How clinical practices in ovarian stimulation is developing; Future of IVF treatment

Nikolaos P. Polyzos, MD, PhD
Centre for Reproductive Medicine, Brussels, Belgium
Why do we need new developments in ovarian stimulation

To provide the most optimal treatment

1. Efficient
   - High pregnancy rates

2. Safe
   - Low risk for OHSS

3. Patient friendly
   - Shorter stimulation
   - Fewer injections
Why do we need to also focus on patient friendliness?

To avoid patients dropping our of treatment
Among 384 couples undergoing IVF treatment, 65 (17%) dropped out.

Reason for Dropout

- Physical or psychological burden of treatment: 28%
- Unknown: 25%
- Relational problems/divorce: 11%
- Ethical objections to ICSI treatment after failed IVF treatment: 9%
- Adoption: 8%
- Poor embryo quality: 8%
- Poor response/signs of ovarian aging: 6%
- Other: 6%

ICSI = intracytoplasmic sperm injection.

Adapted from Verberg et al. *Hum Reprod.* 2008;23:2050.
Dropouts Negatively Impact Real Cumulative Pregnancy Rates

Data from 4102 IVF cycles in 2130 women

ECPR = expected cumulative pregnancy rate; RCPR = real cumulative pregnancy rate.

The evolution in ovarian stimulation
The evolution in gonadotropins

Corifollitropin alfa: the long-acting FSH

FSH = follicle-stimulating hormone; aa = amino acids; $t_{1/2}$ = half life.

Unique pharmacokinetic profile

Fauser et al., RBMonline 2010
Corifollitropin alfa Reduces the Number of Necessary Injections

rFSH = recombinant follicle-stimulating hormone; hCG = human chorionic gonadotropin.
DOSE OF CORIFOLLITROPIN ALFA

Corifollitropin alfa dose should be selected based on body weight

- ≤60 kg------100 µg Corifollitropin alfa
- >60 kg------150 µg Corifollitropin alfa
Rationale for different doses (1)

Similar exposure for both body weight groups

Total Drug Exposure (AUC)

The lowest corifollitropin alfa dose for an optimal chance of treatment success is 100 µg for women weighing ≤60 kg and 150 µg for women weighing >60 kg.

Adapted with permission from de Greef R et al. Clin Pharmacol Ther. 2010
Consequences of Inappropriate Dosing of Corifollitropin Alfa: Risk of Cycle Cancellation or Overstimulation

Effect is at a maximum; this will not result in a much higher ovarian response

Insufficient exposure resulting in a risk of cycle cancellation: Drop of FSH activity below threshold

No reduction of ovarian response

Optimal doses

May lead to overexposure and increase risk of overstimulation

Too high dose: 150-µg in ≤60 kg patient
Optimal dose: 150-µg in 70 kg patient
Optimal dose: 150-µg in 90 kg patient
Too low dose: 100-µg in >60 kg patient

FSH = follicle-stimulating hormone


Corifollitropin alfa. Is it an evolution in ovarian stimulation?

Efficacy

Safety

Patient friendliness

Efficacy
# ELONVA Phase III Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>ENGAGE(^1)</th>
<th>ENSURE(^2)</th>
<th>PURSUE(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>▪ &gt;60 kg</td>
<td>▪ ≤60 kg</td>
<td>▪ ≥50 kg</td>
</tr>
<tr>
<td></td>
<td>▪ 18 to 36 years</td>
<td>▪ 18 to 36 years</td>
<td>▪ 35 to 42 years</td>
</tr>
<tr>
<td><strong>Sample Size / Sites</strong></td>
<td>▪ 1,509</td>
<td>▪ 397</td>
<td>▪ 1,424</td>
</tr>
<tr>
<td></td>
<td>▪ Europe 20, North America 14</td>
<td>▪ Europe 14, Asia 5</td>
<td>▪ United States 33</td>
</tr>
<tr>
<td><strong>Treatment Arms</strong></td>
<td>▪ Corifollitropin alfa 150 µg rFSH 200 IU/d</td>
<td>▪ Corifollitropin alfa 100 µg rFSH 150 IU/d</td>
<td>▪ Corifollitropin alfa 150 µg rFSH 300 IU/d</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>▪ Double-blind RCT 1 cycle</td>
<td>▪ Double-blind RCT 1 cycle</td>
<td>▪ Double-blind RCT 1 cycle</td>
</tr>
<tr>
<td><strong>Primary End Point/Coprimary End Point</strong></td>
<td>▪ Ongoing pregnancy rate Number of oocytes</td>
<td>▪ Number of oocytes</td>
<td>▪ Vital pregnancy rate, assessed 5-6 weeks post-ET</td>
</tr>
</tbody>
</table>

> **3,000 women randomized**

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Phase III RCTs: ALL Similar Regimens

**Investigational group**
- Corifollitropin alfa (150 or 100µg)

**Reference group**
- Placebo
- Corifollitropin alfa

**Placebo rFSH**
- Daily rFSH (daily dose ≤150 or 200 or 300 IU)

**GnRH antagonist (ganirelix 0.25 mg/d)**
- Day 5 through day of hCG
- Stimulation day 5
- Stimulation day 8
- hCG as soon as 3 follicles ≥17 mm (or the day thereafter)

**Daily rFSH**
- (daily dose 150, 200 or 300 IU for 7 days)

**ET**
- 1-2 good-quality embryos (day 3-5)
- 2 good-quality embryos (day 3)

**IVF**
- or ICSI

**Luteal phase support**
ENGAGE Trial

>60 KG
18-36 YEARS OLD
1509 PATIENTS

RCT: Corifollitropin alfa 150 µG vs rFSH 200 IU
Ongoing Pregnancy Rate

Intent-to-Treat Population

Δ = 1.1(-3.8, 5.9)

Δ = (95% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Per attempt</th>
<th>Per embryo transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corifollitropin Alfa 150 μg</td>
<td>39.0</td>
<td>43.9</td>
</tr>
<tr>
<td>recFSH 200 IU</td>
<td>38.1</td>
<td>40.6</td>
</tr>
</tbody>
</table>

N=756, n=295
N=750, n=286
N=672, n=295
N=704, n=286
Cumulus-oocyte-complexes

Intent-to-Treat Population

Oocytes Retrieved (Mean ± SD)

<table>
<thead>
<tr>
<th>Cumulus-oocytes complexes, per attempt</th>
<th>Cumulus-oocytes complexes, per stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corifollitropin Alfa 150 µg (N=756)</td>
<td>recFSH 200 IU (N=750)</td>
</tr>
<tr>
<td>13.8 (n=756)</td>
<td>14.2 (n=732)</td>
</tr>
<tr>
<td>12.6 (n=750)</td>
<td>12.7 (n=742)</td>
</tr>
</tbody>
</table>
ENSURE Trial

<60 KG
18-36 YEARS OLD
397 PATIENTS

RCT: Corifollitropin alfa 100µG vs rFSH 150 IU
Number of Oocytes Retrieved

Intent-to-Treat Population

Δ = 2.5 (1.2; 3.9)

Oocytes Retrieved (Mean ± SD)

Cumulus-oocytes complexes, per attempt
- Corifollitropin Alfa 100 μg (N=268)
- recFSH 150 IU (N=128)

Cumulus-oocytes complexes, per stage
- Corifollitropin Alfa 100 μg (N=266)
- recFSH 150 IU (N=127)

n=268 n=128
n=266 n=127
PURSUE Trial

>50 KG
35-42 YEARS OLD
1,424 PATIENTS

RCT: Corifollitropin alfa 150μG vs rFSH 300 IU
Vital Pregnancy

Full Analysis Set

Percent

Per attempt

Corifollitropin Alfa 150 μg (N=632-694)

recFSH 300 IU (N=647-696)

Per embryo transfer
Number of Oocytes Retrieved

\[ \Delta = 0.5 \pm (-0.2, 1.2)^* \]

<table>
<thead>
<tr>
<th>Group</th>
<th>Oocytes Retrieved (Mean)</th>
<th>( N )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corifollitropin Alfa</td>
<td>10.7</td>
<td>694</td>
</tr>
<tr>
<td>recFSH</td>
<td>10.3</td>
<td>696</td>
</tr>
</tbody>
</table>

\*Non-inferiority margin: Lower bound of the 95% CI of -3 oocytes
Ongoing Pregnancy

Full Analysis Set

Per attempt
- Corifollitropin Alfa 150 μg (N=632-694): 22.2%
- recFSH 300 IU (N=647-696): 24.0%

Per embryo transfer
- Corifollitropin Alfa 150 μg (N=632-694): 24.4%
- recFSH 300 IU (N=647-696): 25.8%
Corifollitropin alfa. Is it an evolution in ovarian stimulation
Safety

In which patients categories should be used?

- **Normal responders**
  Very good pregnancy rates comparable with rFSH and similar OHSS risk (ENSURE, ENGAGE, PURSUE)

- **Low responders**
  Comparable pregnancy rates with short agonist protocol

<table>
<thead>
<tr>
<th></th>
<th>Corifollitropin alfa antagonist</th>
<th>Short flare-up agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive hCG/ ET</td>
<td>21.7%</td>
<td>20.6%</td>
</tr>
<tr>
<td>Ongoing pregnancy/ET</td>
<td>13%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Polyzos et al., Fertil Steril 2013 Feb;99(2):422-6
Safety

OHSS

Comparative incidence of ovarian hyperstimulation syndrome following ovarian stimulation with corifollitropin alfa or recombinant FSH

Corifollitropin alfa (n = 1023)
rFSH (n = 880)

Engage/Ensure

Percentage

Mild Moderate Severe Early onset Late onset

3.0 2.2 1.8 4.6 2.3

3.5 1.3 1.3 3.6 2.4

Reproductive BioMedicine Online (2012) 24, 410–419
Safety

Hyper- responders

Follow the Summary product characteristics!!!!!

Do not use Elonva if you

- have had OHSS
- have previously had a treatment cycle of controlled stimulation with >30 follicles of >11mm
- AFC>20
Can we predict excessive response prior to starting a cycle with corifollitropin?

YES
Excessive ovarian response after corifollitropin alfa

AMH: 3.52 ng/ml
AFC: 16
Unexpected hyper-response…. do not pull the trigger..

GnRH agonist triggering

1500 IU hCG 1 hour after oocyte retrieval and fresh embryo transfer

Freeze all embryos

Humaidan, Polyzos et al.  
Hum Reprod 2013

Devroey, Polyzos et al.  
Hum Reprod 2011
Corifollitropin alfa. Is it an evolution in ovarian stimulation

Patient friendliness

Efficacy

Safety

Patient friendliness
Corifollitropin alfa Reduces the Number of Necessary Injections

rFSH = recombinant follicle-stimulating hormone; hCG = human chorionic gonadotropin.
Patients needing additional rFSH

1/3 of patients met the criteria for hCG injection before or on stimulation day 8

3. MSD data on file.
Does early response compromise pregnancy rates?

<table>
<thead>
<tr>
<th>Criteria for hCG reached….</th>
<th>Early responders* N=166</th>
<th>Normal responders** N=549</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of stimulation (days)</td>
<td>7.9 ± 0.3</td>
<td>10.1 ± 1.2</td>
</tr>
<tr>
<td>Number of oocytes</td>
<td>13.6 ± 7.2</td>
<td>14.5 ± 8.1</td>
</tr>
<tr>
<td>Number of GQE, day 3</td>
<td>4.3 ± 3.6</td>
<td>4.8 ± 4.5</td>
</tr>
<tr>
<td>Number of embryos transferred</td>
<td>1.7 ± 0.6</td>
<td>1.6 ± 0.6</td>
</tr>
<tr>
<td>Ongoing PR</td>
<td>43.4</td>
<td>38.8</td>
</tr>
</tbody>
</table>

*early responders: reaching the criterion for HCG administration on or prior to stimulation day 8
** normal responders: reaching the criterion after stimulation day 8

Values are mean ± SD or n (%).

Summary

- Corifollitropin alfa is a key molecule towards a patient-friendly ovarian stimulation
- Very good pregnancy rates in all age categories
- Very good pregnancy rates for normal and poor responders
- Proven safety in terms of OHSS risk
- Patients and physicians may reduce the burden and complexity of IVF treatment
  - 1/3 of women may reach oocyte retrieval with one injection of corifollitropin alfa
What is eventually our perception for the evolution in ovarian stimulation?

- Efficacy
- Safety
- Patient friendliness
- Complexity
- Lack of safety
- Increased drop outs
Thank you