Synchronization of Slowly Developing Embryos Restores Implantation Success

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Progesterone and clinical outcomes

- Serum Progesterone on day of HCG administration
- 2 critical breakpoints
- Could exogenous LH be the cause?

Late follicular rise in progesterone

- Retrospective study
- 4032 patients
- $P_4 \geq 1.5$ ng/mL associated with lower ongoing pregnancy rates

Bosch E et al. Hum Reprod. 2010; 25:2092-100

Why Do We Attain Elevated Progesterone Levels in the Follicular Phase?

1. Excessive LH Stimulation
   - Exogenous LH/hCG induced luteinization
   - Failure of the GnRH analog to suppress endogenous LH surges

2. High Response
   - Normal Progesterone production per follicle, with the elevation reflecting accumulation from large numbers of follicles

3. A result of excessive FSH stimulation
**Is the Prevalence of Progesterone Elevations Different in GnRH-ant and GnRH-a cycles?**

- RCT
- N=190
- Mean age 32 years
- Stimulation
  - 150-300 IU recFSH
  - No LH/hCG
- Management not altered by presence of P elevation
- Prevalence not altered by choice of analog
- Outcomes diminished by P >1.5 ng/mL

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**Follicular Progesterone Elevations**

*The Two Cell Theory*

- Progesterone
- DHEA-SO₄
- Cholesterol
- Theca Cell
- LH-R
- Estradiol
- Granulosa Cell
- C₂₁ → C₁₉
- C₂₁ → C₂₇
- FSH-R
- Cholesterol
- C₁₉ → C₁₈
Follicular progesterone elevations

The Two Cell Theory

RE-DEFINING THE EFFECT OF EXOGENOUS LH ACTIVITY IN FOLLICULAR STIMULATION: AN ANALYSIS OF 10,280 CYCLES VALIDATING THE IMPORTANCE OF exLH IN PREVENTING A PREMATURE RISE IN PROGESTERONE


* Colors separate statistically definable groups
Ovarian Response versus Elevated Late Follicular Progesterone Levels (>1.5 ng/mL on day of hCG)

Differences between response groups

Ovarian Response versus Elevated Late Follicular Progesterone Levels (>1.5 ng/mL on day of hCG)

Griesinger et al Fertil Steril 2013; 100:1622-8

N=1866

*All comparisons significantly different except that for > 18 oocytes
Live birth rates after IVF are reduced by both low and high progesterone levels on the day of human chorionic gonadotropin administration.

Adjusted for Peak E2, number of COC’s, patient age, number of embryos transferred, and stage of embryo development.

Santos-Ribiero et al Hum Reprod 2014; 29:1698–1705
**DHEA Administration Increases Progesterone Production**

- Case report of cancer patient with POI
- Patient with ovarian tissue transplantation
- Followed sequentially on and off DHEA for intervals of months
- DHEA – 25 mg po tid
- NO change in E2 levels.
- Does this mean that DHEA induces luteinization?

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**Beware of DHEA Interference in your P Assay**

- Patients receiving DHEA have elevated DHEA-SO₄ levels
- These levels may falsely elevate P levels
- Assay dependent

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Forman JARG 2014; 31:645-9

Strauss et al JARG 2014; 31:645-9
A Physiologic Explanation of Impaired Endometrial Receptivity During Stimulated Cycles

What goes wrong?

Late follicular rise in progesterone

- Retrospective study
- 4032 patients
- $P_4 \geq 1.5$ ng/mL associated with lower ongoing pregnancy rates

Progesterone and the Endometrial Transcriptome

Progesterone Pharmacokinetics

Adapted from S. Young, MD, PhD

Use this information for educational purposes only. Always consult with a licensed health care provider for medical advice.
Meta-analysis of late-follicular P levels and clinical outcome

Summary

- Three studies included
- GnRH-antagonist cycles
- Limited sample size
- Outcomes reduced with late follicular P elevation


Progesterone and the Endometrial Transcriptome

Number of genes differentially expressed vs. 40 mg P

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<th>Natural Cycle</th>
<th>10 mg P</th>
<th>5 mg P</th>
<th>2.5 mg P</th>
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<tr>
<td>≥ 2-fold change</td>
<td>0</td>
<td>0</td>
<td>70</td>
<td>236</td>
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<td>≥ 1.5-fold change</td>
<td>0</td>
<td>0</td>
<td>605</td>
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</table>

Young Lab, Unpublished

Adapted from S. Young, MD, PhD
Revisiting the Window of Receptivity


Delayed Implantation versus Poor Embryo Quality

Wilcox et al NEJM 1999
Start with an Endometrium That is Normal in Every Measurable Way...

Integrins
Selectin
Every other molecular marker you can imagine...

Are there other things to think about with endometrial receptivity?

Onset of LH Surge

Ovulation

Embryonic Window of Implantation

Endometrial Window of Implantation
Onset of LH Surge

Progesterone Rise

Synchronous

Dysynchronous

Embryonic Window of Implantation

Endometrial Window of Implantation

Rise in $P_4$ with time after hCG administration

- Onset of LH Surge
- Ovulation
- Progesterone Rise
- Synchronous
- Dysynchronous
- Embryonic Window of Implantation
- Endometrial Window of Implantation

Rise in $P_4$ with time after hCG administration graph:

- Time in hours from hCG administration
- Serum $P_4$

- $<6$
- 6-7
- 8-9
- 10-11
- 12-13
- $>13$
**Embryonic Endometrial Synchrony - Revisited**

- **hCG administration**
- **Ovulation**
- **Progesterone Rise**
- **Embryonic Window of Implantation**
- **Endometrial Window of Implantation**

*Franasiak et al ASRM 2013*

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**Fresh day 5 embryo transfer**

- **<35**
  - **44%**
- **≥35**
  - **18%**
  - **56%**

*p < .001*

*Franasiak et al ASRM 2013*
**Fresh day 6 embryo transfer**

![Bar chart showing implantation rates](chart.png)

- **p < .05**
- **52%** vs **63%** for D5 M-B1 and D5 B2-B6
- **p < .005**
- **32%** vs **48%**

Franasiak et al ASRM 2013

**Frozen synchronous cycle**

![Images of embryos and endometriums](images.png)

- **Progesterone Start**
- **Endometrial Window of Implantation**

**time**
Frozen day 6 embryo transfer

- p = 0.5
- 57% vs. 60%
- p = 0.3
- 37% vs. 42%

Franasiak et al ASRM 2013

Progesterone and Impaired Implantation: A Study of Euploid Embryos

- Sustained implantation rate (%)
- Hours relative to "Closure" of the Window
- All patients had normal P levels prior to the administration of hCG
Older patients are more likely to have “slow” embryos

Proportion of "Slow" Blastocysts

P<0.0001

Forman et al ASRM 2013

Obstetrical Outcomes Following Fresh versus Cryopreserved Embryo Transfer

• Fresh embryos at increased risk for
  • Preterm birth
  • Low birth weight
  • Small for gestational age

Wennerholm et al Hum Reprod 2013 28:2545-53
The supraphysiologic milieu which accompanies superovulation impact low birth weight risk

- Retrospective review of SART data
- 2004-2006
- 56,792 neonates
- Fresh embryo transfer at increased risk for LBW

Embryonic-Endometrial Synchrony

It take two.....