Relation between serum progesterone at the end of controlled ovarian stimulation and treatment outcome across type of gonadotropin preparations

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Introduction
Elevated progesterone levels at the end of controlled ovarian stimulation have been shown to have a detrimental effect on treatment outcome in IVF/ICSI patients. Different threshold values have been suggested, depending on patient characteristics and treatment protocol. The present study investigates the following questions:
• How does serum progesterone at the end of stimulation affect the ongoing pregnancy rate in IVF/ICSI patients according to the type of gonadotropin preparation (HP-hMG versus recombinant FSH) used for controlled ovarian stimulation?
• At which progesterone level can a decline in ongoing pregnancy rate be predicted?

Materials & Methods
This is an analysis of two large randomised controlled trials comparing HP-hMG versus recombinant FSH with respect to ongoing pregnancy rate in controlled ovarian stimulation cycles for IVF/ICSI. One trial included 751 patients treated with 150 IU/day HP-hMG and 818 patients treated with 150 IU/day recombinant FSH (MEGASET1). The second trial included 746 patients in a GnRH antagonist protocol (PREGASET2). The gonadotropin starting dose was 225 IU/day for the long GnRH agonist trial and 150 IU/day for the GnRH antagonist trial, and was fixed for the first 5 days. A total of 1,419 IVF/ICSI patients contributed with data to this analysis; 710 were treated with HP-hMG (Merck Serono, Ferring Pharmaceuticals) and 709 were treated with recombinant FSH (352 with follitropin alfa and 357 with follitropin beta). Of these, 1,209 patients underwent embryo / blastocyst transfer.

Results
Table 1 shows the median (intertquartile range) progesterone concentration at end of stimulation for HP-hMG and rFSH in each of the two trials and in the combined dataset.

Table 1. Serum progesterone concentration at end of stimulation (mmol/L)

<table>
<thead>
<tr>
<th>Drug</th>
<th>GnRH antagonist trial</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP-hMG</td>
<td>2.8 (1.9; 3.6)</td>
<td>3.5 (2.6; 4.4)</td>
</tr>
<tr>
<td>rFSH</td>
<td>2.3 (1.7; 3.0)</td>
<td>2.9 (1.9; 3.5)</td>
</tr>
</tbody>
</table>

For the overall population, the ongoing pregnancy rate decreased with increasing end-of-stimulation progesterone with an OR of 0.87 [0.80; 0.95] per 10 nmol/L increase (N=819), and 0.98 [0.95; 0.99] cycle with embryo transfer (N=1,209). Among the patients treated with recombinant FSH, the impact of increasing end-of-stimulation progesterone was significant with an OR of 0.87 [0.80; 0.95] per 10 nmol/L increase (N=860) but not statistically significantly influenced by progesterone at the end of stimulation.

Similarly, for the overall population the impact of progesterone AUC was also significantly (p<0.01) inversely associated with ongoing pregnancy rate. The findings were consistently observed in both individual trials.

Table 2. Odds ratio (OR) for ongoing pregnancy by increasing serum progesterone concentration at end of stimulation

<table>
<thead>
<tr>
<th>Cycle with transfer</th>
<th>HP-hMG</th>
<th>rFSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.88</td>
<td>0.87</td>
</tr>
<tr>
<td>1</td>
<td>0.92</td>
<td>0.92</td>
</tr>
<tr>
<td>2</td>
<td>0.91</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Among the patients with embryo transfer, the predicted ongoing pregnancy rate declined to below the average observed in the trials when the progesterone concentration at the end of stimulation increased above 2.4 nmol/L (0.87 OR and 0.87 AUC) for patients treated with FSH (2.4 nmol/L in the long GnRH agonist trial and 2.3 nmol/L in the GnRH antagonist protocol) and above 2.7 nmol/L for patients treated with HP-hMG (4.0 nmol/L in the long GnRH agonist protocol and 3.5 nmol/L in the GnRH antagonist protocol).

Figures 1-4 display the predicted ongoing pregnancy rate by end-of-stimulation progesterone levels (solid line is regression line, shaded area is 95% confidence interval, dots/crosses are observed data).

Conclusions
• Overall, ongoing pregnancy rate decreased with increasing serum progesterone concentrations at the end of stimulation in IVF/ICSI patients.
• The relation between end-of-stimulation progesterone concentration and ongoing pregnancy rate appears to be influenced by the type of gonadotropin preparation.
• Progesterone levels at end of stimulation should be interpreted in the context of the type of gonadotropin preparation used.

References

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