Female Infertility 101
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Disclosure
• Nothing to disclose!

Learning Objectives
The fellow should be able to:
1. take an appropriate history and do a physical examination oriented to infertility.
2. evaluate an infertile female.
3. describe and apply to the general management of the infertile couple knowledge related to:
   a. ovulatory disorders, including: correct utilization and interpretation of basal body temperatures, plasma progesterone and endometrial biopsy; diagnoses of causes of anovulation, including polycystic ovary syndrome, syndromes of inappropriate prolactin secretion, and other GnRH causes; selection of ovulation induction utilizing clomiphene, human gonadotropin, bromocriptine and other agents; appropriate monitoring of ovulation induction utilizing estrogen determinations, ultrasound, and LH assays.
   b. tubal disorders, infectious in origin or not, including correct utilization and interpretation of studies of tubal function (e.g., hysterosalpingography and laparoscopy); indications for tubal reparative procedures including the specific indications for microsurgery and laser surgery.
   c. uterine factors, including: correct utilization and interpretation of studies of the uterine cavity, such as hysterosalpingography and hysteroscopy and indications and techniques for corrective procedures.
   d. endometriosis and other peritoneal causes of infertility; knowledge of the medical management of endometriosis (e.g., oral contraceptives, danazol, continuous progestin, androgen therapy, aromatase inhibitors and GnRH and its analogs); indications for surgery for these diseases; the rationale for pharmacologic adjuncts to surgical therapy.
   e. cervical factors, including the several causes of cervical infertility (e.g. chronic cervicitis, inadequate mucus production and cervical antibody formation).
4. cite the incidence of infertility as related to age and the prognosis for treatment of infertility.
5. describe appropriate preconception counseling and screening and explain further diagnostic and therapeutic approaches for couples carrying dominant, X-linked or recessive disorders.

Overview
• Female Reproductive Potential
• Ovarian Factors
• Tubal Factors
• Uterine Factors
• Other options/Therapies

Definitions
• Infertility: one year of unprotected regular intercourse with no conception (6 months if age 35 or greater)  ASRM Committee Opinion 8/2012
• Subfertility: decreased reproductive efficiency
• Fecundability: probability of one cycle resulting in pregnancy (15-20%)
• Fecundity: probability of one cycle resulting in life birth Fritz & Speroff 8th ed

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Average time required for Conception

<table>
<thead>
<tr>
<th>Months of exposure to sperm</th>
<th>Chance of conception (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>57</td>
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<tr>
<td>6</td>
<td>72</td>
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<td>12</td>
<td>85</td>
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<td>24</td>
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</table>

Causes of Infertility

Indications for Evaluation

- ≥ 12 months of unprotected intercourse
- ≥ 6 months if: female age ≥ 35 y o
  - oligo-/amenorrhea
  - known/suspected uterine disease
  - known/suspected tubal disease
  - stage III or IV endometriosis
  - known/suspected male subfertility
- Evaluation of both partners ideally at same time
- Any evaluation starts with thorough H&P

Aging and Fertility

- Decreased fertility with age
- Up to 60% of all conceptions miscarry in 1st trim
- 20-40% of all pregnancy losses unrecognized
- Studies on “natural” populations
- Studies on insemination with donor sperm
- Decreasing fertility of males...

Follicular Depletion

- Rate of follicular depletion increases with decreasing remaining follicles
Endocrinology of Reproductive Aging

- LH concentrations unchanged
- Rise in FSH most apparent during intercycle transition
- Inhibin B declines first (decrease in oocyte number), then Inhibin A
- Follicular phase shorter, earlier rise in estradiol levels, earlier selection of dominant follicle, higher prevalence of dizygotic twinning
- Aging follicles less sensitive to gonadotropins

Age-related Infertility

- Age: THE single most important factor in ART success (regardless if calculated by cycle, oocyte retrieval or per embryo transfer)

  2007 National Survey live birth rate (per embryo transfer):
  - 45.9% for age < 35 years
  - 36.9% for age 35-37 years
  - 27.1% for age 38-40 years
  - 16.0% for age 41-42 years
  - 8.4% for age 43-44 years

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Genetics and Reproductive Aging

- Decreased oocyte quality 2º to meiotic nondisjunction: premature separation of sister chromatids (MI), whole chromosome nondisjunction in MII
- Small chromosomes more prone (smaller chiasma)
- Trisomies > polyploidies > monosomy X
- Risk for aneuploidy: 10% until age 35
  - 30% by age 40
  - 50% by age 43
  - 100% by age 45

Ovarian Reserve Testing

- FSH and Estradiol
- CC challenge test
- AMH
- AFC

Basal FSH and Estradiol

- CD # 2-4
- Can vary within different assays
- FSH > 10 IU/l: specificity 80-100% for poor response to stimulation, sensitivity 30%
- Estradiol > 60 pg/ml – can mask high FSH (advanced follicular depletion)
- Some recommend to repeat once

Clomiphene Challenge Test

- Provocative test (exaggerated FSH increase in older women)
- CD # 2, 3 or 4: basal FSH/Estradiol
- CD # 5-9: Clomiphene 100 mg/d
- CD # 10: stimulated FSH
- Stimulated FSH 10-22 IU/l: 47-98% specificity and 35-93% sensitivity for poor response to stimulation
- Higher sensitivity but lower specificity compared to basal FSH
**Antimüllerian Hormone (AMH)**
- Produced by granulosa cells of preantral and small antral follicles  
  (Duling et al. 1999)
- Gonadotropin independent  
  (Fanchin et al. 2005)
- General IVF population: good predictor for poor ovarian stimulation, but not for pregnancy  
  (Penarrubia et al. 2005)
- More useful in females at risk for decreased ovarian reserve
- 0.2-0.7 ng/ml: 40-97% sensitivity, 78-92% specificity for poor response to stimulation

**Antral Follicle Count**
- CD # 2-4
- Proportional to number of primordial follicles remaining  
  (Scheffer et al. 1999)
- Correlates well with oocyte yield in IVF cycles  
  (Hendricks et al. 2005)
- 3-4 follicles: 73-100% specificity for predicting poor stimulation response and failure to conceive (64-100%) but low sensitivity (9-73%) and 8-33% respectively

**Thyroid function tests**
- TSH: goal < 2.5 mIU/ml  
  (The Endocrine Society Practice Guidelines 8/2012)
- Risk for spontaneous miscarriage 5x increased with TSH > 2.5 mIU/ml or positive TPO-Antibodies  
  (Negro et al. 2010)

**PCOS**
- Diagnosis of exclusion!
  - hypothyroidism
  - hyperprolactinemia
  - late onset CAH
  - DM2
  - ovarian tumor
  - adrenal tumor
  - Cushing syndrome
- Fasting Prolactin
- 17-hydroxy-progesterone
- Testosterone
- DHEAS
- Short Dexa suppression test

**Assessment of Ovulation**
- Menstrual history
- Serum P4 > 3 ng/ml (1 week prior to menses)
- Urinary LH determination – 7% false positive
- Transvaginal sonogram
- ...only positive proof of ovulation: PREGNANCY!
  
  No longer recommended:
  - Basal body temperature
  - Endometrial biopsy

**Indications for Described Tests**
- Ovarian reserve testing:
  - AMA (≥ 35 years old)
  - Hx of chemotherapy/ radiation/ ovarian surgery
  - Smoking
  - Hot flashes/ shorter cycles
  - FHx of early menopause/ POI
  - Unexplained infertility
  - Hx of poor response to stimulation with gonadotropins
- Thyroid evaluation:
  - Every infertile patient  
  (The Endocrine Society Clinical Practice Guidelines 8/2012)
- PCOS labs: oligo-amenorrhea
Lifestyle factors

• Smoking: dose-dependent increase in infertility and time to conception in both female and male
  - accelerated follicle depletion
  - menstrual cycle irregularity
  - gamete and embryo mutagenesis
• Marijuana: inhibits gonadotropin secretion
• Cocaine: tubal disease, impaired spermatogenesis
• Alcohol: reduced fecundability (even small amt)
• Caffeine: < 250 mg/d appears without effect
• NSAIDS: disruption of ovulatory process
• Timed intercourse only if infrequent, 2/week better

Fritz & Speroff 8th ed.

2) Tubal function

Tubal disease

• Prevalence in subfertile women = 30-35 %
• Risk factors: PID
  - Inflammatory bowel disease
  - Ruptured appendicitis
  - Septic abortion
  - History of ectopic pregnancy
  - Endometriosis
  - Tubal surgery
• Risk of hydrosalpinx increases with number of PID episodes: 10, 30 and 60%
  - Westrom 1995
• Proximal occlusion: "all or none"; distal: mild – moderate - severe

Fritz & Speroff 8th ed.

Tubal Diagnostic Studies:

• HSG
• HyCoSy
• Laparoscopy with chromopertubation
• Chlamydia-Antibody titer (CAT)

Hysterosalpingo-contrast-sonography (HyCoSy)

• Acceptable screening for subfertile patients
• Comprehensive, methodologically simple, cost effective and time efficient
  - Saunders et al. 2011
• Information about uterus and ovaries
• No radiation exposure
• Sens and spec comparable to HSG

Hysterosalpingogram (HSG)

• Patency of fallopian tubes
• Size/shape of uterine cavity
• Developmental and acquired uterine abnormalities
• Tubal patency: Sensitivity 65%, specificity 83%
• Unilateral proximal tubal occlusion – 70% open at laparoscopy; bilateral proximal tubal occlusion – 40% open at laparoscopy
  - Swart et al. 1995
• Antibiotics...
• Oil- vs water-based contrast medium
**Chlamydia Antibody Testing (CAT)**
- Role of utility in evaluation of subfertile women is not clearly defined
- Possible tool to triage for HSG vs. LSC
- Lower pregnancy rates with pos CAT even with normal HSG or LSC findings
- Wide variability in different commercial assays
  - different lab methods (immunofluorescence, ELISA preferred)
  - different antigen sources
- Combination of antibodies against CT443 and CT381: sens 67%, spec 100%  
  
**Laparoscopy (LSC)**
- Diagnostic (gold standard) and therapeutic

**Treatment of tubal disease**
- Fimbriolysis vs. Fimbrioplasty vs. Neosalpingostomy
- Mild distal obstruction: 50% live birth rate
  - Severe distal obstruction: 5-20% live birth rate
- Hydrosalpinx – can perform salpingectomy or proximal mechanical occlusion
- “bipolar tubal disease” (both proximal and distal obstruction) – IVF is best option

**3) Uterine Function**

**Uterine abnormalities**
- Congenital malformations
- Leiomyomas
- Intrauterine adhesions
- Endometrial polyps
- Chronic endometritis

**Congenital malformations**
- Prevalence of 2-4%, similar between fertile and subfertile women
  - Septate uterus: live birth rate 40%; resection restores normal chance for term life birth
**Uterine leiomyomata**

- Found in 20 to 40% of all reproductive age women
- Subfertility attributed to:
  - Interference with sperm exposure or sperm transport
  - Interference with ovum capture and transport
  - Impairment of implantation (blood flow, contractions, glandular atrophy)
  - Local decrease in HOX gene expression is required for implantation

**Leiomyomata (2)**

- Best studies: IVF cycles with and without fibroids
- Submucous fibroids decrease pregnancy and delivery rate. 3x increased risk for miscarriage
- Decreased IVF success:
  - 70% for submucous fibroids
  - 30% for intramural fibroids
  - No adverse impact for subserosal fibroids
- Removal of submucous fibroids increases pregnancy rate
- Intramural fibroids: pregnancy rate appears decreased (especially) if large (>5cm)

**Intrauterine adhesions**

- Especially susceptible 2-4 weeks postpartum
- 90% of adhesions: curettage
- HSG: 80% sensitivity and specificity
- Recommend postop HSG or SIS after next menses

**Endometrial polyps**

- Prevalence in subfertile population: 3-10%
- Molecular etiologies: endometrial hyperplasia, overexpression of endometrial aromatase
- Interference with implantation:
  - Resistance of progesterone effects
  - Local inflammatory changes
  - Distortion of uterine cavity
- Polypectomy in infertile females may improve reproductive outcome – need for individualization, depends on size and symptoms

**Saline Infusion Sonogram (SIS)**

- Endometrial pathology
- Detection of polyps and submucosal fibroids: PPV and NPV both > 90%
- Indirect evaluation of tubal patency

**Cervical Abnormalities**

- Sperm capture and reservoir function
- Passage of motile sperm with exclusion of seminal plasma and abnormal sperm
- Glycoproteins biochemically support sperm
- Poor mucus quality can be caused by:
  - Hx of conization/ other surgery
  - Cervicitis
- Postcoital test no longer recommended
- Treatment: IUI
4) Other options/Therapies

Pretreatment Screening Tests
- Blood type and Rh factor, antibody screen
- Pap test
- Cystic fibrosis/ sickle cell
- Rubella
- Varicella
- STIs

Lifestyle Changes
- Weight loss
- Smoking cessation
- Decrease in alcohol intake
- Street drugs
- Occupational/environmental exposure

Unexplained Infertility
- Diagnosis of exclusion
- Untreated patients: cycle fecundability 2-4%
- Likelihood of pregnancy decreases with age of female and increasing duration of infertility
- Both IUI and Clomid on their own show no clinically significant effects
- Clomid plus IUI appear to have higher pregnancy rates
- Gonadotropins alone no better than Clomid plus IUI
- IVF: THE most effective treatment

Unexplained Infertility

<table>
<thead>
<tr>
<th>treatment</th>
<th>Cycle fecundability</th>
</tr>
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<tbody>
<tr>
<td>No treatment</td>
<td>2-4%</td>
</tr>
<tr>
<td>IUI alone</td>
<td>2-4%</td>
</tr>
<tr>
<td>Clomid alone</td>
<td>2-4%</td>
</tr>
<tr>
<td>Clomid/IUI</td>
<td>5-10%</td>
</tr>
<tr>
<td>Gonadotropins</td>
<td>5-7%</td>
</tr>
<tr>
<td>Gonadotropins/IUI</td>
<td>7-10%</td>
</tr>
<tr>
<td>IVF</td>
<td>23-45%</td>
</tr>
</tbody>
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References (1)
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