Mini hCG for Luteal Phase Support - a more Physiologic LPS for ART Treatment

Ovarian Club  Barcelona
16.09.2017
Robert Fischer
MVZ Fertility Center Hamburg
robert.fischer@amedes-group.com
Mini hCG for Luteal Phase Support - a more Physiologic LPS for ART Treatment
Outline

• Why is Luteal Phase support (LPS) required
• Luteal Phase after hCG triggering
• New challenges: GnRH-a triggering
• The more physiological LPS – The evidence
  - The new option

Conclusions
LH-P4 Pulse

Extragonadal activation of endometrial LH receptors and enhancement of implantation

Stimulation of steroidogenesis by the CL

Stimulation of cytokines and growth factors that take part in implantation

Filicori et al., 1984

PULSATILE LH
Is LPS required?

• LP in ALL stimulated IVF cycles is abnormal (vs 8.1% natural cycles)
  Main reason is the inhibition of LH secretion
  (LH pulse frequency and amplitude)
  due to supraphysiological steroid levels and disruption of the feedback mechanisms of the Hypothalamo-pituitary-ovarian axis.

  an insufficient progesterone concentration at the time of implantation or during early pregnancy may cause early pregnancy loss.

Tavaniotou, 2001; Fauser and Devroey, 2003; Edwards, 1980; Fatemi, 2007
Higher Progesterone Level Reduce Pregnancy Loss

Pregnancy loss in relation to the mid-luteal phase progesterone levels in women undergoing ovulation with an agonist trigger

Results from four independent studies

Humaidan et al. (2005) *Hum Reprod.* 20:1213-20
Humaidan et al. (2013) PMID:23753114

Yding Andersen & Andersen, *RBMOnline*, 2014; 28:552
Mid-luteal Progesterone levels are associated with increased pregnancy rates

Viable pregnancies had significantly higher mean P₄ levels in the early luteal phase than non-pregnant. 73% of viable pregnancies, 42% of clinical abortions and 20% of preclinical abortions had a P₄ level exceeding 95 nmol/L in the mid-luteal phase (Liu et al., 1995)

A significant positive association between the mean P₄ concentration during the luteal phase and the clinical pregnancy rate in a study of 544 women undergoing IVF treatment (Mitwally MF et al., 2010)

A significant higher P₄ concentration in patients that became pregnant compared to those who did not (Ellenborgen A et al., 2004)

Yding Andersen & Andersen, RBMOnline, 2014; 28:552
None of the 53 women with a progesterone concentration below 25 nmol/l had a clinical pregnancy and were not included in the present analysis.
Mid-Luteal Phase Progesterone Level as Predictor of Live Birth Rate

Prediction of the chance of a live birth based on the mid-luteal progesterone concentration (multivariate logistic regression model)
Arce J et al., RBMOnline, 2011;22:449
REVIEW

Improving the luteal phase after ovarian stimulation: reviewing new options

Conclusions

Collectively, the present review suggests that: (i) a minimum serum progesterone threshold exists in ovarian stimulation, which needs to be surpassed in order to obtain the most optimal reproductive outcome: this threshold is proposed to be $80-100\,\text{nmol/l}$ during the mid-luteal phase.
The exogenous hCG bolus trigger and the natural/GnRHa trigger induced final maturation of follicles

- 10,000 IU hCG
- Natural mid-cycle surge of LH
- GnRHa trigger induced mid-cycle surge of LH

**Graph Details:**
- **hCG/LH (IU/L)**
- **Time (days):** 0, 1, OPU, OPU+2, OPU+4, OPU+6, OPU+7

**Legend:**
- Red circle: 10,000 IU hCG
- Green circle: Natural mid-cycle surge of LH
- Blue circle: GnRHa trigger induced mid-cycle surge of LH
Levels of progesterone in the luteal phase following the natural menstrual cycle or by the use of hCG bolus trigger.

![Graph showing levels of progesterone (nmol/L) over days after OPU. The graph includes a natural mid-cycle surge and a peak at 10,000 IU hCG.](image-url)
The hCG bolus trigger impacts on the luteal phase

Due to the high concentrations of progesterone and oestradiol the pituitary is inactivated whether down-regulated or not – no LH output

There is a gap of hCG (LH-like activity) in the mid-luteal phase coinciding with the crucial time of implantation

On the other hand the hCG bolus trigger results in a strong luteotropic signal early in the luteal phase

The concentration of progesterone peaks in the early luteal phase and will advance the endometrium

Yding Andersen & Andersen, *RBMOnline* 2014;28:552
Histological dating
in natural and stimulated cycles

Day 0  Day 2  Day 5  Day 7

Histological dating

Natural cycle
Stimulated cycle

P<0.05 (group)
P< 0.001 (interaction)

Bourgain et al, Fertil Steril 2002
Endometrial morphology and pregnancy

Histological dating

Bourgain et al, Fertil Steril 2002
In GnRH antagonist/FSH cycles, advanced endometrial maturation on the day of oocyte retrieval correlates with altered gene expression


According to Noyes' criteria, all endometria taken on the day of oocyte retrieval showed an advanced maturation, ranging from +d2 to +d4. The patients with a subsequent clinical pregnancy all showed a histological dating corresponding to +d2 or +d3.

When comparing endometria +d2-3 to +d4, the microarray results showed a differential expression of 2550 probe sets. Significantly up-regulated genes were SERPINB6, FOXO3A, SOX17 and CDC42. Down-regulated genes of interest were NRP1, HOXA10 and OSF2.
GENE EXPRESSION PROFILING DURING THE WINDOW OF IMPLANTATION - Endometrial Receptivity Array (ERA)

EXPERIMENTAL DESIGN

50 WOMEN

FIVE ENDOMETRIAL BYOIPSIES

AT EACH TIME POINT

AFFIMETRIX

HG-133A

>22,000 genes

LH

Day 1 2 3 4 5 6 7 8 9

hCG

Day 1 2 3 4 5 6 7 8 9

PRE-RECEPTIVE

RECEPTIVE

238 genes / 569 probes

Caucasian
Fertile women with normal cycles
23–39 years
body mass index: 19-25 kg/m2

Horcajadas JA/ Simon C. JCEM 2008
The wide-genomic approach demonstrates a 2-day difference on the cluster of genes governing endometrial receptivity.
Too much of the good?
Experimental evidence suggests prolonged exposure to hCG is detrimental to endometrial receptivity.

This study found that chronic exposure to normal hCG in vitro mediated a down-regulation of LHR in the endometrial epithelial cells and renders cells refractory to acute hCG.
Evidence indicates that supra-physiological levels of hCG during the mid-luteal phase may interfere with successful implantation.
The new challenge: 
GnRH agonist for triggering of ovulation 
and Fresh E.T.

First trials low clinical pregnancy rate – high early pregnancy loss
(Humaidan et al., 2005; Kolibianakis et al., 2005

Low live birth rate after GnRHa versus hCG triggering
(Griesinger et al., Fertil Steril 2007)

Low reproductive outcome attributed to a luteal phase insufficiency
despite supplementation with progesterone and estradiol

GnRHa triggering leads to significantly reduced total amounts of LH released
by the pituitary due to profile and duration of surge.
(Gonen et al., 1990; Itskovitz et al., 1991)

**LH mean mid-luteal phase**
6.0 IU/l in natural cycle
0.2 IU/l hCG trigger
1.5 IU/l in GnRH-a group
(Tavaniotou and Devroey 2003)
(Humaidan et al, 2005)
Serum concentrations of LH (hCG), FSH, E2, and P (during triggering of final stages of oocyte maturation with two GnRH agonist or hCG)

Fauser B C et al. JCEM 2002;87:709-715
Different Strategies for Lut.Phase Support (after GnRH-a Triggering)

- **E2+Progesterone**: (i.m.) high dose until 10 weeks pregnancy  
  
  (Engmann et al. 2008)

- **HCG**: Multi Low-Dose 450 I.U. *(Krause et al. 2006)*  
  Single-Dose 1500 I.U. /Double Dose *(Humaidan et al. 2010; 2013)*  
  Dual–Triggering (GnRHa+1000 I.U. hCG, if E2<4000pg/ml)  
  *(Shapiro et al., 2011; Engmann et al., 2012)*  
  Daily Micro-Dose (125 I.U.) hCG *(C.Y.Andersen et al. 2015))*

- **Rec LH**: Multiple Dose 300 I.U. *(Papanikolaou et al. 2011)*

- **GnRH –Agonist**: Multiple Dose daily *(Pirard et al. 2006, 2015)*  
  *(Bar Hava et al. 2016)*
Pharmacokinetics data: **vaginal route vs IM**

**Plasma progesterone concentrations in steady state**

**Progesterone concentrations in uterine tissue in steady state**

**USE OF EXOGENOUS PROGESTERONE**

Vaginal progesterone provide steady state concentrations around 10 – 12 ng/ml in circulation.

- **Vaginal Pg**
  - 4x200 mg/d
  - 2x50 mg/d

- **IM Pg**
  - 2x1000 mg/d

First uterine pass effect / targeted delivery

*Cicinelli E et al, Obstet Gynecol 2000; 95: 403-6*
Mean $P_4$ concentration in the ovarian vein was 800-fold higher than mean jugular venous levels.

Samples from ovarian veins contralateral to CL-bearing ovaries showed a mean $P_4$ concentration 30 times lower (ipsilateral: $1037 \pm 138$ ng/ml; contralateral: $30 \pm 11$ ng/ml; $P < 0.001$).

Mean progesterone concentration in the uterine vein was approximately 30-fold higher than in jugular and similar in both uterine horns.

**Ovarian production is more likely to cause a direct uterine effect than Vaginal route supplementation**

Daily low-dose hCG stimulation during the luteal phase combined with GnRHa triggered IVF cycles without exogenous progesterone: a proof of concept trial

Claus Yding Andersen¹,², Helle Olesen Elbaek³, Birgit Alsbjerg³,⁴, Rita Jakubcionyte Laursen³, Betina Boel Povlsen³, Lise Thomsen³,⁴, and Peter Humaidan³,⁴

This is a proof-of-concept study conducted as a three arm RCT with a total of 93 patients
Stimulation Protocols:

**hCG trigger**

Control

- **FSH**
- GnRH antagonist
- Progesterone vaginal gel
- Oestradiol tablets

Group 1

- **FSH**
- GnRH antagonist
- hCG 200 IU/day
- hCG 125 IU/day

Group 2

- **FSH**
- GnRH antagonist
- hCG 150 IU/day
- hCG 125 IU/day
Endocrine parameters for women in RCT of follicular phase hCG administration, GnRHa trigger and micro-dose hCG for luteal phase support as compared to a standard protocol (Mean ±SEM)

<table>
<thead>
<tr>
<th></th>
<th>Oestradiol (nmol/L)</th>
<th>Progesterone (nmol/L)</th>
<th>hCG (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Group1</td>
<td>Group 2</td>
</tr>
<tr>
<td>No. women</td>
<td>32</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Day of OT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.0 ±0.7</td>
<td>2.5 ±0.3</td>
<td>3.1 ±0.3</td>
<td>2.6 ±0.2</td>
</tr>
<tr>
<td>7.7 ±1.0</td>
<td>9.4 ±1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.4 ±1.0</td>
<td></td>
<td>2.5 ±0.3</td>
<td>3.1 ±0.3</td>
</tr>
<tr>
<td>Day of OPU</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
</tr>
<tr>
<td>Day of OPU + 7</td>
<td>4.4 ±0.5</td>
<td>5.7 ±0.8</td>
<td>6.8 ±0.6</td>
</tr>
</tbody>
</table>

Yding Andersen et al., Hum Rep 2015;30:2387
hCG during the luteal phase with different dosing

- 125 IU hCG daily
- 1.500 IU hCG on OPU and OPU+5
- 10.000 IU hCG on ovulation trigger
- GnRHa trigger induced mid-cycle surge of LH

hCG (IU/L)

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>OPU</th>
<th>OPU+2</th>
<th>OPU+4</th>
<th>OPU+6</th>
<th>OPU+7</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>96</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>144</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>168</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>192</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>216</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>240</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>264</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>288</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A new concept of Luteal support

By courtesy of C. Yieding Andersen & T. Kelsey
Reproductive outcome of IVF/ICSI treatment in following the antagonist protocol and receiving GnRHa trigger for final oocyte maturation.

<table>
<thead>
<tr>
<th></th>
<th>100 IU hCG daily No exogenous P4 (1 day after OPU for 9 days)</th>
<th>Bolus hCG (1,500 IU) (OPU + individualized OPU 5) 800 mg P4 vag (Ultrogest)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cycles/women</td>
<td>94/84</td>
<td>150/127</td>
<td>NA</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.55 ± 0.43</td>
<td>37.35 ± 0.33</td>
<td>P&gt;0.10*</td>
</tr>
<tr>
<td>Days of stimulation</td>
<td>8.5 ± 0.12</td>
<td>8.5 ± 0.07</td>
<td>P&gt;0.10*</td>
</tr>
<tr>
<td>FSH consumption (IU)</td>
<td>2069 ± 75</td>
<td>2020 ± 59</td>
<td>P&gt;0.10*</td>
</tr>
<tr>
<td>No. oocytes (per cycle)</td>
<td>9.36 ± 0.42</td>
<td>11.58 ± 0.55</td>
<td>P&gt;0.10*</td>
</tr>
<tr>
<td>Normally fertilized (MII oocyte)</td>
<td>478/749 (64%)</td>
<td>925/1411 (66%)</td>
<td>P&gt;0.10**</td>
</tr>
<tr>
<td>Cryopreserved: 2PNs/embryos</td>
<td>44/65</td>
<td>133/74</td>
<td>NA</td>
</tr>
<tr>
<td>No. Embryos for culture</td>
<td>328</td>
<td>610</td>
<td>NA</td>
</tr>
<tr>
<td>No. Embryos used for ET</td>
<td>132/80 (1.7)</td>
<td>234/135 (1.7)</td>
<td>P&gt;0.10**</td>
</tr>
</tbody>
</table>

C.Yding Andersen, R. Fischer et al., JARG, 2016; PMID: 27448021
GnRH-a triggering for ovulation and LPS with only Mini hCG (100 IE s.c. OPU+1 until OPU +9) (<18 Follikel >12mm)

<table>
<thead>
<tr>
<th></th>
<th>100 IE hCG daily no exogenous P4 (Start 1 day after OPU for 9 days)</th>
<th>Bolus hCG (1.500 IE) (OPU + individualised OPU 5) +800 mg P4 vag (Utrogest)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles/Women Age</td>
<td>94/84 36.55 ± 0.43</td>
<td>150/127 37.35 ± 0.33</td>
<td>NA P &gt; 0.10</td>
</tr>
<tr>
<td>Patients with ET (%) /cycle</td>
<td>80 (85 %)</td>
<td>135 (90 %)</td>
<td>P &gt; 0.10</td>
</tr>
<tr>
<td>Nr. pos. hCG (% of ETs)</td>
<td>44 (55 %)</td>
<td>72 (53 %)</td>
<td>P &gt; 0.10</td>
</tr>
<tr>
<td>Biochemical Pregnancies</td>
<td>2 /44 (4.5 %)</td>
<td>13/72 (18,1 %)</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>Clinical Pregnancies(%)</td>
<td>42 (53 %)</td>
<td>59 (44 %)</td>
<td>P &gt; 0.10</td>
</tr>
<tr>
<td>Clinical Miscarriage (%)</td>
<td>3/42 (7.1 %)</td>
<td>10/59 (17 %)</td>
<td>P = 0.09</td>
</tr>
<tr>
<td>Total Pregnancy Losses</td>
<td>5/44 (11.5 %)</td>
<td>23/72 (31.9 %)</td>
<td>P = 0.003</td>
</tr>
<tr>
<td>Ongoing Preg. Day 5 ET</td>
<td>47/75 (63%)</td>
<td>32/64 (50%)</td>
<td>P= 0.028</td>
</tr>
<tr>
<td>OHSS</td>
<td>1 Late Onset-mild</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Yding Andersen, Fischer JARG, 2016;
<table>
<thead>
<tr>
<th></th>
<th>&lt;35</th>
<th>35-39</th>
<th>&gt;= 40</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles</td>
<td>53</td>
<td>85</td>
<td>58</td>
<td>196</td>
</tr>
<tr>
<td>ETs</td>
<td>41 (77,4%)</td>
<td>70 (82,4%)</td>
<td>32 (55,2%)</td>
<td>143 (73,0%)</td>
</tr>
<tr>
<td>Pos.hCG./ET Clin. Preg.</td>
<td>29 (70,7%)</td>
<td>36 (51,4%)</td>
<td>11 (34,4%)</td>
<td>76 (53,2%)</td>
</tr>
<tr>
<td></td>
<td>26 (63,4%)</td>
<td>33 (47,1%)</td>
<td>10 (31,3%)</td>
<td>69 (48,3%)</td>
</tr>
<tr>
<td>Biochem.</td>
<td>3 (13,8%)</td>
<td>3 (8,3%)</td>
<td>1 (9,1%)</td>
<td>7 (9,2%)</td>
</tr>
<tr>
<td>PBGS</td>
<td>15 (28,3%)</td>
<td>38 (44,7%)</td>
<td>49 (84,5%)</td>
<td>102 (52,0%)</td>
</tr>
<tr>
<td>OHSS</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>32,5</td>
<td>37,1</td>
<td>41,8</td>
<td>36,7</td>
</tr>
<tr>
<td>Nr.Oocytes</td>
<td>647 (12,2)</td>
<td>785 (9,24)</td>
<td>399 (6,88)</td>
<td>1831 (9,34)</td>
</tr>
<tr>
<td>MII</td>
<td>535 (82,7%)</td>
<td>662 (84,3%)</td>
<td>336 (84,2%)</td>
<td>1533 (83,7%)</td>
</tr>
<tr>
<td>Fert./MII</td>
<td>361 (67,5%)</td>
<td>403 (60,9%)</td>
<td>231 (68,8%)</td>
<td>995 (64,9%)</td>
</tr>
<tr>
<td>Embryos</td>
<td>69 (1,68)</td>
<td>110 (1,57)</td>
<td>44 (1,38)</td>
<td>223 (1,56)</td>
</tr>
<tr>
<td>Impl.</td>
<td>36 (52,2%)</td>
<td>39 (35,5%)</td>
<td>11 (25,0%)</td>
<td>86 (38,6%)</td>
</tr>
<tr>
<td>Gemini</td>
<td>9 (34,6%)</td>
<td>6 (18,2%)</td>
<td>1 (3,1%)</td>
<td>16 (23,2%)</td>
</tr>
<tr>
<td>Clin.Preg.loss</td>
<td>0</td>
<td>2 (6,1%)</td>
<td>5 (50,0%)</td>
<td>7 (10,1%)</td>
</tr>
<tr>
<td>Total Preg.loss</td>
<td>3/29 (13,8%)</td>
<td>5/36 (13,9%)</td>
<td>6/11 (54,%)</td>
<td>14/76 (18,4%)</td>
</tr>
</tbody>
</table>
### hCG mIU/ml

<table>
<thead>
<tr>
<th>HCG Dosis</th>
<th>Start Tag</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>OPU+1</td>
</tr>
</tbody>
</table>

### P4 ng/ml

<table>
<thead>
<tr>
<th>OPU</th>
<th>HCG mIU/ml</th>
<th>E2 pg/ml</th>
<th>P4 ng/ml</th>
<th>17 OHP µg/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>OPU -2</td>
<td>2199</td>
<td>0.9</td>
<td>1.97</td>
</tr>
<tr>
<td>0</td>
<td>OPU</td>
<td>937</td>
<td>5.4</td>
<td>5.81</td>
</tr>
<tr>
<td>+5</td>
<td>OPU +5</td>
<td>1460</td>
<td>127</td>
<td>28.4</td>
</tr>
<tr>
<td>+7</td>
<td>OPU +7</td>
<td>1697</td>
<td>137</td>
<td>33.6</td>
</tr>
</tbody>
</table>

### hCG Levels in Relation to Oocyte Pick-Up:

- **hCG**:
  - OPU -2: 12704
  - OPU: 22818
  - OPU +5: 22312
  - OPU +7: 23008
  - OPU +14: 22993

- **Progesterone (P4)**:
  - OPU -2: 50
  - OPU: 100
  - OPU +5: 150
  - OPU +7: 200
  - OPU +14: 250

- **Natural Cycle**:
  - Days after OPU:
    - 0: 20
    - 5: 40
    - 10: 60
Conclusions

The luteal phase following a hCG trigger will induce:
- high levels of progesterone in the early luteal phase
- reduced C.L. stimulation during the mid-luteal phase around implantation

In COS a threshold value of P$_4$ of around 80—100 nmol/L exists above which early pregnancy loss is reduced.

The agonist trigger allows a number of new luteal phase protocols to be tested.

A new regime using only daily 100 I.U. hCG s.c. from OPU+1 until OPU+9 is sufficient for LPS after GnRH-a ovulation triggering, showing a P4 luteal phase pattern like the natural cycle and reduced pregnancy loss.
Thank you for your time