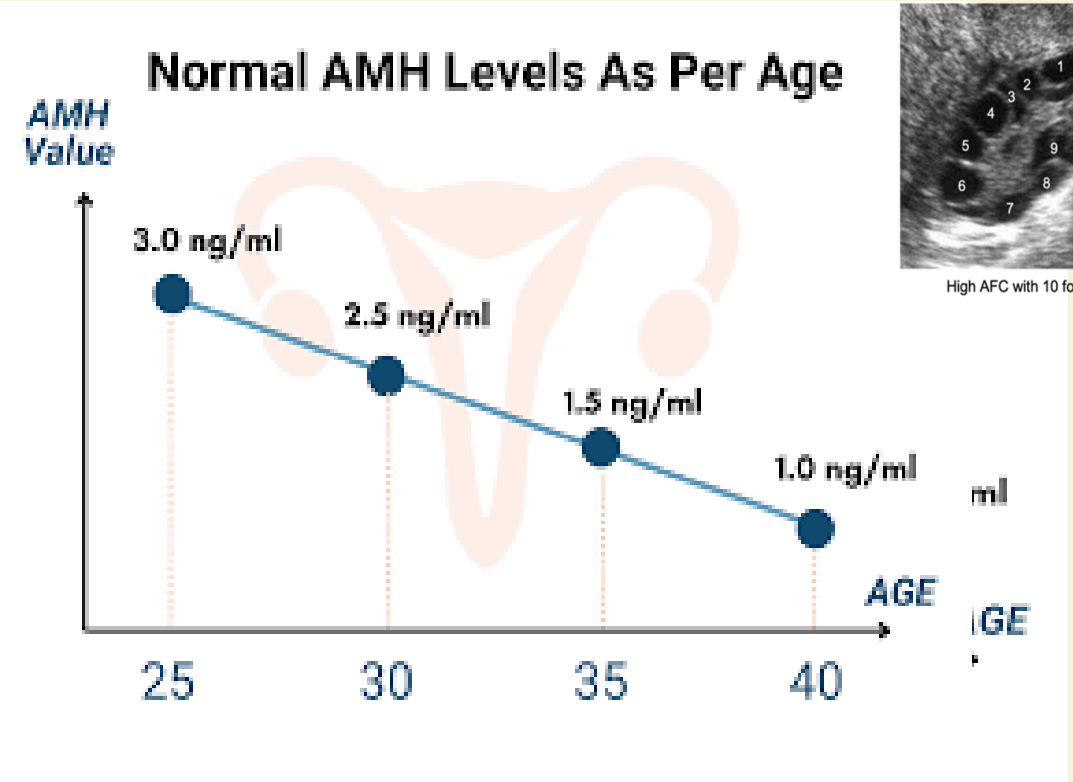
ASRM. Fertility evaluation of infertile women. Fertil Steril 116: 1255-1265,2021

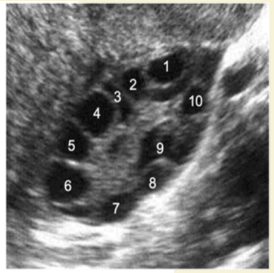
Secondary Tests to Evaluate Ovulatory Disorders

- May disrupt Normal Ovulatory Function
  (if levels are outside the normal range)
  - Cycle Day 3 FSH: <10 mIU/L
  - Cycle Day 3 Estradiol: < 60 pg/ml
  - Any cycle day AMH: 1.5 to 4.0 ng/ml
  - TSH: 1.0 to 4.0 mIU/ml
  - Prolactin: < 25 ng/ml
  - HgbA1c: < 5.7%
  - BMI < 30

ASRM. Fertility evaluation of infertile women. Fertil Steril 116: 1255-1265,2021

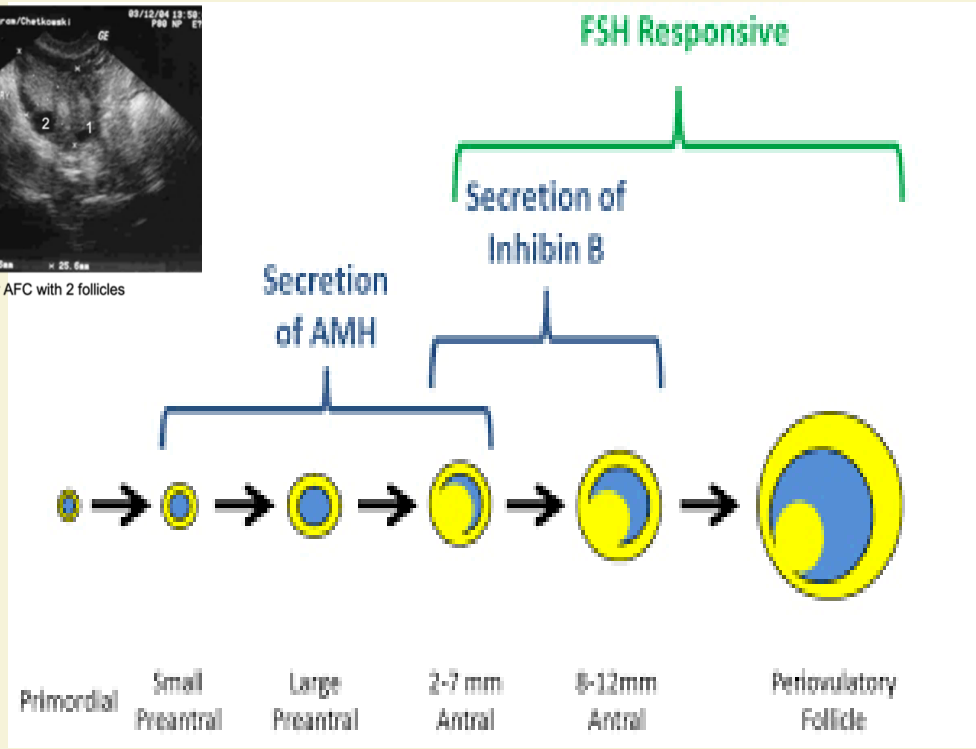
Anti Mullein Hormone (AMH) Correlates with Ovarian Reserve





High AFC with 10 follicles

Low AFC with 2 follicles



Decreased AMH associated with increased age, obesity, tobacco use, endometriosis, ovarian surgery,genetic factors, chemotherapy, radiation therapy

AMH is produced by the small preantral and antral Follicles (2-9mm) and correlates to the ovarian reserve

ASRM Committee Opinion: Measures of Ovarian Reserve. Fertil Steril 114:1151-1157, 2020.

Interpretation of Female Day 3 Hormonal Profile

Lab tests should be used to support your clinical diagnosis

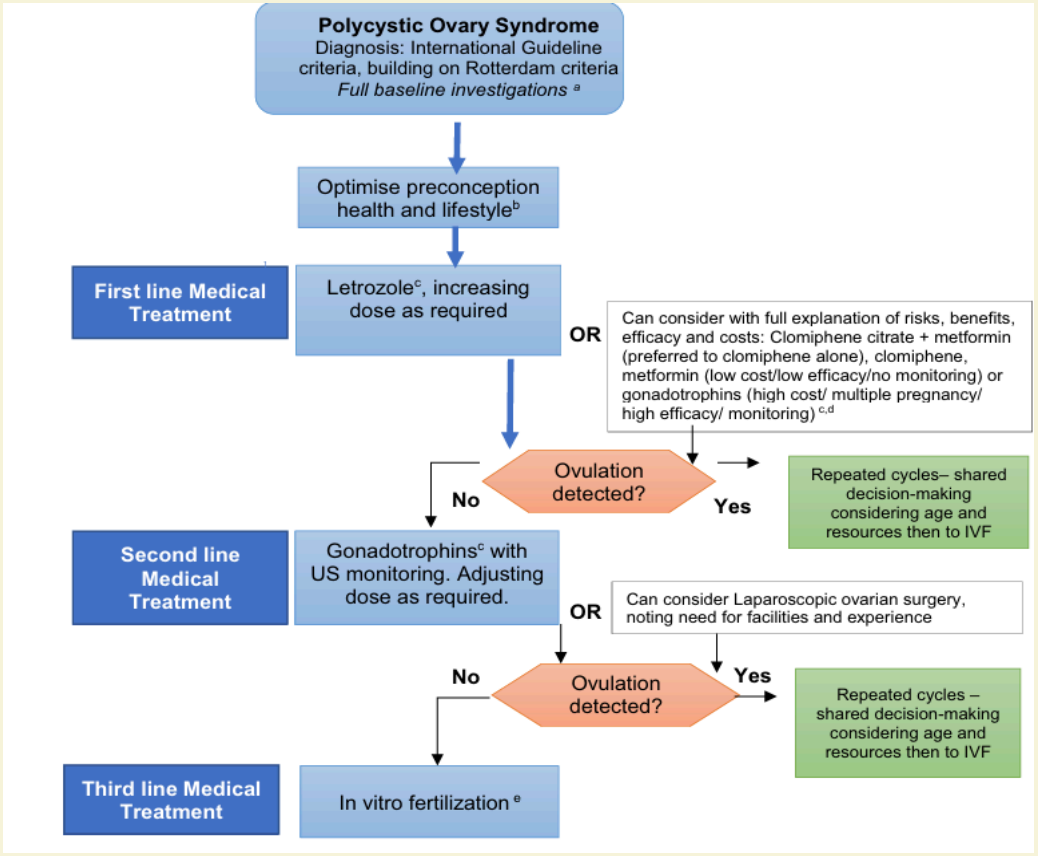
FSH	LH	Estradiol	AMH	Testosterone	Diagnosis
3-10 miu/ml	2-10 miu/ml	<60 pg/ml	1-4 ng/ml	10-70 ng/dl	**Normal range**
3	6	45	3.0	30	**normal**
18	6	Normal or high	>5.0	Normal or elevated	**PCOS**
Often >10, Low if E2 Hi	>10	Normal or high	<1.0	normal or low	**Ovarian hypofunction**
>40	elevated	Often <50	Very low	low	**Ovarian failure**

Premature Ovarian Insufficiency: Evidence-based guideline. Fertil Steril. 123: 221-236, 2025.

DX and TX of Polycystic Ovarian syndrome

Step 1: Irregular cycles + clinical hyperandrogenism
(exclude other causes)* = diagnosis
Step 2: If no clinical hyperandrogenism
Test for biochemical hyperandrogenism (exclude other causes)* = diagnosis
Step 3: If ONLY irregular cycles OR hyperandrogenism
Adolescents ultrasound is not indicated = consider at risk of PCOS and reassess later
Adults - **request ultrasound for PCOM***, if positive (exclude other causes)* = diagnosis

* Exclusion of other causes = TSH, prolactin, 17-OH progesterone, FSH or if clinically indicated exclude other causes (e.g. Cushing's Syndrome, adrenal tumours). For hypogonadotrophic hypogonadism, usually due to low body fat or intensive exercise, exclude clinically and with LH/ FSH.
PCOM = polycystic ovarian morphology on ultrasound



International Guideline for Management of PCOS. Fertil Steril 120:767-793, 2023.
ACOG Practice Bulletin No. 194 PCOS. Obstet Gynecol 131:e157-e171, 2018.

Fertility Treatments to Induce Ovulation

- Use Clomiphene 50 mg cycle days 3 to 7 ($30.00/5)
- Use Letrazole of 2.5 mg cycle days 3 to 7 ($2.00/5)
- For PCOS patients (with elevated HgbA1c > ~ 5.8))

  -Metformin ER 500 to 750 mg po daily to BID ($28.00/180)
- Vaginal progesterone supplements 3 days after LH surge
  - Vaginal suppository compounded 100 mg ($2.50/each)
  - Endometrin Micronized vaginal tablet 100 mg ($15/tablet)
  - Crinone 8% vaginal gel daily ($40/applicator)
  - Prometrium capsule 100 mg used vaginally-off label ($3.50/each)

Rule of 7's for Ovulation Induction

Treatment Cycle	Rule	Days
• Use Clomiphene 50 mg cycle days 3 to 7 or Use Letrazole of 2.5 mg cycle days 3 to 7	7	3-7
• Expect ovulation in 7 days after last pill	14	10-18
• Monitor CD 21 Progesterone in 7 days	21	19-23
• Check pregnancy test 7 days later	28	28-30

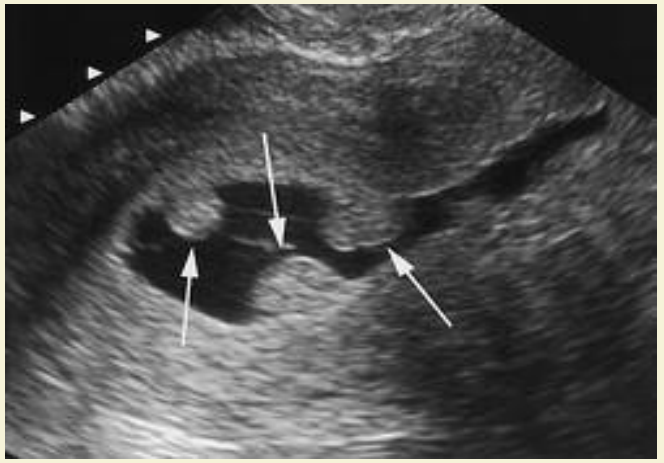
Triple stripe 10 mm endometrium CD 14

19 mm dominant follicle CD 14

Causes of Female Infertility: Uterus and Tubes

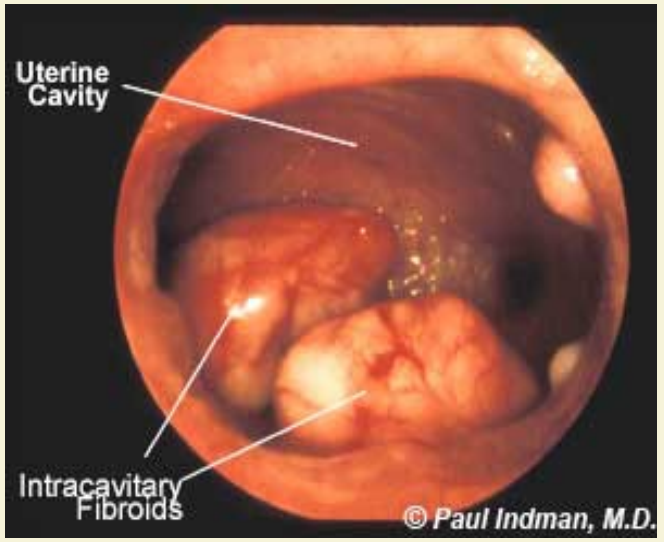
Uterine Factors

- Fibroids
- Polyps
- Asherman's syndrome Scarring
- Endometriosis/Adenomyosis
- Congenital anomalies

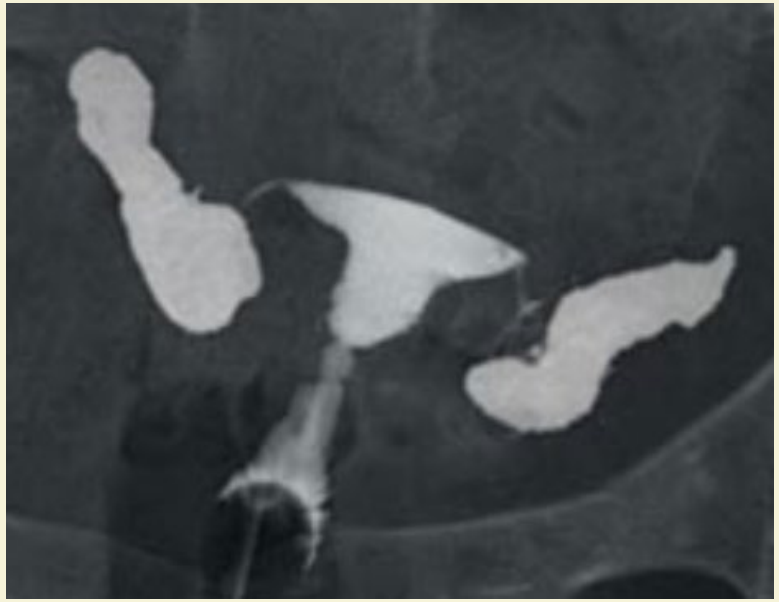


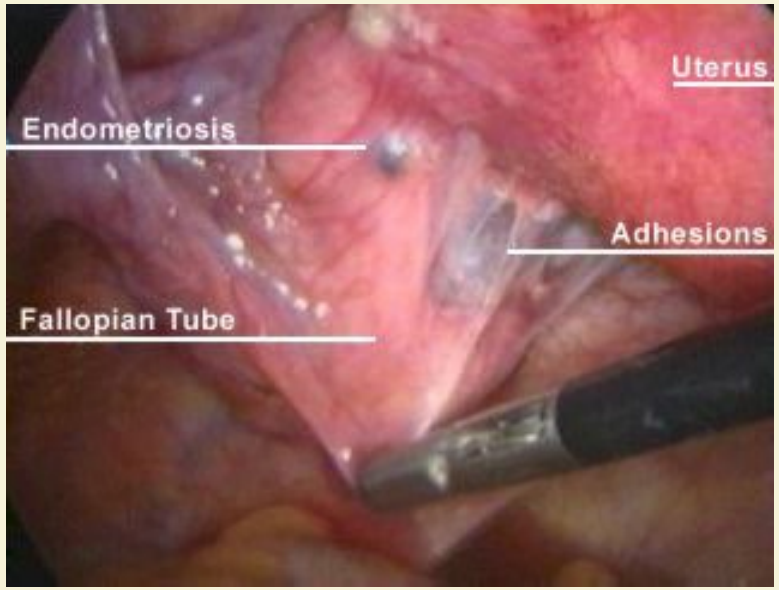
Tubal Factors

- Hydrosalpinges
- Blocked or damaged tubes
- Prior infection
- Prior surgery



Fertility treatments: Anatomic Abnormalities





– **Diagnosis**

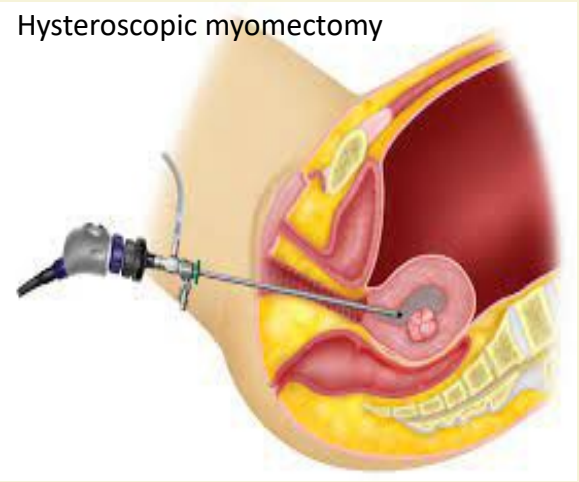
HSG

Laparoscopy

SHG

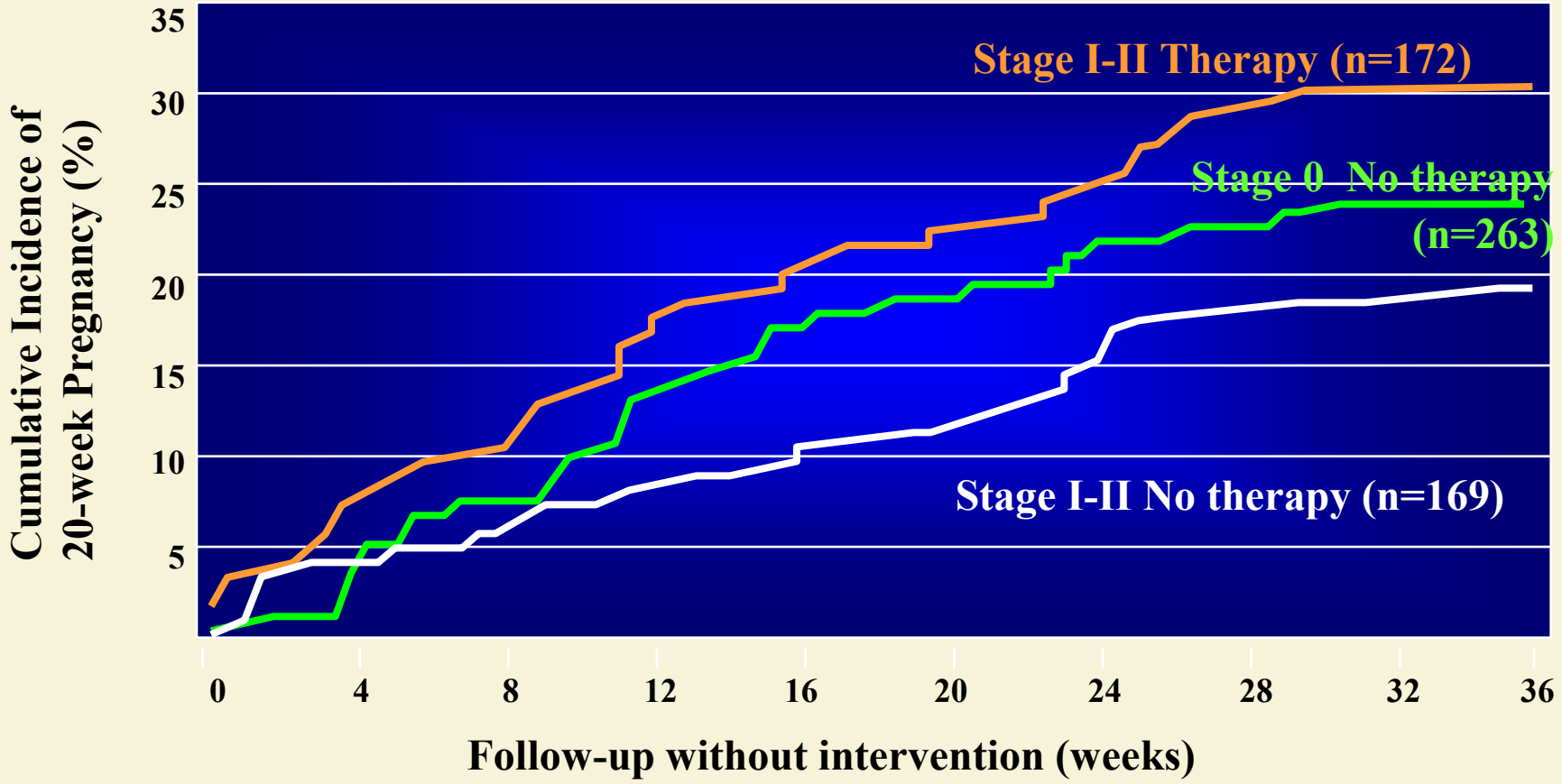
– **Surgical intervention**

- Hysteroscopy
- Laparoscopy
- Open abdominal surgery



Natural Fecundability After Surgical Treatment of Endometriosis

349 women with 1 year of infertility and a negative evaluations were diagnosed with Stage I-II endometriosis. Randomized at the time of laparoscopy to sham surgery or ablation.



Marcoux S. ENDOCAN Study. New England J Med 1997;337:269

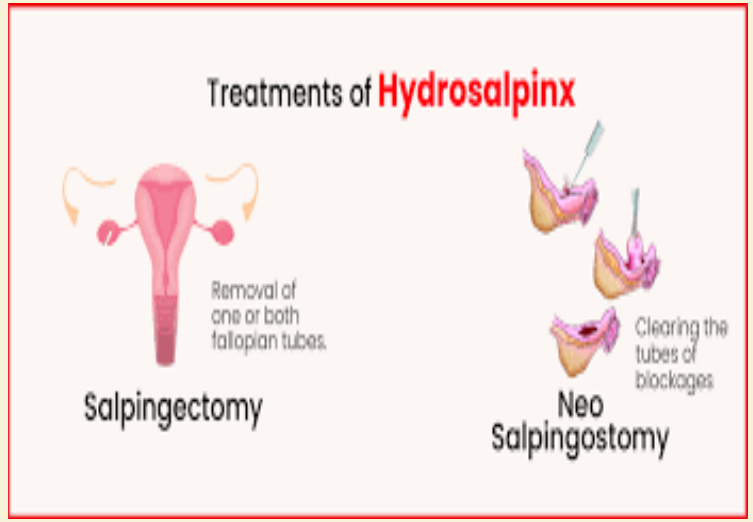
Hydrosalpinx Treatment Options

- Antibiotics if Pelvic Inflammatory Disease

- Salpingectomy (tubal removal)-usually best
- Salpingostomy (tubal repair)-ectopic risk

- In vitro fertilization- after tubal removal or occlusion
  -reduces negative impact of tubal fluid
  -reduces embryotoxic cytokines
  -reduces fluid drainage through uterus
  -enhances embryo implantation

- Proximal occlusion without hydrosalpinx does not require surgical intervention



Meyer WR et al. Hydrosalpinges adversely affect markers of Endometrial receptivity. Human Reprod. 12:1293-8, 1997.

Causes of Male Factor Infertility

OBSTRUCTIVE CAUSES

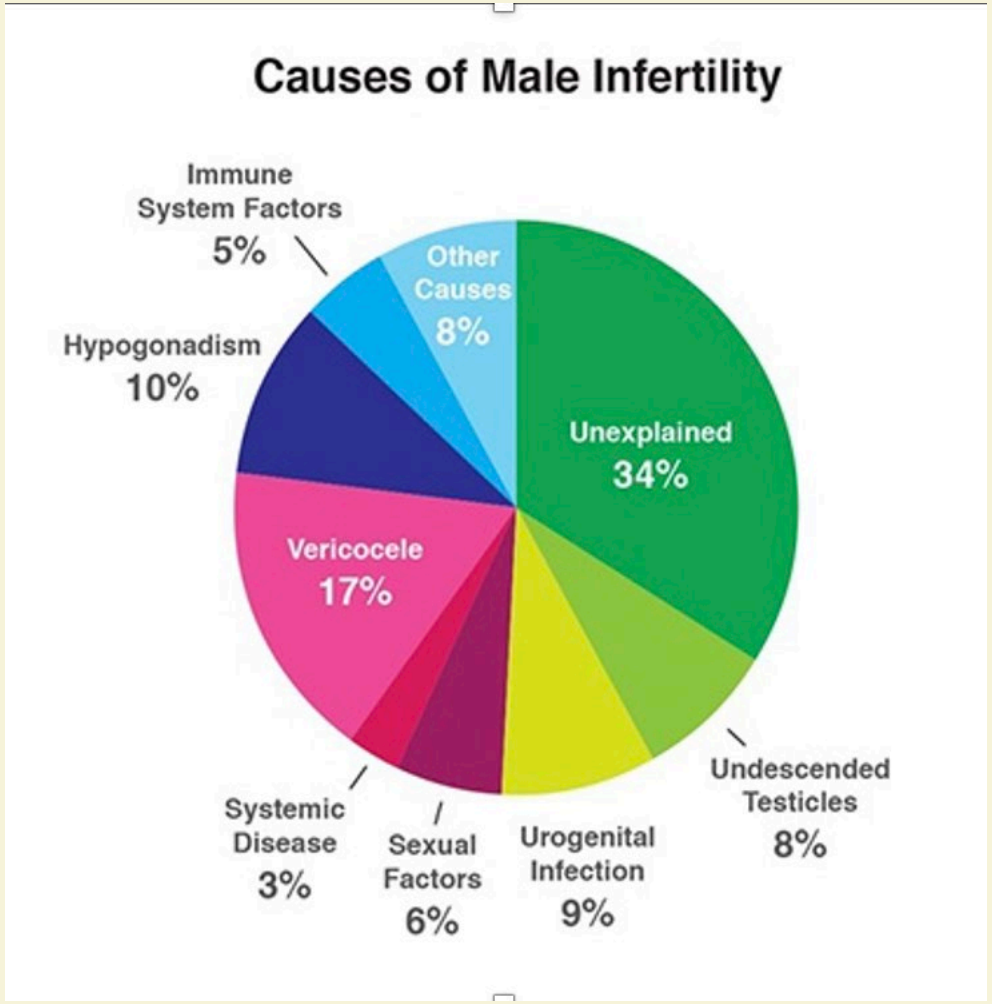
Azoospermia
Absence of the vas deferens (CFTR)
Retrograde ejaculation
Vasectomy

(Check for CF mutation)

NON-OBSTRUCTIVE CAUSES

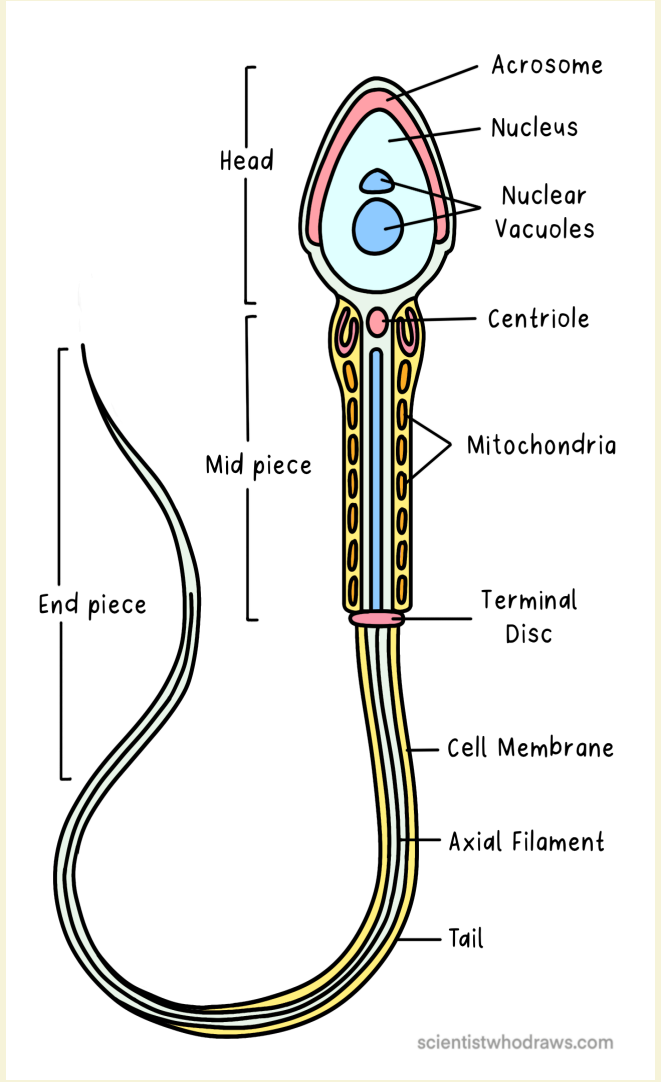
Testicular insufficiency
Erectile dysfunction
Oligospermia (low count)
Asthenospermia (low motility or normal forms)
Hypothalamic

(Check FSH, LH, Testosterone, TSH, Prolactin,
Karyotype, Y-chromosome microdeletion, DNA Fragmentation)



Normal Sperm Parameters

Parameter	Lower reference limit
Semen volume (ml)	1.5 (1.4–1.7)
Total sperm number (10^6 per ejaculate)	39 (33–46)
Sperm concentration (10^6 per ml)	15 (12–16)
Total motility (PR+NP, %)	40 (38–42)
Progressive motility (PR, %)	32 (31–34)
Vitality (live spermatozoa, %)	58 (55–63)
Sperm morphology (normal forms, %)	4 (3.0–4.0)
Other consensus threshold values	
pH	≥7.2
Peroxidase-positive leukocytes (10^6 per ml)	<1.0



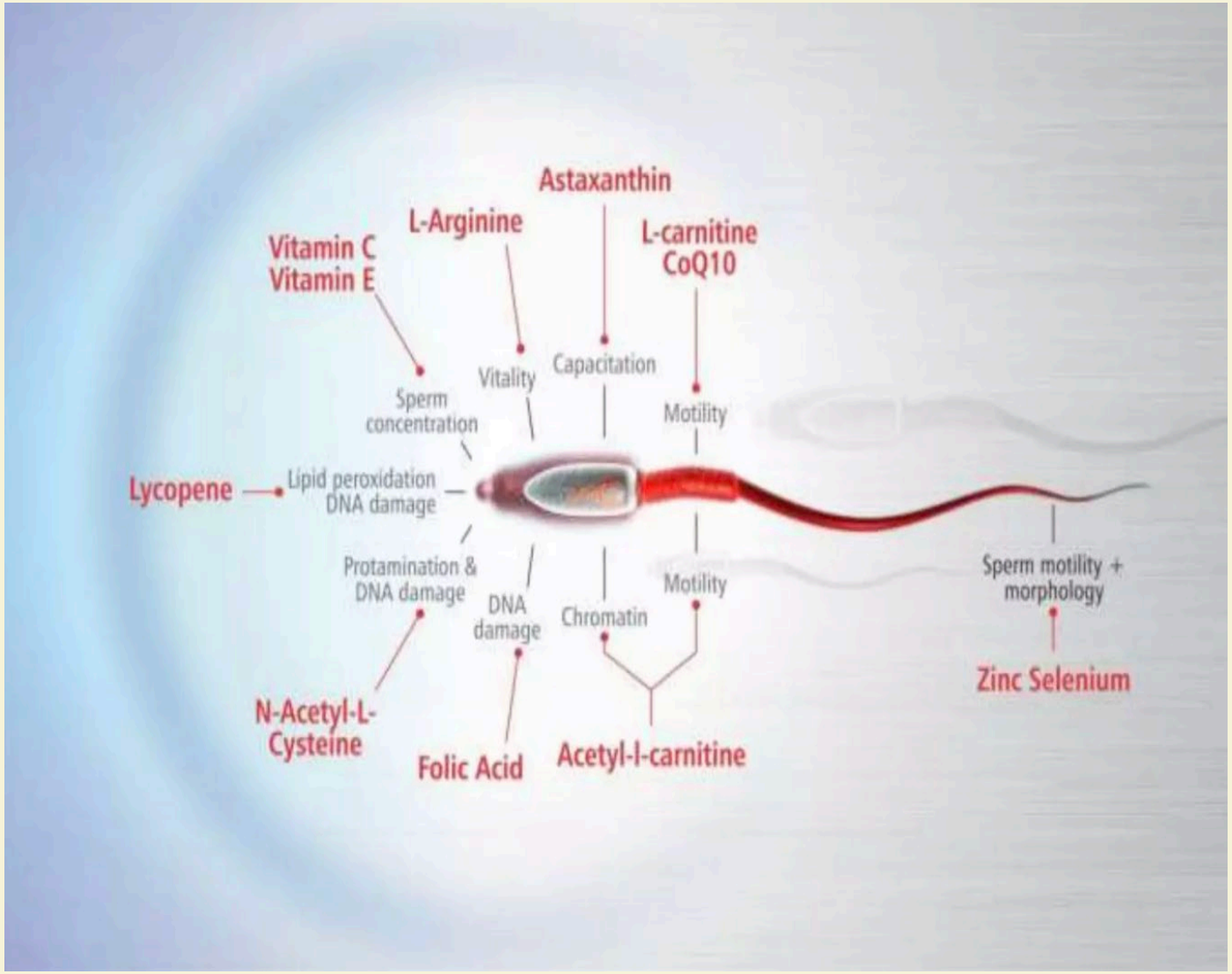
World Health Organization laboratory manual for the examination and processing of human semen. 6th Edition 2021.

Interpretation of Male Hormonal Profile

Lab tests should be used to support your clinical diagnosis

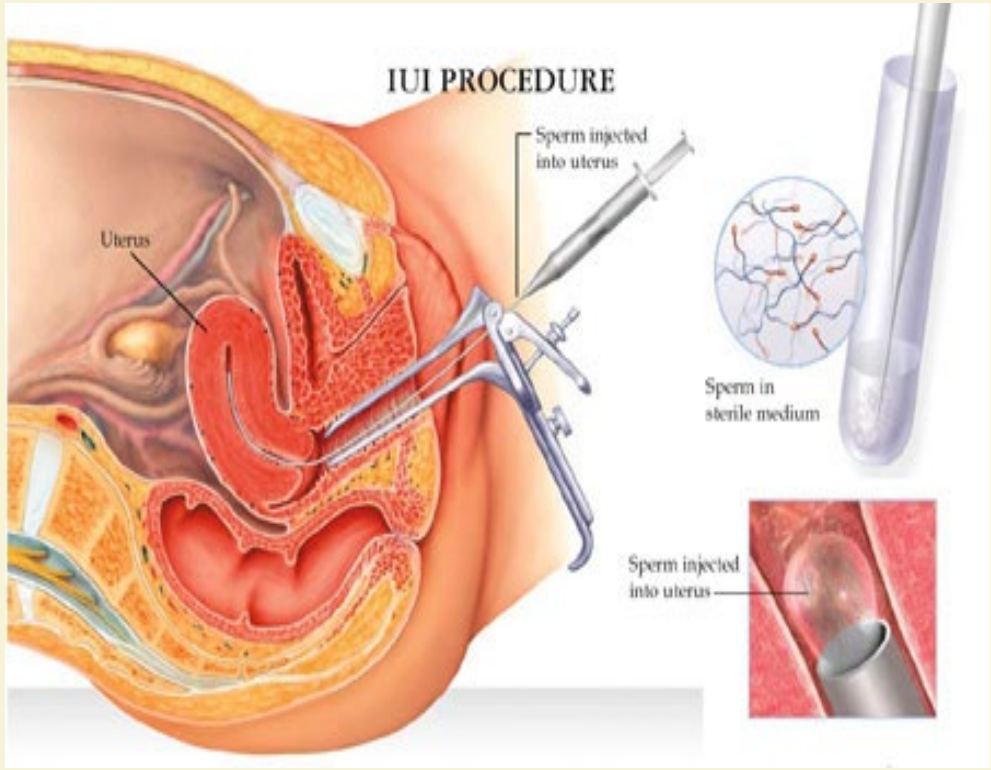
Increased FSH	Increased LH	Low testosterone	Testicular failure
Increased FSH	Normal LH	Normal testosterone	Failure of Spermatogesis
Decreased FSH	Decreased LH	Low testosterone	Hypogonadotropic hypogonadism

Supplements and Lifestyle modification may improve some male factors



Fertility Treatments: Male + Ovulatory Factor
Ovulation Induction with Intrauterine Insemination

- **Maximize every aspect of the cycle**
  - More mature eggs
  - Trigger shot to boost ovulatory signal
  - Higher concentrations of sperm
  - Sperm placed “Upstream” past cervix
  - Progesterone support



Intrauterine Insemination (IUI) Treatment Protocol

- **Monitoring and Timing are important**
  - Day 1 – Call with start of menses
  - Days 3 to 7-Take letrazole 2.5 mg po daily
  - Days 10 to 20 – check 2nd urine of the day for LH (PreMom ovulation kits from Amazon)

  ~ Day 14 (12 to 16)

  -If patient is ovulatory, morning of LH surge

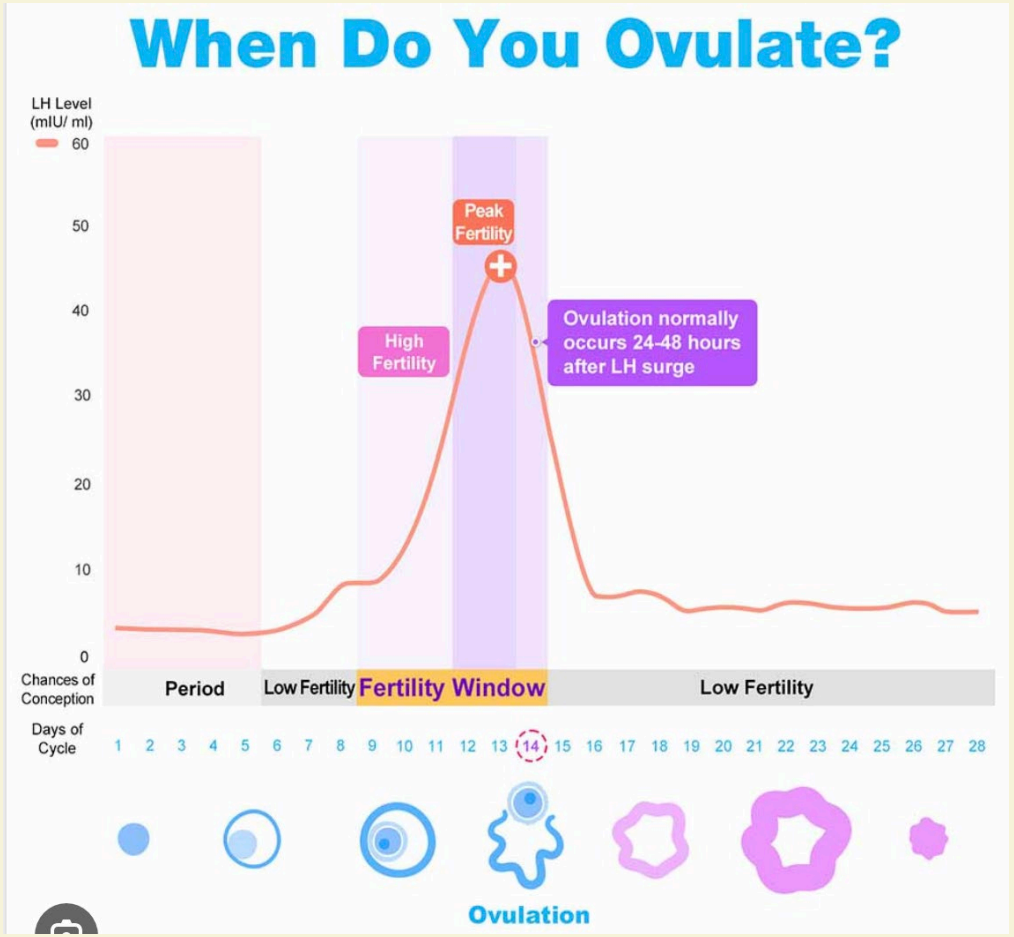
  -If patient is not ovulatory, HCG trigger shot

  ~ Day 15 morning - perform IUI

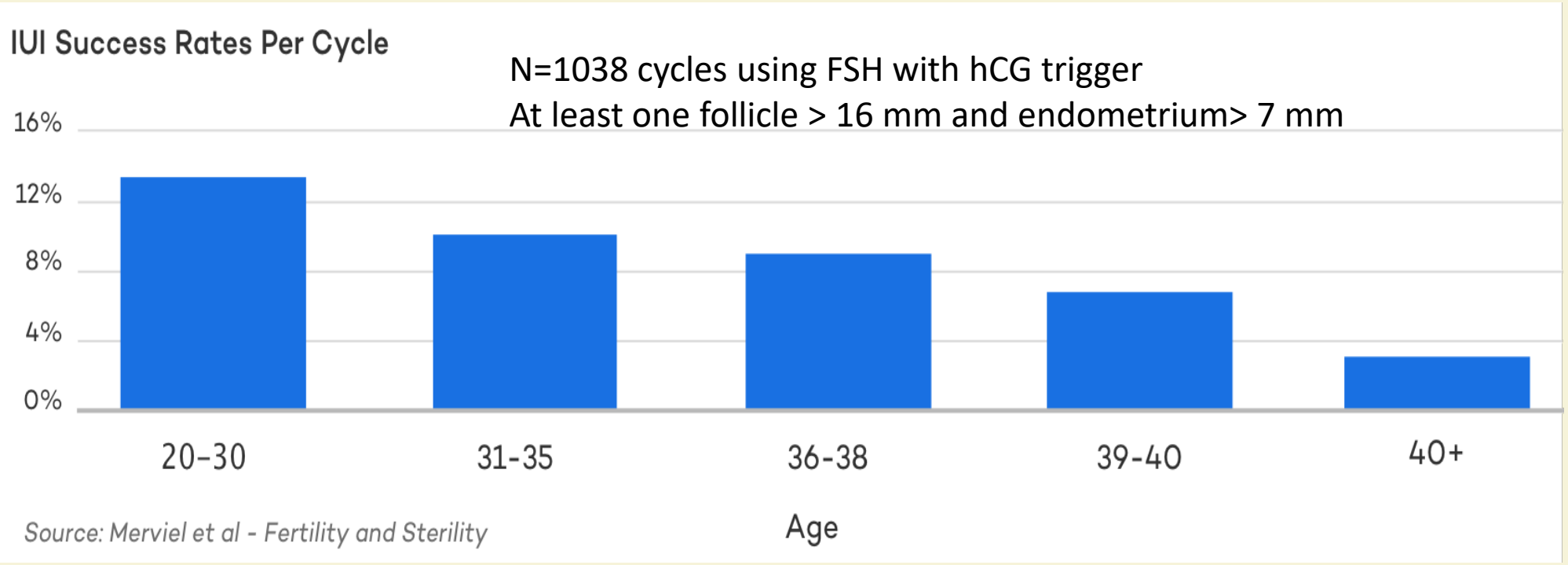
  (encourage intercourse unless < 10 million sperm

  ~ Day 18 – start vaginal progesterone support

  - Day 28 to 32 – pregnancy test if no menses



Success Rates with Ovulation Induction + IUI



- Lower success rates with other identified causes of infertility
  - Endometriosis
  - Tubal factors
  - Abnormal semen parameter

- Tobacco use
- Obesity
- Pelvic adhesions

-Age >35 years
-AMH < 1.0

Merviel P et al. Predictive factors for a pregnancy after IUI. Fertil Steril 93:79-88, 2010.
Zippi AL et al. Predicting success of IUI using a clinically based scoring system. Arch Gynecol Obstet 306:1777-86, 2022.

What to do with Unexplained Infertility

(Ovulatory, normal HSG, normal Semen analysis, lifestyle issues addressed)

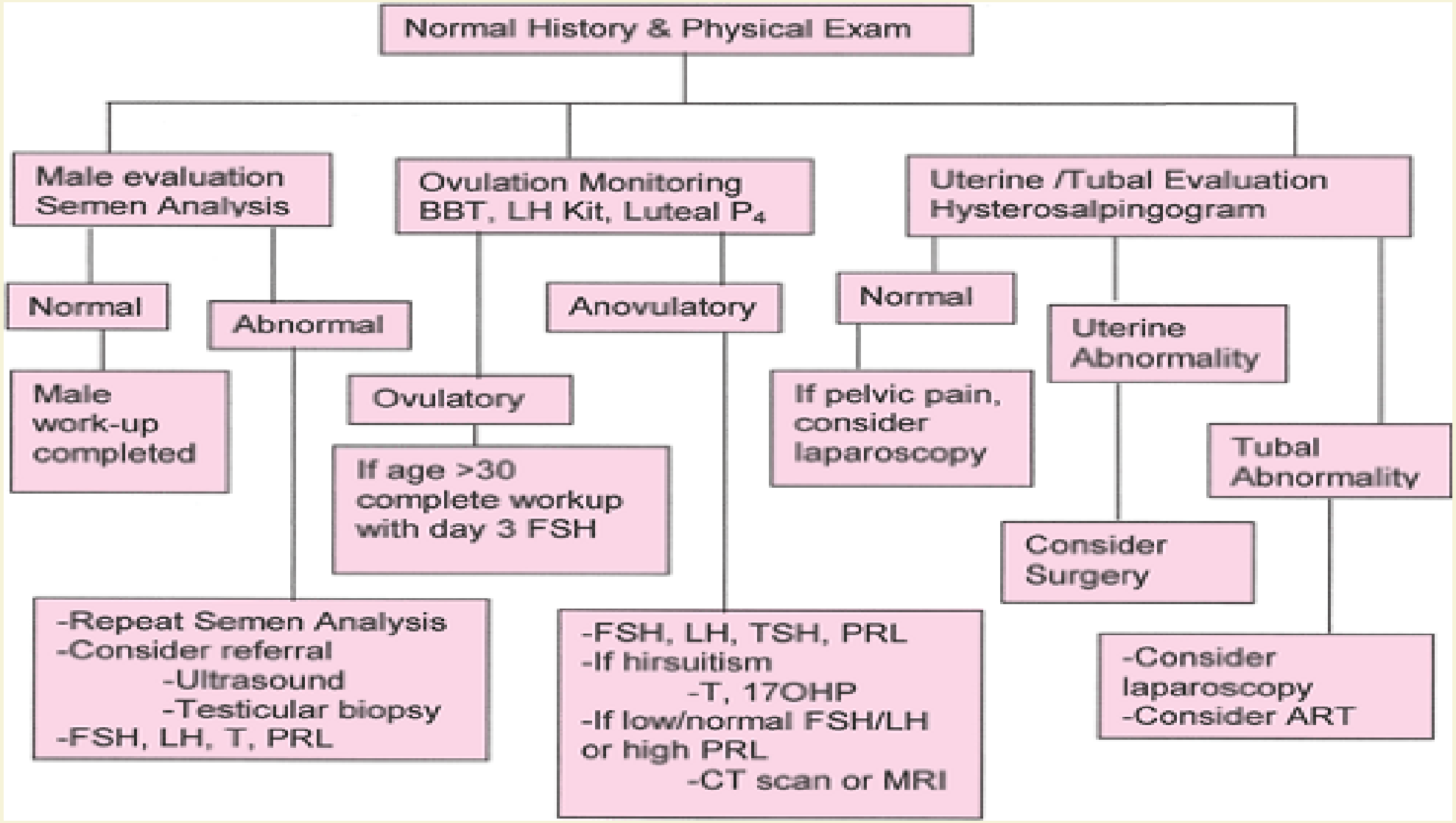
If woman is younger than 30 years old,

- try empiric clomiphene or letrazole for 3 - 4 months
- 75-90% ovulate – check progesterone
- 8-10% twins, 0.5% triplets
- 85% of pregnancies occur in first 3 ovulatory months
- 75% of pregnancies occur with Clomid 100mg or lower or Letrazole 5 mg or lower (best for PCOS)
- Do not:
  - use supplemental estrogen until after LH surge
  - arbitrary use of hCG for ovulation triggering

When to Refer Your Patient- Depends on You

- Female age greater than 35
- Patient of any age with low AMH (<1.0 to 1.5)
- Patient of any age with day 3 FSH > 10
- Abnormal semen analysis
- Infertility with multiple etiologies
- Young patient with infertility of more than 24 months
- No success after 4 to 6 months of ovulation induction
- Patient frustration or expectation level is high

Summary: Algorithm for the Evaluation of Infertility



Infertility for the Generalist

Thank you!

Questions?