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Crescent Journal of Medical and Biological Sciences
Vol. 7, No. 1, January 2020, 110–115
eISSN 2148-9696

Effect of Estrogen Priming in Antagonist Cycles in Women With Poor Response to IVF Treatment

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Abstract

Objectives: Despite inconsistencies in existing studies, the results of some research studies indicate that treatment with estrogen priming and gonadotropin-releasing hormone (GnRH) antagonist look promising for poor-responder patients.

Materials and Methods: The study was conducted on 2 groups of poor-responder patients under treatment with GnRH antagonist and gonadotropin. Each group had 53 patients. The treatment was performed after considering the patients' age, the number of previously failed in-vitro fertilization (IVF), antral follicles count and mean serum level of follicular stimulating hormone (FSH3), anti-Müllerian hormone (AMH), and estradiol (E2). In the intervention group, 4 mg of estradiol valerate was administered daily from the 21st day of the cycle before IVF and continued up to the second day of the cycle. Then, stimulation was initiated with human menopausal gonadotropin (HMG) and follicle-stimulating hormone (FSH) and the GnRH antagonist was implemented on the eighth day and continued until the prescription of human chorionic gonadotropin (HCG).

Results: The average number of obtained large follicles (2.9±1.8 against 2.3±1.6), M2 oocytes (3.6±0.3 against 2.8±0.3) and embryo quality type II (1.3±0.2 against 0.9±0.1) and type III (0.7±0.1 against 0.3±0.1) in the intervention group was significantly higher compared to the control group (P value was respectively 0.05, 0.05, 0.05, and 0.01). The rate of successful pregnancy was higher in the intervention group (8.3%) than in the control group (6.7%). However, it was not statistically significant ($P=0.50$).

Conclusions: Estrogen priming has positive effects on GnRH antagonist cycles with an increase in the number of large follicles and better quality oocytes and embryos.

Keywords: Estrogen Priming, Gonadotropins, GnRH

Introduction

All female follicles and oocytes are formed in ovaries in utero while metaphase stops in meiotic prophase I. The continuance of cell division depends on the completion of menstrual cycles and occurrence of fertilization (1). With age, disorders occur in the process of chromosome segregation and meiosis division, especially in meiosis I (2-4).

One of the most widely used assisted reproductive techniques (ART) in case of such disorders is in vitro fertilization (IVF). IVF requires ovarian hyper-stimulation to facilitate the release of the ovum by several follicles for fertilization to occur. Endometrial implantation after fertilization is closely associated with hormonal conditions. Owing to this, the ovarian hyper-stimulation process due to follicular overgrowth and increased serum concentrations of estradiol leads to an early increase in progesterone. This could, however, lead to implantation failure (5,6).

The aforesaid factors are the reasons for the failure of assisted reproductive techniques. They eventually cause patients to respond poorly to treatments and lower the success rate. Studies have shown that the rate of poor response to assisted reproductive techniques is 5.6% to 35.1% (7,8). Regardless of conflicting definitions, poor response and treatment failure finally leads to increased rates of implantation failure, less activated oocytes, a reduced number of embryos derived from IVF and lower chance of fertility compared to people with a natural response to treatment (9,10).

So far, several treatments have been introduced to improve the conditions of patients with poor response among which short protocol is the most common method of treatment. According to this method, low-dose agonist or antagonist is used. In this protocol, a higher endogenous follicular stimulating hormone (FSH) level is used to increase the number of follicles. An initial FSH increase in short protocol could result in follicular growth.

Received 29 November 2017, **Accepted** 26 April 2018, **Available online** 17 May 2018

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However, a simultaneous increase in luteinizing hormone (LH) may cause follicle apoptosis. Similarly, standard treatment antagonists cause the developing oocytes in patients exposed to androgen production in vivo to be in circulation during the six to seven days of stimulation before the follicle growth. Even low levels of androgens in highly sensitive people could have improper effects (11,12). The results of the studies conducted in this field have been inconsistent (13-16). Given the existence of contradictory information in this regard, and the absence of a comprehensive and efficient study in Iran, similar or different endocrine changes in some patients as well as the low cost or absence of complications arising from short-term estrogen therapy, we applied this method to treat people who did not previously respond to the stimulation method. Accordingly, the prescribed estrogen while coming in contact with androgen resulted in improved growth, better quality of ovum and embryo, and increased implantation rate. Besides, prescribed estrogen may activate the patient's response to FSH because it activates the estrogen of FSH receptors.

Materials and Methods

This was a randomized controlled clinical trial involving 106 women who volunteered for IVF with a history of poor response. They had been referred to Al-Zahra hospital of Tabriz in north-west Iran in 2015. Al-Zahra hospital is the nation's most well-equipped women's infertility center. It serves over 6 million people in north-west Iran. After receiving their consent, they were randomly placed under treatment with gonadotropin-releasing hormone (GnRH) antagonist protocol, with or without estrogen priming.

Based on a study by Fisch et al (17), the fertility rate in the women studied was estimated to be 27% on an average. If α is 0.05, power is 95% and there is 27% difference between 2 control and intervention groups based on ratio comparison. A sample size of 42 people was estimated for each group. Considering that 25% of the people were excluded from the study, the sample size for each group was 53 and the total sample size was 106 people. Randomization was also conducted using a random number table.

Women in the age group of 19 to 42 years with low ovarian reserve, borderline FSH (over 10), low anti-Müllerian hormone (AMH) (below 1), and low number of antral follicles who had previously not responded to treatment with short-term antagonist and gonadotropin protocol or their retrieved oocytes was equal to or less than 3 met the inclusion criteria. Those excluded were women who had not responded to treatment at all, had a follicle or a canceled cycle or changed into intrauterine insemination (IUI), or had certain diseases such as hypothyroidism (hypothyroidism is an underactive thyroid gland) or hyperprolactinemia (is the presence of abnormally high levels of prolactin in the blood).

In this study, the women who did not respond to conventional therapies with antagonist protocol were categorized as intervention group and were included in the treatment cycle with antagonist and GnRH following the administration of estrogen priming. From the 21st day of the previous IVF cycle, a daily dosage of oral estradiol valerate (4 mg) was prescribed for these patients. This was continued to the second day of the cycle. The control group members were also included in the treatment cycle with GnRH antagonist and gonadotropin groups with conditions similar to the intervention group with the exception of receiving estrogen priming. Since intervention and control group members were not in contact with each other and were not aware of being included in intervention or control group, the confounding effect arising from Halo effect was controlled as much as possible. From the second day of the cycle, ovarian stimulation was initiated in both groups with human menopausal gonadotropin (HMG) and FSH. After follicle maturity to 12 to 14 mm, GnRH antagonist was started and continued until the day of human chorionic gonadotropin (HCG) injection. After observation of at least 2 follicles with a size of 18 mm or more, oocyte retrieval was conducted for both groups within 34-35 hours after HCG injection by transvaginal ultrasound machine, made by Honda, Japan. The ultrasonography result was interpreted by 2 experienced gynecologists. After dissecting the oocyte, sperms were injected into the cytoplasm of oocytes and embryos were cultured in ISM media (is a growth medium for culturing embryos). Then 4 to 8 cell embryos were scored and transferred to the uterus under abdominal ultrasound for assessing pregnancy. About 12 to 14 days after embryo transfer, BHCG was evaluated by the enzyme-linked immunosorbent assay (ELISA) kit. If the result was positive, a transvaginal ultrasound was performed to evaluate the clinical pregnancy rate 14 days later. Therefore, fertilization, implantation, and clinical pregnancy were examined.

The data were analyzed using SPSS software version 20.0. The normal distribution of quantitative data was conducted using the Kolmogorov-Smirnov test. The quantitative data were compared using *t* test for independent groups and qualitative data were compared using chi-square and Fisher exact tests. $P \leq 0.05$ was considered statistically significant. In this study, there was no compulsion on the participants and they did not bear any cost, so the number of the missing subject was zero.

Results

According to the findings of the present study, the mean age of case and control groups was 34.8±4.1 (21-24) and 33.5±5.1 years (21-42). According to the independent *t* test, no statistically significant difference was observed between 2 groups ($P=0.14$). The cause of infertility was poor ovarian reserve in all cases. All patients also had a history of IVF treatment. The results of the comparison between the 2 groups are shown in Table 1.

Table 1. Comparison of Factors Affecting Fertility and Successful Implantation in Intervention and Control Groups

Variable	Intervention Group Mean ± SD	Range	Controlled Group Mean ± SD	Range	*P* Value
Mean age of patients	34.8±4.1	24-41	33.5±5.1	21-42	0.14
Mean age of patients' husband	38.1±5.9	27-56	38.0±5.6	27-56	0.89
Average number of IVF replications	1.1±0.3	1±2	1.1±0.3	1±2	0.80
Average number of previously mature follicles	5.4±2.1	1±10	5.9±2.9	2-17	0.32
Average number of previously obtained oocyte	4.5±2.2	1±10	4.8±2.9	1±17	0.67
Average number of antral follicles	3.5±0.8	2-5	3.4±0.9	2-5	0.37
Mean FSH3 level in serum (mIU/mL)	7.4±1.9	3.9-14.7	7.9±2.1	5.5-15.9	0.15
Mean AMH level in serum (mg/mL)	1.0±0.5	0.3-3.1	0.9±0.1	0.3-4.7	0.93
Mean E2 level in serum (pg/mL)	84.5±29.4	22.8-206	89.1±33.2	37-226	0.42
Mean estrogen level at HCG injection (pg/mL)	1983.1±1002.6	325-4800	1843.8±1024.3	4800-310	0.47
Mean progesterone level at HCG injection (pg/mL)	0.7±0.2	1.3-0.3	0.7±0.2	1.3-0.4	0.73
Average endometrial thickness at HCG injection (mm)	7.9±0.9	6-9	8.1±0.8	6-9	0.18

Abbreviations: IVF, in-vitro fertilization; FSH, follicular stimulating hormone; AMH, anti-Mullerian hormone; E2, estradiol; HCG, human chorionic gonadotropin.

The study showed that the number of transferred embryos in the intervention group was 1 in 4 patients, 2 in 13 patients, 3 in 33 patients, and 4 or more in 3 patients. The number of embryos conveyed in the control group was 1 in 4 patients, 2 in 24 patients, 3 in 23 patients and 4 or more in 2 patients. Two-day-old embryos were transferred in 30 cases and three-day-old embryos were transferred in 23 cases. Two-day-old embryos were transferred in 28 women in the control group and three-day-old embryos were transferred in 25 women in the control group. According to the chi-square test, there was no statistically significant difference between the 2 groups ($P=0.70$). The results of this study are shown in Table 2 for further comparison of the effects of estrogen priming.

Moreover, the canceled cycle was observed in 5 cases in the intervention group and 7 cases in the control group. According to the chi-square test, there was no statistically significant difference between the 2 groups ($P=0.50$).

Discussion

The present study was conducted to examine the effect of estrogen priming on GnRH antagonist cycles in poor-responder patients. According to the findings, estrogen priming resulted in more developed follicles and oocytes as well as high-quality embryos compared to the control group. Although relevant results obtained in terms of the frequency of the canceled cycle and successful pregnancy were better in the intervention group, this difference was not statistically significant.

Several studies have been conducted in this area, but heterogeneous and conflicting results have been reported. The results of the present study are consistent with the study by Fanchin et al. The study indicated that by using negative and natural feedback of the hypothalamic-pituitary, estrogen priming could effectively prevent the increment of FSH at intervals between cycles, improve simultaneous homogenous growth of follicles, and finally

Table 2. Comparison of the Impact of Estrogen Priming on Intervention and Control Groups

Variable	Intervention Group Mean ± SD	Range	Controlled Group Mean ± SD	Range	*P* Value
Average number of small follicles	1.6±0.2	0-5	1.4±0.2	0-7	0.44
Average number of medium follicles	2.6±0.3	0-10	2.2±0.2	0-10	0.33
Average number of large follicles	2.9±1.9	0-7	2.3±1.6	0-5	0.05
Average number of obtained oocytes M1	1.6±0.6	0-4	1.3±0.1	0-3	0.07
Average number of obtained oocytes GV	1.1±0.1	0-4	1.0±0.2	0-6	0.77
Average number of obtained oocytes M2	3.6±0.3	0-10	2.8±0.3	0-10	0.05
Average number of grade I quality embryos	2.6±1.4	0-8	2.5±1.4	0-6	0.65
Average number of grade II quality embryos	1.3±0.2	0-5	0.9±0.1	0-4	0.05
Average number of grade III quality embryos	0.7±0.1	0-4	0.3±0.1	0-3	0.01
Mean number of gonadotropins injections of recent cycle	35.2±4.5	24-45	34.6±5.5	2-45	0.47
Mean number of gonadotropins injections of last cycle	27.9±4.8	18-38	28.5±3.6	18-36	0.41

Abbreviations: M1, metaphase 1; GV, germinal vesicle; M2, metaphase 2.

bring about better growth and mature follicles (18,19).

The study by Dragisic et al indicated that estrogen priming in GnRH antagonist protocol in poor-responder patients could improve ovarian stimulation and lead to more uniformity in follicular development and increase pregnancy rates (20). Although the findings of the present paper are consistent with the aforesaid study, no statistically significant difference was found between 2 groups in terms of clinical pregnancy rate.

The study by Frattarelli et al conducted on 60 poor-responder patients indicated that estrogen priming in standard IVF protocol compared with the method without estrogen priming would significantly increase the number of resultant ovum and embryos. Despite its slight impact on pregnancy rate, it leads to an improvement in overall performance, which was consistent with the findings of the present paper (21).

The study by Hill et al examined the effect of estrogen priming on 57 poor-responder patients compared with the standard protocol conducted on 228 controlled patients. This led to an increased number and higher quality of ovum and embryos. The result of pregnancy in the intervention group was more desirable compared to the control group but did not reach a significant level which is consistent with the present study (22).

Weitzman et al conducted a study on 57 patients under estrogen priming treatment and compared the results with the control group. Similar to 2 previous studies, the number and quality of the resulted ovum and embryos were significantly better. This was consistent with the present study. However, no statistically significant difference was found in terms of pregnancy rate (23).

The study by Ata et al compared the results of applying estrogen priming in GnRH antagonist cycle with the results obtained from the application of microdose flare-up protocol. The number of follicles and oocytes resulting from the 2 methods were similar. But the number of high quality transferred embryos, as well as clinical pregnancy rate in the 2 groups had no statistically significant difference (24). The reason for disconformity between the aforesaid study and present study was the absence of a proper control group.

In contrast to our findings, the study by DiLuigi et al indicated that estrogen priming in GnRH antagonist cycle had no serious effect on IVF results in terms of number and quality of resultant follicles and oocytes and outcomes of clinical pregnancy compared to the control group which may be due to heterogeneous poor-responder patients (25).

The study by Elassar et al compared the fertilization results in terms of estrogen priming in GnRH antagonist cycle between 2 intervention and control groups. Accordingly, the total dose of prescribed gonadotropin and E2 levels during the administration of HCG was significantly low in the intervention group. However, the number and quality of the resultant follicles and oocytes, cycle cancellation and pregnancy rate were reported to be the same in both groups (26). Unlike the results of the aforesaid study, there was no statistically significant difference in terms of the total number of GnRH ampoules prescribed in the present study. The difference between patients in terms of the severity of abnormal position and other features associated with poor response to treatment could be due to the differences in the 2 studies. Another study by Elassar et al in the same group indicated that estrogen priming in GnRH antagonist cycle had no clear influence on IVF outcome in poor-responder patients (27).

In the study by Shastri et al, the effect of estrogen priming in GnRH antagonist cycle was compared with oral contraceptive pill microdose leuprolide method in patients with poor response. The IVF results and pregnancy was reported to be the same in both groups (28). The contradiction between the results could be justified based on the dissimilarities of the control groups in 2 recent studies and the present paper.

The study by Chang et al examined the effect of estrogen priming during the luteal phase and ovarian stimulation during GnRH Antagonists cycle. A total number of 155 poor-responder patients were studied in 3 groups: In one group (86 patients), the estrogen priming (4 mg of estradiol valerate per day) was initiated from the 21st day of the luteal phase and was stopped on the third day of menstruation (28 patients). In the other group, it was initiated during the ovarian stimulation period and continued until the prescription of HCG (58 patients). The Pentagon protocol of GnRH was also performed on 69 patients using the normal method. It was finally discovered that estrogen priming intervention in both methods exhibited significantly reduced percentage of the cases with canceled cycles compared with the control group. Simultaneously, the number of retrieved ovum, normal embryo, and higher quality embryos significantly increased. There was no major difference between 2 methods of estrogen priming (15) which was consistent with the results of the present study.

In a meta-analysis study by Chang and Wu, the effect of estrogen priming on IVF results in poor-responder patients was examined. The findings of 32 studies including 450 patients in the intervention group and 606 patients in the control group were examined. It was found that estrogen priming in the luteal phase would significantly increase the stimulation period, number and maturity of the resultant oocytes and decrease the number of canceled cycles. However, there was no statistically significant difference between the 2 groups in terms of successful pregnancy rate (14).

In another meta-analysis study by Reynolds et al, the effect of estrogen priming in the luteal phase was examined. It was found that the rate of cycle cancellation was reduced in this method while the rate of clinical pregnancy increased. Unlike other studies, the aforesaid study indicated that there was no statistically significant

difference between the 2 groups in terms of the number of retrieved ovum and embryos (16).

The study by Yucel et al on 121 poor-responder patients discovered that estrogen priming had no noticeable effect on the improvement of response to treatment in microdose GnRH agonist flare-up protocol. It only increased the number of oocytes (13).

It seems that the difference in severity of disease in the population studied, differences in sample size and various risk factors such as treatment failure or poor response to it could explain the conflicting results. It was also shown that some of these studies did not evaluate and follow up the clinical efficacy of these interventions and the patients themselves were used as controls while the previous failed cycles belonging to these patients were used as the control. Moreover, in several studies, a proper schedule was not determined for GnRH prescription after estrogen priming (15). The use of estrogen priming in IVF is proposed based on the fact that follicular growth and granulosa cell proliferation will be improved by estrogen and FSH (29), which is consistent with the findings of the present study.

Conclusions

Racial differences between various communities may result in endocrine differences and this may provide the justification for different outcomes in different studied populations. Obviously, due to the heterogeneity of poor-responder patients, prescribing or recommending a particular treatment for these patients has never been possible. However, efforts to increase the chances of pregnancy in these patients will continue until these problems are overcome. Therefore, it is recommended to conduct similar and simultaneous researches in different parts of the world using the same treatment method and larger sample size..

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

The study was approved by the Ethics Committee of Tabriz University of Medical Sciences (ethics No. TBZMED. REC.1394.1003) and registered on the Iranian Registry of Clinical Trials website (identifier: IRCT201602075942N3; https://irct.ir/trial/6417). .

Financial Support

The department of Obstetrics and Gynecology at the Women's Reproductive Health Research Center affiliated to Tabriz University of Medical Sciences, Iran supported the study.

Acknowledgments

This paper is extracted from a thesis written as a part of a specialist degree in Obstetrics and Gynecology at the Women's Reproductive Health Research Center.

The authors would like to appreciate the support of the department of Obstetrics and Gynecology at the Women's Reproductive Health Research Center affiliated to Tabriz University of Medical Sciences, Iran..

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