



# EVALUATION OF FEMALE INFERTILITY

FLAME LECTURE: 222A

PERCIVAL/BURNS 9.9.15

# Learning Objectives

- ▶ Define infertility
- ▶ Describe causes of female infertility
- ▶ Describe the evaluation of an infertile couple
- ▶ Discuss the psychosocial issues associated with infertility
- ▶ Prerequisites:
  - ▶ FLAME LECTURES: 213A-B – Menstrual Cycle and Ovulation
- ▶ See also – for closely related topics
  - ▶ FLAME LECTURE 222B – Evaluation of Male Infertility
  - ▶ FLAME LECTURE 222C – Management of Infertility
  - ▶ FLAME LECTURES: 208-209 – Evaluation & Treatment of PCOS

# Etiology of Infertility

- ▶ Approximately 8-15% of couples are unable to conceive after 1 year of unprotected intercourse
- ▶ **Primary infertility**: a woman has **never** been able to get pregnant
- ▶ **Secondary infertility**: a woman has been pregnant in the past, but now has not been able to conceive for >1 year
- ▶ **Fecundability**: the probability of achieving a pregnancy within one menstrual cycle
  - ▶ Even for a normal young healthy couple, the chance is 20-25%
  - ▶ After 12 months, 85% of couples should conceive
  - ▶ Varies significantly with maternal age

# Etiology of Infertility

- ▶ Evaluation is warranted after 1 yr of trying for women <35 yo, and after 6 months of trying for women > 35 yo
- ▶ Earlier evaluation may also be justified based on medical history and physical findings:
  - ▶ Oligomenorrhea or amenorrhea
  - ▶ Known or suspected uterine/tubal/peritoneal disease or severe endometriosis
  - ▶ Known or suspected male subfertility

## Causes of Infertility

Male Factor	26%
Ovulatory Dysfunction	21%
Tubal Damage	14%
Endometriosis	6%
Coital Problems	6%
Cervical Factors	3%
Unexplained	28%

# The Voweled Etiology of Infertility

## A → Anatomic

- Tubal infertility, Ashermann's syndrome, other endometrial cavity pathology, endometriosis

## E → Endocrine

- Thyroid disease, hyperprolactinemia

## I → Intercourse

- Timing, frequency, use of products/lubricants

## O → Ovulation

- PCOS, hypogonadotropic hypogonadism, idiopathic anovulation

## U → You. As in "your fault" while you point towards your male partner ☹️

# Evaluation of Infertility - HISTORY

- ▶ **PGH**: regularity of menses (ovulatory/uterine factors)
  - ▶ Dysmenorrhea, dyspareunia, dyschezia (endometriosis)
  - ▶ Hx of STIs (chlamydia, gonorrhea, PID) (tubal factor)
- ▶ **POBH**: recurrent pregnancy loss (uterine factor)
- ▶ **PMH**: obesity, hirsutism (PCOS), galactorrhea, thyroid problems
- ▶ **PSH**: abdominopelvic or thyroid surgeries
- ▶ **SH**: caffeine intake, EtOH, tobacco, illicit drug use, toxic exposures, excessive exercise
- ▶ **FH**: hx of developmental delay/birth defects, infertility, early menopause
- ▶ **ROS**: symptoms of thyroid dz?, pituitary dz?

# Evaluation of Infertility- *Physical Exam*

- ▶ **General:** Weight, BMI, blood pressure, pulse, signs of androgen excess (hirsutism/virilization), acanthosis nigricans
- ▶ **HEENT:** Thyroid enlargement, nodules, tenderness
- ▶ **Breast Exam:** Breast characteristics & evaluation for secretions
- ▶ **Pelvic Exam:**
  - ▶ Vaginal or cervical abnormality, secretions, or discharge
  - ▶ Pelvic or abdominal tenderness, organ enlargement, or masses
  - ▶ Uterine size, shape, position, mobility
  - ▶ Adnexal masses or tenderness
  - ▶ Cul-de-sac masses, tenderness, nodularity



Navigate:

[Etiology](#)

[Female  
History](#)

[Female  
Physical](#)

[Female Lab  
Evaluation](#)

[Overview](#)

[Psych  
Impact](#)

# Evaluation of *Ovulatory Dysfunction*

- ▶ Ovulatory dysfunction will be identified in ~15% of all infertile couples and accounts for up to 40% of infertility in women
  - ▶ Failure to achieve pregnancy after 3-6 cycles of successful ovulation induction is an indication to perform additional testing
- ▶ Common causes: PCOS, obesity, strenuous exercise, thyroid dysfunction, hyperprolactinemia

## EVALUATION OF OVULATORY DYSFUNCTION

Menstrual History	Serial basal body temperature	Ovulations Predictor Kits
<ul style="list-style-type: none"><li>• Regular cycles: Q21-35 days</li><li>• Some degree of variation is normal</li></ul>	<ul style="list-style-type: none"><li>• Most ovulatory cycles have a progesterone-mediated biphasic pattern</li><li>• Not reliable for defining the time of ovulation &amp; tedious</li><li>• Not a preferred method for evaluating ovulatory function</li></ul>	<ul style="list-style-type: none"><li>• OPKs are purchased over the counter to examine urine for the LH surge which triggers ovulation, thus + OPK = + ovulation!</li><li>• The day of and day after the + LH surge are the interval of highest fertility</li></ul>



Navigate:

[Etiology](#)

[Female  
History](#)

[Female  
Physical](#)

[Female Lab  
Evaluation](#)

[Overview](#)

[Psych  
Impact](#)

# Eval of *Ovulatory Dysfunction* – cont'd

## TESTS TO EVALUATE FOR OVULATORY DYSFUNCTION

Serum progesterone	Endometrial Biopsy	Transvaginal ultrasound	Other tests
<ul style="list-style-type: none"><li>• Can be tested 1wk before expected next menses, rather than on specific day of cycle (ex: cycle day 21)</li><li>• Should be &gt;6 ng/mL or increasing</li></ul>	<ul style="list-style-type: none"><li>• Looking for secretory phase tissue can't distinguish fertile from infertile women</li><li>• Not recommended!</li></ul>	<ul style="list-style-type: none"><li>• Evaluate for:<ul style="list-style-type: none"><li>• <math>\uparrow/\downarrow</math> Antral Follicle Count (AFC) or ovarian volume</li><li>• Ovarian luteum cysts as sign of ovulation</li><li>• Endometrial stripe thickness</li></ul></li><li>• Not high yield for helping with ovulatory dysfunction diagnosis, however helpful for other female causes</li></ul>	<ul style="list-style-type: none"><li>• TSH</li><li>• Prolactin</li><li>• AMH, Cycle day 2-3 FSH and estradiol (to evaluate for: premature ovarian failure, hypothalamic amenorrhea)</li></ul>

# Evaluation of 'Ovarian Reserve'

- ▶ "Ovarian reserve" describes reproductive potential as a function of number and quality of oocytes
  - ▶ Diminished ovarian reserve (DOR) – women of reproductive age having regular menses whose response to ovarian stimulation or fecundity is reduced compared to women of comparable age
- ▶ Ovarian reserve tests help to predict response to stimulation and therapies like in vitro fertilization
- ▶ But remember, poor results never imply an absolute inability to conceive

## Women at increased risk for DOR:

- > 35 yo
- Family hx of early menopause
- Single ovary
- Hx of ovarian surgery which can affect the blood supply
- Chemo/RT
- Smoking
- Asian ancestry

Navigate:

[Etiology](#)

[Female History](#)

[Female Physical](#)

[Female Lab Evaluation](#)

[Overview](#)

[Psych Impact](#)

# Evaluation of 'Ovarian Reserve'

## TESTS TO EVALUATE FOR OVARIAN RESERVE

FSH & E2	Anti-Müllerian Hormone	Clomiphene Challenge Test	Antral Follicle Count
Drawn on cycle day 2-4	Is gonadotropin-independent, thus levels remain consistent throughout menstrual cycle; AMH is produced by granulosa cells of early follicles	Draw FSH on both CD 3 & CD 10 (w/ 100mg Clomiphene given on CD 5-9)	TVUS in early follicular phase to measure sum of follicles ('egg houses') in both ovaries
<ul style="list-style-type: none"><li>• ↑ FSH (&gt;12) assoc w/ poor response to stimulation</li><li>• Cycle to cycle variability can occur, but peak FSH values have the highest predictive value for IVF outcome</li><li>• When FSH is normal, but E2 is ↑, this is still considered abnormal</li></ul>	<ul style="list-style-type: none"><li>• ↓ AMH is assoc w/ poor response to stimulation, poor embryo quality, and poor pregnancy outcomes with IVF.</li><li>• Recent studies show that levels may be diminished with exogenous hormone use (OCPs, GnRH agonist, etc.), obesity, and hypogonadotropic hypogonadism</li></ul>	<ul style="list-style-type: none"><li>• Elevated FSH after Clomid suggests diminished ovarian reserve</li><li>• Not done often because AMH and AFC are simpler and highly predictive of ovarian response</li></ul>	<ul style="list-style-type: none"><li>• An AFC &lt;10 is low, (&lt;6 is assoc. w/ poor response to stimulation during IVF, but does not predict failure to conceive)</li><li>• Antral follicles are generally 2-10 mm in diameter</li><li>• Suppressed by exogenous hormones such as OCPs</li></ul>

# Evaluation of *Uterine Abnormalities*

- ▶ Uncommon cause of infertility, but should be excluded

## TESTS TO EVALUATE FOR UTERINE ABNORMALITIES

Ultrasound (2D & 3D)	Hysterosalpingogram (HSG)	Sonohysterogram (Saline infusion sonogram)	Hysteroscopy
<ul style="list-style-type: none"> <li>• Good for evaluating for fibroids or congenital malformations</li> </ul>	<ul style="list-style-type: none"> <li>• X-ray image of uterus/fallopian tubes</li> <li>• Defines size and shape of uterine cavity</li> <li>• Gold standard for viewing:               <ul style="list-style-type: none"> <li>• Mullerian anomalies</li> <li>• Tubal occlusion (next slide)</li> </ul> </li> <li>• Low sensitivity and PPV for polyps, submucous myomas, and synechiae</li> </ul>	<ul style="list-style-type: none"> <li>• TVUS during injection of saline into uterine cavity</li> <li>• High PPV and NPV for detection of intrauterine pathology (ex. polyps)</li> <li>• Can push bubbles into uterine cavity and watch them pass through tubes to assess for patency as well (not as good as an HSG)</li> </ul>	<ul style="list-style-type: none"> <li>• Definitive method for diagnosis and treatment of intrauterine pathology</li> <li>• Costly and invasive</li> </ul>

Navigate:

[Etiology](#)

[Female History](#)

[Female Physical](#)

[Female Lab Evaluation](#)

[Overview](#)

[Psych Impact](#)

# Evaluation of *Tubal Patency*

- ▶ Tubal disease is an important cause of infertility and should be excluded. Tubal disease and pelvic adhesions can impair oocyte/sperm motility and access for fertilization
- ▶ Associated with history of PID, endometriosis, ectopic pregnancy, past abdominal/pelvic surgery

## TESTS TO EVALUATE FOR TUBAL PATENCY

### Hysterosalpingogram (HSG)

- X-ray image of uterus/fallopian tubes
- Can document proximal and distal tubal occlusion, demonstrate salpingitis isthmica nodosa, fimbrial phimosis or peritubal adhesions
- Findings suggesting proximal tubal obstruction require further evaluation to exclude spasm

### Saline infusion sonogram (SIS)

- Looks for bubbles in tubes
- Can also just look for fluid in cul-de-sac, but this does not differentiate unilateral vs. bilateral tubal patency

### Laparoscopy with chromotubation

- Chromotubation dye injected into tube to visualize potential tubal obstruction
- Only method available to make specific diagnosis of endometriosis or pelvic/adnexal adhesions

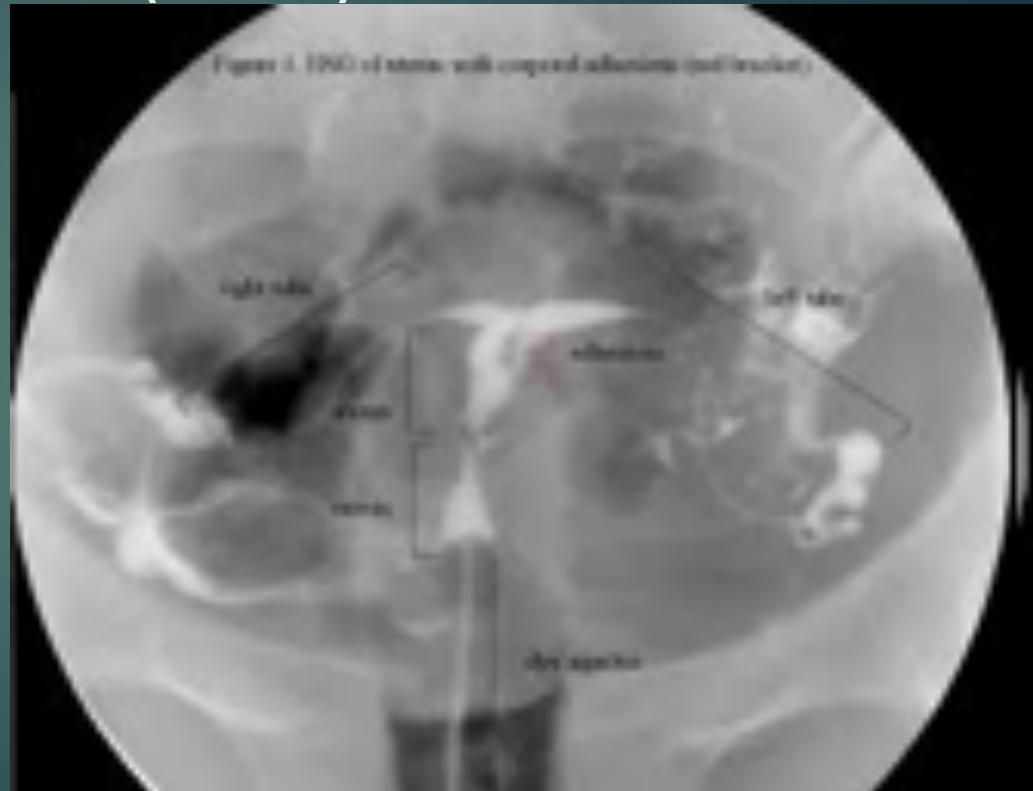
### Fluoroscopic/hysteroscopic selective tubal cannulation

- Will confirm or exclude proximal tubal occlusion seen on HSG, but rarely done given evidence limited



# Hysterosalpingogram (HSG)

- ▶ Normal HSG showing normal tubal anatomy with dye filling the uterus and spilling out of tubes into the abdominal cavity
- ▶ However, this picture notably also displays an area in the uterine cavity that is not being filled up with dye which is concerning for a polyp, or in this case, uterine adhesions





# Evaluation of *Cervical Factors*

- ▶ Abnormalities of *cervical mucous production* or *sperm mucous interaction* are rarely the sole or principal cause of infertility
- ▶ *Postcoital test*
  - ▶ Cervical mucous obtained shortly before ovulation and is examined microscopically for presence of motile sperm within hours after intercourse
  - ▶ May be used for couples for whom formal semen analysis is not accessible or feasible
  - ▶ *No longer recommended* as part of routine evaluation because test is subjective, has poor reproducibility, is inconvenient for the patient, rarely changes clinical management, and does not predict inability to conceive.

## Evaluation of Infertile Female - *Other*

- ▶ Serum TSH with reflex T4 to assess for thyroid disease which can affect ovulation and/or TSH-producing pituitary tumor
- ▶ Serum prolactin to assess for hyperprolactinemia which can affect ovulation and/or prolactinoma
  - ▶ Mechanism: prolactin inhibits GnRH secretion
  - ▶ Is low yield if no concerning clinical signs such as galactorrhea or oligomenorrhea
- ▶ Stress can even play a role! (next slide)

# Infertility – Psychosocial Consequences

- ▶ Psychosocial stress can both contribute to infertility and be a consequence of it and shouldn't be underestimated
- ▶ However the relationship is complex:
  - ▶ ↑ baseline stress correlated w/ poor biologic end points like oocytes retrieved/fertilized, pregnancy, live birth rate, and birth weight<sup>1</sup>
  - ▶ ↑ stress is also associated with higher treatment drop-out rate
  - ▶ Stress reduction education during treatment can lead to increased treatment outcomes

## Psychosocial Stress Assessment

- ▶ Do you feel uncomfortable being around pregnant women and/or children or babies?
- ▶ Do you find that you try to avoid situations where there may be pregnant women or babies/small children?
- ▶ Is your sexual relationship very satisfying, satisfying, or dissatisfying? And if it is dissatisfying, do you feel that your infertility has had a negative impact on your sex life?
- ▶ Do you only make love during the fertile times of your cycle?
- ▶ Do you feel that you and your partner mostly agree about how to proceed with infertility treatment?
- ▶ Do you feel that your partner is sympathetic and supportive of you?
- ▶ How is your mood? How have you been feeling? Are you able to enjoy your usual activities?
- ▶ Are you worried? Do you have difficulty concentrating or sleeping? Are you restless?
- ▶ Has your appetite changed?

# SUMMARY OF FIRST STEPS

- ▶ Take a thorough History & PE
- ▶ Begin with the least invasive testing:
  - ▶ **Ovulatory factor:**
    - ▶ Menstrual history and history of positive ovulation prediction kits?
    - ▶ Cycle Day 3 FSH, E2
    - ▶ Baseline Antral Follicle Count and serum AMH
    - ▶ Serum Prolactin and TSH
  - ▶ **Tubal and Uterine Factor:**
    - ▶ TVUS to evaluate for non-cavity uterine pathology (ex. fibroids)
    - ▶ Hysterosalpingogram to evaluate uterine cavity and tubal patency
  - ▶ **Male Factor:**
    - ▶ Semen analysis (*see FLAME: Male infertility*)
  - ▶ **STI testing** is required in most states for males and females before fertility treatments may begin

# IMPORTANT LINKS / REFERENCES

- ▶ Uptodate – Causes of Female Infertility
  - ▶ Uptodate – Evaluation of Female Infertility
  - ▶ Uptodate – Psychological Stress and Pregnancy
  - ▶ <http://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/How-I-Practice/Infertility-Workup>
1. Klonoff-Cohen et al (*Fertility and Sterility* 2001)