GnRH antagonists in ART

Which patients will benefit most?

Peter Humaidan
The Fertility Clinic, Skive, Denmark

Rome 2007
GnRH antagonists in ART

Proponents:
Most patients benefit from GnRH antagonist treatment
GnRH antagonists in ART

- GnRH antagonist versus GnRH agonist facts:
  - Suppression of the endogenous LH level within a few hours
  - No flare up effect
  - No risk of GnRH agonist induced cyst formation
  - No estrogen deprivation symptoms
  - FSH consumption reduced
  - Duration of stimulation shortened – less costly
  - 21 days shorter treatment duration
  - Unintended administration during early pregnancy avoided
  - Reduction in severe OHSS rate

(Al-Inany et al., 2007; Tarlatzis et al., 2006; Klingmuller et al., 1993; Varney et al., 1993)
GnRH antagonists in ART

And what about the psychological impact:

Significantly fewer symptoms of depression 1 week after treatment termination in women experiencing failure (two or more trials) after GnRH antagonist treatment as compared to long GnRHα treatment (De Klerk et al., 2007)

Significantly lower drop-out rate (Heijnen et al., 2007)
GnRH antagonists in ART

Opponents:

- Less flexible programming

OCP programming is feasible
(Kolibianakis et al., 2006; Fischel et al., 2001)

- Significant difference in clinical pregnancy rate in favour of GnRH antagonist
  on an intention to treat basis
  (number needed to treat to benefit in favour of agonist: 21)

(Al Inany et al., 2007)
GnRH antagonists in ART

But are the GnRH antagonist trials comparable?

- mixture of flexible and fixed protocols
- se-progesterone levels on cd 2
- size of follicle at time of GnRH ant (flexible protocols)
- size of follicle on day of triggering ovulation
- se-progesterone levels on day of hCG

All factors of importance for the receptivity of the endometrium (Kolibianakis et al., 2005, 2004; Bosch et al., 2003)
GnRH antagonists in ART

Assertion:

After a “learning curve”, for the clinician, the majority of normo-responder patients will have a pregnancy outcome with GnRH antagonists similar to that of GnRHa – with the benefits of a “milder” protocol.
Apart from the normo-responder patient will a specific sub-group of patients benefit more than others?
GnRH antagonists in ART

- The low/poor responder patient
- PCOS
- Patients at risk of OHSS/previous OHSS
Poor/low responder

In theory:

GnRH antagonist blocks the GnRH receptors of the pituitary immediately and reduces LH and FSH secretion within hours – LH reduction more pronounced than FSH.

No suppression of FSH in early follicular phase

Theoretically GnRH antagonist could be optimal in patients with decreased ovarian reserve
Poor/low responder

- Recent meta-analysis:

Franco et al., 2006 – 6 studies (407 patients) - long GNRHa/GnRHant (2 studies); short GnrHa/GnRH ant (4 studies)

Result:
- Oocytes ↑ in favour of GnRH ant when comparing long GNRHa/GnRH ant
- Oocytes ↑ in favour of GnrHa when comparing short GNRHa/GnRH ant

No differences in clinical outcome parameters
Recent meta-analysis:

Griesinger et al., 2006 – 8 studies (575 patients) – long
GNRHa/GnRH ant (2 studies); short GnRHa/GnRH ant (6 studies)

Result:
No oocytes ↑ in favour of GnRH ant when long GNRHa/GnRH ant
No significant. difference between short GnRHa/GnRH ant

No differences in clinical outcome parameters
Poor/low responder

CRASH – a modified GnRH antagonist protocol

- 3mg GnRH antagonist cd 23 (luteolysis and synchronization)
- Flexible GnRH antagonist protocol with high dose FSH

follicles ↑ oocytes↑ embryos↑ IR 18.4 PR 38.5%


BUT:
studies in poor/low responders are small, variation in definition, heterogeneity.

More studies needed
Recent meta-analysis:

Griesinger et al., 2006, GnRH ant versus GnRHa – 4 studies (305 randomized patients)

Result:
Duration of stimulation reduced in GnRH ant cycles

No difference regarding consumption and number of oocytes
No difference in clinical outcome parameters
No difference in grade I and II OHSS
No grade III (severe) OHSS reported
GnRH agonist for triggering of ovulation

GnRHa displaces the GnRH antagonist from the GnRH receptors in the pituitary triggering a surge of both LH and FSH which effectively stimulates ovulation and final oocyte maturation

(Gonen et al., 1990; Itskovitz et al., 1991)
Risk of OHSS/Previous OHSS

- Triggering of final oocyte maturation with a bolus of GnRHa – reducing the risk of moderate and severe OHSS
GnRH antagonists in ART

When GnRHa was used to trigger ovulation, we have previously seen unacceptably:

- Low IR
- Low PR
- High rates of early pregnancy loss

Due to a luteal phase insufficiency

Despite luteal phase support with vaginal progesterone and oral oestradiol

(Humaidan et al., 2005; Kolibianakis et al., 2005)
Patients at risk of OHSS

- Triggering of ovulation with GnRHa
- Elective cryopreservation
- Stimulated FER

- Proof of concept study
- 20 patients – 19 FER – ongoing PR 31.6% per first ET
- No cases of moderate or severe OHSS

Griesinger et al., 2007
GnRH agonist for triggering of ovulation – a new modified protocol

Is it possible to transfer in a fresh cycle after triggering of ovulation with GnRHa without compromising the clinical outcome of the patient?

Results of a recent trial
1500 IU hCG secures a normal pregnancy outcome in IVF/ICSI GnRH antagonist cycles in which ovulation was triggered with GnRH agonist

Humaidan P., Ejdrup Bredkjær H., Westergaard L.G. and Yding Andersen C.

1The Fertility Clinic, Viborg Hospital (Skive), Denmark, 2The Fertility Clinic, Holbæk Hospital, Denmark, 3The Fertility Clinic, Odense University Hospital, Denmark, 4Laboratory of Reproductive Biology, University Hospital of Copenhagen.
Reproductive Outcome in 0.5mg GnRHa/1500 IU hCG versus 10.000 IU hCG triggered ovulation

<table>
<thead>
<tr>
<th></th>
<th>GnRHa/hCG</th>
<th>hCG</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>153</td>
<td>152</td>
<td></td>
</tr>
<tr>
<td>Rate of transfer, n (%)</td>
<td>132 (86%)</td>
<td>138 (91%)</td>
<td>NS</td>
</tr>
<tr>
<td>Pos. hCG per ET, n (%)</td>
<td>67 (51%)</td>
<td>72 (52%)</td>
<td>NS</td>
</tr>
<tr>
<td>CP/ET, W7, n (%)</td>
<td>50 (38%)</td>
<td>55 (40%)</td>
<td>NS</td>
</tr>
<tr>
<td>IR, n (%)</td>
<td>60/211 (28%)</td>
<td>71/235 (30%)</td>
<td>NS</td>
</tr>
<tr>
<td>Early pregnancy loss, n (%)</td>
<td>18/67 (27%)</td>
<td>14/72 (19%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*) Fishers exact test

Humaidan et al., ESHRE 2007. O-203
## Reproductive Outcome

<table>
<thead>
<tr>
<th></th>
<th>GnRha</th>
<th>GnRha + hCG 1500</th>
<th>hCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>55</td>
<td>153</td>
<td>152</td>
</tr>
<tr>
<td>Rate of ET, n (%)</td>
<td>48 (87%)</td>
<td>132 (86%)</td>
<td>138 (91%)</td>
</tr>
<tr>
<td>Pos. hCG/ET, n (%)</td>
<td>14 (29%)</td>
<td>67 (51%)</td>
<td>72 (52%)</td>
</tr>
<tr>
<td>CP/ET,W7, n (%)</td>
<td>3 (6%)</td>
<td>50 (38%)</td>
<td>55 (40%)</td>
</tr>
<tr>
<td>IR, n (%)</td>
<td>3/89 (3%)</td>
<td>60/211 (28%)</td>
<td>71/235 (30%)</td>
</tr>
<tr>
<td>Early PL, n (%)</td>
<td>11 (79%)</td>
<td>18/67 (27%)</td>
<td>14/72 (19%)</td>
</tr>
</tbody>
</table>

*) Fishers exact test (Humaidan et al., 2005; Humaidan et al., ESHRE 2007. O-203)
Conclusion

Supplementation with 1500 IU hCG 35 hours post triggering of ovulation with GnRHa:

- Rescues the luteal phase
- Provides a clinical pregnancy rate similar to that of hCG induced ovulation
- Tendency towards more MII oocytes

(Humaidan et al., RBM 2006; Humaidan et al., ESHRE 2007. O-203)
And what about OHSS risk in high responder patients?

- 50 patients in the hCG arm > 10 oocytes
- 42 patients in GnRHa/hCG arm > 10 oocytes

- hCG arm: 3 cases (2%) : 1 severe, 2 moderate
- GnRha/hCG arm: 0 cases

Humaidan et al., ESHRE 2007. O-203
GnRH antagonists in ART

Which patient will profit most from GnRH antagonist treatment?

- All patients – from the patient’s perception
- Most patients – from the clinician’s perception
- More studies needed in subgroups to draw firm conclusions
Thank You

The Fertility Clinic
Skive Hospital