Clinical Experience With Corifollitropin alfa

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Our team has no financial interaction with MSD company, nor has received any support for the medications used by the patients.
Corifollitropin alfa

- rFSH = recombinant follicle-stimulating hormone
- hCG = human chorionic gonadotropin

Direct gonadotropin suppression

<table>
<thead>
<tr>
<th>Time</th>
<th>Corifollitropin alfa</th>
<th>rFSH</th>
<th>hCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- ≤ 60 kg : 100 µg
- > 60 kg : 150 µg
Inclusion criteria

- First cycle
- All infertility etiologies excluding PCOS
- AFC > 5
- D3 FSH < 10 mIU / mL and E₂ < 80 pg / mL
- Ejaculate sperm
- Age < 42
### Patient and cycle characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33.7 (range 25-42)</td>
</tr>
<tr>
<td>Mean number of oocytes and MII oocytes retrieved / OPU</td>
<td>11.2 and 7.2</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>68</td>
</tr>
<tr>
<td>Mean number of embryos transferred / cycle</td>
<td>1.4 embryo / transfer</td>
</tr>
<tr>
<td>Pregnancy rate per transfer</td>
<td>% 66</td>
</tr>
<tr>
<td>Clinical pregnancy rate per transfer</td>
<td>% 57</td>
</tr>
<tr>
<td>Ongoing pregnancy rate per transfer</td>
<td>% 50</td>
</tr>
</tbody>
</table>
Specific problems of antagonist cycles

**Definition**

D5 of stimulation

- Lead follicle $\geq 14$ mm
- the rest $\leq 10$ mm

Asynchronous follicular growth
Specific problems of antagonist cycles

**Definition**

D5 of stimulation

Lead follicle \( \geq 14 \text{ mm} \)

+ 

the rest \( \leq 10 \text{ mm} \)

1 in 30 cycles
Day when hCG criteria was met

1/3 rd of patients had not required additional rFSH

Data on file.
How long did the stimulation last?

number of patients

stimulation period (days)

<table>
<thead>
<tr>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>11</td>
<td>12</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
How long did the stimulation last?

% 87 completed the stimulation with a maximum of single dose

% 47 completed the stimulation without any extra dose
Did the outcome differ in cycles reaching hCG criteria with a single corifollitropin alfa shot (quick responders)?

![Bar chart showing pregnancy rate per embryo transfer]

- **Quick responders**: 71%
- **Slower responders**: 62%

**Pregnancy rate per embryo transfer**
Additional dose requirement

In 15 cycles that have not reached the criteria for hCG triggering within 7 days of corifollitropin alfa injection, the mean additional dose requirement per patient was:

310 IU of gonadotropin per patient
Peak serum E$_2$ levels on the day of hCG

<table>
<thead>
<tr>
<th>pg / mL</th>
<th>Number of Patients</th>
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<tr>
<td>&lt; 500</td>
<td>2</td>
</tr>
<tr>
<td>500-1000</td>
<td>5</td>
</tr>
<tr>
<td>1000-1500</td>
<td>9</td>
</tr>
<tr>
<td>1500-2000</td>
<td>8</td>
</tr>
<tr>
<td>2000-2500</td>
<td>1</td>
</tr>
<tr>
<td>2500-3000</td>
<td>1</td>
</tr>
<tr>
<td>3000-3500</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 3500</td>
<td>3</td>
</tr>
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</table>
Peak serum $E_2$ levels on the day of hCG

87% relatively safe zone for OHSS

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Peak serum $E_2$ levels on the day of hCG

- Median $P_4$ on the day of hCG:
  - $0.9 \text{ ng / mL}$
Peak serum $E_2$ levels on the day of hCG

<table>
<thead>
<tr>
<th>$E_2$ Concentration (pg/mL)</th>
<th>Number of Patients</th>
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<td>500-1000</td>
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<td>1</td>
</tr>
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<td>1</td>
</tr>
<tr>
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</tr>
<tr>
<td>$&gt; 3500$</td>
<td>3</td>
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</table>

Median $P_4$ on the day of hCG:
- 0.6 ng/mL
- 0.9 ng/mL
What about $P_4$ elevation in follicular phase?

<table>
<thead>
<tr>
<th>Serum $P_4$ on the day of hCG</th>
<th>Number of cycles</th>
</tr>
</thead>
<tbody>
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<td>$\geq 1.5$ ng / mL</td>
<td>0</td>
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What about $P_4$ elevation in follicular phase?

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<table>
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<tr>
<th>cases</th>
<th>Peak estradiol (pg / mL)</th>
<th>Corresponding $P_4$ (ng / mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>5412</td>
<td>1,01</td>
</tr>
<tr>
<td>18</td>
<td>3802</td>
<td>0,4</td>
</tr>
<tr>
<td>26</td>
<td>4926</td>
<td>0,7</td>
</tr>
</tbody>
</table>
Unexpected poor response rate

<table>
<thead>
<tr>
<th>number of cycles with ( \leq 3 ) eggs retrieved</th>
<th>( n ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 / 30 ( %10)</td>
<td></td>
</tr>
</tbody>
</table>
### 3.2.2 Cancellation rate per woman randomized

<table>
<thead>
<tr>
<th>Study</th>
<th>Women randomized</th>
<th>Women randomized</th>
<th>Cancellation</th>
<th>Cancellation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corifollitropin alfa study</td>
<td>53</td>
<td>242</td>
<td>15</td>
<td>83</td>
</tr>
<tr>
<td>Devroy 2004</td>
<td>11</td>
<td>75</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Engage study 2009</td>
<td>62</td>
<td>756</td>
<td>41</td>
<td>750</td>
</tr>
<tr>
<td>Ensure study group 2010</td>
<td>22</td>
<td>268</td>
<td>8</td>
<td>128</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1341</strong></td>
<td></td>
<td><strong>985</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events 148

Heterogeneity: $\chi^2 = 1.16$, $df = 3$ ($P = 0.76$); $I^2 = 0$

Test for overall effect: $Z = 2.49$ ($P = 0.01$)

### 3.2.3 Cancellation due to overstimulation

<table>
<thead>
<tr>
<th>Study</th>
<th>Women randomized</th>
<th>Women randomized</th>
<th>Cancellation</th>
<th>Cancellation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engage study 2009</td>
<td>6</td>
<td>756</td>
<td>0</td>
<td>750</td>
</tr>
<tr>
<td>Ensure study group 2010</td>
<td>6</td>
<td>268</td>
<td>1</td>
<td>128</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1024</strong></td>
<td></td>
<td><strong>878</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events 12

Heterogeneity: $\chi^2 = 0.70$, $df = 1$ ($P = 0.40$); $I^2 = 0$

Test for overall effect: $Z = 2.03$ ($P = 0.04$)

### 3.2.4 Cancellation due to understimulation

<table>
<thead>
<tr>
<th>Study</th>
<th>Women randomized</th>
<th>Women randomized</th>
<th>Cancellation</th>
<th>Cancellation (95% CI)</th>
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<td><strong>1024</strong></td>
<td></td>
<td><strong>878</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events 41

Heterogeneity: $\chi^2 = 0.02$, $df = 1$ ($P = 0.88$); $I^2 = 0$

Test for overall effect: $Z = 0.55$ ($P = 0.58$)
no cancellation in this first series of patients
% of patients

<table>
<thead>
<tr>
<th></th>
<th>Corifollitropin alfa (n=30)</th>
<th>Engage trial</th>
<th>Ensure trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hafif</td>
<td>3.3</td>
<td>2.9</td>
<td>3.0</td>
</tr>
<tr>
<td>Orta</td>
<td>0</td>
<td>2.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Şiddetli</td>
<td>0</td>
<td>1.9</td>
<td>1.8</td>
</tr>
</tbody>
</table>
Day of ET

- D5 transfer: 14
- D2 transfer: 1
- D3 transfer: 15

Embryo quality

- grade I: 44
- grade II-IV: 56
## Day 2 vs Day 3 Initiation of Stimulation

<table>
<thead>
<tr>
<th>Corifollitropin alfa</th>
<th>Cycle Day 2 (n=343)</th>
<th>Cycle Day 3 (n=368)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of stimulation, days</td>
<td>9.8 (1.4)</td>
<td>9.4 (1.5)</td>
</tr>
<tr>
<td>Estradiol on day of hCG, pmol/L</td>
<td>4239 (1512, 11,891)</td>
<td>4899 (1762, 11,671)</td>
</tr>
<tr>
<td>Number of oocytes retrieved</td>
<td>14.1 (8.1)</td>
<td>14.0 (7.9)</td>
</tr>
<tr>
<td>Ongoing pregnancy rate, % (n)</td>
<td>37.9 (130)</td>
<td>43.5 (160)</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless otherwise stated.

*aRestricted to patients treated with hCG.

*bData are median (P5, P95).
# D2 vs D3 start of corifollitropin alfa

<table>
<thead>
<tr>
<th></th>
<th>D2</th>
<th>D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulation phase in days (median)</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Duration of antagonist use in days (median)</td>
<td>5</td>
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</tr>
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<td>Number of oocytes retrieved per OPU (mean)</td>
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<td>Pregnancy rate / ET (%)</td>
<td>63 %</td>
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</thead>
<tbody>
<tr>
<td>Stimulation phase in days (median)</td>
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<td>8 (-1)</td>
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D2 vs D3 start of corifollitropin alfa

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<th>D3</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulation phase in days (median)</td>
<td>9</td>
<td>8</td>
<td>-1</td>
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<td>5</td>
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<td>-1</td>
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<td>+4</td>
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<td>9.6 (+3)</td>
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<td>Pregnancy rate / ET (%)</td>
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<td>75 % (+12)</td>
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</tbody>
</table>
Conclusions

- Corifollitropin alfa can be adopted easily to clinical practice without any compromise in cycle outcomes.

- It has additional benefits of simplicity and patient friendliness.

- Just like the introduction of antagonists into COH, this mode of ovarian stimulation will have a prominent role in the management of IVF cycles.