Recent Developments in Infertility Treatment

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Disclosures

• I don’t have financial interest or other relationships with industry relative to the topics being discussed.

Audience Response Question #1

• In the last five years the evaluation and treatment of infertility has become:
  – A) more complicated
  – B) less complicated
  – C) stayed the same

There is no right answer
Audience Response Question #2

- As a result of trends you've seen over the last five years, the chance that you will refer an Infertility patient to a specialist is:
  - A) more likely
  - B) less likely
  - C) no change

Two Main Topics

- The work-up of the Infertile patient has just been simplified.
- There is a new technology in ART that will change the way infertility treatment is performed (and its not PGS)

Infertility: When to Evaluate

<table>
<thead>
<tr>
<th>Patient</th>
<th>Evaluate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A healthy woman having unprotected intercourse</td>
<td>After year</td>
</tr>
<tr>
<td>Healthy woman over 35 yrs.</td>
<td>After 6 months</td>
</tr>
<tr>
<td>Irregular menses, known or suspected uterine/tubal disease, Stage 3-4 endometriosis, male factor</td>
<td>Don't wait</td>
</tr>
</tbody>
</table>
With outcomes-based medicine, many diagnostic steps are no longer recommended

- Post-coital test of cervical mucus
- Rubin’s test or sono contrast test of tubal patency
- Endometrial biopsy for luteal phase deficiency or for culture
- Sperm function tests (e.g. anti-sperm antibodies)
- Chlamydia antibody testing
- Varicocele assessment
- Routine diagnostic laparoscopy
- Routine diagnostic hysteroscopy

With outcomes-based medicine, many diagnostic steps are no longer recommended

- The Clomiphene Challenge Test has been replaced by better methods (Anti-Müllerian Hormone and Antral Follicle Count)

Infertility: How to Begin

**Patient**
- Comprehensive medical, family, social and reproductive history
- Physical exam
- Consider ultrasound, ovarian reserve testing

**Partner**
- Semen analysis
- PMHx
- PSHx
Infertility: What to Ask

• C  Coitus?
• O  Ovulation?
• S  Sperm?
• T  Tubes?

Infertility: What to Ask

• Coitus?
  • Frequency, dyspareunia, ED, premature ejaculation, timing, out of town travel, other sexual dysfunction

• Ovulation?
  • Can be assumed to be normal if the patient has regular 24-35 day cycles

ASSESSMENT OF OVULATION

History
Menstrual calendar
BBT charting
Progesterone over 3 ng/mL
Ovulation predictor kits
Endometrial biopsy
Sonography
# Ovulatory dysfunction: The First Step
Correct the Underlying Disease

- BMI < 20: Gain weight
- Hyperprolactinemia: Medical correction
- Androgen Excess: Medical correction
- Thyroid Disorder: Medical correction
- BMI > 30: Lose weight

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**Ovarian Reserve Assessment:**

**Reasonable candidates:**
- Women of advanced age (>35)
- Women with unexplained infertility at any age
- Prior chemo/XRT/oophorectomy/ovarian cystectomy
- Smoking
- Family history of early menopause
- Poor response to gonadotropins

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**Ovarian Reserve Assessment:**

These are associated with poor response to ovarian stimulation and failure to conceive

- Day 2-3 FSH: high values (over 10 to 14)
- Antral Follicle Count: less than 10 follicles (measuring 2-9 mm)
- Anti-Müllerian Hormone: low (less than 1 ng/mL)
Male Factor Infertility
Male factor accounts for 35-40% of infertility

Semen analysis should be early diagnostic step

• If abnormal, any invasive diagnostic procedures in the woman should be held until decisions are reached regarding the man.

• If normal, attention directed to the female.

Normal values for semen analysis

1. Volume: > 1.5mL (was >2.0)
2. pH: > 7.2
3. Sperm concentration: > 15 x 10^6/mL (was >20)
4. Total sperm count: > 39 x 10^6/ejaculate
5. Motility: > 58%, progressive motility > 32%
6. Morphology: > 4% using “Strict criteria”

Based on samples from 4000 men whose time to pregnancy exceeded 12 months. 1-sided lower reference limit with 95% conf. intervals

WHO Laboratory Manual, 2015

Hysterosalpingogram

• Contrast injected through the cervix
• Can evaluate uterine cavity and patency of fallopian tubes
• Laparoscopy is more expensive but can identify endometriosis and adhesions
Diagnostic Evaluation of Infertility in the Female

• Evidence based
• Cost effective
• Greatly simplified
• Should always involve both partners

ASRM Practice Committee Guidelines 2015

Audience Response Question #3

• In the setting of IVF, controlling for the same number of embryos at transfer, which would have a higher live birth rate:
  – A) fresh embryo transfer
  – B) thawed, previously frozen embryo transfer
  – C) no significant difference

This time, there is a right answer

Cryopreservation of Reproductive Tissues

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sperm</td>
<td>1953</td>
</tr>
<tr>
<td>Embryos</td>
<td>1983</td>
</tr>
<tr>
<td>Oocytes</td>
<td>2013</td>
</tr>
</tbody>
</table>
**Summary of Trends**

**Fresh vs Frozen**

- IVF typically gives us lost of eggs/embryos to work with
- There is a trend towards putting back fewer embryos in order to reduce multiples
- Cryopreservation started in mid-1980s
- Frozen embryo technology provided a place for surplus embryos

**Two types of freezing methods were discovered in the 1980s. Fast and slow:**

- When a cell freezes two bad things happen, water leaves the cell to form external ice, and the intracellular ice crystals form and damage organelles.

**Embryo surrounded by crystal formation**
Traditionally, pregnancy rates in Frozen cycles lagged behind Fresh cycle PR

- Suboptimal transfers
- Embryo prioritization
- By definition, the patient will always be older
- Cryo-thaw survival (70%)

However

There were certain clinical conditions where you skipped a fresh transfer, and did not prioritize embryos into Fresh and Frozen groups

Ovarian Hyperstimulation Syndrome

- Elective cryopreservation of all embryos
- Frozen cycle PR > Fresh cycle PR
  - Queenan JT et al. *Hum Reprod* 1997
  - D’Angelo A. *Semin Reprod Med* 2010
RCT: IVF patients randomized to fresh or frozen-thawed embryo transfer

"ATTRIBUTABLE RISK OF IMPLANTATION FAILURE D/T ENDOMETRIAL RECEPTIVITY IN FRESH GROUP: 64.7%"

Shapiro B et al Fertil Steril 2011;96:344-8

Vitrification
The process of freezing where a substance turns to glass

Amorphous Ice: Solid form of water where the molecules stay randomly arranged.

Vitrification

• Made possible oocyte freezing + thawing
  – Oncofertility
  – Egg banking
  – Donor egg banking
A small hole is made by the laser between two cells for fluid to escape.

In a hyperosmotic (sucrose) bath, water is drawn out and the blast begins to collapse.

Fully collapsed and ready to be frozen. After thawing, re-inflation occurs in about 2 hrs.

Embryo Cryopreservation Thaw Survival Rates

<table>
<thead>
<tr>
<th>Method</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow-freeze/slow thaw</td>
<td>70%</td>
</tr>
<tr>
<td>Vitrification</td>
<td>94-98%</td>
</tr>
</tbody>
</table>

2016 SART National Trends in Clinical Outcomes
Infants born following IVF are at increased risk for:

- Preterm birth
- Low birth weight
- Perinatal mortality
- Congenital anomalies

And these are not solely related to multiple gestations


Pregnancies from fresh IVF cycles are more likely to be affected by disorders of placentation:

- IUGR
- Pre-eclampsia
- First trimester pregnancy loss rate
- Stillbirths

Than pregnancies conceived following frozen embryo transfer

Marino et al. JPIIF 51:11-50, 2014
Summary

- The infertility workup has been simplified and is much easier than before
- Technologic advances in freezing of eggs and embryos will lead to fewer multiple gestations, higher pregnancy rates and better outcomes

Questions?