Infertility Evaluation and Basic Management: Logistical and Clinical Considerations

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• There are no relevant financial relationships with any commercial interests to disclose for Michael Policar

• Jordan Vaughan is a consultant for EMD Serono
Objectives

• Discuss evaluation for both male and female patients
• Discuss ovarian reserve testing
• Discuss the management of anovulatory women including pharmacologic options
• Identify efforts to maximize natural fertility
• Identify patients warranting referral to a specialist for further evaluation
Should Generalist ObGyns, PCP’s and FP Clinics Offer Infertility Services?

- Set referral points based on your expertise, resources
- Referral points to explained patient(s) early on
- Relationship with REI practice(s)
  - Consistent work-up plans
  - Phone consults during work-up
  - Detailed referral points
  - Maintain continuity of care
Infertility: Definitions

• Infertility
  – No pregnancy in 12 mo of unprotected intercourse (<35) and 6 months (>35)

• Pregnancy rates with “normal” fertility
  – 1 month: 25%
  – 6 months: 60%
  – 9 months: 75%
  – 12 months: 85%
  – 18 months: 90%
Primary and Secondary Infertility

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Infertility</td>
<td>70%</td>
<td>• F: never conceived</td>
</tr>
<tr>
<td>Secondary Infertility</td>
<td>30%</td>
<td>• F: previously conceived, but later unable</td>
</tr>
</tbody>
</table>
Infertility: Definitions

• Initiate the infertility evaluation
  – Woman < 35 years old: @ 12 months of UPI
  – Woman 35-39 years old: @ 6 months
  – Woman > 40 years old: @ 3 months
  – History of, or risk factors, for infertility: @ 0-6 months
  – After 6 or more cycles insemination

• 1/2 couples pregnant in within 1 year

UPI: unprotected intercourse
Diagnostic evaluation of the infertile female: a committee opinion

Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama
## Causes of Infertility in Couples

<table>
<thead>
<tr>
<th>Proportion</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>Male factor</td>
</tr>
<tr>
<td>30%</td>
<td>Tubal/peritoneal factor</td>
</tr>
<tr>
<td>20%</td>
<td>Ovulatory factor</td>
</tr>
<tr>
<td>15%</td>
<td>Unexplained</td>
</tr>
<tr>
<td>5%</td>
<td>Unusual (cervix, uterus)</td>
</tr>
</tbody>
</table>
Causes of Female Infertility

• Tubal/Peritoneal Factor
  – Tubal occlusion (prior episode of PID, previous ectopic)
  – Peritoneal adhesions (prior peritonitis or surgery)
  – Endometriosis

• Ovulatory Factor
  – Anovulation: PCOS, hyperprolactinemia
  – Luteal phase insufficiency
  – Poor “quality” ovulation (poor ovarian reserve)

• Cervical Factor
  – “Hostile” mucus: anti-sperm antibodies, infection
  – Scant mucus: “hypoestrogenic” effect
  – Surgery on cervix
Male Causes of Infertility

• Poor sperm production
  – Chronic “overheating” of testicles
  – Varicocele (varicosity of testicular vein)
  – Toxin exposure (environmental, occupational, drugs)
  – Mumps orchitis
Causes Male of Infertility

• **Scarring of the vas deferens**
  – Epididymitis (GC, chlamydia, ureasplasma)
  – Prior vasectomy or other genital tract surgery
  – Disorders of the GU tract (Congenital Bilateral Absence of the Vas Deferens CBADV)

• **Hypogonadism**
  – Low gonadotroptins (LH, FSH)
  – Low testicular testosterone production
  – Aging, especially >50 years old
Visit 1: Female History

• Previous pregnancies; outcomes and complications
• Prior infertility; results of evaluation, treatments
• Frequency of intercourse; sexual dysfunction
• History of PID; postpartum, post-abortion infection
• Pelvic pain, dysmenorrhea; endometriosis
Visit 1: Female History

- Medical: diabetes, thyroid; pelvic surgery
- Medications, alcohol, street drugs
- Cigarette smoking
- Occupation; exposure to environmental hazards
- Galactorrhea
- Menstrual patterns
  - Cycle length range (best 25-35 days apart)
  - Molimenal symptoms (if present, ovulating)
Visit 1: Female Examination

- BP, weight, BMI, waist circumference (PCOS)
- Skin: axial hirsuitism, acne, male-pattern balding (PCOS)
- Thyroid enlargement; any nodules or tenderness
- Breasts: galactorrhea (▲ prolactin)
- Cervix: mucopus, friability (infection)
- Uterine corpus
  - Size, shape (fibroids, uterine anomalies)
  - Corpus tenderness (PID)
  - Fixed retroflexion: endometriosis (EM)
- Adnexa: tenderness (PID, EM), mass (EM, tumor)
Does the Partner Need to Be Involved?

• Evaluation should focus on the couple
• Both encouraged to attend each visit
• Both partners understand the rationale for tests and procedures
• An ongoing process to ensure that all medical, emotional, and financial concerns are addressed
Visit 1: Male History

Past medical history
• Fathered previous pregnancies within 3 years
• Genital trauma or surgery
• Genital infections; GC, Chlamydia, mumps
• Environmental heat: spa, pants, sitting time

Coital factors
• Coital frequency
• Coital technique, esp ejaculation factors
Visit 1: Male History

Current exposures

- Drugs: b-blockers, Ca channel blockers, cimetidine, HMG-CoA reductase inhibitors
- Toxic chemicals, esp. metals and dyes
- Street drug and alcohol use
- Cigarette smoking
Visit 1: Male Examination

- Utility is controversial
  - “Preferable” to do exam, but little contribution if semen analysis is normal
- Male examination
  - Masculine traits
  - Varicocele
  - Hypospadias
  - Urethral discharge
  - Prostatitis
Visit 1: Laboratory

- **Women**
  - CBC, ESR
  - TSH, prolactin
  - Screen for gonorrhea, chlamydia (if indicated by age; risks)
  - Screen for HIV (if never screened, or as indicated by risks)
  - If amenorrhea, serum FSH and estradiol ($E_2$)
  - If indicated, ovarian reserve testing

- **Men**
  - Semen analysis (if has not caused pregnancy in >3 years)
    - Abstain for 3 days before sampling
    - *Check with your lab for collection rules*
Visit 1: Pelvic Ultrasound

- Diagnostic pelvic ultrasound
  - >10 to 12 follicles per ovary (PCOS)
  - Persistent hemorrhagic cysts with low-level echoes (endometriosis)
  - Anatomical conditions: fibroids, polyps, and Müllerian anomalies (uterine septum)
  - Decreased ovarian volume and reduced antral follicle count associated with reduced fertility

- Serial TV ultrasound used to document ovulation
Visit 1: Counseling

- Preconception care advice
- Optimal timing of intercourse
- Stop smoking (both partners)
  - Offer nicotine replacement
  - Group therapy
- If BMI > 30, recommend/assist with weight loss
- Discuss emotional issues and support, financial costs of planned infertility services, etc.
- Which questions can I answer?
Visit 1: Counseling

• Preconception care
  – Folic acid 400 mcg PO per day
  – Rubella serology; immunize if seronegative
  – Cystic fibrosis screening if risk factors (screen 1 partner, screen the 2\textsuperscript{nd} only if the 1\textsuperscript{st} is identified as a carrier)
  – Change medications to safer FDA pregnancy category
    • Antihypertensives
    • Anti-epileptic drugs
  – Blood glucose control in diabetics
The Fertile Window

Day-Specific Probability of Pregnancy

Day Relative to Ovulation

Probability of pregnancy by cycle day, involving recurrent intercourse, by age. Data from Stanford and Dunson 2007 (16).

Achieving Pregnancy

- Fertility rates are lower among women who
  - Are very thin (BMI <19) or obese (BMI >35)
  - Consume high levels of caffeine (e.g., >5 cups per day, fecundability reduced by 45%)
  - Smoke (infertility RR increased by 60%)
  - Consume alcohol > 2 drinks/day (RR increased 60%)
  - Use recreational drugs (RR increased 70%)
  - Exposure to toxins, solvents (RR increased 40%)

Frequency of Intercourse

• Misperception: frequent ejaculation decreases fertility
  – With daily ejaculation, quality, count, motility normal
  – If oligozoospermia, count and motility may be highest with daily ejaculation
• After abstinence of ≥ 10 days, semen results deteriorate
• Efficiency highest when UPI occurs every 1-2 days
  – To reduce anxiety, optimal frequency best defined by couple preference
ASRM: Coital Practices

- Sperm at midcycle cervix found in tubes ≤ 15 min
- No evidence that coital position affects fecundability
- No relationship between female orgasm and fertility

ASRM: Vaginal Lubricants

• Water-based lubricants, olive oil, and saliva inhibit sperm motility in vitro by 60-100%
• Canola oil and mineral oil have no effect
• ASRM
  – “It seems prudent to recommend mineral or canola oil, or hydroxyethylcellulose lubes, when needed

Ovulation Prediction Kits (OPK)

- Replaced BBT to confirm ovulation
- Positive with LH surge; ovulation in 14-26 hours later
  - Highest fertility on day of the surge and next 48 hours
  - Best: sex or insemination the day after a + result
- Accuracy: 98% for LH surge; slightly less for ovulation
- Result is “visual” positive or meter-read
  - Positive test indicates presence of ovulation (natural or induced)
  - Ideal timing for intercourse or IVF
Ovulation Prediction Kits (OPK)

- 5-9 urine dipsticks/ cycle; all have control stripe or box
- Perform at time of day listed in package insert
- Start testing 4-5 days before expected ovulation
- Retail cost example...from reputable on-line source
  - $32 for 20 test sticks
  - $8 per cycle if 5 sticks used each cycle
Semen Analysis

• WHO 2010 Reference Ranges
  - Volume: ≥ 1.5 ml (1.4-1.7ml)
  - Concentration: ≥ 15 million/cc
  - Total sperm count > 39 million

Based upon 5%ile of 1,990 men in 8 countries

- Motility: ≥ 40%
- Progressive: ≥32%
- Normal forms: ≥ 4%

• Definitions
  - Conception increases to 50 million/mL, then plateaus
  - Oligospermia: sperm density <20 million/mL
    - Severe oligospermia < 5 million/mL
  - Odds of male infertility increases with the number of semen parameters in the subfertile range
Semen Analysis

Management of results

• Normal: proceed with evaluation
• Oligospermia: repeat after at least 4 weeks
• If repeat semen analysis is low
  – Measure FSH and total testosterone
  – Evaluation by Urologist or REI sub-specialist
• Thresholds for treatment
  – 2-20 million: IUI
  – < 2 million: ICSI (ART program)
Infertility: Visit 2

• Review lab results
  – If hyperprolactinemia, evaluate
  – If hypothyroidism, treat with $T_4$ replacement
  – If abnormal SA x 2, refer to urologist or ART

• Review menstrual calendar and OPK results
  – If ovulatory, proceed HSG
  – If clearly anovulatory, induce ovulation
  – If polymenorrhea or cycle irregularity, evaluate for luteal phase defect
Visit 2: Documentation of Ovulation

- Regular menstrual cycles with intervals of 24–35 days
- Consistent pattern of molimena
- Mid-luteal phase progesterone $\geq 3$ ng/mL
  - Time blood draw 7 days before expected menses
  - Evaluate result relative to onset of actual menses
- Positive ovulation prediction kit
- Pelvic ultrasound evidence of ovulation
- Outdated indicators
  - Secretory endometrium on endometrial biopsy
  - Basal body temperature elevation
Ovarian Aging

- Peak Fertility is between 20-24 years old
- Women have fixed number of oocytes
- At 20 weeks of gestation a female fetus has 6 million oocytes
- Decline in fertility begins in 30s
  - Remaining oocytes are more likely to be aneuploid

Visser JA, de Jong FH, Laven JSE, Themmen, APN, 2006
Pavone ME, Hirshfeld-Cytron JE, Kazer RR, 2011
Ovarian Reserve Testing

Indications

- >35 years or risk factors
- Unexplained infertility
- Ovarian surgery
- Family history of premature menopause
- History of endometriosis
Ovarian Reserve Testing

Follicle Stimulating Hormone/Estradiol level

- Cycle days 2-4
- FSH Typically 3.5-12 IU (>10 concerning)
- Estradiol > 70 pg/mL abnormal
  - Early follicular development, poor oocyte pool
- An elevated estrogen level may suppress FSH early
  - False negative day 3 FSH
- Approximately $50.00

Pavone ME, Hirshfeld-Cytron JE, Kazer RR, 2011
Ovarian Reserve Testing

Elevated FSH predicts poor response
• <10% pregnancy rate with IVF
• Young women with diminished reserve

Older woman with normal FSH
• Prognosis is age-based
• “Normal” test does not improve prognosis

Single abnormal test is predictive
Ovarian Reserve Testing

Antral Follicle count
- <10mm mean diameter
- 5-10 antral follicles assoc with good IVF response
- Best when combined with bloodwork
- $100-200.00

Key Point: Screening tests
- Counseling couples, discussing options
Ovarian Reserve Testing

**AMH (anti-Mullerian hormone)**

- Secreted by granulosa cells/involved in the regulation/recruitment of primordial follicle
- May be drawn at any time of menstrual cycle
- Avoid drawing while on hormonal birth control
- Approximate cost $50-$60.00

AMH vs. FSH

• AMH is a measurement of primordial follicle pool
• Levels decline early ovarian aging
• Elevated levels of FSH do not occur until cycles are already irregular
• Only AMH level shows decline over time

de Vet et al. Fertility and Sterility 2002; 77:357-362
AMH is Secreted by Pre-antral & Antral Follicles

La Marca A et al, Hum Reprod Update 2010
© The Author 2009. Published by Oxford University Press on behalf of the European Society of Human Reproduction and Embryology.

www.DrOsuphi.com
AMH Predictor Of Live Birth

- Study published in 2010 examined an AMH cutoff that discriminates between better and poorer live birth chances
- AMH level <1.05 suggests correlation to FSH 10mIU/ml
- Clinical pregnancies are established at all AMH levels

Fertility and Sterility, 2010:94:7
Uterine Evaluation

- Hysterosalpingogram
- Transvaginal ultrasound
- Saline-infusion sonogram
- Hysteroscopy
- Laparoscopy
Hysterosalpingogram (HSG)

- Water or lipid soluble contrast media is introduced into the cavity
- Done after menses and before ovulation (CD 5-10)
- Can document proximal and distal tubal occlusion and salpingitis
- Approximate cost $200-300
Hysterosalpingogram (HSG)

• Good for confirming tubal patency (83% spec)
• Low specificity for tubal occlusion (65%)
  – Poor accuracy for PROXIMAL obstruction
  – Poor assessment of peritubal disease
• Not to be done if a patient has a history of PID (or treat with doxycycline)
• If normal, may have timed intercourse with or without oral medication for 3-6 cycles

Practice Committee for the ASRM  Diagnostic evaluation of the infertile female: a committee opinion
Fertil Steril. 2015;103(6)e44-e50
Hysterosalpingogram

• Abnormal HSG should be followed up
  – Bilateral tubal blockage, refer
  – Endometrial abnormality - Sonohystogram (SIS)
  – Hysteroscopy
Saline Infusion Sonography (SIS)

- Transvaginal ultrasound with the induction of saline
- High predictive value (>90%) for detection of pathology
- Can cost upwards of $800.00

Practice Committee for the ASRM  Diagnostic evaluation of the infertile female: a committee opinion. Fertil Steril. 2015;103(6)e44-e50
Laparoscopy/Hysteroscopy

• Definitive method for diagnosis and treatment of uterine pathology

• Laparoscopy with chromotubation can document tubal patency and identify fimbrial phimosis or adhesions

• Laparoscopy is diagnostic for endometriosis and peritoneal factors
  – Not recommended for routine evaluation without pelvic pathology or indications
Causes of Ovulatory Dysfunction

- Polycystic ovary syndrome (PCOS)
- Obesity
- Extremes of weight gain or loss
- Eating disorders
- Strenuous exercise
- Thyroid dysfunction
- Hyperprolactinemia
Anovulation: Presentations

- Amenorrhea, oligomenorrhea, or dysfunctional bleeding
- Absence of menstrual symptoms
- Cycle length <24 or >34 days
- Prior need for ovulation induction
- Physical findings of PCOS
  - Obesity
  - Axial hirsuitism, acne
- Galactorrhea
- No ovulation with OPK or low luteal-P level
Clomiphene Citrate

- Initial treatment of choice for most anovulatory or oligo-ovulatory women
- Used with hypothalamic pituitary dysfunction
- Selective estrogen receptor modulator
- Binds to receptors in the hypothalamus
- Increases FSH/LH and causes mid cycle surge
- Use lowest effective dose
- Generic Rx: $4.00-10.00/cycle

Practice Committee of the ASRM. Use of clomiphene citrate in infertile women: a committee opinion
Clomiphene Citrate

- Dose: 50mg (52%), 100mg (22%)
  - 5 days: Cycle days 3-7 or 5-9
  - Higher doses not approved by FDA
  - LH surge 5-12 days after treatment
- Approximately 80% will ovulate
  - Ovulation must be documented
- 15% cycle fecundability
Clomiphene Citrate

- Begin after spontaneous or induced menses
  - May induce menses with progestin x 10 days
  - Ovulation usually occurs 5-7 days after last pill
- OPK starting 3-4 days after last clomiphene or serum progesterone level 12-14 days after last clomiphene
- If spotting or no menses, do a pregnancy test
- If ovulation is documented and pt is not pregnant after 4 cycles, consider HSG
Clomiphene Citrate

Adverse Effects

• Twins: 5-8%, Triplets 0.3%
• Hyperstimulation is rare
• Impairment of endometrial growth
• Cancer
  – Limited studies
  – No causal relationship to breast or ovarian cancer

More than 6 cycles is rarely successful

Clomiphene Citrate

• Predictors of good response
  • Lower BMI
  • Young age
  • Oligomenorrhea
    • Not amenorrhea!
<table>
<thead>
<tr>
<th>Age</th>
<th># Pts</th>
<th>PR/Cycle</th>
<th>PR/Pt</th>
<th>&gt;5 cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>983</td>
<td>11.5%</td>
<td>24.2%</td>
<td>18</td>
</tr>
<tr>
<td>35-37</td>
<td>422</td>
<td>9.2%</td>
<td>18.5%</td>
<td>3</td>
</tr>
<tr>
<td>38-40</td>
<td>265</td>
<td>7.3%</td>
<td>15.1%</td>
<td>4</td>
</tr>
<tr>
<td>41-42</td>
<td>81</td>
<td>4.3%</td>
<td>7.4%</td>
<td>0</td>
</tr>
</tbody>
</table>

Fertil Steril 2008;90:2281-6
Glucophage

- Insulin sensitizing agent
  - Reduces circulating insulin/androgen levels
  - Helps to restore normal ovulation in some women
  - GI side effects are most common

- Dose should be slowly increased
  - 500mg up to 1500 as tolerated
  - Approx. $4.00

Fritz MA, Speroff L. Clinical Gynecologic Endocrinology and Infertility. 2011
Clomiphene, Metformin, or Both for Infertility in the PCOS

RCT 626 women with PCOS treated for 6 months

<table>
<thead>
<tr>
<th></th>
<th>Clomiphene</th>
<th>Metformin</th>
<th>Both</th>
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</thead>
<tbody>
<tr>
<td>Ovulation</td>
<td>49%</td>
<td>29%</td>
<td>60%</td>
</tr>
<tr>
<td>Conception</td>
<td>30%</td>
<td>12%</td>
<td>38%</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td>6%</td>
<td>0</td>
<td>3%</td>
</tr>
<tr>
<td>Live birth</td>
<td>22.5%</td>
<td>7.2%</td>
<td>26.8%</td>
</tr>
</tbody>
</table>
Legro RS et al., NEJM 2007; 356:551-566
Letrozole

Aromatase Inhibitor (AI)
• Increases GnRH and FSH pulsatility
• Doses 2.5-5.0 mg taken cycle days 3-7 or 5-9
• Half life 2 days (vs 2 weeks for clomiphene)
• Comparable to clomiphene for ovulation
• Better endometrial profile
• Not FDA approved for this indication
• Approx. $10-20.00

J Obstet Gynaecol Can 2007;29:668
Fertil Steril 2006;85:1761
Letrozole vs. Clomiphene Citrate

- CC 50 mg daily or letrozole 2.5 mg daily
  - Start on cycle day 3; use for 5 days
  - Up to five menstrual cycles
- Dose increased if nonresponse
- Maximum daily dose (both given for 5 days)
  - CC = 150 mg/d
  - Letrozole 7.5 mg/d

Letrozole vs Clomiphene

• Conclusions
  – Decreased serum estradiol with letrozole
  – Research is conflicting
  – Ovulation rate: 61.7% letrozole, 48.3% CC
  – Live birth rate: 27.5% letrozole, 19.1% CC
Letrozole vs Clomiphene

- Comparable ovulation and pregnancy rates
- May benefit CC resistant pts
- Letrozole may have beneficial endometrial profile
- Majority of studies with PCOS patients
- Letrozole good option, but not FDA approved for this purpose (off-label indication)
Office Based Infertility Evaluation

High Risk Conditions

• Age > 35 (or 40) years old
• Infertile > 3 years
• Anatomical defect (tubal damage, adhesions, myoma)
• Major maternal medical condition
• Severe endometriosis
• Unexplained infertility, not responsive to treatment
  – Poor ovarian reserve
  – Ovarian failure (premature, natural)
  – Surgical oophorectomy
Office Based Infertility Evaluation

“High Risk” factors

None

Ovulation status (Hx, Ovulation predictor kit or P level) +/- FSH/AMH

Ovulatory

S.A/HSG

Pregnant

Normal

Next

Abnormal

Anovulatory

Not pregnant

Poor ovarian reserve

Next

Refer for ART
Ovulatory, HSG normal

Wait 3-6 months/CC, then either

Diagnostic laparoscopy with tubal dye

- Normal
  - "Unexplained infertility"
    - IUI + induce ovulation x4 cycles
      - Pregnant
      - Not pregnant

- Abnormal
  - Refer for ART

Refer for ART

strong suspicion of advanced stage endometriosis, tubal occlusive disease, or peritoneal factors.
Artificial Reproductive Technologies

• Intrauterine Insemination
• IVF
• Donor egg/Donor Sperm
• Donor embryo
• Gestational surrogacy
• Preimplantation Genetic Diagnosis
• Oocyte cryopreservation
Intrauterine Insemination (IUI)

- Used in
  - Cervical factor infertility
  - Unexplained infertility
- Can be done with partner or donor semen
- Sample in lab; washed of antigens, antibodies
- Place 1-4 days before expected ovulation
In Vitro Fertilization

A process by which fertilization take place outside the body
Conclusions

• Diagnostic evaluation for infertility should include assessment of ovulatory function, tubal patency, and semen analysis

• Ovarian reserve testing may be considered for women over 35, family history of early menopause, single ovary or ovarian surgery, chemotherapy, unexplained infertility, or undergoing assisted reproductive technologies

• Routine laparoscopy should not be performed unless there is suspicion of endometriosis or peritoneal factors
Conclusions

• Clomiphene citrate should be considered for anovulatory/oligo-ovulatory clients and is the first line treatment

• When ovulation is documented by menstrual calendar, LH urine kit, or progesterone level, and HSG should be considered to evaluate tubal patency

• Referral to a reproductive specialist should be considered for anovulatory women who are not pregnant after 4-6 cycles of documented ovulation with clomiphene citrate, abnormal HSG evaluation, and an abnormal semen analysis
Conclusions

• When the definition of fertility is not met, efforts should be maximize to maximize fertility
• Time to conceive increases with age....efforts should be made to complete childbearing by mid to late 30s
• The fertile window spans a 6 day interval ending on the day of ovulation.
• Intercourse every 1-2 days during the fertile window increases the likelihood of pregnancy.
• Monitoring ovulation with detection devices might be beneficial.
• Tobacco, alcohol consumption, illicit drugs, and vaginal lubricants should be discouraged
References (MP)

• ASRM. Optimizing natural fertility: a committee opinion. Fertil Steril 2013; 100 (3): 631-7


• Fritz MA and Speroff L. Clinical Gynecologic Endocrinology and Infertility, 8th edition, 2011: Chapter 27 (Female infertility), Ch 30 (Male infertility)


References (JV)


References (JV)


References (JV)

References

• Negro R, Schwartz A, Gismondi R, et al. Increased Pregnancy Loss Rate in Thyroid Antibody Negative Women with TSH Levels Between 2.5 and 5.0 in the First Trimester of Pregnancy. JCEM 2010 95(9);E44-48.


