Advanced age, poor responders and the role of LH supplementation

C. Alviggi
University “Federico II”, Naples, Italy
Paracrine activity

Since intermediate follicular phase

Expression of LH receptors in the granulosa

Jeppesen et al., JCEM, 2012

- Sustain of FSH-dependent granulosa activities, including aromatase induction and growth factors release (IGF-1, EGF etc…)
- Optimization of steroidogenesis
- Reduction of progesterone production (?)
Role of LH during intermediate folliculogenesis

Who requires LH supplementation?

All patients?

Advanced reproductive age?

Hyporesponders?

Pharmacogenomics?

Antagonists?

Since intermediate follicular phase

(Expression of LH receptors in the granulosa)

- Sustain of FSH-dependent granulosa activities, including aromatase induction and growth factors release (IGF-1, EGF etc…)
- Optimization of steroidogenesis
- Reduction of progesterone production (?)
Among patients treated with FSh and GnRH analogues for in vitro fertilization, is the addition of recombinant LH associated with the probability of live birth? A systematic review and meta-analysis

Kolibianakis EM et al., 2007

7 RCT's (701 patients), among which 5 reported agonist and 2 antagonist cycles.
Recombinant LH supplementation to recombinant FSH during the final days of controlled ovarian stimulation for in vitro fertilization. A multicentre, prospective, randomized, controlled trial


RCT - 526 normogonadotrophic women

Randomization on day 6

**Group 1** \((n = 261)\) r-FSH monotherapy

**Group 2** \((n = 265)\) supplementation with rLH (75 IU <35 years - 150 IU >35 years)

*Hum Reprod, 2008*


Pregnancy rates and outcomes.

<table>
<thead>
<tr>
<th></th>
<th>r-HFSH (n = 68)</th>
<th>r-HFSH + r-HLH (n = 63)</th>
<th>P-value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT population analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive β-HCG test</td>
<td>16.2 (11/68)</td>
<td>28.6 (18/63)</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical pregnancy rate</td>
<td>14.7 (10/68)</td>
<td>27.0 (17/63)</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical pregnancy rate per transfer</td>
<td>18.5 (10/54)</td>
<td>30.4 (17/56)</td>
<td>NS</td>
</tr>
<tr>
<td>Implantation rate</td>
<td><strong>11.3 (16/141)</strong></td>
<td><strong>18.1 (26/144)</strong></td>
<td><strong>0.049</strong></td>
</tr>
<tr>
<td>Live birth rate per started cycle</td>
<td>7.4 (5/68)</td>
<td>19.0 (12/63)</td>
<td><strong>0.047</strong></td>
</tr>
<tr>
<td>Live birth rate per transfer</td>
<td>9.3 (5/54)</td>
<td>21.4 (12/56)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>PP population analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive β-HCG test</td>
<td>18.5 (12/65)</td>
<td>25.4 (16/63)</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical pregnancy rate</td>
<td>16.9 (11/65)</td>
<td>25.4 (16/63)</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical pregnancy rate per transfer</td>
<td>21.2 (11/52)</td>
<td>28.6 (16/56)</td>
<td>NS</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>10.0 (14/140)</td>
<td>17.4 (24/138)</td>
<td>NS</td>
</tr>
<tr>
<td>Live birth rate per started cycle</td>
<td>7.7 (5/65)</td>
<td>17.5 (11/63)</td>
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<tr>
<td>Live birth rate per transfer</td>
<td>9.6 (5/52)</td>
<td>19.6 (11/56)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are percentage (number/total).

HCG = human chorionic gonadotrophin; ITT = intention-to-treat; NS = not statistically significant; PP = per protocol; r-HFSH = recombinant human FSH; r-HLH = recombinant human LH.

\(^a\)Chi-squared test.
Impact of luteinizing hormone administration on gonadotropin-releasing hormone antagonist cycles: an age-adjusted analysis

Ermesto Bosch, M:D:, Elena Labarta, M.D., Juana Crespo, M.D., Carlos Simon, M.D., José Remohi, M.D. And Antonio Pellicer, M.D.

No significant differences between the two stimulation protocols in terms of implantation, pregnancy, and ongoing pregnancy rates in patients aged <36 years old.

The implantation rate was significantly better in those patients given rFSH + rLH in the 36 to 39 years old age group. Clinical and ongoing pregnancy rates were also better in this group, but not statistically significant.
At least two of the following three features must be present:

• Advanced maternal age (≥40 years) or any other risk factor for POR (Turner syndrome, X-fragile mutations, history of chemotherapy etc.)

• A previous poor ovarian response (POR) (≤3 oocytes with a conventional stimulation protocol);

• An abnormal ovarian reserve test (i.e., AFC 5–7 follicles or AMH 0.5–1.1 ng/ml).

  o Two episodes of POR after maximal stimulation are sufficient to define a patient as a poor responder;
  o Patients over 40 years age with an abnormal ovarian reserve test should be more properly defined as expected poor PORs patient.
Hypo-response to rFSH

• Hypo-responders are women with normal ovarian reserve who can achieve ‘adequate’ number of oocytes retrieved and oestradiol production

BUT…

There is an increase in the cumulative rFSH dose (i.e. >3000 IU) and in the stimulation length

Alviggi et al., RBMOnline 2006; RBMOnline 2009; Devroey et al., Hum Reprod Update 2009
Cochrane review 2007 - rLH for controlled ovarian stimulation in hyporesponders

Ongoing PR per woman randomized

<table>
<thead>
<tr>
<th>Study</th>
<th>rLH and rFSH n/N</th>
<th>rFSH alone n/N</th>
<th>Odds Ratio (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Odds Ratio (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrenetxea 2008</td>
<td>8/38</td>
<td>7/38</td>
<td></td>
<td>25.7</td>
<td>1.18 [0.38, 3.70]</td>
</tr>
<tr>
<td>De Placido 2005</td>
<td>19/65</td>
<td>13/65</td>
<td></td>
<td>43.5</td>
<td>1.85 [0.74, 3.71]</td>
</tr>
<tr>
<td>Ferraretti 2004</td>
<td>22/54</td>
<td>11/54</td>
<td></td>
<td>30.8</td>
<td>2.80 [1.14, 6.33]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>155</td>
<td>155</td>
<td></td>
<td>100.0</td>
<td>1.85 [1.10, 3.11]</td>
</tr>
</tbody>
</table>

Total events: 40 (rLH and rFSH), 31 (rFSH alone)
Test for heterogeneity chi-square=1.40 df=2 p=0.50 I²=0.0%
Test for overall effect z=2.32 p=0.02

Favours r-hFSH          Favours r-hFSH + r-hLH

No difference in LH endogenous levels during stimulation

Mochtar MH, Cochrane Database, 2007, Issue 2
Comparison of peak oestradiol concentrations in studies evaluating human menopausal gonadotrophin (HMG) or recombinant (r) LH and rFSH only. All values in the figure are statistically significantly different (P<0.05)

Hill et al., Reprod Biomed Online, 2012
Recombinant LH supplementation to recombinant FSH during induced ovarian stimulation in the GnRH-antagonist protocol: a meta-analysis

RLR Baruffi, Al Mauri, CG Petersen, V Felipe, AMC Martins, J Cornicelli, M Cavagna, JBA Oliveira, JG Franco Jr

<table>
<thead>
<tr>
<th>Trial</th>
<th>Trial</th>
<th>rFSH + rLH</th>
<th>rFSH</th>
<th>WMD</th>
<th>95% CI fixed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean ± SD</td>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levi-Setti et al., 2006</td>
<td>18</td>
<td>6.9 ± 2.1</td>
<td>18</td>
<td>0.4</td>
<td>-1.1, 1.9</td>
</tr>
<tr>
<td>Griesinger et al., 2005</td>
<td>46</td>
<td>6.57 ± 4.17</td>
<td>41</td>
<td>0.08</td>
<td>-1.7, 1.8</td>
</tr>
<tr>
<td>Sauer et al., 2004</td>
<td>21</td>
<td>14.6 ± 9.5</td>
<td>21</td>
<td>0.9</td>
<td>-4.1, 5.9</td>
</tr>
<tr>
<td>Acevedo et al., 2004</td>
<td>22</td>
<td>7.4 ± 1.6</td>
<td>20</td>
<td>2.2</td>
<td>0.98, 3.4</td>
</tr>
<tr>
<td>Cédrin-Durnerin et al., 2004</td>
<td>107</td>
<td>8.2 ± 4.1</td>
<td>93</td>
<td>0.4</td>
<td>-0.73, 1.53</td>
</tr>
<tr>
<td>Total</td>
<td>214</td>
<td>193</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled effect size: fixed</td>
<td></td>
<td></td>
<td></td>
<td>0.88</td>
<td>0.21, 1.54</td>
</tr>
<tr>
<td>(Mulrow–Oxman)</td>
<td></td>
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</tbody>
</table>

Z (test WMD + differs from 0) = 2.58, P = 0.0098
Non-combinability of studies, Cochran Q = 6.196684 (df = 4), P = 0.18.
CI = confidence interval; r = recombinant; WMD = weighted mean difference.
Use of LH and pregnancy

CONCLUSION

• RCTs and one meta-analysis have demonstrated that recombinant LH (rLH) supplementation does not improve neither ovarian response nor outcome of IVF in patients treated with GnRH-analogues

• There is evidence (RCTs and one meta-analysis) that women with ‘ovarian resistance’ (hyporesponse) to rFSH benefit from rLH supplementation (irrespective of basal and post-GnRH-a LH levels) – Hypo-response: high consumption of FSH in a previous cycle or initial slow response to standard rFSH doses despite “normal” ovarian reserve
  Common LH polymorphism is associated with hypo-response:
  pharmacogenetic bases for personalizing controlled OS protocols
  (higher FSH doses - LH supplementation)

• Evidence (RCTs, stratification analysis from RCTs and meta-analysis) suggesting that rLH improves outcome of IVF in women 36 – 39 years old

• Efficacy of rLH in antagonist cycles to be proven in larger RCT (evidence of significant increase in Estradiol levels and number of mature oocytes)

• No evidence that rLH is useful in poor responders (women with reduced ovarian reserve)