The luteal phase in a natural and stimulated cycle

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Which hormones seem to be crucial during the luteal phase in a natural cycle?
The role of LH in the luteal phase

Crucial!

→ Totally responsible for steroidogenic activity of the corpus luteum (Casper and Yen, 1979)
→ Upregulation of growth factors, VEGF-A, FGF2 (Sugino et al., 2004; Wang et al., 2002)
→ Upregulation of cytokines involved in implantation (Licht et al., 2001)
→ Stimulation of LH receptors in endometrium (Rao, 2001; Tesarik et al., 2003)
The role of progesterone

- Induces secretory transformation of the endometrium in the luteal phase (Bourgain et al., 1990)

- Progesterone deficiency delays endometrial maturation (Dallenbach-Hellweg, 1984)

- Removal of CL prior to 7 weeks of gestation leads to pregnancy loss (Csapo, 1972)

- Normal pregnancy was sustained when progesterone was given after removal of CL (Csapo, 1973)
Luteo-placental shift

Scott et al., 1991

The prevalence of a luteal phase defect in natural cycles in normo-ovulatory patients with primary or secondary infertility = **8.1%** (Rosenberg et al., 1980).
Causes of luteal phase defect in a natural cycle

- Disordered folliculogenesis
- Defective corpus luteum function
- Abnormal luteal rescue by the early pregnancy
- A variety of clinical conditions, such as
  - hyperprolactinemia
  - hyperandrogenic states
  - weight loss
  - stress
  - athletic training may result not in oligo- or anovulation, but rather may be manifest as LPD (Ginsburg, 1992).
How to define a luteal phase defect in a natural cycle?

- Serum mid-luteal progesterone levels < 10ng/ml (Jordan et al., 1994)

- Mid-luteal progesterone levels do not always reflect the endometrial maturation (Batista et al., 1994)

- “Most reasonable” consensus = a lag of more than two days in endometrial histological development compared to the expected day of the cycle (Jones, 1991; Dawood, 1994).
The luteal phase in stimulated cycles

- **Long agonist protocol**
  - D21
  - Start stimulation

- **Short agonist protocol**
  - D1
  - Start stimulation

- **Antagonist protocol**
  - Luteal phase support

- Pregnancy test
- 7-12 weeks of pregnancy
Luteal phase defect in all stimulated cycles

Schematic representation of changes in luteal phase length and progesterone profile induced by ovarian hyperstimulation for IVF (Macklon et al., 2006)
Endometrial biopsy on the day of ovulation, natural cycle

No secretory features
Endometrial biopsy on the day of oocyte retrieval, GnRH agonist and gonadotrophin stimulation cycle

Clear secretory features
Etiology of luteal phase defect

- Oocyte retrieval?
  - Removal of granulosa cells

- hCG?
  - Suppressing LH

- GnRH agonist? GnRH antagonist?

- Combination of these factors?
LH concentration during the luteal phase (post hCG) in GnRH agonist and gonadotrophin stimulation cycles

Smitz HR 1988

Fig. 9: Mean (± SEM) serum LH concentrations in the luteal phase (day 0 = day of HCG injection) of buserelin/HMG and CC/HMG (controls) treated patients.
GnRH antagonist can be safely administered in gonadotrophin stimulated IUI cycles without luteal phase supplementation

Ragni HR 2001
Is this statement in contradiction with the lecture?

**Answer:** No

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>FSH + antagonist</th>
<th>FSH alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean no of follicles</td>
<td>2.7</td>
<td>3.2</td>
</tr>
<tr>
<td>FSH units</td>
<td>1080</td>
<td>1054</td>
</tr>
<tr>
<td>E2 (ng/ml) (pre hCG)</td>
<td>500</td>
<td>900</td>
</tr>
<tr>
<td>LH (U/L) (day 4 post hCG)</td>
<td>1.8</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*Ragni HR 2001*
Is the luteal phase LH concentration (post hCG) in antagonist – gonadotrophin cycles normal or decreased?
### Is luteal support necessary in GnRH antagonist cycles?

<table>
<thead>
<tr>
<th></th>
<th>r-hCG (n = 11)</th>
<th>r-LH (n = 13)</th>
<th>GnRH agonist (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration follicular phase (d)</td>
<td>11 (9–14)</td>
<td>12 (10–14)</td>
<td>12 (9–16)</td>
</tr>
<tr>
<td>No. days GnRH antagonist</td>
<td>4 (3–8)</td>
<td>4 (3–6)</td>
<td>4 (2–7)</td>
</tr>
<tr>
<td>No. follicles ≥ 11 mm</td>
<td>7 (5–16)</td>
<td>8 (2–18)</td>
<td>9 (3–13)</td>
</tr>
<tr>
<td>No. oocytes retrieved</td>
<td>7 (3–23)</td>
<td>7 (1–26)</td>
<td>10 (1–17)</td>
</tr>
<tr>
<td>No. patients achieving embryo transfer$^b$</td>
<td>9</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Pregnancy$^b$</td>
<td>2 (18%)</td>
<td>1 (8%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Ongoing pregnancy$^b$</td>
<td>2 (18%)</td>
<td>0 (0%)</td>
<td>1 (7%)</td>
</tr>
</tbody>
</table>

Support of corpus luteum function remains mandatory after ovarian stimulation for IVF with GnRH antagonist co treatment.

Beckers et al 2003 JCEM
Iatrogenic luteal phase defect is due to supraphysiological steroid levels in stimulated cycles

(Fatemi et al, HRU, 2007)
The use of progesterone in IVF

Table 5. Meta-analysis of the relative risk and 95% CI of patients using various routes of progesterone vs. placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>Progesterone n/N</th>
<th>Placebo n/N</th>
<th>OR (95% CI fixed)</th>
<th>Weight %</th>
<th>OR (95% CI fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albert et al. [14]</td>
<td>14/43</td>
<td>8/43</td>
<td></td>
<td>9.2</td>
<td>2.11 (0.78, 5.73)</td>
</tr>
<tr>
<td>Belaisch-Allart et al. [19]</td>
<td>27/141</td>
<td>20/145</td>
<td></td>
<td>27.3</td>
<td>1.48 (0.79, 2.78)</td>
</tr>
<tr>
<td>Leeton et al. [17]</td>
<td>14/72</td>
<td>12/80</td>
<td></td>
<td>15.7</td>
<td>1.37 (0.59, 3.19)</td>
</tr>
<tr>
<td>Polson et al. [15] GIFT</td>
<td>13/34</td>
<td>5/42</td>
<td></td>
<td>4.7</td>
<td>4.58 (1.43, 14.64)</td>
</tr>
<tr>
<td>Polson et al. [15] IVF</td>
<td>6/58</td>
<td>10/58</td>
<td></td>
<td>15.4</td>
<td>0.55 (0.19, 1.64)</td>
</tr>
<tr>
<td>Van Steirteghem et al. [16]</td>
<td>18/68</td>
<td>19/100</td>
<td></td>
<td>19.4</td>
<td>1.53 (0.74, 3.20)</td>
</tr>
<tr>
<td>Yovich et al. [18]</td>
<td>11/77</td>
<td>5/60</td>
<td></td>
<td>8.3</td>
<td>1.83 (0.60, 5.60)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>103/493</td>
<td>79/528</td>
<td></td>
<td>100.0</td>
<td>1.57 (1.13, 2.17)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 7.35$, d.f. = 6, $p = 0.29$.  
Test for overall effect: $z = 2.70$, $p = 0.007$. 

Nosarka et al., 2005
Progesterone in LPS

- IM P
- Oral P
- Vaginal P
IM Progesterone

Effective

Physiological serum levels

Painful (long, thick needles)

Occasional sterile abscess

Occasional allergic reaction (oil vehicle)

Needs to be administered by nurse, husband

Acute eosinophilic pneumonia associated with IM administration of progesterone as luteal phase support after IVF: 4 case reports
Vaginal progesterone

First uterine pass effect /targeted delivery

Migration through cervical tissue and lower segment of uterus up to the fundus

Vaginal application of Progesterone
Endometrial Diffusion: Vaginal progesterone

One hour after application

Four hours after application

Progressive diffusion of progesterone from the cervix to the fundus of the uterus

### IM vs Vaginal progesterone

**Intramuscular versus vaginal P administration: ongoing pregnancy per ET.**

<table>
<thead>
<tr>
<th>Study</th>
<th>IM Progesterone n/N</th>
<th>Vaginal Progesterone n/N</th>
<th>Odds Ratio (Fixed) 95% CI</th>
<th>Odds Ratio (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>With GnRHa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smutz 1992</td>
<td>25/131</td>
<td>40/131</td>
<td>1.86 (1.05, 3.30)</td>
<td></td>
</tr>
<tr>
<td>Abate 1999</td>
<td>15/52</td>
<td>6/52</td>
<td>0.32 (0.11, 0.91)</td>
<td></td>
</tr>
<tr>
<td>Sucedo 2000</td>
<td>11/40</td>
<td>11/37</td>
<td>1.12 (0.41, 3.00)</td>
<td></td>
</tr>
<tr>
<td>Propst 2001</td>
<td>39/99</td>
<td>25/102</td>
<td>0.50 (0.27, 0.91)</td>
<td></td>
</tr>
<tr>
<td>Sucedo 2003</td>
<td>7/50</td>
<td>15/50</td>
<td>2.63 (0.97, 7.17)</td>
<td></td>
</tr>
<tr>
<td>Dal Prato 2008</td>
<td>38/138</td>
<td>32/137</td>
<td>0.80 (0.47, 1.38)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (therapeutic doses)</strong></td>
<td><strong>135/510</strong></td>
<td><strong>129/509</strong></td>
<td><strong>0.94 (0.71, 1.26)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Zarutskie et al., FS, 2009
Vaginal vs IM Progesterone

- 544 women undergoing GnRH agonist long luteal phase IVF-ET
- 399 women IM P4
- 145 women vaginal micronized P4

- No difference in clinical pregnancy rates or in pregnancy loss rates

Mitwally et al, Fertil Steril, 2010
Patients prefer Vaginal progesterone over IM

Easier to administer [n=498] 6.6
Less painful [n=497] 6.7
Takes less time [n=496] 6.5
Preferred over IM [n=500] 6.4

Disagree Agree

Levine H., 2000
Oral progesterone ineffective?

- Progesterone administered orally:
  - degradation to its $5\alpha$- and $5\beta$-reduced metabolites. (Penzias, 2002)

- Bourgain (1990) and Devroey (1988): absence of any secretory transformation of the endometrium in patients treated with oral micronised progesterone compared to I.M. or vaginal micronised progesterone
Oral progesterone ineffective?

- Dydrogesterone (DG), a retroprogesterone with good oral bioavailability, which has an anti-estrogenic effect on the endometrium causing a secretory transformation (Whitehead, 1980)

- Chakravarty et al. (2005) in a prospective, randomised study compared the efficacy of vaginal micronised progesterone with oral dydrogesterone as luteal phase support after IVF

Both dydrogesterone (DG) and micronised progesterone (P) were associated with similar rates of successful pregnancies (24.1% vs. 22.8%, respectively; p=0.81).
Oral progesterone ineffective?

- Relatively retarded endometrial development in artificial cycles treated with oral dydrogesterone has been reported in several studies (Pellicer et al., 1989; Li et al., 1994, Fatemi et al., 2007).

- The oral DG might be sufficient for luteal supplementation in IVF cycles, however; more large randomized controlled trails are needed, before a conclusion can be made.
Oral DG versus Vaginal progesterone

**Figure 1.** Representative endometrial biopsy on day 21 of an artificial cycle after micronized progesterone. Patients with premature ovarian failure received estrogen from days 1 to 21 and vaginal progesterone from days 15 to 21. (Coiled glands with active secretion and minimal residual vacuoles. Stromal oedema.) Absence of mitotic activity. The maturation corresponds to day 6 of the luteal phase (haematoxylin and eosin staining, ×200).

**Figure 2.** Representative endometrial biopsy on day 21 of an artificial cycle after oral dydrogesterone. Small glands with minimal coiling and persistent homogeneous subnuclear vacuoles and pseudostratified nuclei. (No stromal edema. Focal mitotic activity.) The maturation corresponds to days 2–3 of the luteal phase (haematoxylin and eosin staining, ×200).
<table>
<thead>
<tr>
<th></th>
<th>Vaginal prog</th>
<th>Vaginal prog + $E_2V$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET (n)</td>
<td>183</td>
<td>195</td>
</tr>
<tr>
<td>Pregnancies (n)</td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td>%</td>
<td>35</td>
<td>32</td>
</tr>
</tbody>
</table>

Smitz HR 1993
**Estradiol supplementation - RCT**

**Pilot trial RCT n = 176**

<table>
<thead>
<tr>
<th>Ongoing pregnancy rate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prog (200 mg bid)</td>
<td>34 / 81 (42 %)</td>
</tr>
<tr>
<td>Prog + E2 patches (100 μg / day, twice / week)</td>
<td>33 / 79 (42 %)</td>
</tr>
</tbody>
</table>

*Serna FS 2008
Similar in meta-analysis Gelbaya FS 2008*
## Vaginal progesterone (Utrogestan) versus vaginal progesterone and estradiol valerate (E₂)

<table>
<thead>
<tr>
<th></th>
<th>Vaginal progesterone</th>
<th>Vaginal progesterone + E₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean) (years)</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Days of stimulation</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>(mean)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH units (mean)</td>
<td>1796</td>
<td>1807</td>
</tr>
<tr>
<td>COC (mean)</td>
<td>12.3</td>
<td>11.9</td>
</tr>
<tr>
<td>Embryos transferred</td>
<td>1.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>

*Fatemi HR 2006*
## Pregnancy outcome in GnRH antagonist cycles

<table>
<thead>
<tr>
<th>Ongoing pregnancies per rand. patients (%)</th>
<th>Vaginal prog</th>
<th>Vaginal prog + E₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg retrieval (%)</td>
<td>26 / 126 (26.0)</td>
<td>30 / 101 (29.7)</td>
</tr>
<tr>
<td>ET (%)</td>
<td>26 / 97 (26.8)</td>
<td>30 / 99 (30.3)</td>
</tr>
<tr>
<td></td>
<td>26 / 90 (29.9)</td>
<td>30 / 92 (32.6)</td>
</tr>
</tbody>
</table>

*Fatemi HR 2006*
A systematic review Gelbaya et al., FS, 2008
Is hCG in the luteal phase superior to progesterone?

hCG does not provide better results than progesterone, and is associated with a greater risk of OHSS.

What is the best timing of luteal support?

- The administration of progesterone before oocyte retrieval is associated with a lower pregnancy rate than the administration of progesterone after oocyte retrieval. (Sohn et al., 1999)

- Decrease of 24% was seen when luteal phase support was delayed until 6 days after OR compared to 3 days after OR (Williams et al., 2001)

- No difference was found when luteal phase support was started at OR compared to starting at ET (Baruffi et al., 2003)
200 mg vaginal progesterone three times daily during 14 days from the day of transfer until the day of a positive HCG test. The study group (n = 150) withdrew vaginal progesterone from the day of positive HCG. The control group (n = 153) continued administration of vaginal progesterone during the next 3 weeks of pregnancy.

**Prolongation of progesterone supplementation in early pregnancy has no influence on the miscarriage rate, and thus no effect on the delivery rate.**

**Progesterone supplementation can safely be withdrawn at the time of a positive HCG test.**

Andersen et al., 2002
Conclusions

- Ovarian stimulation destroys luteal phase receptivity
- Role of supraphysiological levels of steroids
- Vaginal progesterone and progesterone IM do provide similar pregnancy rates
- There is no benefit of addition of estrogens