The role of GnRH agonists/antagonists in assisted reproduction

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Disclosure

• Travel grants from Ferring and IBSA.
• No other commercial relationships to disclose.
Objectives

• To compare basic differences between GnRH antagonists and GnRH agonist.

• To describe different protocols of the use of GnRH antagonist.

• To suggest other options for the use of GnRH antagonist.

• To evaluate the outcome of IVF treatment using antagonist as compared to agonist.
Introduction of GnRHa during stimulation for IVF prevented premature LH surge and improved the pregnancy rate (Fleming et al., 1988)
The improved pregnancy rate was due to prevention of premature LH surge and production of a larger cohort of follicles.
No available data in SART/ASRM IVF registry or ESHRE European IVF registry on the percentage of IVF/ICSI cycles stimulated with GnRH antagonist protocols.
• There is a consensus that GnRh agonist was used in the majority of IVF cycles worldwide.

• It is believed that there is a clear shift towards the use of more GnRh antagonist cycles in recent years.
• The Spanish registry for year 2012 showed that GnRH antagonist was used in 55% of IVF/ICSI (Barri 2014, personal communication)
Mode of action of GnRh analogues
The difference in stimulation: Agonist vs. antagonist

1. Synchronized follicles after GnRH down regulation
2. Day 2 ovary without any down-regulation (antagonist protocol)
Mechanism of action

**Antagonist**
- Receptor blockage
- Competitive inhibition
- Immediate suppression
- Rapid reversibility

**Agonist**
- Initial flare-up
- Receptor down regulation
- Pituitary desensitization
- Slow reversibility
Mechanism of action of GnRH agonist inhibition of endogenous LH surge
MECHANISMS OF GnRH AGONIST ACTION

- GnRH receptor internalization and post-receptor block of gonadotropin synthesis
- **non competitive** process
- **late pituitary suppression** (1-2 weeks)
Mechanism of action of antagonists
Prevention of premature LH surge

Fatemi 2002, Antalya 2003
MECHANISMS OF GnRH ANTAGONIST ACTION

- competitive pituitary
  GnRH receptor block
- immediate pituitary
  suppression
GnRH Antagonist Vs Long GnRH Agonist Cycles

Flare-up

Pituitary downregulation

Direct gonadotropin suppression

LH

Time

Advantages of antagonist protocols

- Shorter treatment (several weeks)
- Smaller doses of gonadotrophins
- No ovarian cyst formation
- Lower incidence of OHSS
- Immediate recovery of pituitary
Why antagonist did not replace agonist for controlled ovarian hyperstimulation in ART cycles?
Cochrane review: pregnancy outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>GnRH antagonist</th>
<th>GnRH agonist</th>
<th>OR (95% CI Fixed)</th>
<th>OR (95% CI Fixed)</th>
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<td>European-Middle East</td>
<td>73/226</td>
<td>40/111</td>
<td>0.85 (0.52, 1.37)</td>
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<td>North American</td>
<td>66/196</td>
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<td>0.87 (0.53, 1.45)</td>
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<td>Olivennes 2000</td>
<td>26/126</td>
<td>11/43</td>
<td>0.75 (0.33, 1.73)</td>
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<tr>
<td>Total (95% CI)</td>
<td>308/1211</td>
<td>176/585</td>
<td>0.79 (0.63, 0.99)</td>
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</tbody>
</table>

Al-Inany and Aboulghar 2002
Cochrane review: pregnancy outcome.

- The clinical pregnancy rate was significantly lower in the antagonist group.
- The absolute treatment effect (ATE) was calculated to be 5%. The number needed to treat (NNT) was 20.
- This means that for every 20 subfertile couples undergoing IVF/ICSI program, one additional successful pregnancy added to the 5-8 expected pregnancies in the GnRH agonist treated group.

Al-Inany and Aboulghar 2002
Lower pregnancy rate in antagonist cycles??
Effect of antagonist on endometrium and implantation

• Dose finding study: 2 mg of Ganirelix had very low pregnancy rate (1).
• Negative effect on endometrial receptivity (2). However, this was criticized by Mannaerts and Gordon 2000 (3).
• Pregnancies from frozen-thawed embryos from antagonist cycles are similar to agonist cycles, suggesting an effect of antagonist on endometrium and not on oocytes (4).

1. Ganirelix dose-finding study group 1998
2. Hernandez et al 2000
3. Mannaerts and Gordon 2000
4. Kol 1999
Learning curve and fine-tuning

• Some major European clinics use antagonist only with good results

• Meta-analysis comparing agonist and antagonist showed the difference in pregnancy rate to be very small

Fauser and Devroey 2005
GnRH antagonist vs GnRH Agonist: Success Rates
Better in Centers With Experience

Values represent unadjusted means and SE.
Borm and Mannaerts. 2000
Trials to improve pregnancy rate in antagonist protocol

Several studies investigated different options to improve the pregnancy rate

- Flexible protocol
- Use of oral contraception
- Increase dose of FSH on start of antagonist
Flexible versus fixed protocol
Flexible protocol

• 323 women were treated with fixed antagonist protocol (started day 6) versus 119 women who started antagonist later depending upon size of lead follicle. Comparable implantation rate 30.4% versus 33.7%, clinical pregnancy rate 47% versus 52.9% (Tannus et al., 2013)
GnRH antagonist fixed versus flexible protocols: Meta-analysis

- Only 4 randomized studies met the criteria.
- There was no statistically significant difference in pregnancy rate between fixed and flexible protocol (0.7, 95% CI 0.42-1.1).
- There was a trend towards higher PR with fixed protocols particularly if antagonist is started beyond day 8.

Al-Inany et al 2005
Oral pills for cycle scheduling prior to IVF cycles stimulated by GnRH antagonist protocol

• 1799 cycles were studied.
• OCP – pretreated cycles required longer stimulation and higher doses of FSH but implantation and pregnancy rates were not affected. (Pinkas et al., 2008)
• The same results were achieved by Garcia-Velasco et al, (2011).
Oral contraceptive pill pretreatment for women undergoing ART Cochrane review

- The combined OCP in GnRH antagonist cycles, compared to no pre-treatment, is associated with fewer clinical pregnancies (OR 0.69, P = 0.03) and more days and a higher amount of gonadotrophin therapy (respectively: P < 0.0001; and P < 0.00001).

Smulders et al 2010
Increasing FSH dose with start on GnRH antagonist

• In a randomized study, increasing the dose of hMG on day of GnRH antagonist administration had no effect on improving the pregnancy rate (1)
• In a randomized study, increasing the dose of rFSH after starting GnRH antagonist did not alter E2 response or improve implantation and pregnancy rates (2).

1. Aboulghar et al 2004  
2. Propst et al 2006
Rec LH supplementation in GnRH antagonist cycles: a Cochrane review

- Three randomized trials are included (216 patients)
- There is no evidence of a difference in clinical pregnancy rate (OR 0.79, 95% CI 0.95 -1.56) or ongoing pregnancy rate 0.83, 95% CI 0.39-1.80)

Mochtar et al 2007

• 22 RCT
• 3176 Subjects
• Livebirth (from manuscript in 10 studies and by conversion of pregnancy rate to live birth rate using special formula in 12 studies (Arce et al 2005)
• Both long and flare up agonist protocols were included
• No significant difference between PR in agonist and antagonist protocols (OR, 0.86; 95% CI, 0.72-1.02)

Al-Inany et al Cochrane Database Syst Rev. 2006 Jul 19;3:CD001750

- 27 RCT included
- Only long GnRH protocol was included
- Published studies and abstracts in major meetings were included
- Clinical pregnancy rate was significantly lower in the antagonist group (OR = 0.84, 95% CI = 0.72-0.97)
- Ongoing pregnancy rate and live birth rate showed the same significant lower pregnancy rate in the antagonist group (P = 0.03; OR 0.82, 95% CI 0.69-0.98)
- OHSS was significantly lower in the antagonist arm (P=0.01, RR 0.61, 95% CI 0.42-0.89)
Authors’ conclusions (Al-Inany et al 2006)

• GnRH antagonist protocol is a short and simple protocol with good clinical outcome with significant reduction in OHSS and amount of gonadotropins used, but with significantly lower pregnancy rate.

Cochrane Database Syst Rev. 2006 Jul 19;3:CD001750
New Cochrane review (1) (Al-Inany et al. 2011)

• In a recent Cochrane review
• 45 RCT = 7511 cycles
• Comparing long GnRHs versus GnRH antagonist
• There was no significant difference in the lifebirth rate (9 RCT OR: 0.086, 95% CI 0.69-1.88)

Cochrane Database Syst Rev. 2011 May 11;(5):CD001750
New Cochrane review (2) (Al-Inany et al. 2011)

• There was no significant difference in ongoing pregnancy rate (29 RCT OR: 0.87, 95% CI 0.77-0.99)

• There were a statistically significant lower incidence of OHSS in GnRH antagonist group (29 RCT, OR: 0.43; 95% CI 0.33 – 0.57, P<0.00001)

Cochrane Database Syst Rev. 2011 May 11;(5):CD001750
Meta-analysis of agonist versus antagonist in poor responders

- 6 trials included, there was no significant difference between GnRH antagonist and agonist long or flare-up protocol with respect to cycle cancellation rate, number of oocytes and clinical pregnancy rate per cycle initiated (Franco et al Reprod Biomed Online. 2006 Nov;13(5):618-27.).
Soft protocol randomized trial for IVF (404 patients)

(Heijnen et al Lancet. 2007 Mar 3;369(9563):743-9.)

Mild stimulation + GnRH antagonist protocol + Single ET

Standard stimulation + Long GnRH a protocol + Double ET

End Point

Cumulative PR within 1 year from randomization, Total costs up to 6 weeks after delivery, and Overall discomfort of patient

Cumulative pregnancies that resulted in deliveries within a year

43.4% 44.7%

Multiple pregnancy (P<0.0001)

0.5% 13.1%

Total cost in Euro

8333 10745

No significant difference in anxiety, depression, or discomfort
GnRh antagonist and OHSS
# Meta-analyses Confirm That GnRH Antagonists Have a Better Safety Profile vs GnRH Agonists

<table>
<thead>
<tr>
<th></th>
<th>Kolibianakis</th>
<th>Al-Inany</th>
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<tr>
<td>Risk of severe OHSS</td>
<td>RR 0.46* (0.26, 0.82; P=0.01)</td>
<td>OR 0.61 (0.42, 0.89; P=0.01)</td>
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<td>Interventions to prevent OHSS</td>
<td>OR 0.44 [0.21, 0.93] vs. agonist; P=0.03</td>
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*For every 59 women treated with a GnRH agonist vs GnRH antagonist, one additional case of severe OHSS will occur.

OR = Odds ratio; RR = Risk ratio

## Hospital admission due to OHSS

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<th>Citation</th>
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<th>Rate2</th>
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<td>0.47</td>
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**Favor agonists**

**Favor antagonists**

**RR : 0.47**

~ 2 times less risk for hospital admission due to OHSS with GnRH antagonists

Kolibianakis et al. Hum Reprod Update 2006
Triggering ovulation with GnRHa
Griesinger et al. 2006

23 Studies

Final oocyte maturation

GnRH agonist
0.5 bolous

- Pregnancy rate: 0.21, 0.05-0.84, \( p=0.03 \)
- OHSS: Significant drop
- First trimester pregnancy loss: 0.05 increase

hCG 10,000 IU

- Higher pregnancy rate
- Higher OHSS rate
- Lower first trimester pregnancy loss
In a small randomized study, Humaidan et al. 2006 suggested that triggering ovulation with GnRHa supplementation with 1500 IU hCG 35 hours later seemd to secure a normal luteal phase and a normal clinical pregnancy outcome.
Rescue of luteal phase after triggering ovulation by GnRHa

- A prospective randomized study on 305 IVF patients treated by gonadotropin-releasing hormone (gonadotropin-releasing hormone (GnRH) antagonist were randomized to either GnRHa 0.5 and 1500 IU on the day of oocyte retrieval or 5000 IU hCG.
- Clinical pregnancy rate was not significantly different between both groups.
- There was a non-significant difference of 7% in delivery rate in favor of hCG triggering.

Humaidan et al. 2010
GnRHa versus hCG for oocyte triggering in GnRH antagonist protocol: Cochrane Review (Youssef et al 2011)

- 11 RCTs n = 1055
- 8 fresh antagonist studies
- GnRH agonist was less effective than hCG in term of live birth rate (0.44, 95% CI 0.29 – 0.68) and ongoing pregnancy rate (0.45, 95% CI 0.3 – 0.65)
- For a group with 30% live birth rate in hCG group, the LBR in GnRHa triggering will range between 12 – 22%
- OHSS rate was significantly lower in GnRHa group (OR 0.10, 95% CI 0.01 – 0.82) for a group with 3% OHSS rate with hCG, the rate would be between 0% and 2.6% with GNRHa.
High clinical pregnancy rate and low incidence of OHSS by a modified GnRHa trigger of ovulation (Iliodromiti et al., 2013)

- A large retrospective study (275 women at high risk for OHSS used GnRHa to trigger ovulation followed 1 h later with 1500 IU of hCG.
- The clinical pregnancy rate was 41.8% with 2 cases of severe OHSS 0.72%
Agonist trigger with aggressive luteal support

- GnRHa trigger is effective in the prevention of OHSS.
- Lower conception rates have been reported.
- Intensive LPS is an effective approach to improve implantation rates in women with peak E2 levels $\geq 4,000$ pg/mL.
- A dual trigger with GnRHa and 1,000 IU hCG and intensive LPS to improve implantation rates.

Engmann and Benadiva2012
Two randomized studies on GnRHa and hCG support for patients at risk of OHSS (Humaidan 2013)

On day of Triggering of ovulation, based on the number of follicles

High risk for OHSS (Follicles ≥ 11 mm, = 15 to 25)

- **G A = 60**
  - 0.5 GnRHa + 1500 IU hCG after oocyte retrieval
  - No OHSS

- **G B = 58**
  - 5000 IU hCG
  - 2 moderate late onset OHSS

Low risk for OHSS (Follicles ≥ 11 mm, N ≤ 14)

- **G C = 125**
  - Bolus of 0.5 GnRHa + 1500 IU hCG after oocyte retrieval + 1500 IU hCG 5 days after oocyte retrieval
  - 2 late onset OHSS

- **G D = 141**
  - 5000 IU hCG
  - No OHSS
An OHSS-free clinic by segmentation of IVF treatment
Devroey et al., 2011

• Urinary GnRH antagonist protocol and trigger ovulation by a bolus of GnRHa if there is a risk for OHSS, freeze all oocytes or embryos for later use. This will prevent completely OHSS.
• Severe OHSS after GnRHa trigger and freeze-all approach in GnRH antagonist protocol occurred in 2 patients with no hCG injection. They required hospitalization and drainage of ascitic fluid (Fatemi et al., 2014)
GnRH antagonist during stimulation of high risk patients

Forty-seven patients at high risk for OHSS because of markedly elevated $E_2$ were treated with ganirelix acetate. Despite being pretreated with GnRH agonist and without withholding gonadotropins, serum $E_2$ decreased by 49.5% of pretreatment value after initiation of ganirelix, and 68.1% of the patients became pregnant (Gustofson et al 2006).
Antagonist for prevention of OHSS

190 patients at risk for OHSS

randomized

94

GnRH antagonist administration

No cases of OHSS in both arms

- Significantly more high quality embryos
- Significantly less days than coasting

96

Coasting

GnRH antagonist for treatment of early OHSS

- In 3 patients with severe early OHSS, GnRH antagonist was given daily for a week, symptoms subsided and embryos were cryopreserved at blastocyst stage for future ET.

Lainas et al 2009
• For PCO patients, GnRH antagonist is the protocol of choice. It gives the opportunity to trigger ovulation with GnRHa and possibly freeze all embryos (Kol et al., 2012)
Evidence of GnRH antagonist escape in obese women (Rolls et al 2014)

- Comparing 10 obese and 10 normal-weight women who received GnRH antagonist showed that LH rise occurred in 50% of the obese women.
- The authors suggested that the dose of GnRH antagonist in obese women may be increased in accordance with increase in the dose of FSH.
A case series of 19 patients stimulated by the long GnRHa protocol and became at risk of OHSS, agonist was stopped and antagonist started, later triggering of ovulation was done by hCG in 14 patients and GnRHa in 5 patients. They achieved 42% PR from fresh ET (Martinez et al., 2014)
Outcome of babies after antagonist protocol

• Follow up of phase two and three of Ganirelix production were compared with long GnRHa protocol (432 babies versus 184 babies). Complications during pregnancy and delivery did not differ between the 2 groups. Congenital malformation were 7.5% in antagonist versus 5.5 agonist. No significance was found (Boerrigter et al., 2002)
Conclusion 1

• GnRH antagonist protocol provides significant advantages:
  – Shorter stimulation periods
  – Option for the use of soft friendly protocol
  – No cyst formation
  – Lower incidence of OHSS
  – Less stressful
Conclusion 2

- GnRH antagonist results in:
  - Similar pregnancy rates compared to GnRHa long protocol.
  - Similar pregnancy outcome.
  - Similar babies’ outcome.
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