Protocols agonists vs antagonists

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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.
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.
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
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?
<table>
<thead>
<tr>
<th>Study</th>
<th>GnRH antagonist</th>
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<th>OR (95% CI Fixed)</th>
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<td>Total (95% CI)</td>
<td>308/1211</td>
<td>176/585</td>
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<td>0.79 (0.63,0.99)</td>
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Al-Inany and Aboulghar Hum Reprod 2002:874-85. 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 Hum Reprod 2002:874-85. 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. Hernández 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

GnRH antagonist vs GnRH Agonist: Success Rates
Better in Centers With Experience

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

Several studies investigated different options to improve the pregnancy rate

• Flexible protocol
• Early start of GnRH antagonist
• Use of oral contraception
• Increase dose of FSH on start of antagonist
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.

Triggering ovulation with GnRHa

• In a systematic review of 23 studies GnRH agonist versus hCG were compared for triggering final oocyte maturation in GnRH antagonist protocol. Triggering ovulation by GnRH agonist reduced significantly the pregnancy rate 0.21, 0.05-0.84; p = 0.03) and also reduced significantly the OHSS.

• The odds of first trimester pregnancy loss is also increased 0.05).

Rescue of luteal phase after triggering ovulation by GnRHa

- A prospective randomized study on 305 IVF patients treated by GnRH antagonist were randomized to either GnRHa 0.5 and 1500 IU on the day of oocyte retrieval.
- There was a non-significant difference of 7% in delivery rate in favor of hCG triggering.

Humaidan et al. Fertil Steril 2010; 847-54
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 affective 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 Benadiva. Fertil Steril 2012
Oral contraceptive pill pretreatment for women undergoing ART

- 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<0.000001).

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).

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 on going pregnancy rate 0.83, 95% CI 0.39-1.80)

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%

8333  10745

Total cost in Euro

No significant difference in anxiety, depression, or discomfort

- 22 RCT
- 3176 Subjects
- Livebirth (from manuscript in 10 studies and by convenrsion 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
• 46 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
GnRh antagonist and OHSS
Meta-analyses Confirm That GnRH Antagonists Have a Better Safety Profile vs GnRH Agonists

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<th>Kolibianakis</th>
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<tr>
<td><strong>Risk of severe OHSS</strong></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><strong>Interventions to prevent OHSS</strong></td>
<td>OR 0.44 [0.21, 0.93] vs. agonist; (P=0.03)</td>
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</table>

*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

#### RR: 0.47

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

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<th>Rate2</th>
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**Favor agonists**

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**Favor antagonists**

Kolibianakis et al. Hum Reprod Update 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.

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 to GnRHa long protocol
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  - L. Mansour, M. D.
  - M. Metwally, M. D.
  - H. Aboulghar, M. D.
  - M. Aboulghar, M. D.
  - H. Al Inany, M. D.
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    - H. Fanous, B.Sc.
    - A. Mohamed, B.Sc.