DIAGNOSIS AND MANAGEMENT OF INFERTILITY

Women’s Health Conference, Jayme S. Bosler, MD
April 21, 2023
Objectives

- Discuss how to optimize natural fertility
- Define Infertility
- Review of an appropriate infertility evaluation
- Basic overview of treatment options
- Knowing when to refer
OPTIMIZING NATURAL FERTILITY
Before getting started

- Start a prenatal vitamin
- Adopt a healthy lifestyle
- Optimize any medical or genetic conditions
What are my chances?

• Conception rates in young fertile heterosexual couples
  ▪ First 3 months of trying (20-37%)
  ▪ 85% by one year
  ▪ 93% by two years

• These rates are lower in older couples
  ▪ Women over age 35
  ▪ Men over age 50
What should be on the menu?

- Myth: Eating certain foods will help you get pregnant
- Fact: Eating a well-balanced diet is most important

- No evidence for any of the following
  - Vegetarian diet
  - Low fat diet
  - Vitamin-enriched diets
  - Antioxidant or herbal remedies

- Evidence for harm
  - Overconsumption of sea food
  - Mercury poisoning
Lifestyle factors that affect infertility.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Impact on fertility</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity (BMI &gt;35)</td>
<td>Time to conception increased 2-fold</td>
<td>Clark (38)</td>
</tr>
<tr>
<td>Underweight (BMI &lt;19)</td>
<td>Time to conception increased 4-fold</td>
<td>Clark (38)</td>
</tr>
<tr>
<td>Smoking</td>
<td>RR of infertility increased 60%</td>
<td>Augood (39)</td>
</tr>
<tr>
<td>Alcohol (&gt;2 drinks/d)</td>
<td>RR of infertility increased 60%</td>
<td>Eggert (40)</td>
</tr>
<tr>
<td>Caffeine (&gt;250 mg/d)</td>
<td>Fecundability decreased 45%</td>
<td>Wilcox (41)</td>
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<tr>
<td>Illicit drugs</td>
<td>RR of infertility increased 70%</td>
<td>Mueller (42)</td>
</tr>
<tr>
<td>Toxins, solvents</td>
<td>RR of infertility increased 40%</td>
<td>Hruska (43)</td>
</tr>
</tbody>
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Note: BMI = body mass index; RR = relative risk.
Reprinted from the document of the same name, last published in 2013 (Fertil Steril 2013;100:631-7).

What needs to go right?

Only 1% of sperm make it through the cervix!
• Myth: Infertility is mostly a female issue

• Fact: There is an equal likelihood that either heterosexual partner will have a problem
  ▪ 1/3 of cases are related to problems with the woman
  ▪ 1/3 of cases are related to problems with the man
  ▪ 1/3 of cases are related to problems with both partners
What does age got to do with it?

- For Women
  - Marked decrease after age 35
  - Related to egg quality

- For Men
  - Semen parameters decline noticeably after age 35
  - Fertility not affected until age 50
Infertility Facts

Figure 1

Trends in the Fertility Rate (births per 1,000 women ages 15-44): Selected Years, 1950-2013

Don’t tell me to relax!

• Myth: Being stressed causes infertility

• Fact: Unhealthy behaviors in response to stress are the real culprits

• Studies linking stress and infertility fail to account for indirect effects
  ▪ Smoking
  ▪ Drinking
  ▪ Infrequent intercourse
  ▪ Comfort foods
How often is too often?

- Myth: frequent ejaculations decrease male fertility

- Fact: abstinence intervals as short as 2 days have no adverse effect

- In normal men
  - No change in semen quality, sperm concentration, or sperm motility with daily ejaculation

- Longer abstinence periods are worse
  - >5 days may adversely effect counts
  - >10 days cause semen parameters to deteriorate significantly
When should we be trying?

• The “Fertile Window”
  ▪ 6-day interval ending on the day of ovulation

• Highest probability
  ▪ 3-day interval ending on day of ovulation
When is the egg being released?

- Monitoring ovulation
  - Cervical mucous
  - Urinary LH kits (ovulation predictor kits)
  - Basal Body Temperature
Cervical mucous, really?

- Inexpensive

- Probability of pregnancy
  - Highest when mucous is slippery and clear

- Volume increases with increasing estrogen
  - Peaks 2-3 days prior to ovulation
Ovulation Predictor Kits

- Detect the midcycle LH surge

- The surge is a brief event
  - Lasts 48-50 hours from start to finish
  - Typically only positive on a single day

- Second void of the day

- Ovulation follows 14-26 hours after the surge

- Greatest Fertility
  - Few days leading up to Day of Detection and next day
What about sex?

- Myth: Certain positions increase your chance

- Fact: No evidence to support one position over another
  - Sperm can be found in the cervical canal seconds after ejaculation
  - Labeled particles placed in the vagina can be found in the tubes within 2 minutes

- Some lubricants can poison sperm
  - Harmful: water-based lubricants (Astroglide, K-Y Jelly), olive oil, saliva
  - Safe: hydroxyethylcellulose based (Pre-Seed, ConceivEase), canola oil
DEFINING INFERTILITY
Infertility

- Definition: Failure to achieve pregnancy after 12 months of regular, unprotected heterosexual intercourse or due to an impairment of a person’s capacity to reproduce either as an individual or with her/his partner.

- Known impairment to a person’s capacity to reproduce (ie. irregular menstrual cycles, anovulation, previous tubal surgery, no access to sperm or ovaries/uterus)

- Evaluation:
  - If a woman is over 35 years old, evaluation should begin after 6 months of attempts
  - If a woman is over 40 years old or has a known impairment, immediate evaluation is warranted

Causes of Infertility

- Tubal and pelvic pathology: 35% for Couples, 40% for Women
- Ovulatory dysfunction: 15% for Couples, 40% for Women
- Unexplained infertility: 10% for Couples, 10% for Women
- Unusual problems: 5% for Couples, 10% for Women
- Male problems: 35% for Couples
EVALUATING INFERTILITY
Infertility Evaluation

- First:
  - Appropriately screened, vaccinated, and sufficiently healthy or has clearance from Maternal-Fetal Medicine to proceed with pregnancy?

- Then:
  - Perform a systematic and organized evaluation to determine appropriate therapy.
    - Ovulation/Eggs/Ovarian Reserve
    - Fallopian Tubes/Peritoneal
    - Uterus/Cervix
    - Male
    - Other Medical Conditions
Anovulation

- Normal Menstrual Cycle 21-35 days
- Test with Ovulation Predictor Kits (OPKs)
- Most common cause is Polycystic Ovarian Syndrome (PCOS)
Ovarian Factor Infertility

• TSH -- hypo/hyperthyroidism
• Prolactin – pituitary microadenoma
• AMH best test for ovarian reserve
• Day 3 FSH (w/ Estradiol only!)
  ▪ -- low value – failure to centrally stimulate follicular growth
  ▪ -- high value – ovarian failure, few eggs remaining to stimulate
Diminished Ovarian Reserve

- Women never make more eggs!
  - 3 blood tests and a vaginal ultrasound
    - Anti-Mullerian Hormone
    - Day 3 Follicle Stimulating Hormone
    - Day 3 Estradiol
    - Antral Follicle Count (AFC)
Egg Quality

- Humans are not efficient at producing normal oocytes
- By the third decade only one out of three eggs will be euploid (33%)
- Age 36/37: five out of six abnormal (17% normal)
- Age 40: eight out of nine are abnormal (11% normal)
- Age 45: 14 of 15 are abnormal (7% normal)
Tubal Factor

• **Fallopian Tubes/Peritoneal**
  - History: STDs, number of partners, appendectomy, prior surgery, endometriosis, myomectomy, ectopic pregnancy

• Testing: HSG, Laparoscopy **get records**

• **All hydrosalpinx need to be addressed, lower implantation rate by 50%, salpingectomy or segmental resection**
  - ESSURE no longer recommended
Tubal Factor

Hysterosalpingograms (HSGs)

Center for Reproductive Health and Gynecology, Beverly Hills, CA,
Tubal factor

- 50% tubal infertility rate after 3 PID episodes
- >50% of cases no history of infection
- Silent chlamydia infections
Tubal factor

• HSG get films, do them yourself
  ▪ 10% False Positive and
  ▪ 10% False Negative

• Laparoscopy with chromopertubation if any doubt
Uterine factor

• Normal uterine cavity is important

• Abnormal cavity
  ▪ Endometrial Polyps
  ▪ Uterine Leiomyomata
  ▪ Intrauterine adhesion
  ▪ Endometrial hyperplasia
Filling defect on HSG
Uterine Factor - Saline Ultrasound

Submucosal Fibroid

Saline fluid injected into uterine cavity

Lower cavity

Adhesion Band

Upper cavity

Oblique view of uterus
Uterine Leiomyomata

- Dense ‘ball’ of myometrial cells and fibrous tissue
- Disrupt uterine cavity
- Lower implantation
Male Factor

- **Semen Analysis**
  - Genetic
  - Anatomic
    - Varicoceles
    - Previous Surgery
  - Hormonal
    - Low Testosterone
    - High FSH
  - Lifestyle Factors
    - Cigarette smoking
    - Alcohol intake
    - Use of illicit drugs
    - Obesity
    - Psychological stress
    - Advanced Paternal Age
    - Diet
    - Caffeine intake

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WHO 1999</th>
<th>WHO 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (mL)</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>Concentration (million/mL)</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Motility, %</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>Normal forms, %</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Live forms, %</td>
<td>60</td>
<td>58</td>
</tr>
</tbody>
</table>
Treatments

• Ovulatory factor: Ovarian stimulation
• Uterine factor: Hysteroscopy, Myomectomy
• Tubal factor: In Vitro Fertilization (IVF)
• Unexplained: Intrauterine insemination, IVF
• Male Factor: Mild – IUI; Severe – IVF with ICSI
TREATING INFERTILITY
Infertility Treatment Options

• Ovulation induction with medications
• Intrauterine insemination (IUI)
• In Vitro Fertilization (IVF) with or without pre-implantation genetic testing (PGT)
• Donor egg, sperm, or embryo
• Gestational Carrier
Ovulation Induction

- Clomiphene citrate
- Letrozole
- Injectable Gonadotropins
- Trigger ovulation with human chorionic gonadotropin (hCG)
Intrauterine Insemination
In Vitro Fertilization

- Stimulation with Injectable Gonadotropins (FSH and LH)
- Oocyte Retrieval
- Fertilization with Intracytoplasmic Sperm Injection (ICSI)
- Embryo Transfer
Third Party Reproduction

- Donor sperm
- Donor egg
- Donor embryo
- Gestational Carrier

Seattlespermbank.com  Eggdonationfriends.com  Embryodonation.com
REFERRING TO REI
When should I seek help?

• After one year of trying without success
• After 6 months if over 35 years
• Earlier if concerning history…
When should I seek help?

- Earlier if you’re female and…
  - Irregular or no menstrual periods
  - LH tests never turn positive
  - History of STDs
  - Prior pelvic or abdominal surgery
  - Single or same-sex relationship

- Earlier if you’re male and…
  - Known problems with the testicles or genitals
  - Problems with ejaculation
  - History of STDs
  - Single or same-sex relationship
If ONLY issue is anovulation…

- For providers that feel comfortable with ovulation induction agents, ie. Clomiphene citrate or Letrozole, **3-6 cycles** before referring to REI

- When starting a new medication or new dose, recommend midcycle transvaginal ultrasound to assess for quantity of developing follicles

- Would not recommend attempting conception with >3 follicles measuring 14mm or over
QUESTIONS?
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