Original Article

A boon for infertility patients: Ovarian stimulation with GnRH antagonist

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Abstract

OBJECTIVE: To assess the clinical outcomes using gonadotropin-releasing hormone (GnRH) antagonist protocol in *in vitro* fertilization (IVF) cycles in a private practice set up in India.

DESIGN: Retrospective analysis.

SETTING: Private IVF center, New Delhi.

PATIENTS: Between July 2014 and December 2015, 510 self cycles were evaluated.

INTERVENTIONS: Controlled ovarian stimulation (COH) was started on cycle day 2 using gonadotropins (225–450 IU daily) and GnRH antagonist was added on the day when follicle reached 13–14 mm. When follicle reached 18 mm, transvaginal ultrasound guided oocyte aspiration was performed before 36 h of human chorionic gonadotropin (hCG) trigger. Embryo transfer (ET) was done on day 2/3/5, according to the embryo growth and beta-hCG was done after 14 days of ET.

Keywords: gnrh antagonist, ovarian stimulation, pregnancy rates

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INTRODUCTION

Ovarian stimulation is an important factor for the success of *in vitro* fertilization (IVF). There are two mechanisms involved in controlled ovarian stimulation (COH) – gonadotropin-releasing hormone (GnRH) agonist and antagonist protocol. GnRH agonists initially produce a stimulation of the gonadotrophs resulting in secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) and the expected gonadal response. Although continuous administration initially has the same effect, it is subsequently followed by down-regulation and inhibition of the pituitary–gonadal axis by clustering and internalization of the specific receptors. GnRH antagonists promptly suppress pituitary gonadotropin by competitive GnRH-receptor binding, thereby avoiding the initial stimulatory phase of the agonists and induce a rapid decrease in FSH and LH levels, preventing and interrupting premature LH surges and do not require desensitization period, so can be used in late follicular phase.[1] GnRH antagonist protocol produced a comparable ovarian response, embryo development, and pregnancy rates to GnRH agonist regime requiring lesser amounts of gonadotropins. Moreover, GnRH antagonist protocol required a shorter stimulation period plus fewer side-effects.[2] In India, the agonist protocol is time tested and still very popular. The infertility specialists are more familiar with agonist protocol and the batching is easier with this protocol. The antagonist protocol is just gaining popularity and in our center, we are using the antagonist protocol in 90% cases. The aim of the present study

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was to assess the clinical outcomes using GnRH antagonists in self-cycles in a private center in Delhi, India.

MATERIALS AND METHODS

A retrospective analysis was made of all GnRH antagonist cycles undergoing self-IVF-embryo transfer (IVF-ET) cycles. Between July 2014 and December 2015, 510 patients underwent ovarian stimulation using the GnRH antagonist protocol.

Protocol

Ovarian stimulation was started on day 2 with gonadotropins, recombinant human FSH (rhFSH, Folisuge; Intas Pharmaceuticals Ltd, India or Gonal F; Merck Serono S.p.A, Italy), or highly purified menotrophin human menopausal gonadotropin (hpHMG, Menopur; Ferring GmbH, Germany) in the dose of 225–450 IU, depending on the patient's profile [age, body mass index (BMI), previous dose of gonadotropins] till day 6 of period followed by transvaginal follicular monitoring and the dose was adjusted according to ovarian response. When follicles reached 13–14 mm, daily subcutaneous injection of GnRH antagonist, 0.25 mg Cetrorelix (Cetrotide, Merck Serono S.p.A, Italy) was added. When follicles reached 18 mm, 500 μg recombinant human chorionic gonadotropin (hCG) (rhCG, Ovitrelle; Merck Serono S. p.A, Italy) was given to trigger ovulation.

Transvaginal oocyte aspiration was performed before 36 h, under ultrasound guidance, using Wallace OPU needle and Cooks gamete buffer media. Embryos were further cultured in Cooks fertilization/cleavage/blastocyst media.

ET was done on day 2/3/5, according to the embryo growth under transabdominal USG guidance (with full bladder). After gentle insertion of speculum and suction of cervical mucus, soft outer sheath was inserted till the level of internal os. It was followed by insertion of the soft Cooks Guardia Access echotip ET catheter containing embryos in 10 μl media and 5 μl air bubble on both sides of the media and then embryos were placed in mid-uterine cavity.

Luteal support was added in the form of vaginal and injectable progesterone. Beta-hCG was done after 14 days of ET.

Statistical analysis

The measured outcomes included days of stimulation (DOS), total dose used, number of oocytes retrieved, number of embryo transferred, pregnancy, and clinical pregnancy rates. Pregnancy rates were defined as the number of positive beta-hCG cases (beta-hCG was done after 2 weeks of ET) and clinical pregnancies were defined as the presence of a fetal heart beat on ultrasonographic examination.

RESULTS

The demographic profile for the patients is summarized in Table 1. The mean age was 31.6 (range 24–40) years. All patients had normal cycle day 2 serum FSH levels (5–8 mIU/ml) and serum estradiol levels (35–50 pg/ml). Among all 510 subjects recruited, 313 (61.4%) presented with primary infertility and the rest 197 women (38.6%) were associated with secondary infertility. The mean duration of infertility was 6.3 years, ranging from 2 to 18 years.

Pregnancy rates

According to age group, higher pregnancy rates were seen in age <35 years [Table 2].

The average numbers of DOS were 10.3 ranging from 10 to 12 days and the total doses used were between 2400 IU and 4500 IU. The mean number of oocytes retrieved was 13.6 ranging from 11 to 16. All ETs were done on day 2/3/5 and average number of embryos transferred was 2.9 [Table 3]. There was no cancelation of cycle due to poor response. No ovarian hyperstimulation syndrome (OHSS) case had been noted during the study period. The total pregnancy rate was 43.7% (223/510) and out of 223 pregnancies, 16 were biochemical pregnancies. Thus, the clinical pregnancy rate was 40.6%.

Table 1: Demographic profile

Parameters	Value
No. of patients	510
Age (years)	31.6
BMI (kg/m^2)	20.8
Basal FSH levels (mIU/ml)	6.4
Basal estradiol levels (pg/ml)	40.2
Duration of infertility (years)	6.3
Infertility (%)	
Primary	313 (61.4%)
Secondary	197 (38.6%)
Causes of infertility (%)	
Ovarian factor	81 (15.9%)
Tubal factor	142 (27.8%)
Male factor	130 (25.5%)
Unexplained	68 (13.3%)
Mixed	89 (17.5%)

Table 2: Age distribution

Age (years)	No. of patients (*n*)	Pregnancy rate (PR)	CPR
<30	120	61 (50.8%)	58 (48.3%)
30–35	194	96 (49.5%)	90 (46.4%)
35–38	102	38 (37.3%)	35 (34.3%)
38–40	94	28 (29.8%)	24 (25.5%)
Total	510	223 (43.7%)	207 (40.6%)

Table 3: IVF ET results

Parameter	Value
Days of stimulation	10.3
No. of doses used (IU)	3125
No. of oocytes	13.6
No. of embryo transferred	2.9
Pregnancy rate (%)	43.7
Clinical pregnancy rate (%)	40.6

DISCUSSION

The present study evaluated the effectiveness of GnRH antagonist in IVF cycles. The aim of using GnRH antagonists in IVF is the inhibition of a premature LH rise which could lead to premature luteinization, follicle maturation arrest, and asynchrony of oocyte maturation. The use of GnRH antagonists in IVF is characterized by many advantages:[3]

1. Prevention of premature LH increase is easier and takes less time. GnRH antagonists act within a few hours after their administration and thus they can be administered only when there is a risk for an LH surge. This is in contrast to GnRH agonists where pituitary down-regulation occurs only after 7–10 days.

2. The initial stimulation by GnRH agonists can induce cyst formation, which is avoided with GnRH antagonists.

3. No hot flushes are observed with GnRH antagonists, as their use does not result in profound hypo-estrogenaemia observed with GnRH agonists.

4. Inadvertent administration of the GnRH analog in early pregnancy can be avoided, as GnRH antagonist is administered in the mid-follicular phase.

5. Requirements for exogenous gonadotropins are reduced, rendering ovarian stimulation less costly.

6. Duration of ovarian stimulation protocols is shortened, improving patient comfort and compliance.

In India, most of the IVF specialists are using long protocol with agonist and are still doing batching. GnRH antagonist protocol produced a comparable ovarian response, embryo development, and pregnancy rates to GnRH agonist regime requiring lesser amounts of gonadotropins. Lainas *et al.*[4] compared the flexible GnRH antagonist and the GnRH agonist long protocols in 220 polycystic ovary syndrome (PCOS) patients undergoing IVF treatment, and found that the flexible GnRH antagonist protocol was associated with a similar ongoing pregnancy rate (50.9 versus 47.3%), lower incidence of OHSS grade II, lower gonadotropin requirement, and shorter duration of stimulation, compared with GnRH agonist. Devroey *et al.*[5] performed meta-analyses of various studies and stated that the treatment with antagonists was associated with similar live birth rates but reduced treatment burden (duration and side effects) and less risk of ovarian stimulation syndrome, compared with GnRH agonist long protocols. In an update of a Cochrane review, 45 randomized controlled trials (RCTs) ($n = 7511$) comparing the antagonist to the long agonist protocols were included and concluded that the use of antagonist compared with long GnRH agonist protocols was associated with a large reduction in OHSS [29 RCTs; odds ratio (OR) 0.43, 95% confidence interval (CI) 0.33–0.57] and there was no evidence of a difference in live-birth rate (9 RCTs; OR 0.86, 95% CI 0.69–1.08) or ongoing pregnancy (28 RCTs; OR 0.87, 95% CI 0.77–1.00).[6] In poor responders also, GnRH antagonist had effective role. Kim *et al.*[7] investigated the effectiveness of GnRH antagonist multiple-dose protocol (MDP) with oral contraceptive pill (OCP) pretreatment in 120 poor responders undergoing IVF/ICSI, compared with GnRH antagonist MDP without OCP pretreatment and GnRH agonist low-dose long protocol (LP) and concluded that GnRH antagonist MDP with OCP pretreatment was at least as effective as GnRH agonist low-dose LP in poor responders and can benefit the poor responders by reducing the amount and duration of FSH required for follicular maturation.

CONCLUSION

GnRH antagonists in ovarian stimulation for IVF is a very friendly protocol, requiring smaller dose of gonadotropins and shorter stimulation period, requiring only 2–3 times of follicular monitoring in experienced hands with good pregnancy rate.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Olivennes F, Cunha-Filho JS, Fanchin R, Bouchard P, Frydman R. The use of GnRH antagonists in ovarian stimulation. Hum Reprod Update 2002;8:279–90.

2. Rashid MR, Ong FB, Omar MH, Ng SP, Nurshaireen A, Sharifah-Teh NS, *et al.* GnRH agonist and GnRH antagonist in intracytoplasmic injection cycles. Med J Malaysia 2008;63:113–7.
3. Tarlatzis BC, Fauser BC, Kolibianakis EM, Diedrich K, Devroey P, On Behalf of the Brussels GnRH Antagonist Consensus Workshop Group. GnRH antagonists in ovarian stimulation for IVF. Hum Reprod Update 2006;12:333–40.
4. Lainas TG, Sfontouris IA, Zorzovilis IZ, Petsas GK, Lainas GT, Alexopoulou E, *et al.* Flexible GnRH antagonist protocol versus GnRH agonist long protocol in patients with polycystic ovary syndrome treated for IVF: A prospective randomised controlled trial (RCT). Hum Reprod 2010;25:683–9.
5. Devroey P, Aboulghar M, Garcia-Velasco J, Griesinger G, Humaidan P, Kolibianakis E, *et al.* Improving the patient's experience of IVF/ICSI: A proposal for an ovarian stimulation protocol with GnRH antagonist co-treatment. Hum Reprod 2009;24;764–74.
6. Al-Inany HG, Youssef MA, Aboulghar M, Broekmans F, Sterrenburg M, Smit J, *et al.* GnRH antagonists are safer than agonists: An update of a Cochrane review. Hum Reprod Update 2011;17:435.
7. Kim CH, You RM, Kang HJ, Ahn JW, Jeon I, Lee JW, *et al.* GnRH antagonist multiple dose protocol with oral contraceptive pill pretreatment in poor responders undergoing IVF/ICSI. Clin Exp Reprod Med 2011;38:228-33.