RESEARCH ARTICLE

Ovarian hyper-stimulation protocols in good prognosis patients: Agonist versus Antagonist protocol, an Iraqi view

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Abstract

Objective: To elucidate the most appropriate stimulation protocol for intracytoplasmic sperm injection (ICSI) among good prognosis patients.

Methods: A cross sectional study including 100 sub-fertile couples with good prognosis profile (women younger than 38 years, with a dose of 1200-3600 IU follicle-stimulating hormone (FSH), retrieving >3 oocytes in their first or second ICSI cycle), were divided into two groups based on stimulation protocol. There were 40 patients treated with GnRH-agonist in group 1 and 60 patients treated with GnRH-antagonist. The total dose of gonadotropins, days of stimulation, endometrial thickness (ET), estradiol (E2) at the day of human chorionic gonadotropin hCG, ICSI outcome, ovarian hyperstimulation syndrome (OHSS) and pregnancy rate were analyzed and compared between the two groups.

Results: The study showed that in comparison with the GnRH-agonist stimulation protocol, the GnRH-antagonist stimulation protocol resulted in less use of gonadotropins, more retrieval of oocytes, lower risk of OHSS and higher pregnancy rate in good prognosis patients (1890.00 ± 143.81 vs 1572.50 ±111.67, 10.25 ±1.13 vs 11.17±1.21 and 20% vs 10%, 45% vs 53.3%) respectively but without significant differences (P-value $\geq$ 0.05).

Conclusion: The GnRH-antagonist stimulation protocol is as effective as the GnRH-agonist stimulation protocol for good prognosis patients.

Keywords: GnRH-agonist, GnRH-antagonist, Good prognosis, ICSI outcome. (JPMA 71: S-51 [Suppl. 9]; 2021)

Introduction

Infertility is defined as failure to conceive after 12 months of regular unprotected intercourse; maternal age is a cornerstone factor affecting fertility.[1,2] Artificial reproduction technique (ART) is a group of skills that include organized programmes to get pregnant using fertility-enhancing medications, intrauterine insemination, intracytoplasmic sperm injection (ICSI), assisted reproductive technique (ART) and surrogacy.[2] Controlled ovarian hyperstimulation (COH) has an important role in reproductive medicine and is a cornerstone in achieving pregnancy by ART. COH is associated with increased implantation and pregnancy rates compared with the natural cycle.[3]

During ART, the COH has three important aims: pituitary desensitization, multiple follicle growth stimulation, and ovulation induction.[4] Many ways were found to achieve the COH in patients involved in the ART, and each one of them has some degree of advantage and disadvantage.[5] The gonadotropin-releasing hormone (GnRH) agonists act by preventing the premature luteinizing hormone (LH) surge during COH by pituitary desensitization, increasing the number of retrieved ova and decreasing the cycle cancellation rate. This is a good property, but they are not safe due to ovarian hyperstimulation syndrome (OHSS) and other complications.[6] Although the GnRH agonists were used for several decades, the antagonists have recently become more popular as they provide faster pituitary desensitization without the risk of initial flare (shorter duration of stimulation and fewer injections) together with reducing the risk of OHSS.[7] However, despite the numerous studies, the difference in the effect of any of these protocols on implantation and live birth rates is still controversial.[8]

The GnRH agonists act by binding to their specific receptors on the pituitary gland and causing gland desensitization by maintaining the signal for a long time, and by this, the downregulation of gonadotropin secretion is achieved.[9] On the other hand, the GnRH antagonist acts by binding to the pituitary receptors and blocking them almost straight away, suppressing the gonadotropin secretion in a few hours.[8]

Although the mechanism of action of the GnRH agonist and GnRH antagonist is well understood, it is still unclear which protocol gives better results in practice.

A patient with a good prognosis profile is a; woman younger than 38 years age, receiving a total dose of follicle-stimulating hormone (FSH) 1200-3600 IU, having

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their first or second ICSI cycle with retrieving more than three oocytes, whatever the cause of infertility. To unravel the controversy regarding the usefulness of the stimulation programme, this study compared the outcome of both protocols in good prognosis patients in cross sectional study designs.

Patients and Methods

Cross sectional study was performed in the Iraq, Al-Sader Medical City, Al-Najaf fertility centre from May 2021 to August 2021 on couples seeking treatment for their sub-fertility problem. The data were collected from the patient's records in the fertility centre. One hundred couples seeking treatment for their sub-fertility problem were involved; only patients with good profiles were chosen. Ethical approval was taken from the ethical committee of the University of Kerbala college of medicine. The whole study was explained to the participants, and informed written consent was obtained.

The following formula was used for sample size calculation for comparison between two groups when the endpoint is quantitative data:[10]

Sample size = [2SD2 ($Z\alpha 2 + Z\beta$)2]/d2

SD = standard deviation from previous studies, $Z\alpha 2$= 1.96, $Z\beta$ = 0.84, d = suspected difference between mean values.

Sample size= [2 (4.9)2 (1.96=0.84)2]/22 =94

This study included 100 patients to meet the sample size.

The study included only the good prognosis patients who received GnRH flexible antagonist and GnRH short agonist stimulation protocol. The good prognosis profile is women younger than 38 years age, who have received a total FSH dose of 1200-3600 IU during their first or second intracytoplasmic sperm injection cycle and have yielded more than three oocytes upon completion, irrespective of the cause of infertility. Patients with body mass index (BMI) <18 kg/m^2 or ≥40 kg/m^2, processes in which clomiphene citrate was used, cancelled cycles, frozen-thawed embryos and oocytes donation were excluded.

The GnRH antagonist protocol was used for 60 patients, and the GnRH agonist short protocol was used for 40 patients. This type of protocol for each patient was made based on the patients' age, BMI, hormonal profile and the type and cause of infertility.

The GnRH antagonist protocol involved the flexible regimen, at first ovarian stimulation with daily recombinant FSH (Gonal-f, Merck Serono Specialities Pvt. Ltd., Italy) given subcutaneously (s.c) starting from the second day of the menstrual cycle of the female partner (dose range from 150 - 450 IU) and continued till the day of ovulation trigger. On obtaining an adequate ovarian response, represented by serum E2 levels more than 500 pg/ml and the size of the larger follicle being (14-15 mm), cetrotide 0.25 mg (Merck Serono, Italy), the GnRH antagonist, was given daily by subcutaneous injection and continued until there were minimally three follicles ≥17 mm in diameter. This was followed by hCG.

The agonist protocol involved a short regimen for the patient. On the second day of the female partner's menstrual cycle, she was given decapeptyle 1.0 mg s.c daily (GnRH agonist for pituitary desensitization) lasted till the day of hCG injection. Then, on the 2nd or 3rd day of the cycle, recombinant FSH (Gonal-f, Merck Serono Specialities Pvt. Ltd., Italy) was given in a daily dose of 150-450 IU by subcutaneous injection for ovarian stimulation. This was continued till one day before hCG administration.

When the ovarian response to the stimulation protocol was adequate, and there were more than three follicles of more than 17 mm in diameter, ovulation trigger was done by s.c injection of Hcg (Pregnyl 10000 IU) for both groups. Ova pick up was carried out under general anaesthesia and by ultrasound guidance 36 hours later.

In the metaphase two (MII), the male partner's sperms were injected in the ova (intracytoplasmic sperm injection ICSI). The injected ova were incubated in a special atmosphere, and 16-18 hours later, fertilization was done by identifying the two pronuclei (2PN). On days 2-3 post-injection, the quality of the embryos was assessed, and maximally, three good quality embryos were transferred. Luteal support was carried out by administering progesterone (Duphaston tab) three times per day in a total dose of 30 mg/ day from the day of oocyte retrieval up to ten weeks of pregnancy. A pregnancy test (PT) was done 14 days after the transfer of embryos.

The essential data of the patients, including the age, duration of infertility, type of infertility, basal serum hormones, (follicular stimulating hormone (FSH), luteinizing hormone (LH) and estrogen (E2) were noted. The protocols used were compared between the two groups. The protocol characters included were, the total dose of gonadotropin, serum E2 and endometrial thickness (ET) on the day of ovulation trigger and the days of stimulation. The ICSI outcome was noted in the form of the numbers of retrieved oocytes, mature oocytes, immature oocytes, two pronuclei (2PN), fertilization rate, cleavage rate, number and quality of embryos, numbers

of transferred embryos, the occurrence of OHSS and pregnancy rate.

Our data from the ICSI were analyzed for the outcome of the two stimulation protocols (GnRH short agonist protocol and GnRH flexible Antagonist) by using Microsoft Office Excel 2016. For the analysis SPSS programme (Statistical Package for social sciences) version 21 was used. The numeric variables were compared by the independent t-test and expressed as mean±SD and the categorical variable by the Chi-square test, which was expressed in numbers and percentages. P-value < 0.05 was considered statistically significant.

Results

In this study, the primary infertility was present in 76 (76%) women, and secondary infertility was seen in 24(24%) women. The group treated with the Agonist protocol comprised of 40 women. Of these 26(65%) had primary infertility and 14(35%) had had secondary infertility.

Whereas, for the patients treated with antagonist protocol, 50(83.3%) had primary infertility and 10(16.7%) had secondary infertility. The initial investigations of the two groups did not show any statistically significant difference (Table-1).

Although the total dose of received gonadotropins was noticeably less in patients with antagonist protocol, the difference was not statistically significant. Moreover, there was no significant difference between the two groups in the remaining factors. The ICSI outcomes were better in patients receiving the agonist protocol but the difference was not statistically significant (Table-2). OHSS was less in patients receiving the GnRH-antagonist protocol [8(20%) vs 6(10%)] with no significant difference (P= 0.31). The pregnancy rate itself was higher in the antagonist group [18(45%) vs 32(53.3%)], but again there was no statistical difference (p =0.66).

Discussion

The current study results showed a trend of higher pregnancy rate and lower occurrence of OHSS with no meaningful differences regarding the outcome of the two stimulation protocol among good prognosis patients.

Table-1: The essential data of the enrolled patients (n=50).

Variables	Agonist group (n= 40 mean±SD)	Antagonist group (n=60 mean ±SD)	P-value
Age (years)	30.10 ± 0.97	27.90± 0.97	0.09
Duration of infertility (years)	7.25 ± 0.73	6.57 ± 0.67	0.5
Basal FSH (mIU/mL)	6.06 ± 2.7	5.59 ± 1.7	0.47
Basal LH (mIU/mL)	3.55 ± 2.05	4.77 ± 2.7	0.11
Basal E2(pg/ml)	28.54 ± 13.14	36.44 ± 18.1	0.13

FSH: follicular stimulating hormone; LH: luteinizing hormone; E2: Oestrogen.

Table-2: Comparing the stimulation protocol characters and their outcome.

Variables	Protocols of COH		P-value
	Agonist group (n=40 mean ± SD)	Antagonist group (n=60mean± SD)	
Days of stimulation	9.30 ± 1.55	9.47 ± 2.14	0.08
Total dose of gonadotropins (IU)	1890.00 ± 643.15	1572.50±611.68	0.76
ET at the ovulation trigger (mm)	9.25 ±1.94	9.70 ± 2.07	0.47
Serum E2 at the ovulation trigger (pg/ml)	2118.98 ±152.71	1892.50 ± 77.72	0.44
Retrieved oocytes (per cycle)	10.25 ±5.05	11.17±6.64	0.60
Mature oocytes (per cycle)	8.75 ±4.9	9.60 ±6.2	0.61
Fertilized oocytes (2PN)	6.65 ±3.8	6.63 ± 4.05	0.92
Fertilization rate	72.710 ± 26.75	69.15 ± 25.69	0.64
Total no. of Embryos per cycle	6.30 ±3.7	6.03 ± 3.8	0.80
Cleavage rate	91.130 ± 22.98	94.11 ± 12.78	0.55
Good quality embryos	5.45 ±3.6	5.07± 3.3	0.70
Transferred embryos per cycle	2.40 ± 0.99	2.72 ±0.64	0.17

ET: Endometrial thickness; S.E2: serum Oestrogen; PN: Pronuclei; OHSS: Ovarian hyper-stimulation syndrome.

The assumption, that the switch from the previously widely used GnRH-agonist to the GnRH-antagonist is associated with a lower dose of gonadotropins used and shorter duration of treatment; needs to be reconsidered. Our study showed no significant difference in the ICSI outcome, OHSS, pregnancy rate between the two studied protocols. This result may be attributed to our inclusion criteria, where both groups had similar fertility potentials as indicated by their age, duration of infertility, type of infertility, and the similar hormonal analysis of both groups. Grow et al.[6] agreed with our results as they reported that the numbers of retrieved oocytes and the numbers of embryos transferred (≥2) are not significantly different between the studied groups. Likewise, Bhawana et al.[11] and Prapas et al.[12] observed in their studies, that the number of retrieved oocytes were similar in both GnRH-agonist and GnRH-antagonist protocols. The results of Johnston-MacAnanny et al.[13] were in accordance with our findings as they concluded that the ICSI outcome and clinical pregnancy rate were the same for good prognosis patients using GnRH-antagonist or GnRH-agonist stimulation protocols. However, Shrestha et al.[14] reported a higher number of retrieved oocytes with the GnRH-agonist protocol used in their study.

Al-Inany[15] revealed that the occurrence of OHSS is significantly less with GnRH-antagonist protocols, while our analysis confirmed a trend of non-significant OHSS rates in antagonist protocol. Grow et al.[5] declared that

GnRH-antagonist protocol lowers the risk of the OHSS.

Lambiek et al.[16] and Usonienë[17] showed that the agonist group's pregnancy rate was significantly higher. Regarding the days of stimulation, the total dose of gonadotropins, ET and E2 at the day of hCG, showed no significant difference between the two groups, while Xiao et al.[18] found that the ET was similar in both groups, but the other parameters were significantly lower in GnRH-antagonist group. Lai et al.[19] also did not find any significant difference in the ET between the two studied protocols, while Huang et al.[20] and Orvieto et al.[21] encountered a thicker endometrium in women using the GnRH agonist protocol. On the contrary, Stimpfel et al.[5] disagreed with our results; they observed that the GnRH-antagonist protocol was the most effective protocol for good prognosis patients as it was associated with better ICSI outcome in the form of retrieved oocytes, number of 2PN, number of good quality embryos, less OHSS and higher pregnancy rate.

Our study recruited 100 patients only as a bigger sample could not be retrieved due to incomplete records of the Fertility Centre. Nevertheless, the study recruited good prognostic patients, all less than 38 years of age, an important risk factor in many obstetrical problems.[1,22,23] The novelty of the current study was identifying the appropriate stimulation protocol for good prognosis patients and understanding the benefit of each stimulation protocol in different patients. Therefore, our findings can help the team of the IVF centres and guide the clinical decision in choosing the right protocol for the right patient aiming for decreasing the burden on IVF patients by means of treatment trial and cost.

Further studies are warranted on this subject with larger sample size and at a different region to emphasize how the stimulation protocol can affect the outcome of the ICSI procedure and improve the success rate.

Conclusion

Despite the higher pregnancy rate and lower occurrence of OHSS, the differences were non-significant, and the GnRH-antagonist stimulation protocol is as effective as the GnRH-agonist stimulation protocol for good prognosis patients.

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