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Original article

Exploring the effect of adding low dose human chorionic gonadotropin on oocyte maturation in women undergoing intracytoplasmic sperm injection: A randomized control trial

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Abstract

Background: The aim of this study was to examine the effect of adding low dose human chorionic gonadotropin (hCG) on oocyte maturity and hyper-stimulation syndrome in women undergoing Intra-cytoplasmic Sperm Injection (ICSI).

Methods: In a randomaized clinical trail, 150 eligible patients undergoing a long GnRH agonist protocol were randomly divided into three groups of 50 women. The women in the first group received recombinant FSH alone (rFSH). The women in the second group received rFSH by 100 IU hCG daily. All participants in the three groups received rFSH by 200 IU hCG daily. The mean numbers of mature oocytes retrieved (MII oocytes) for normal responders as the primary outcome, and the occurrence ovarian hyperstimulation syndrome (OHSS) as the secondary outcome were measured for each group. A P-value of less than 0.05 was considered as statistically significant.

Results: There was no significant difference in the comparison of the incidence of mature oocytes formation among the three groups. The number of OHSS was significantly lower in third group compared with those of the other groups (6% vs 14% and 18%, respectively; P = 0.03).

Conclusion: The addition of 200 hCG to recFSH throughout the stimulation in a long GnRH agonist protocol only benefited a lower number of OHSS.

Keywords: Intracytoplasmic sperm injection cycle, Low dose hCG, Ocyte maturation

Introduction

Hyperstimulation is one of the most important components of the assisted reproductive technique (ART), whose aim is to produce enough follicles without the degradation of follicle quality. It is generally believed that during the natural cycle of the ovary, various pituitary hormones are responsible for the growth of follicles (1, 2). It is also assumed that in the early stages of the cycle, follicle-stimulating hormone (FSH) is responsible for the growth of the follicle, but it declines in the middle of the cycle, and the luteinizing hormone (LH) plays a more important role. In addition, the more controlled ovarian hyper-stimulation (COH) protocols are more similar to normal hormone changes, the more efficient they will be (3, 4).

In most infertile patients, it is thought that the administration of FSH for ovarian mobility is sufficient. In these patients, the dominant follicles also contain LH receptors, which can respond to endogenous LH. While some patients do not respond to the treatment with FSH alone, others react to it pretty well. In these patients, the administration of the LH in the middle or at the end of the follicular phase is helpful. It is estimated that the dministration of the LH can reduce the amount of FSH received and increase the response of the follicles (5, 6).

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Researchers have shown that various groups of patients can benefit from the treatment with LH more than others. These groups include patients who are over the age of 35, patients who have given abnormal initial responses with FSH, and patients with poor ovarian responses (7-9).

On the other hand, the LH with the effect on theca can produce androgenic secretion. The androgens are converted to estradiol by the aromatase enzyme. It is presumed that the rising levels of estradiol in the environment can result in a higher level of oocytes. In fact, one effective way to administer LH and human chorionic gonadotropin (HCG) is by raising the level of estradiol (10, 11).

It is also thought that HCG is a natural analogue of the LH. It is assumed that HCG can selectively bind to LH receptors and can stimulate similar activity of LH. The half-life of HCG is greater than LH. HCG can fill LH receptors for more than 24 hours and stimulate stable receptors. HCG is also 6 times stronger than LH. Other sources of stimulation such as human menopausal gonadotropin (HMG) are cheaper LH functions. It is staggering that 200 units of HCG is equal to 1200 units of LH (12).

New COH protocols for ovarian stimulation are used in low doses of HCG (200-50). It is estimated that the onset of HCG is in the middle of the cycle or it begins when the size of the follicles reaches 10-12 mm. At this time, LH receptors on the follicle surface have the ability to stimulate follicle growth without FSH. It is thought that the use of low doses of HCG (when follicles are larger than 12 mm) can reduce the use of gonadotropins. The use of HCG can also reduce the number of small pre-ovulatory follicles, and the risk of ovarian hyper stimulation syndrome (OHSS) can consequently decrease (13). Other effects of HCG are angiogenesis and the increase in the thickness of the endometrium. It can also increase the implantation rate (14). The result of another study has shown that the administration of HCG in ovarian stimulation regimens has been associated with a smaller number of immature oocytes in polycystic ovary syndrome (PCOS) patients (5).

In the current study, we strove to investigate the effect of adding HCG to the ovarian stimulation regimen with FSH. The final result was a comparison based on the maturation of oocytes between the three groups and the occurrence of OHSS.

Materials & Methods

This was a prospective, parallel, and randomized study, which was carried out at the Fatemeh Zahra Infertility Center in Babol, Iran, from May 2017 to March 2019. The study was approved by the Babol University ethics committee and registered in the Iranian Clinical Trial (IRCT2017012932284N1).

Women between ages 20-40 were included in the study. The women with abnormal hysterosalpingography, a previous infertility treatment, and the history of a chronic disease were excluded from the study. A total number of 162 women participated in this study, among whom 150 were selected based on the inclusion and exclusion criteria. All participants were informed regarding the aim of the study and were asked to sign the written informed consent. Then we randomly divided patients to three groups using block randomization method (block size=6).

All women underwent a long GnRH agonist protocol and received 150 IU rFSH injections (Cinnal-f , Sinajen Company, Iran). The women in the first group received rFSH injections until appropriate number of mature follicles were developed. The women in the second group received rFSH injections from cycle day until the main follicle reached the diameter of 14 mm. Then the daily injections of 100 IU of human chorionic gonadotropin (hCG, DarouPakhsh, Iran) started, and the dose of rFSH was reduced from 150 to m75 IU daily for all patients. In third group, when the main follicle reached 14 mm in diameter, rFSH injections were stopped, and the treatment with the daily injections of 200 IU of human chorionic gonadotropin started. The treatment of women in the three groups continued until appropriate numbers of mature follicles were developed. When at least two or three follicles reached 18-20 mm in diameter, 10,000 IU human chorionic gonadotropin was injected. Then all mature follicles were retrieved 36 hours after the human chorionic gonadotropin trigger shot and were then fertilized with standard intracytoplasmic. The mean number of mature oocytes retrieved (MII oocytes) as the primary outcome and the occurrence OHSS as the secondary outcome were measured in each group. In this study, all three mild, moderate and severe OHSS categories were considered as occurrence OHSS. The incidence of follicle count greater than 13 mm or follicle size greater than 11 mm was defined as the

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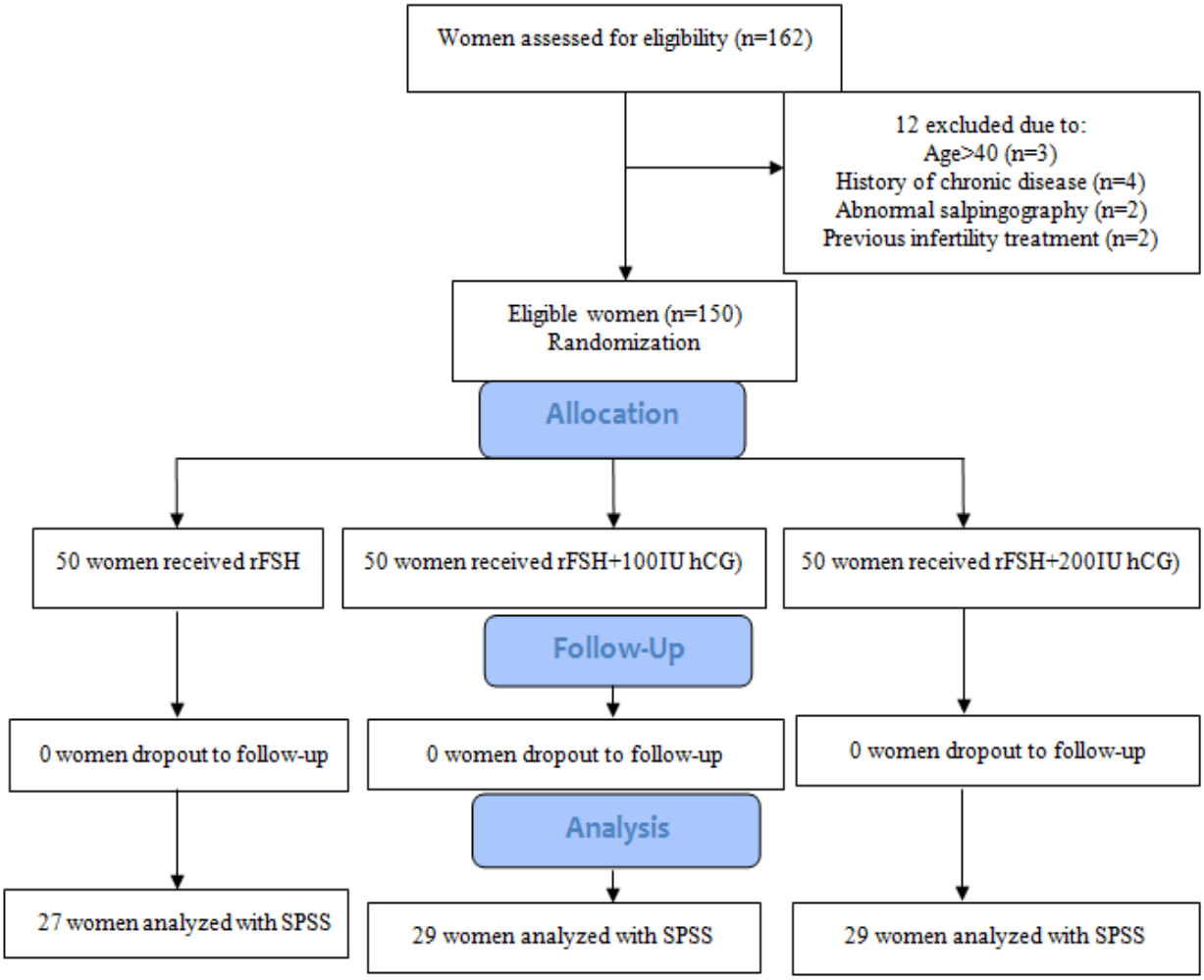


Figure 1. Flow diagram of the participants

predictor of overgrowth of ovarian stimulation. Ovarian excitation cases were evaluated in all three groups with the same definition (Figure 1).

Sample size calculations estimated that in order to obtain significant differences with a 0.05 significance level and a power of 80 %, a sample size of at least 50 patients in each group would be needed.

Data analysis was done using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 20. ANOVA (one way analysis of variance) was used to compare the means from the quantitative variables with normal distribution among the three groups. The qualitative variables were analyzed by the Chi-Square analysis. A P-value of less than 0.05 was considered as statistically significant.

Results

The age and body mass index (BMI) of the three groups were used to confirm the consistency of the groups. The data from the groups were compared, and no significant difference was found between the three groups, indicating that the groups were appropriate. The average number of mature oocytes in each group was calculated. The mean numbers of mature oocytes in women who received rFSH only, 100 IU hCG and 200 IU hCG were 9, 9.7, and 8.7, respectively. The difference of the mean mature oocytes in the three groups was not statistically significant among the three groups (Table 1).

Table 1. Baseline characteristics of participants in the three treatment groups

	Group1*	Group2**	Group3***	P-Value
	Mean (Min-Max)	Mean (Min-Max)	Mean (Min-Max)	
Age (Years)	31.1 (20-40)	31.9 (21-38)	30.6 (21-38)	0.299
FSH (IU/l)	6.1 (4-16)	6.5 (5-12)	6.2 (5-18)	0.314
BMI (Kg/m^2)	27 (19-34)	26.5 (20-35)	26.8 (21-32)	0.793

* rFSH; ** rFSH + 100 IU hCG ; *** rFSH + 200 IU hCG

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None of the groups experienced severe OHSS. The incidence of excessive ovarian stimulation was 14% in the first group, 18% in the second group, and 6% in the third group. The difference in the incidence of OHSS in the third group was significantly less than the other two groups ($p \leq 0.0001$). The incidence of OHSS in the second group was higher than that of the first group, and this difference was separately statistically tested. The difference between the first and the second groups was not significant (Table 2).

Table 2. Number of mature oocytes retrieved and occurrence ovarian hyperstimulation syndrome (OHSS) in the three treatment groups

	Group1*	Group2**	Group3***	P-Value
Mature oocyte retrieved: Mean(Min-Max)	9 (2-25)	9.7 (4-26)	8.7 (3-24)	0.576
OHSS: n (%)	7 (14)	9 (18)	3 (6)	$<10^{-4}$

* rFSH; ** rFSH + 100 IU hCG ; *** rFSH + 200 IU hCG

Discussion

The present study illustrated that adding hCG to rFSh did not increase the mature oocyte retrieved in normal responders undergoing ICSI. A similar result reported that higher mature oocytes were not found in normal responders who received LH or hCG compared to those who received rFSH only (15). Nonetheless, a randomized controlled trial on poor responders showed that adding100 IU hCG to rFSH was associated with the increased number of the mature oocytes retrieved compared to those who received rFSH only (13). In addition, a study on women over the age of forty demonstrated that the number of mature oocytes was higher in women who received low doses of hCG and rFSH compared with those who received rFSH only (5).

Also, our study demonstrated a significant difference in the reduced occurrence of OHSS in normal responders who received 200 hCG IU compared with those who received 100 IU hCG or rFSH only. Several studies have shown that the use of low dose of hCG in addition to rFSH is associated with reduced OHSS (5, 16, 17). A possible explanation for the difference in occurrence OHSS among the three groups might be the difference in the production of endothelial growth factor under the effect of hCG injection. The previous studies showed that the occurrence of OHSS was due to endothelial growth factor, which was produced by mature oocyte through hCG injection. This hormone can also be produced by immature oocyte after the retrieval of mature oocytes, and might result in higher occurrence OHSS (18, 19). In the present study, we only calculated the total number of MII oocyte retrieved. But the number of MI oocytes, germinal vesicle oocyte, and atretic oocytes was not defined. However, the number of mature oocyte was the same in all age groups. The occurrence of lower OHSS in the women reached 200 IU hCG, and there was no difference found in the number of mature oocyte retrieved, which was probably due to the demographic factors and small sample size. Accordingly, other studies did not report any better outcomes in normal responders who received low dose hCG compared with those who received rFSH only (20, 21).

Conclusion

The addition of 200 hCG to rFSH throughout the stimulation in a long GnRH agonist protocol benefited a lower occurrence of OHSS only. But it is vital to conduct future clinical randomized clinical trials with larger and more homogenous women to confirm the beneficial effect(s) of adding 200 hCG IU to rFSH in normal responders undergoing ICSI.

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Conflicts of Interest

We declare that we have no competing interests.

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