Disclosures

Speakers Bureau EMD Serono

Board of Directors

Nurse Practitioners in Women’s Health (NPWH)
Objectives

• Review human reproduction and necessary components to achieve pregnancy

• Discuss the effects of weight and fertility

• Identify treatment options for the overweight fertility client
Definition of Infertility

• <35 inability to conceive after 12 months of more of unprotected intercourse.

• >35 inability to conceive after 6 months of unprotected intercourse

• Other considerations
  – History of severe endometriosis
  – Male factor fertility
  – Ovarian factors
Male & Female Factors Are Equal
Among couples with identifiable causes of infertility

Couples
- Tubal and pelvic pathology: 35%
- Ovulatory dysfunction: 15%
- Male problems: 35%
- Unexplained infertility: 10%
- Unusual problems: 5%

Women
- Tubal and pelvic pathology: 40%
- Ovulatory dysfunction: 40%
- Unexplained infertility: 10%
- Unusual problems: 10%
Hormones (gonadotropins)

GnRH

- Produced/released from hypothalamus in pulses, triggered by drop in estrogen and progesterone levels
- Targets anterior pituitary to produce/release LH/FSH
- Stress may effect production of GnRH
  - Impacts entire cycle
Hormones (gonadotropins)

- **FSH**
  - Produced/secreted from anterior pituitary
  - Release triggered by GnRH
  - Stimulates follicle development (ovaries)

- **LH**
  - Produced/secreted from anterior pituitary gland
  - Completes follicular maturation
  - Level increases 6 to 10 fold - “LH surge”
  - Rise of LH begins about 36 hours prior to ovulation
  - Post ovulation: causes “luteinization” of theca and granulosa cells - creates the corpus luteum
Menstrual Cycle

DAYS
1  7  14  21  28

FOLLICULAR PHASE  LUTEAL PHASE

OVARIAN CYCLE

OVARUM

OVULATION

UTERINE CYCLE

MENSES  PROLIFERATIVE  SECRETORY

www.womenshealth.gov
Follicular Development / Ovulation
Modifiable Factors

• Weight management
  • Preferred BMI 19-25
  • Women with BMI >27 have higher risk of ovulatory dysfunction

• Personal habits
  • Smoking
  • Exercise
  • Caffeine and Alcohol
<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 two-fold</td>
<td>Hassan and Killick, 2004</td>
</tr>
<tr>
<td>Underweight (BMI&gt;19)</td>
<td>Time to conception increased four-fold</td>
<td>Hassan and Killick, 2004</td>
</tr>
<tr>
<td>Smoking</td>
<td>RR of infertility increased 60%</td>
<td>Clark et al., 1998</td>
</tr>
<tr>
<td>Alcohol (&gt;2 drinks/day)</td>
<td>RR of infertility increased 60%</td>
<td>Eggert et al., 2004</td>
</tr>
<tr>
<td>Caffeine (&gt;250mg/day)</td>
<td>Fecundability decreased 45%</td>
<td>Wilcox et al., 1998</td>
</tr>
<tr>
<td>Illicit drugs</td>
<td>RR of infertility increased 70%</td>
<td>Mueller et al., 1990</td>
</tr>
<tr>
<td>Toxins, solvents</td>
<td>RR of infertility increased 40%</td>
<td>Hruska et al., 2000</td>
</tr>
</tbody>
</table>
Weight and Fertility
Weight and Fertility

- Anovulation
- Menstrual disorders
- Infertility
- Decreased success with ART
- Altered ovarian response and quality
- Miscarriage
- Adverse pregnancy outcomes
Mechanism

- Increased conversion of androgens to estrogen in adipose tissue (estrone)
- Decreased gonadotropins
- Disturbed LH pulsatility
- Insulin stimulates increased production of androgen from the ovaries
- Decreased SHBG levels by insulin
- Changes in the production of adipokines
Mechanism

• Gonadotropin secretion affected
  – Increased peripheral aromatization of androgens to estrogen

• Hyperinsulinemia leads to hyperandrogenemia
  – Granulosa cell apoptosis and impaired ovarian function

• Adipose tissue regulates energy homeostasis
  – Secrete adipokines to regulate physiological processes

• Sex hormone binding globulin (SHBG) and growth hormone (GH) are decreased and leptin levels increased – Increased androgens
## Effects of Adipokines on Reproduction

<table>
<thead>
<tr>
<th>Adipokines</th>
<th>Serum level in obesity</th>
<th>Effects on reproduction</th>
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</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>Increases (resistance)</td>
<td>Inhibits insulin induced steroidogenesis</td>
</tr>
<tr>
<td>Leptin</td>
<td>Increases (resistance)</td>
<td>Inhibits LH stimulated estradiol production by granulosa cells</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Decreases</td>
<td>Plasma insulin levels increase</td>
</tr>
<tr>
<td>Resistin</td>
<td>Increases</td>
<td>Causes insulin resistance</td>
</tr>
<tr>
<td>Visfatin</td>
<td>Increases</td>
<td>Increased insulin sensitivity</td>
</tr>
<tr>
<td>Omentin</td>
<td>Decreases</td>
<td>Increased insulin sensitivity</td>
</tr>
</tbody>
</table>
Obesity and Female Reproduction

• Excess weight increases the risk of menstrual abnormalities
  – Menstrual irregularities occur more frequently in women 175% of ideal body weight compared to less than 150%

• Obese women with regular menstrual cycles still may have decreased fertility
  – Dutch study 3,029 ovulatory women with a BMI >29 had a 4% lower spontaneous pregnancy rate

Practice Committee for the American Society for Reproductive Medicine. Obesity and reproduction: a committee opinion. Fertil Steril. 2015;104(5):1116-1126
Obesity and Female Reproduction

• Obese women have lower chance of conception within 1 year of stopping contraception
  – Insulin induced SHBG reduces gonadotropin secretion
  – Reduced follicular amplitude, not frequency
  – Diminished luteal progesterone levels

Obesity and Female Reproduction

• Systematic review of 27 IVF studies showed 10% lower live birth rate for women with BMI >25
  – Obesity caused by diet causes follicle apoptosis, oxidative stress, reduced embryo survival and abnormal fetal growth

• Women with regular cycles still have decreased fecundity
  – Dutch study found a 4% lower spontaneous pregnancy rate per kg increase in women with a BMI >29 kg
Obesity and Female Reproduction

• Amenorrhea, anovulation, sub fertility, and infertility increases with higher body weight

• Obese women are 3 times more likely to experience irregular menses, anovulation, androgen excess, and infertility
  – Particularly when excess weight gain occurred in adolescence
  – Adolescent obesity is associated with a 3x increased risk of lifetime nulliparity and a 4x increased risk of nulligravity

Adolescent obesity and lifetime nulliparity

Figure 1

Lifetime nulliparity and nulligravidity %

Adolescent obesity and lifetime nulliparity

Female body weight and **number of oocytes**
Miscarriage rate and BMI

![Bar chart showing miscarriage rates by BMI categories (Clinical and Total).](chart.png)
Polycystic Ovary Syndrome
Pathophysiological Characteristics of the Polycystic Ovary Syndrome (PCOS).
Pathophysiology

• Hypothalamic pituitary ovarian dysfunction

• Increased LH (pulse frequency/amplitude)
  – Increased LH:FSH ratio
    • Stimulates ovary to increase androgen production

• Insulin resistance

• Androgen excess
Multiple contributors to PCOS

• Ovary:
  – Increased androgen production from theca cells
    • Increased androgen basal levels and increased LH

• Adrenals:
  – Increased
    • adrenocortical production of androgens
    • DHEAS (40 to 70%)

• Peripheral conversion of androgen precursors

• Decreased SHBG – increased free testosterone
Multiple contributors to PCOS

- Hypothalamic-pituitary-ovarian-uterine axis (HPOU) dysfunction:
  - LH pulse amplitude/frequency higher
  - GnRH pulsatility abnormal
  - Increased LH = Increased androgenic symptoms
  - Decreased FSH = no dominant follicle
Treatment Options for the Obese Client

• Lifestyle Modification – Weight loss
  – Goal BMI < 35
    • Low glycemic/high fat yielded more improvement than high glycemic/low fat
      – Lower insulin resistance
    – Dutch study of anovulatory women lost 10kg (22lbs)
      • 90% achieved ovulation; 78% pregnancy

• Oral Agents
  – Clomiphene Citrate, Letrozole, Metformin

• Injectable Gonadotropins

Fertil Steril. 2015;104(5)1116-1126
Clomiphene Citrate

- Clomiphene Citrate
  - 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

Clomiphene Citrate

• Dosing 50mg (52%), 100mg (22%)
  – Taken for 5 days
  – Higher dose not approved
  – LH surge 5-12 days after

• Baseline ultrasound not needed

• Approximately 80% ovulate; 15% cycle fecundability

• Unexplained Infertility
  – 2-4% CC; 5-10% + IUI
Clomiphene Citrate

- **Adverse Effects**
  - Twins: 5-8%, Triplets 0.3%
  - Impairment of endometrial growth

- **Cancer**
  - No causal relationship to breast or ovarian cancer

- **Predictors of good response**
  - Lower BMI
  - Young age
  - Oligomenorrhea
    - Not amenorrhea!

** More than 6-9 cycles is rarely successful

Letrozole

• Aromatase Inhibitor
  – Increases GnRH and FSH pulsatility
  – Doses 2.5mg or 5.0 mg taken 5 days
  – Comparable to clomiphene citrate for ovulation
    • Not FDA approved
    • Half life 2 days (vs 2 weeks for Clomid)

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

• In PCOS:
  • 5mg Letrozole (n=218), 100mg Clomiphene (n=220)
  • No follicles: 4.4 vs. 6.8
  • Ovulation rate: 67.5% vs. 70.9%
  • Preg Rate/cycle: 15.1% vs. 17.9% (p=0.72)

• Conclusions:
  • Decreased serum estradiol with letrozole
  • No advantage of letrozole over clomiphene

Begum et. Al. Fertility and Sterility 2009
Letrozole vs Clomiphene Citrate

• Clomiphene Citrate Resistant:
  – PCOS (n=64) failed ovulation on 100mg Clomiphene
    • Letrozole 7.5mg (n=32) vs. Clomiphene Citrate 150mg (n=32)
    • Ovulation: 62.5% vs. 37.5% ($p<0.05$)

  – Pregnancy rate over 6 cycles
    • Letrozole: 13/32 (40.62%)
    • Clomiphene citrate: 6/32 (18.75%) $p>0.05$

Begum et. Al. Fertility and Sterility 2009
Letrozole vs Clomiphene Citrate

• 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
Metformin

• 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

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>
</tr>
</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>
Male obesity
Evidence varies as to whether it:

- Alters sperm function
- Increases sperm DNA damage
- Decreases sperm mitochondrial activity
- Induces seminal oxidative stress
- Impairs blastocyst development
- Reduces pregnancy outcome in ART
- Increases miscarriage in ART

Practice Committee of ASRM, 2015 Fertil. Steril. 104, 1116-26
Conclusions

• Obesity has a negative impact on the fertility potential

• Obese women may have menstrual irregularities and lower possibility to conceive (even from adolescence)

• There is reduced response to ovulation inducing agents

• Oocyte quality is affected and endometrial function may be impaired

• The role of men’s obesity needs further investigation

• Lifestyle modification is recommended but it increases natural conceptions only in anovulatory infertile women


