INFERTILITY FOR THE PRIMARY CARE PROVIDER

Top Ten Myths

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NOTHING TO DISCLOSE
The top ten myths
Educational Objectives

1. Review the basic workup of the infertile couple.
2. Gain better understanding of the uses of modern modalities to document ovulation.
3. Understand the costs of advanced Infertility treatments.
4. Gain insight into the medical coverage of these treatments.
The top ten myths

1. Day 3 FSH is important
2. BBTC is the best way to predict ovulation
3. Endometrial biopsy is useful
4. One sonogram is enough for evaluation
5. Infertility is a woman’s problem
6. Infertility is not covered and expensive
7. You can’t do IVF without breaking a few embryos
8. IVF causes multiple births
9. IVF causes autism
10. IVF docs are all the same
1. Day 3 FSH is important

- Not by itself
- Day 3 Estradiol is just as important
- Less than 80 is good
- Less than 60 is better
- AMH may be able to replace both (0.9-9.5)
<table>
<thead>
<tr>
<th>FSH (mIU/ml)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 (7-12)</td>
<td>Normal</td>
</tr>
<tr>
<td>10-20</td>
<td>Less fertile</td>
</tr>
<tr>
<td>&gt;20</td>
<td>“Donor eggs”</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Menopause</td>
</tr>
<tr>
<td>Variable from cycle to cycle</td>
<td></td>
</tr>
<tr>
<td>Does not give long term prognosis</td>
<td></td>
</tr>
<tr>
<td>2 babies with FSH 100</td>
<td></td>
</tr>
</tbody>
</table>
Comparison of previously published studies evaluating the prognostic value of $E_2$ in patients undergoing ART cycles to the current study.

<table>
<thead>
<tr>
<th>Study</th>
<th>ART cycles$^a$</th>
<th>$E_2$ threshold (pg/mL)</th>
<th>ART cycles above threshold$^b$</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Licciardi et al., 1995</td>
<td>592</td>
<td>&gt;30</td>
<td>332</td>
<td>Decreased pregnancy rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;60</td>
<td>86</td>
<td>Decreased oocyte number</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;75</td>
<td>30</td>
<td>No pregnancies</td>
</tr>
<tr>
<td>Smotrich et al., 1995</td>
<td>292</td>
<td>$\geq$80</td>
<td>27</td>
<td>Increased cancellation rates, decreased pregnancy rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\geq$100</td>
<td>15</td>
<td>No pregnancies</td>
</tr>
<tr>
<td>Evers et al., 1998</td>
<td>231</td>
<td>&gt;60</td>
<td>16</td>
<td>Decreased oocyte number, increased cancellation rates, and no pregnancies</td>
</tr>
<tr>
<td>Vazquez et al., 1998</td>
<td>248</td>
<td>&gt;25</td>
<td>?</td>
<td>Decreased implantation and pregnancy rates only in patients older than 35 years</td>
</tr>
<tr>
<td>Frattarelli et al., 2000</td>
<td>2,476</td>
<td>$&lt;20$</td>
<td>350</td>
<td>Increased cancellation rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\geq$80</td>
<td>92</td>
<td>Increased cancellation rates</td>
</tr>
</tbody>
</table>

$^a$ Total number of ART cycles evaluated in the published article.

$^b$ Total number of ART cycles above the published threshold $E_2$ level.

AMH: Anti-Mullerian Hormone

- AMH can be run at any point in the cycle
- AMH can be used to predict poor prognosis
- Can also be used to predict ovarian hyperstimulation syndrome
- May be useful in dosing infertility meds
- May test while patient is on OCP, therefore useful in egg donors
2. BBTs can predict ovulation

- Inexpensive
- Good 40 years ago
- Studies find 15 to 40% correlation with ovulation
- Increases stress
- Not reproducible
- Occurs after ovulation
2. Urinary LH Kits don't work

### Table 1. Comparison of Previous Studies Involving Urinary LH Tests and the Present Study

<table>
<thead>
<tr>
<th>Primary author</th>
<th>ULH kit</th>
<th>Test site</th>
<th>Subjects</th>
<th>Cycles</th>
<th>Frequency of monitoring</th>
<th>Predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luciano⁴</td>
<td>First Response*</td>
<td>Laboratory &amp; home</td>
<td>50 infertile</td>
<td>40 spont, 10 CC</td>
<td>Daily first AM ULH Daily SLH Daily US</td>
<td>44/47* (94%) collapse within 2 d of +ULH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Daily late AM ULH Daily SLH Daily US</td>
<td></td>
</tr>
<tr>
<td>Vermesh⁵</td>
<td>First Response*</td>
<td>Laboratory</td>
<td>27 infertile</td>
<td>30⁷</td>
<td>Daily ULH Daily SLH Daily US</td>
<td>16/30 (53%) collapse on d of surge</td>
</tr>
<tr>
<td></td>
<td>OvuStick⁴</td>
<td></td>
<td></td>
<td>24⁷</td>
<td>Daily ULH Daily SLH Daily US</td>
<td>24/24 (100%) collapse within 2 d of +ULH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 CC</td>
<td>Daily ULH Daily SLH Daily US</td>
<td>Combined: 90% collapse d of +ULH</td>
</tr>
<tr>
<td>Elkind-Hirsch¹³</td>
<td>OvuStick³</td>
<td>Laboratory</td>
<td>55 infertile</td>
<td>20 spont</td>
<td>Twice daily ULH Daily SLH Daily US</td>
<td>Spont: 16/20 (80%) collapse 24–40 h after +ULH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17 CC</td>
<td>Daily ULH Daily SLH Daily US</td>
<td>CC: 11/17 (65%) collapse 24–40 h after +ULH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>38 GnRH</td>
<td>Daily ULH Daily SLH Daily US</td>
<td>GnRH: 24/24 (100%) collapse 24–40 h after +ULH</td>
</tr>
<tr>
<td>Pearstone¹⁶</td>
<td>Ovukit¹</td>
<td>Home</td>
<td>145 infertile</td>
<td>93 spont</td>
<td>Daily ULH Daily US</td>
<td>Spont: 88/93 (95%) collapse within 2 d of +ULH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>176 CC</td>
<td>Daily ULH Daily US</td>
<td>CC: 172/176 (98%) collapse within 2 d of +ULH</td>
</tr>
<tr>
<td>Miller</td>
<td>Ovuquick²</td>
<td>Home</td>
<td>26 normal</td>
<td>26 spont</td>
<td>Daily ULH Twice daily SLH + US</td>
<td>24/26 (92%) collapse within 2 d of +ULH</td>
</tr>
</tbody>
</table>
3. Endometrial biopsy is useful

- Confirms ovulation and allows dating
- Detects rare subclinical endometritis

- But
  - Pain
  - Cost
  - Poor reproducibility
    - Same slide, same pathologist- 24% agreement
    - Can’t do in conception cycle

- SHOULD NOT BE ROUTINE!

*Noyes et al, Fertil Steril, 1950,*
*Li et al,Fertil Steril 1989*
*ASRM Practice Committee Report 2000*
Submyth: “Day 21” Progesterone should be measured

- Don’t rely on the calendar
- Day 10 – 12 follicle check
- LH kit
- Measure Prog 8 days after surge
- If P₄ > 2.0 ng/mL, patient ovulated
P4 Minute-Minute Variation

NORMAL
Luteal Phase

Progesterone (nmol/L)

Hours

Progesterone (ng/ml)

0 4 8 12 16 20 24

0 4 8 12 16 20

0 10 20 30 40 50 60

confirmed the earlier findings that in women with LBD, LH surge
confirmed the earlier findings in a number of women. We now extend the
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Progesterone levels

- Nat cycle 10
- Clomid cycle 15
- Pregnancy 10-20 controversial
Progesterone supplementation: no PO!

- Prometrium gelcaps: 200-400 bid
- Endometrin tablets: 100 tid (100/200)
- Compounded suppositories: 400 mg bid
- Crinone 8% adhesive cream 90gm qam
- Progesterone in oil 50 mg IM daily
- Stop at 10 weeks if not bleeding
- Wean slowly to 12 weeks if some bleeding
4. Sonograms are not routine

- Fertility evaluation
- Natural Timed Intercourse
- Clomid Timed Intercourse
- Assessment of cysts
- Assessment of fibroids
- Assessment of pain
- Suspicion of endometriosis
- Diagnosis of hydrosalpinx
Fertility Evaluation

- Dx : Fertility testing (V26.21)
- Day 3 FSH/E2
- Day 3 Sonogram (baseline)
- Day 5-10 HSG
- Semen analysis any time in cycle
- Day 10 – 12 Sonogram (follicle check)
- Day “21” Progesterone
- CPT : 76830
Natural Timed Intercourse

- DX : Unexp Infertility (628.9 or V26.1)
- Day 3 FSH/E2 + Sono (76830)
- Day 10 – 12 Follicle check
- Clear Blue Digital
- TIC qday when smiling
- +/- Prog
Clomid Timed Intercourse

- DX: 256.4 (PCO) vs 628.0
- Day 3 FSH/E2/HCG + Sono
- Day 10 – 12 Follicle check Sono
- Repeat Follicle check Sono in 3 – 4 days
- LH kit when follicle > 14mm
- TIC

- Check Prog in 1st cycle
- Patient should be referred if not pregnant after 3 cycles
Half Time Highlights

- Day 3 FSH has limitations
- BBTs are not accurate
- LH kits work well
- Endometrial Bx is not useful
- Day 21 Progesterone shouldn’t always be measured
- One sonogram is never enough
5. Infertility is a woman’s problem
Sperm

Semen analysis (WHO)

- Concentration: $>15 \text{ mill/ml}$
- Motility: $>40\%$
- Morphology:
  - $>30\% \text{ WHO}$
  - $>14\% \text{ strict}$
  - $<4\% \text{ ICSI}$
6. Infertility is not covered
Is infertility covered? A Quiz

- Not at all
- Sometimes
- Most of the time
- All of the time
Submyth: All infertility treatments are expensive

- IUIs are hundreds of dollars
- IVF is about $10000-$15000
- IVF costs have not changed significantly in 20 years
- IVF success rates have improved 4-fold in some centers
Why is IVF expensive?

<table>
<thead>
<tr>
<th>Service</th>
<th>Code</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>OV/Sonos/Bloods</td>
<td>76830/99213</td>
<td>$1608</td>
</tr>
<tr>
<td>Complex prep w/ SA</td>
<td>89263</td>
<td>$378</td>
</tr>
<tr>
<td>Oocyte Identification</td>
<td>89254</td>
<td>$2025</td>
</tr>
<tr>
<td>Retrieval</td>
<td>58970</td>
<td>$1550</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>00940</td>
<td>$640</td>
</tr>
<tr>
<td>US guidance @ Retrieval</td>
<td>76948</td>
<td>included</td>
</tr>
<tr>
<td>Insemination of oocytes</td>
<td>89268</td>
<td>$250</td>
</tr>
<tr>
<td>Culture of embryos</td>
<td>89250</td>
<td>included</td>
</tr>
<tr>
<td>Embryo prep for transfer</td>
<td>89255</td>
<td>included</td>
</tr>
<tr>
<td>Embryo transfer with ultrasound</td>
<td>58974</td>
<td>$1850</td>
</tr>
<tr>
<td>Trail transfer</td>
<td>76942</td>
<td>$165</td>
</tr>
</tbody>
</table>

Total cost = $8474
Micromanipulation Table
PGD- Abnormal Embryo
7. You can’t do IVF without breaking a few embryos

- **Vitrification**: Egg freezing allows the successful freezing of unfertilized eggs.
- It is possible to limit the number of eggs that are fertilized and freeze the remainder of unfertilized eggs.
- **Vitrification** is new, but becoming mainstream.
How Many???
8. IVF causes multiple births

- SET pregnancy rates approach pregnancy rates of 2 or 3 embryos
- In women under 40, there is virtually no difference in pregnancy rates between transfer of 2 vs 3 embryos in our lab
- Scott, et al compared SET 41% PR vs SET + chromosomal analysis 55% PR
9. IVF causes autism

- Danish study Hvidtjorn et al 1995-2003
- 588,967 children
- 5.6 % born from ART. 0.68% with ASD
- Natural conceptions 0.61% with ASD
- Statistically significant!
- But significance disappears when controlling for parental age

10. All IVF Docs are the same

- Survey of 591 new patients (1/09)
- 81 IVF recommended (14%)
- 510 Dx or OI/IUI
- Most patients don’t want or need IVF
- The best IVF Doc knows when not to do IVF
Outreach sites
The top ten myths

1. Day 3 FSH is helpful in some cases
2. LH kit is the best way to predict ovulation
3. Endometrial biopsy is no longer useful
4. One sonogram is never enough for evaluation
5. Infertility is a couple’s problem
6. Infertility is sometimes covered and has remained the same cost for 20 years
7. Vitrification allows IVF without freezing or excess embryos
8. IVF prevents multiple births
9. IVF does not increase risk of autism, and PGD decreases risk of genetic disease
10. The best infertility docs offer the easiest cheapest treatment that works for the patient
If only we were rabbits