Infertility Evaluation and ART

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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

Disclosure

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

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

Wallace and Kelsey, PLoS 2010

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

Battaglia et al, Human Reproduction 1996

Increasing Rates of Chromosomal Abnormalities with Age

Aneuploidy Rates in Couples Undergoing IVF

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>38</td>
<td>35</td>
</tr>
<tr>
<td>75%</td>
<td>37</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>90%</td>
<td>32</td>
<td>27</td>
<td>23</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>

Habbema et al. Human Reproduction 2015

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**Evaluation of the Infertile Couple**

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

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**Center for Reproductive Health**
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)

Dyer et al. NEJM 2017
Evaluation of the Infertile Couple

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

Optimizing Natural Fertility

| TABLE 1 |
|———|
| **Lifestyle factors that affect infertility.** |
| **Factor** | **Impact on fertility** | **Study** |
| Obesity (BMI >35) | Time to conception increased 2-fold | Clark (38) |
| Underweight (BMI <19) | Time to conception increased 4-fold | Clark (38) |
| Smoking | | |
| Alcohol | | |
| (>2 drinks/day) | | |
| Caffeine | FEV1 decreased 4% | Wilcox (41) |
| (>250 mg/dl) | RR of infertility increased 60% | Augood (39) |
| Bitch drugs | RR of infertility increased 70% | Mueller (42) |
| Toxic solvents | RR of infertility increased 40% | Hirokawa (43) |

Note: BMI = body mass index, RR = relative risk

Adapted from the document of the same name, last published in 2013 (until ASRM. Optimizing natural fertility. Fertil Steril 2016.)

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

**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

**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 +
- Ultrasound on day 10
- Intercourse or IUI 12-24 hours after +kit
- hCG trigger
- Intercourse or IUI 24-36 hours after hCG trigger

**Artificial Insemination (AI) or Intrauterine Insemination (IUI)**

- Center for Reproductive Health
- UCSF Center for Reproductive Health
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

**Table 1. Outcomes with Regard to Live-Birth, Ovulation, Pregnancy, Pregnancy Loss, and Fertility**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clomiphene Group [No. (n)]</th>
<th>Letrozole Group [No. (n)]</th>
<th>Absolute Difference [mg (n)]</th>
<th>Raw Ratio ± 95% CI [mg (n)]</th>
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<td>Live birth — no. (%)</td>
<td>72 (23)</td>
<td>56 (21)</td>
<td>16 (0.52) ± 16 (0.52)</td>
<td>0.66 ± 0.04 (0.52)</td>
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<td>Pregnancy — no. (%)</td>
<td>92 (25)</td>
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<td>4 (0.04) ± 4 (0.04)</td>
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<td>Pregnancy loss — no. (%)</td>
<td>43 (10)</td>
<td>38 (9)</td>
<td>5 (0.12) ± 5 (0.12)</td>
<td>0.80 ± 0.05 (0.12)</td>
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<td>Infant mortality — no. (%)</td>
<td>2 (0)</td>
<td>1 (0)</td>
<td>1 (0.5) ± 1 (0.5)</td>
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**IVF**

- 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
IVF Procedure

Center for Reproductive Health

- FSH+LH
- Egg Retrieval
- hCG trigger

Intracytoplasmic Sperm Injection (ICSI)

Preimplantation Genetic Screening

- PGS vs PGD
- Benefits of PGS for women > 37:
  - Decreased risk of early miscarriages from aneuploidy
  - Decreased risk of chromosomally 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