Infertility Evaluation and ART

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Disclosure

No one involved in the planning or presentation of this activity has any relevant financial relationships with a commercial interest to disclose.

Infertility is a Common Disease

- 12% of reproductive age women in the US have infertility
- WHO ranks infertility as the 3rd most serious disease worldwide

Age is the #1 Predictor of Fertility

- Women are less likely to conceive and more likely to miscarry as they get older
Decreasing Egg Quantity with Age

- Finite number of follicles at birth
- 12% remaining at age 30
- 3% remaining at age 40

Abnormal Spindles in Older Eggs

- 20-25 year old eggs: 17% of eggs with abnormal spindle assembly
- 40-45 year old eggs: 83% of eggs with abnormal spindle assembly

Increasing Rates of Chromosomal Abnormalities with Age

Aneuploidy Rates in Couples Undergoing IVF

Battaglia et al., Human Reproduction 1996

Franasiak et al., Fertility and Sterility 2014
Age at which to start trying to conceive

Maximum female age for starting families with 1, 2 or 3 children with a 50, 75 and 90 percent chance of success:

<table>
<thead>
<tr>
<th>Chance of success</th>
<th>1-child family</th>
<th>2-child family</th>
<th>3-child family</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without IVF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>41</td>
<td>18</td>
<td>35</td>
</tr>
<tr>
<td>60%</td>
<td>22</td>
<td>27</td>
<td>33</td>
</tr>
<tr>
<td>With IVF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>42</td>
<td>39</td>
<td>36</td>
</tr>
<tr>
<td>75%</td>
<td>39</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>90%</td>
<td>35</td>
<td>31</td>
<td>28</td>
</tr>
</tbody>
</table>

Haldeman et al. Human Reproduction 2015

Evaluation of the Infertile Couple

- Ovarian Reserve Testing
- Tubal Patency Assessment
- Semen Analysis
- Other Indicated Testing

Evaluation of the Infertile Couple

- Anti-Mullerian Hormone (AMH)
  - The most reliable predictor
  - Produced by granulosa cells of pre-antral and small antral follicles
  - Drawn at any time in the menstrual cycle
  - Can be drawn while on hormonal contraceptives (long-term use may suppress levels)
  - The higher the level, the higher the reserve
  - “Normal” level is age-dependent
Ovarian Reserve Testing

- Follicle Stimulating Hormone (FSH)
  - Indirect marker of ovarian reserve
  - Produced by the pituitary in response to negative feedback from estradiol and inhibin B
  - Drawn on day 2-3 of the menstrual cycle along with an estradiol (E2)
  - The higher the level, the lower the reserve
  - Normal is <10-12 IU/L

Antral Follicle Count (AFC):
- The number of follicles <10mm
- Assessed via transvaginal ultrasound at any time in the cycle
- The higher the AFC, the higher the reserve

There is no screening test for egg QUALITY, only quantity

Tubal Patency Assessment

- Hysterosalpingogram (HSG)
- Sono HSG (FemVue)

- Hysterosalpingogram (HSG)
  - Oil-based better than water-based

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Oil-Based</th>
<th>Water-Based</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ectopic pregnancy — no (%)</td>
<td>10.7(5.1)</td>
<td>15.5(23.7)</td>
<td>0.72 (0.55, 0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Clinical pregnancy — no (%)</td>
<td>82.1(3.1)</td>
<td>91.7(3.8)</td>
<td>0.89 (0.83, 0.96)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Miscarriage — no (%)</td>
<td>15.2(4.3)</td>
<td>17.5(16.4)</td>
<td>1.10 (0.93, 1.29)</td>
<td>0.28</td>
</tr>
<tr>
<td>Live birth — no (%)</td>
<td>21.9(10.1)</td>
<td>22.5(11.3)</td>
<td>0.97 (0.77, 1.19)</td>
<td>0.70</td>
</tr>
<tr>
<td>Stillbirth — no (%)</td>
<td>0.0(0.0)</td>
<td>0.0(0.0)</td>
<td>0.0 (0.0, 1.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Twin fetal death — no (%)</td>
<td>0.0(0.0)</td>
<td>0.0(0.0)</td>
<td>0.0 (0.0, 1.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median duration of pregnancy — no (%)</td>
<td>37.9(14.4)</td>
<td>37.9(14.4)</td>
<td>0.80 (0.65, 0.99)</td>
<td>0.08</td>
</tr>
<tr>
<td>Median pregnancy rate — no (%)</td>
<td>25.0 (23.3)</td>
<td>25.0 (23.3)</td>
<td>1.00 (0.90, 1.12)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

All p values and 95% confidence intervals are compared. Of 704 females, 635 completed IVF cycles, and 99 completed HSG. If FSH values are missing, the median value of the available data points is used. Patients are stratified by the number of previous HSGs and pregnancy outcomes are compared. Rates are compared using the Fisher’s exact test. Data were not available for all outcomes.
Evaluation of the Infertile Couple

- Semen Analysis
- Other Indicated Testing
  - Thyroid
  - Prolactin
  - PCOS labs
  - Other imaging

Optimizing Natural Fertility

<table>
<thead>
<tr>
<th>Table 1: Lifestyles factors affecting infertility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
</tr>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Body Mass (BMI: &gt; 25)</td>
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<tr>
<td>Underweight (BMI: &lt; 18)</td>
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<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Alcohol (2+ drinks/day)</td>
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<tr>
<td>Oral agents (Clomid, Letrozole)</td>
</tr>
<tr>
<td>Injectable FSH/LH (Gonal-F, Follistim, Menopur)</td>
</tr>
<tr>
<td>Often used in conjunction with intrauterine insemination (IUI)</td>
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</tbody>
</table>

Assisted Reproductive Technology (ART) Options

- Superovulation
  - Ovulation of >1 egg to overcome the age effect
  - Oral agents (Clomid, Letrozole)
  - Injectable FSH/LH (Gonal-F, Follistim, Menopur)
  - Often used in conjunction with intrauterine insemination (IUI)
Clomiphene Citrate (Clomid)

- Selective Estrogen Receptor Modulator (SERM)
- ER antagonist at the hypothalamus
- Inhibits negative feedback of estrogen
- Increased GnRH pulsatility
- Increased pituitary FSH and LH secretion

Clomid Instructions
Based on a 28 day cycle

- Take 50-150mg (1-3 tabs) daily x 5 days
- Start on cycle day 3 (days 3-7)
- Check ovulation kit starting day 10 until +
- Intercourse or IUI 12-24 hours after +kit
- Ultrasound on day 10
- Intercoourse or IUI 24-36 hours after hCG trigger

Potential Side Effects of Clomid

- Increased multiple pregnancy rate (7%)
- Mood swings
- Hot flushes
- Headaches
- Bloating
- Visual symptoms and light sensitivity
- Decreased endometrial thickness
- Decreased cervical mucus

Artificial Insemination (AI) or Intrauterine Insemination (IUI)
Letrozole (Femara)

- Aromatase inhibitor (AI)
- Blocks conversion of androgens into estrogen
- Inhibits negative feedback of estrogen
- Increased GnRH pulsatility
- Increased pituitary FSH and LH secretion

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Letrozole (Femara)

- 2.5-7.5mg (1-3 tabs) daily x 5 days
- Not FDA approved for fertility use
- More expensive
- Fewer side effects (fatigue and dizziness)
- Increased success rates in PCOS patients
  - Legro et al., NEJM 2014
  - 750 infertile women 18-40 years of age
  - Randomized to Letrozole or Clomid with intercourse for up to 5 cycles
  - Higher ovulation, pregnancy and live-birth rates in Letrozole group

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IVF Procedure

Egg Retrieval

FSH+LH

Days

hCG trigger

Intracytoplasmic Sperm Injection (ICSI)

Preimplantation Genetic Screening

- PGS vs PGD
- Benefits of PGS for women > 37:
  - Decreased risk of early miscarriages
  - Decreased risk of genetically abnormal pregnancies
  - Decreased number of embryo transfer attempts
  - Decreased risk of multiple gestation
Preimplantation Genetic Screening

- Risks of PGS:
  - Increased cost
  - Increased manipulation of the embryo
  - Decreased total number of embryos for transfer (possible decrease in cumulative pregnancy rate)
  - Error rates and mosaicism

Summary

- Fertility rates decrease and miscarriage rates increase as women get older
- Initiate infertility evaluation and refer to REI after 12 months of trying to conceive in a woman < 35 yrs, and after 6 months in a woman > 35 yrs
- Treatment options include superovulation / IUI and IVF (+/- PGS)

Thank you