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

<table>
<thead>
<tr>
<th>Causes of Infertility</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Factor</td>
<td>26%</td>
</tr>
<tr>
<td>Ovulatory Dysfunction</td>
<td>21%</td>
</tr>
<tr>
<td>Tubal Damage</td>
<td>14%</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>6%</td>
</tr>
<tr>
<td>Coital Problems</td>
<td>6%</td>
</tr>
<tr>
<td>Cervical Factors</td>
<td>3%</td>
</tr>
<tr>
<td>Unexplained</td>
<td>28%</td>
</tr>
</tbody>
</table>
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, hypogonadotrophic 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
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

<table>
<thead>
<tr>
<th>Menstrual History</th>
<th>Serial basal body temperature</th>
<th>Ovulations Predictor Kits</th>
</tr>
</thead>
</table>
| • Regular cycles: Q21-35 days  
• Some degree of variation is normal | • Most ovulatory cycles have a progesterone-mediated biphasic pattern  
• Not reliable for defining the time of ovulation & tedious  
• Not a preferred method for evaluating ovulatory function | • OPKs are purchased over the counter to examine urine for the LH surge which triggers ovulation, thus + OPK = + ovulation!  
• The day of and day after the + LH surge are the interval of highest fertility |
### Tests to evaluate for Ovulatory Dysfunction

<table>
<thead>
<tr>
<th>Serum progesterone</th>
<th>Endometrial Biopsy</th>
<th>Transvaginal ultrasound</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| • Can be tested 1wk before expected next menses, rather than on specific day of cycle (ex: cycle day 21) | • Looking for secretory phase tissue can’t distinguish fertile from infertile women | • Evaluate for:  
  - ↑/↓ Antral Follicle Count (AFC) or ovarian volume  
  - Ovarian luteum cysts as sign of ovulation  
  - Endometrial stripe thickness | • TSH  
• Prolactin  
• AMH, Cycle day 2-3 FSH and estradiol (to evaluate for: premature ovarian failure, hypothalamic amenorrhea) |
| • Should be >6 ng/mL or increasing | • Not recommended! | • Not high yield for helping with ovulatory dysfunction diagnosis, however helpful for other female causes | |

---

**Eval of Ovulatory Dysfunction – cont’d**
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 simulation 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
## Evaluation of ‘Ovarian Reserve’

### Tests to Evaluate for Ovarian Reserve

<table>
<thead>
<tr>
<th>FSH &amp; E2</th>
<th>Anti-Müllerian Hormone</th>
<th>Clomiphene Challenge Test</th>
<th>Antral Follicle Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drawn on cycle day 2-4</td>
<td>Is gonadotropin-independent, thus levels remain consistent throughout menstrual cycle; AMH is produced by granulosa cells of early follicles</td>
<td>Draw FSH on both CD 3 &amp; CD 10 (w/ 100mg Clomiphene given on CD 5-9)</td>
<td>TVUS in early follicular phase to measure sum of follicles ('egg houses') in both ovaries</td>
</tr>
</tbody>
</table>

- **↑ FSH (>12)** assoc w/ poor response to stimulation
- **→** AMH is assoc w/ poor response to stimulation, poor embryo quality, and poor pregnancy outcomes with IVF.
- **Recent studies show that levels may be diminished with exogenous hormone use (OCPs, GnRH agonist, etc.), obesity, and hypogonadotropic hypogonadism
- **Elevated FSH after Clomid suggests diminished ovarian reserve**
- **Not done often because AMH and AFC are simpler and highly predictive of ovarian response**
- **An AFC <10 is low, (<6 is assoc. w/ poor response to stimulation during IVF, but does not predict failure to conceive)**
- **Antral follicles are generally 2-10 mm in diameter**
- **Suppressed by exogenous hormones such as OCPs**
**Evaluation of Uterine Abnormalities**

- Uncommon cause of infertility, but should be excluded

### Tests to Evaluate for Uterine Abnormalities

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound (2D &amp; 3D)</td>
<td>• Good for evaluating for fibroids or congenital malformations</td>
</tr>
<tr>
<td>Hysterosalpingogram (HSG)</td>
<td>• X-ray image of uterus/fallopian tubes</td>
</tr>
<tr>
<td></td>
<td>• Defines size and shape of uterine cavity</td>
</tr>
<tr>
<td></td>
<td>• Gold standard for viewing:</td>
</tr>
<tr>
<td></td>
<td>- Mullerian anomalies</td>
</tr>
<tr>
<td></td>
<td>- Tubal occlusion (next slide)</td>
</tr>
<tr>
<td></td>
<td>• Low sensitivity and PPV for polyps, submucous myomas, and synechiae</td>
</tr>
<tr>
<td>Sonohysterogram (Saline infusion sonogram)</td>
<td>• TVUS during injection of saline into uterine cavity</td>
</tr>
<tr>
<td></td>
<td>• High PPV and NPV for detection of intrauterine pathology (ex. polyps)</td>
</tr>
<tr>
<td></td>
<td>• Can push bubbles into uterine cavity and watch them pass through tubes</td>
</tr>
<tr>
<td></td>
<td>to assess for patency as well (not as good as an HSG)</td>
</tr>
<tr>
<td>Hysteroscopy</td>
<td>• Definitive method for diagnosis and treatment of intrauterine pathology</td>
</tr>
<tr>
<td></td>
<td>• Costly and invasive</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Tests to evaluate for Tubal Patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterosalpingogram (HSG)</td>
</tr>
<tr>
<td>X-ray image of uterus/fallopian tubes</td>
</tr>
<tr>
<td>Can document proximal and distal tubal occlusion, demonstrate salpingitis isthmica nodosa, fimbrial phimosis or peritubal adhesions</td>
</tr>
<tr>
<td>Findings suggesting proximal tubal obstruction require further evaluation to exclude spasm</td>
</tr>
<tr>
<td>Saline infusion sonogram (SIS)</td>
</tr>
<tr>
<td>Looks for bubbles in tubes</td>
</tr>
<tr>
<td>Can also just look for fluid in cul-de-sac, but this does not differentiate unilateral vs. bilateral tubal patency</td>
</tr>
<tr>
<td>Laparoscopy with chromotubation</td>
</tr>
<tr>
<td>Chromotubation dye injected into tube to visualize potential tubal obstruction</td>
</tr>
<tr>
<td>Only method available to make specific diagnosis of endometriosis or pelvic/adnexal adhesions</td>
</tr>
<tr>
<td>Fluoroscopic/hysteroscopic selective tubal cannulation</td>
</tr>
<tr>
<td>Will confirm or exclude proximal tubal occlusion seen on HSG, but rarely done given evidence limited</td>
</tr>
</tbody>
</table>
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.

Image from Wikipedia
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 with poor biologic end points like oocytes retrieved/fertilized, pregnancy, live birth rate, and birth weight.
  - 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?

---

1. Klonoff-Cohen et al (Fertility and Sterility 2001)
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

1. Klonoff-Cohen et al (*Fertility and Sterility* 2001)