The uses of antagonist in IVF/ICSI cycle

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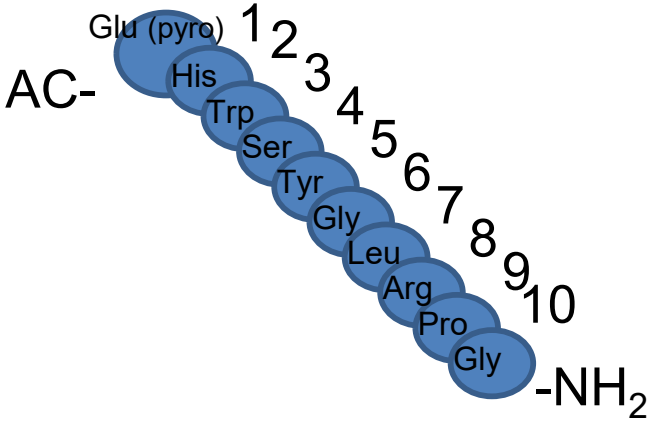
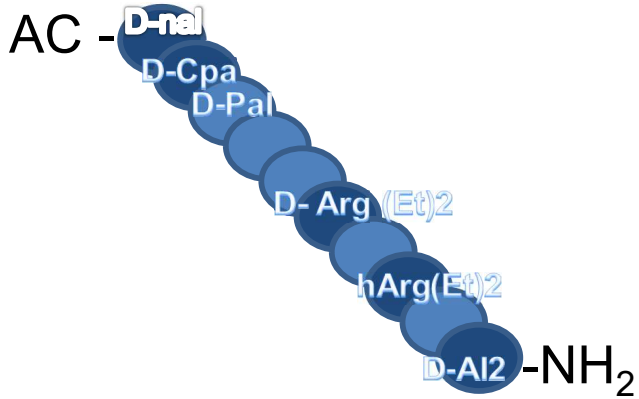
GnRH agonist/ antagonist

Chemical struture

GnRH

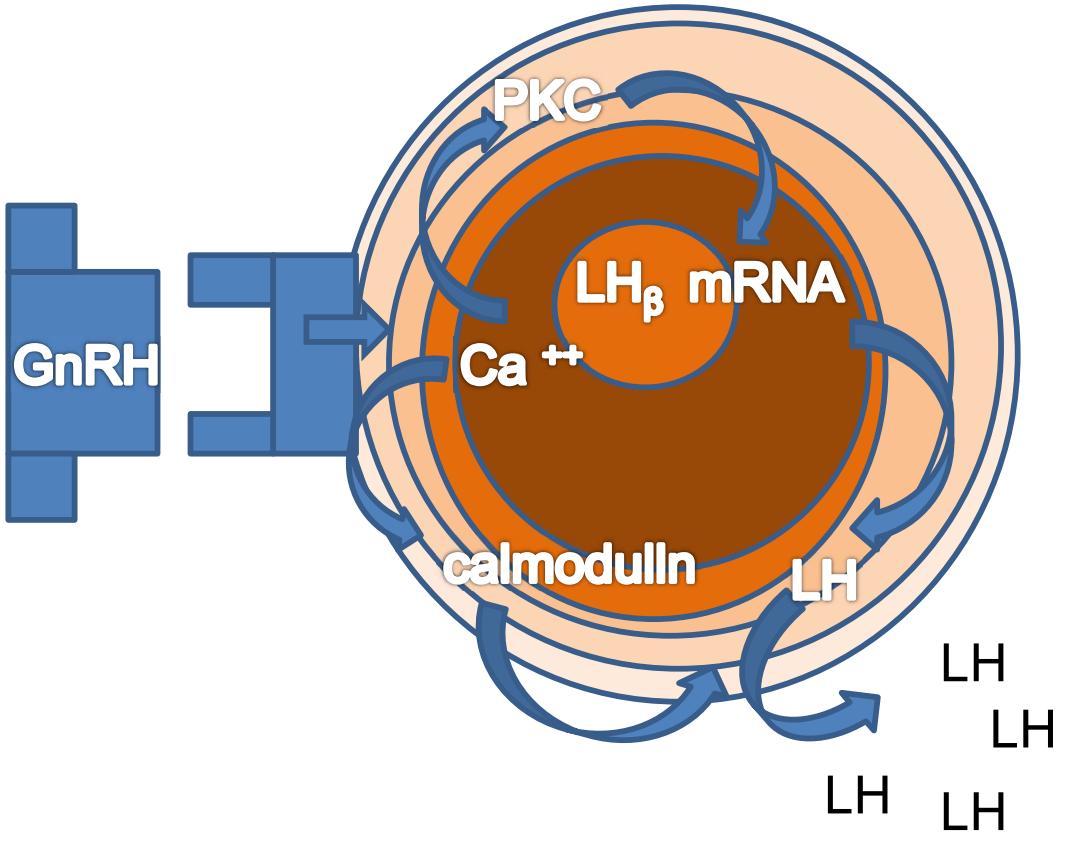


GnRH antagonist

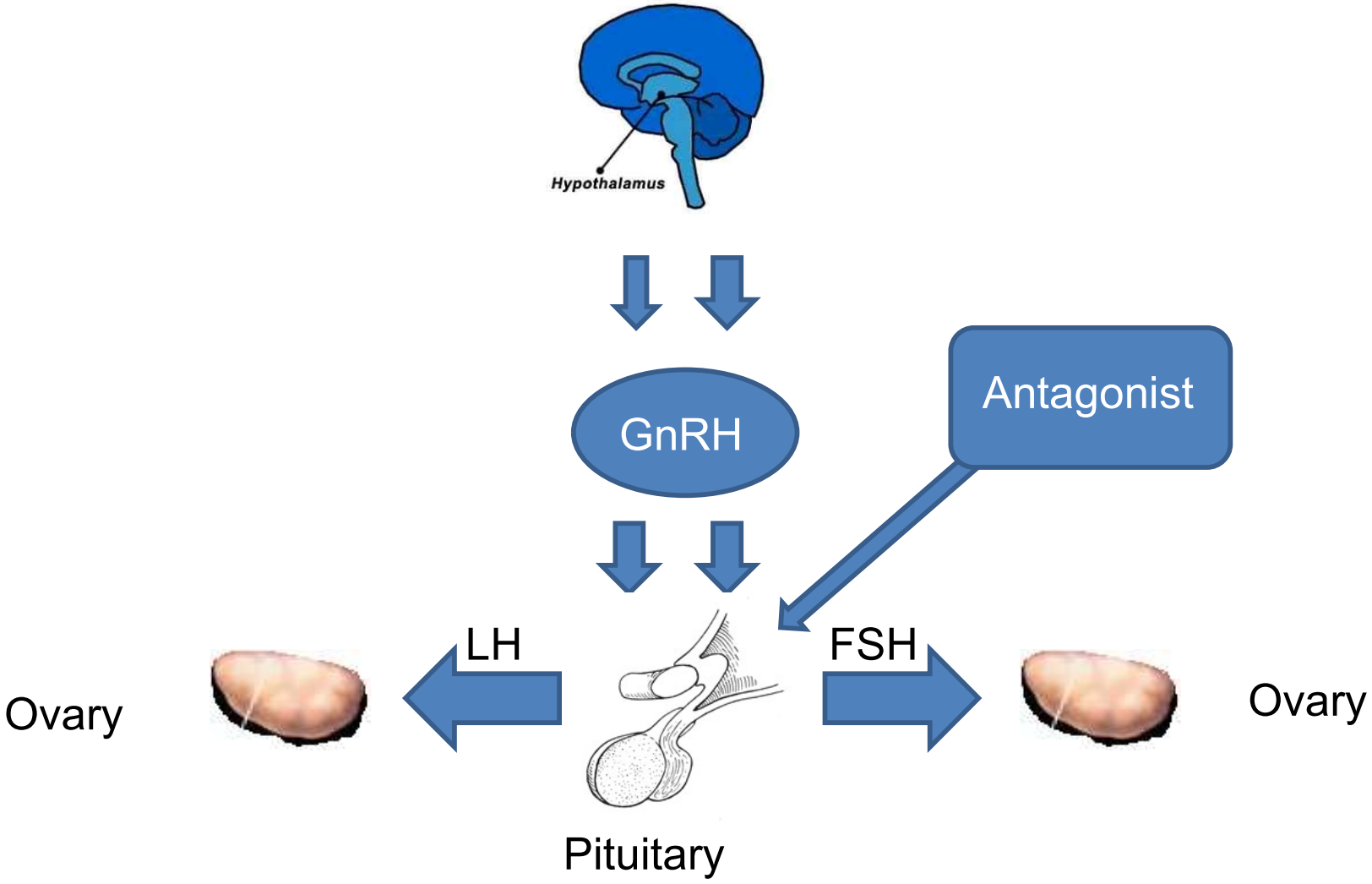


Mechanism of Action of GnRH Agonist

- GnRH receptor internalization and post-receptor block of gonadotropin synthesis.
- Non competitive process.
- Late pituitary suppression (1-2 weeks)

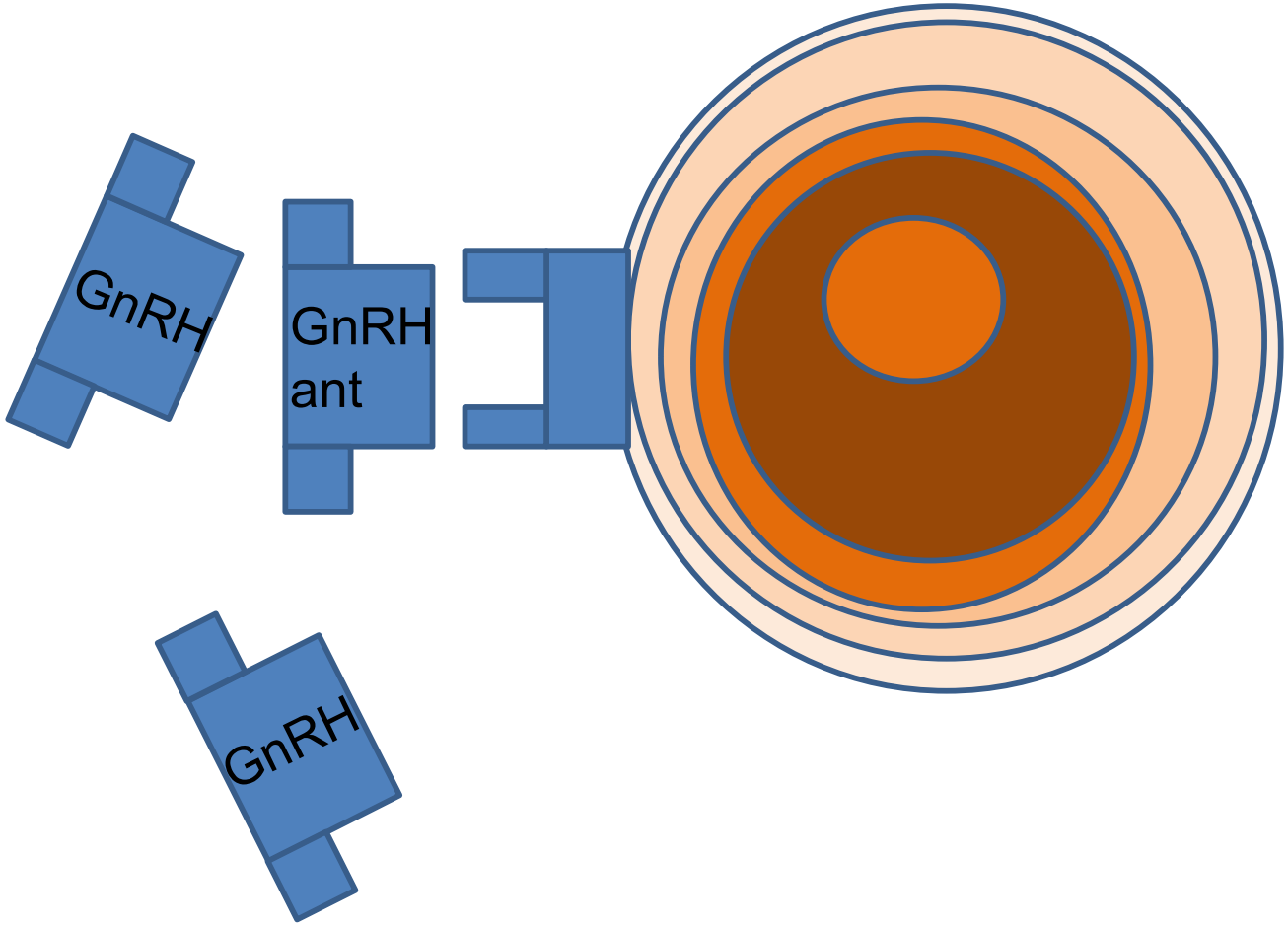


Mechanism of action of antagonists Prevention of premature LH surge



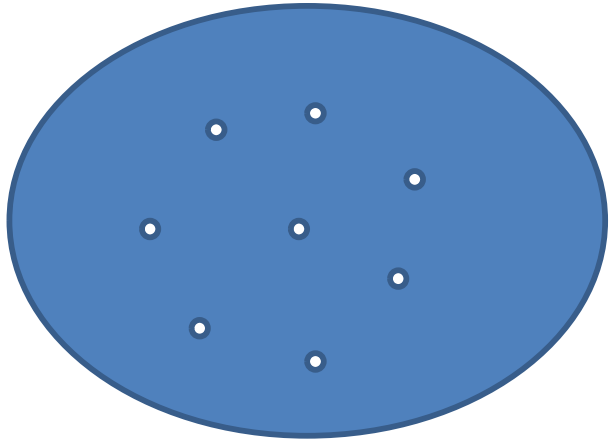
Mechanisms of GnRH antagonist action

- Competitive pituitary GnRH receptor block.
- Immediate pituitary suppression.



The difference in stimulation: Agonist vs. Antagonist

1:



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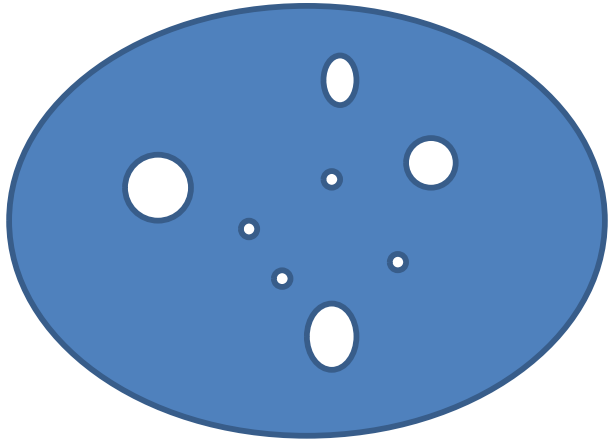

1. Synchronization follicles after GnRH down regulation.
2. Day 2 ovary without any down-regulation (antagonist protocol).

Advantages for the use of GnRH antagonists in IVF

- No initial flare-up, act within a few hours (Klingmuller et al., 1993)
- No cyst formation, no stimulation (Tarlatzis, 2006)
- No estrogen deprivation symptoms (Varney et al., 1993)
- Shorter treatment
- Reduced gonadotropin use
- Rapid reversibility

Stimulation in IVF cycle can be by using:

- Long protocol (Agonist)
- Short protocol (Agonist)
- Antagonist fixed protocol
- Antagonist flexible protocol
- Normal cycle protocol ± Flexible antagonist protocol

Agonist protocol

- Using suppression (Down regulation) through short acting Decapeptyl 0.1 mg SC or Long acting 3.6 mg SC.

Antagonist/ Suppression of LH during stimulated cycle

- Fixed required multiple injection or
- flexible requires one or two injection of 0.25mg.

Fixed protocol

- Start from D5 or D6 of the cycle.
- Daily 0.25mg SC injection of Orgalutran or Cetrotid (sc), up to the time of giving HCG.

Flexible protocol

- To start the ovarian stimulation without any down regulation
- When the follicle become 14 to 15 mm in diameter, antagonist should be given once or repeated next day
- It should be given at least 12 hours before the HCG

Ovarian stimulation

- For any protocol, you may use the urinary HMG or recombinant human FSH.

From the history

HMG is coming from:

. Pregnant Mare serum in 1930

. Pig pituitary gland extracts in 1935

. Human Menopausal gonadotropin (HMG) in 1950 where extracted from post menopausal women.

. Urinary HMG 1980

. FSH (75 IU) + LH (75 IU) + Some urinary proteins

. Humegon, Pergonal, Menogon, IVFM, Menipure + small amount of HCG.

Recombinant human FSH

- FSH β subunit gene encoding, 1983.
- Recombinant human FSH, 1995

  Follitropin alpha (Gonal F) 75 IU

  Follitropin Beta (Puregon) 50 IU/100IU

HMG vs. Rec-FSH

• HMG urinary	Rec-FSH
• Extracted from the urine of PM women gives batch to batch inconsistency	Batch to Batch consistency
• Used for many years successfully for ovarian stimulation and still used.	Free from urinary protein
• Cheaper in price	More expenses
• Almost no side effect a part from hyper-stimulation ovarian syndrome (OHSS).	In over all results of in pregnancy out come both have some results. Less OHSS.

In ART many variables impact the success rates:

- Patient age
- Infertility type and causes
- Media
- Laboratory facilities and experience of emberiologist
- Protocols and clinical experience
- Embryo transfer procedure

Success rates in ART affected by:

- Type of stimulation regimen and protocol
- Gonadotrophin preparation and stores
- Dose calculation
- Time of Antagonist and HCG administration ± pick up.

Psychological and physical treatment

- Will reduce the dropout and increase the success

In our IVF centre ‘Lamis’

- We are using both protocols antagonist and agonist.
- I use the antagonist (flexible protocol).
- I start the ovarian stimulation by using the recombinant or HMG (Menogon or IVFM)

- For this short trial in four months, the total number of patients 400.
- All ages were included from 21-50 years old.
- All types and causes of infertility are included
- It is a randomised trial

Drugs for stimulation

- Starting by fixed doses
- 200 IU of Puregon or
- 300 IU of HMG

The results

- Total number of patients who used antagonist 400 patient over 4 months from 1st Dec 2009 till 31 Mar 2010

Age group 21 to 50 years old

Age group	21-30	31-35	36=40	>41
No of patients	85	115	120	80
% of pregnancy	40	60	55	15

Results

- No. of patients who use recombenent FSH (Puregon) 310
- No. Of patients who use HMG urinary was 90

Fertilization

- Group of HMG was 81 where only 9 not fertilized (90%)
- Recombenant group 279 were 31 not fertilized (90%)

Embryo transfer

- In HMG group 72 (80%)
- In recombenant group 248 (80%)

Pregnancy rate

- Pregnancy is about 46% in both groups

Discussion

Pooled GnRH antagonist clinical studies: Data on neonatal outcomes pooled from 5 clinical studies in women with ongoing pregnancy (N=474)

	GnRH anatagonist n (%)	GnRH agonist n (%)
Mean gestational age, weeks	38	37.4
Term birth	306 (73)	107 (59.8)
Pre-term birth (≥33 weeks and <37 weeks)	87 (20.8)	47 (26.3)
Very pre-term birth (<33 weeks)	27 (6.2)	25 (14)
Mean birth weight, g	2834	2716
Congenital malformations (%)	7.5	3.3
Major malformations (%)	4.5	3.3

Boerrigter P. Et al., Hum Reprod. 2002; 17:2027

Discussion

- Two recent meta-analyses evaluated randomized controlled trials of GnRH antagonists vs GnRH agonists in IVF[1,2] .

- These meta-analyses included different studies, used different measures of efficacy, and reached different conclusions regarding relative efficacy.

1. Al-inany et al. Cochrane Database Syst Rev. 2006; 3: CD001750
2. Kolibianakis et al. Hum Reprod Update. 2006; 12:651

Meta-analysis of GnRH anatagonists vs GnRH agonists: Pregnancy Outcomes

The 2 studies had different results for pregnancy outcomes.

	GnRH Antagonist vs	GnRH Agonist
Live Birth Rate	Al-Inany[1]	Kolibianakis[2]
Odds Ratio	0.82	0.86
95% confidence interval	0.69, 0.98	0.72, 1.02
P value	0.03	0.085

1. Al-inany et al. Cochrane Database Syst Rev. 2006; 3: CD001750
2. Kolibianakis et al. Hum Reprod Update. 2006; 12:651

Differences in study design may have affected results of meta-analyses

Characteristic	Al-Inany et al 2006 (Cochrane)	Kolibianakis et al 2006
Last date searched	Feb 2006	Dec 2005
No. of studies	27	22
Included non per-reviewed data	Yes	No
Included studies on IUI	Yes	No
Total patients	3865	3176
Primary outcome	Ongoing pregnancy or live birth rate	Live birth rate

1. Al-inany et al. Cochrane Database Syst Rev. 2006; 3: CD001750
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Meta-analysis confirm that GnRH anatagonist have a better safety

	Kolibianakis	Al-Inany
Duration of analog treatment	-19.48 days (-21.05, -17.91)	-20.90 days (-22.20, -19.60)
Duration of ovarian stimulation	-1.13 days (-1.83, -0.44)	-1.54 days (-2.42, -0.66; P= .0006)
Risk of severe OHSS	RR 0.46 (0.26, 0.82; P= .01)	OR 0.61 (0.42, 0.89; P=.01)
Interventions to prevent OHSS		OR 0.44 [0.21, 0.93] Vs. Agonist; p=.03

OR = Odd ratio; RR = Risk ratio

1. Al-inany et al. Cochrane Database Syst Rev. 2006; 3: CD001750
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GnRH antagonist as a key component of patient-centred therapy

- Good pregnancy rates
- Reduced risk of OHSS
- Reduction of stress associated with physical and psychological treatment burden
    - No side effects related to flare up
    - Fewer injections
    - Shorter treatment cycles
    - Shorter duration of stimulation

Devroey et al. Human Reproduction. 2009; 24:764-774.

Stress Impacts IVF Success

Indicators of stress:

- Significantly higher in women undergoing simulated IVF compared to unstimulated IVF or undergoing gyneaclogical surgery not related to infertility[1].
- Prolactin, cortisol, and state anxiety score all increased during stimulated in-vitro fertilization (IVF) treatment.

Anxiety associated with IVF leads to inadvertent noncompliance with recommended gonadotropin dosing, a poor or excessive ovarian response, and possibly a poor cycle outcome[2].

1. Harlow et al. Human Reproduction. 1996; 11:274-9.
2. Noorhasan et al. Fertil Steril. 2008; 90:2013. e1-e3.

Stress Impacts IVF Success

- COS with less complicated treatment regimens – fewer injection: Less stress[1].
- The psychological burden of IVF treatments was the primary reason cited among couples who discontinued treatment before achieving success[2,3].
- Stress and anxiety have a significant negative impact on IVF outcomes (pregnancy)[4]

1. Hojgaard et al. Hum Reprod. 2001; 16:1391. 2. Olivis et al. Fertil Steril. 2004; 81:258
3. Verberg et al. Hum Reprod. 2008; 23:2050. 4. Smeenk et al. Hum Reprod. 2001; 16:1420.

Summary

- In contrast to GnRH agonist, GnRH antagonists produce immediate control of LH secretion (Fatemi et al., 2002), allowing shorter duration of administration
- Phase III studies comparing GnRH antagonist to a long agonist protocol demonstrate that GnRH antagonist provides
  - An equivalent number of good quality embryos
  - Comparable pregnancy rates
  - Shorter duration of stimulation
  - Lower FSH requirement
  - Similar obstetric, perinatal, and neonatal outcomes

Summary

Meta-analyses of trials comparing studies on GnRH antagonist protocols vs. GnRH-agonist stimulation protocols have indicated

- Comparable rates of ongoing pregnancy and live birth, or efficacy differences too small to matter in real world scenarios
- Significantly lower risk of OHSS.

The reduced treatment burden associated with GnRH antagonists in combination with SET is associated with

- Lower rates of dropout
- Equivalent cumulative pregnancy rates
- Lower costs per pregnancy

Conclusion

- Antagonist protocol can be used as alternative to agonist protocol long and short
- In the end, I feel stronger to accommodate antagonist protocol in my practice using both types, Fixed and flexible.
- Flexible is cheaper and gives comparable results

Thank you