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The Pretreatment Effect of Myoinositol on Improving Egg Quality in Infertile Patients with Polycystic Ovary Syndrome

Abstract:

Polycystic ovary syndrome is one of the most common causes of endocrine disorders in women and the most common cause of infertility due to lack of ovulation, which affects 6-10% of women of reproductive age. The current study aimed to investigate the pretreatment effect of myoinositol on improving egg quality in infertile patients with polycystic ovary syndrome. In the current study, about 54 candidates for IVF diagnosed with polycystic ovary syndrome were included and divided into case and control groups by block randomization. The data was analyzed using descriptive and analytical statistics in the Strata software. The significance level was considered at p<0.05. The average number of administrations of CETROTIDE and rFSH as well as the number of immature eggs of the MI-GV stage, were lower in the case group compared to the control group. The positive healing effects of myoinositol on the reduction of the number and dosage of the medicines used to treat women with polycystic ovary syndrome have made it a good alternative to treat patients with this syndrome.

Keywords: *Polycystic ovary syndrome, CETROTIDE, Rfsh,infertility*

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Introduction

Polycystic ovary syndrome is one of the most common causes of endocrine disorders in women and the most common cause of infertility due to lack of ovulation, which affects 6-10% of women of reproductive age [1, 2]. This syndrome is named after the presence of large ovaries containing a large number of small cysts (in most affected women and not in all patients) located in the outer layer of each ovary. Women suffering from this disease have common symptoms such as menstrual disorders, hyperandrogenism symptoms such as hirsutism and acne, hair loss, and infertility. Patients are exposed to severe complications such as the increased risk of endometrial and breast cancer, dyslipidemia, high blood pressure, cardiovascular diseases, and diabetes [3]. The prevalence of obesity and dyslipidemia in patients with polycystic ovary syndrome is higher than in healthy women. 40% of affected women are obese, and 75% are infertile [4]. This disease is seen in approximately 6 to 10 percent of women of reproductive age. The cause of this disease is unknown. Affected women face difficulty in getting pregnant due to problems in ovulation. Researchers believe that hereditary factors and diabetes play are effective in its emergence. On the other hand, early diagnosis and initiation of treatment can help prevent long-term complications such as type 2 diabetes, heart disease, and stroke [5, 6].

Normal fertility cycles are regulated by changes in the levels of hormones produced by the pituitary gland in the brain and ovaries. The pituitary gland secretes follicle-stimulating hormones and luteinizing hormones, which control the growth and release of eggs in the ovaries [7]. During a one-month cycle, ovulation occurs approximately two weeks before menstruation. Ovaries secrete estrogen and progesterone hormones that prepare the uterine wall to receive a fertilized egg. The ovaries are also responsible for producing male hormones (androgens), such as testosterone. If pregnancy does not occur after ovulation, the secretion of estrogen and progesterone decreases, and the uterine wall falls during menstruation [8]. In polycystic ovary syndrome, the pituitary may secrete high amounts of corpus luteum-producing hormone, and the ovaries also produce high amounts of androgens. This disrupts the normal menstrual cycle and can also cause infertility, hirsutism, and acne. Although scientists are not sure about the cause of polycystic ovary syndrome, several factors are involved in the occurrence of this syndrome, among which the following can be mentioned [9].

In 2012, Lisi et al. conducted a pilot study in which the pretreatment effect of myoinositol on IVF cycles of people without polycystic ovary syndrome was investigated. In this study, 100 women under the age of 40 without polycystic ovary syndrome were divided into two groups. One group received myoinositol and folic acid, while the other only took folic acid. The addition of myoinositol to folic acid in patients without polycystic ovary syndrome undergoing multiple follicular stimulations for IVF reduces the number of immature oocytes and rFSH while maintaining the number of pregnancies. In addition, a significant increase in the incidence of implantation was observed in the group treated with myoinositol [10]. In an article entitled "the effect of myoinositol in polycystic ovary syndrome" by Biradar et al. (2014), myoinositol has been

investigated as an alternative medicine to metformin in the treatment of polycystic ovary syndrome. It aimed to replace metformin and reduce the side effects of this drug. Based on this research, it has been shown that myoinositol, as a substance in follicular fluid, plays an important role in the cytoplasmic and nuclear growth of the egg. Also, it has been concluded that myoinositol not only affects the level of insulin sensitivity but also improves the adversaries such as acne, hirsutism, reduces the side effects for patients with polycystic ovary syndrome, and regularizes menstrual cycles [11]. Caprio et al. (2015) investigated the therapeutic effect of myoinositol on patients who had a poor response to the IVF process. In this study, 76 patients were divided into two groups; one group received myoinositol and folic acid, and the other received only folic acid for three months. This study showed that myoinositol positively affects the quality and number of eggs and can increase ovarian response to gonadotropins. This research recommended that myoinositol be used as adjuvant therapy in weak IVF cycles [12]. Many studies aim to improve egg quality and reduce the side effects of IVF cycles in these patients worldwide. Some of these studies have addressed the role of insulin resistance in the background of these complications. The current study also aims to reduce insulin in circulation and decrease free androgen and estrogen, thus reducing side effects such as ovarian hyperstimulation, which probably occurs following an excessive increase in blood estrogen [13, 14]. The exact balance of steroids in the follicular fluid strongly affects the quality of the recovered eggs and the fertility rate.

Methods and Materials:

The current research was a double-blind, randomized clinical trial. The statistical population includes all infertile women with polycystic ovary syndrome who are candidates for IVF at Shahrekord's Hazrat Zahra Infertility Center. Using a study reported the average number of days of ovarian stimulation to be 11.4±0.9 and 12.4±1.4 in ICSI. Taking α=0.05 and the power of the study at 0.85, the sample size was obtained as 54 people with 24 patients in the case and 30 in the control groups, respectively [15].

Inclusion and exclusion criteria are as follows:

Inclusion Criteria:

- Infertile women with polycystic ovary syndrome under the age of 35 who are candidates for IVF.
- Sperm test-reviewed and normal hysterosalpingogram.
- Patient consent to participate in the study.

Exclusion Criteria:

- The use of another drug during the study.
- The presence of any underlying disease, abdominal and pelvic surgery history, male infertility, hysterosalpingography, and abnormal prolactin.
- The patient withdrew from participating in the study.

After measuring the basic tests of FSH, LH, estrogen, prolactin, anti-müllerian hormone, and fasting insulin on the third day of menstruation, they were divided into two groups by computerized block randomization. In one group, only folic acid was prescribed for three months with a dosage of 400 mg per day, and the second group received myoinositol 2000 mg + folic acid 400 mg per day for three months. Subsequently, both groups entered the cycle of ovulation stimulation using the antagonist protocol, and according to the conditions, a dose of 150 units of rFSH was considered until the 18 mm follicle was obtained for the patient. Moreover, after a mature follicle (14 mm) appeared on the ovarian surface, the antagonist was prescribed daily as a subcutaneous CETROTIDE. After observing the 18-22 mm follicle in the ovarian surface, 10,000 units of HCG were injected, and ovulation was observed after 36 hours. The information obtained through the checklist was recorded, and the descriptive statistics and calculation of central tendency and dispersion indices and, analytical statistics T-test, chi-score correlation coefficient in strata software were used for the data analysis. It should be noted that the Ethics Committee approved this study of Shahrekord University of Medical Sciences.

Results:

Distribution of the Case Study's Patients in the Research Groups:

In the current study, 54 women with polycystic ovary syndrome who were candidates for IVF were studied in the case (24 women) and control groups (30 women) (Table 1).

Table 1: Distribution of IVF-candidate infertile women with polycystic ovary syndrome in the research groups

Group	Frequency	Percentage
Case	24	44.44
Control	30	55.56
Total	54	100

Average Number of CETROTIDE and rFSH Injections for the Samples:

Table 2: Comparison of average numbers of CETROTIDE and rFSH injections in IVF-candidate women with polycystic ovary syndrome in the research groups

Group	Frequency	Standard deviation ± mean	Significance level
CETROTIDE			
Case	24	4.20 ± 0.65	0.00 = P*
Control	30	5.96 ± 1.12	
Total	54	5.18 ± 1.28	
rFSH			
Case	24	11.25 ± 0.73	0.00 = P*
Control	30	12.96 ± 1.12	
Total	54	12.20 ± 1.29	

*is indicative of significance level at $p<0.05$

As seen in Table 2, the average number of injections of CETROTIDE in infertile women with ovarian cysts in the case and control groups shows a significant difference between the patients in the case and control groups. The average number of steroid injections in the case group was (4.20 ± 0.65), which is significantly lower than that of the control group (5.96 ± 1.12) (P = 0.00). Also, there is a significant difference in the average rFSH injection between case and control group patients. The average rFSH injection in patients of the case group (11.25 ± 0.73) was significantly lower than that of the control group (12.96 ± 1.12) (Pr = 0.00).

The Number of Immature and Degenerate Eggs in the Sample Patients:

Table 3: Comparison of average numbers of degenerate and immature eggs in IVF-candidate women with polycystic ovary syndrome in the research groups

Group	Frequency	Standard deviation ± mean	Significance level
Case	24	5.83 ± 1.88	P -0.008
Control	30	8.1 ± 2.89	
Total	54	7.9 ± 2.72	

*is indicative of significance level at $p<0.05$

A significant difference was observed in the number of immature and degenerate eggs between control and case group patients. Table 3 shows that the number of immature and degenerate eggs in the case group was significantly (P = 0.0008) lower than that of the control group.

The number of Mature Eggs in the Sample Patients:

Table 4: Comparison of average numbers of mature eggs in IVF-candidate women with polycystic ovary syndrome in the research groups

Group	Frequency	Standard deviation ± mean	Significance level
Case	24	9.12 ± 1.22	P -0.002
Control	30	8.06 ± 1.36	
Total	54	8.53 ± 1.39	

*is indicative of significance level at $p<0.05$

The number of metaphase II mature eggs in the control group was significantly higher than in the case group. The total number of eggs in the case group was 219, and the total in the control group was 242. Also, as shown in Table 4, the average number of metaphase II mature eggs in the case group was significantly higher than the number of eggs in the control group. This number was 9.12 ± 1.22 in the intervention group and 8.06 ± 1.36 in the control group.

The Number of Freeze Cycles in the Sample Patients:

The number of cycles that led to the freezing in patients of the case and control groups is shown in Table 5. The number of freeze cycles in the control group was higher than in the case group. The average freezing cycles in case group patients were significantly higher than in control group patients (6.12 ± 1.87 versus 4.32 ± 1.84).

Table 5: Comparison of average numbers of freeze cycles in IVF-candidate women with polycystic ovary syndrome in the research groups

Group	Frequency	Standard deviation ± mean	Significance level
Case	24	6.12 ± 1.87	P -0.000
Control	30	4.32 ± 1.84	
Total	54	5.15 ± 2.05	

*is indicative of significance level at $p<0.05$

Discussion:

The current study aimed to investigate the effect of pretreatment with myoinositol on improving egg quality in IVF/ICSI treatment in infertile patients with polycystic ovary syndrome. The results showed that the average number of CETROTIDE, rFSH, and immature MI-GV eggs in the group that received myoinositol was lower compared to the control group.

Inositol and especially myoinositol are essential molecules that play an important role in the early development of the embryo. Studies have shown that the serum level of these molecules in fetuses and newborn babies is several times higher than in adults. Administering it during pregnancy reduces the risk of gestational diabetes in humans. The concentration of myoinositol in the reproductive system of female mammals is higher than its amount in blood serum, indicating this molecule's positive role in fertility. Its levels in follicular fluid and blood serum have a direct and significant relationship with egg quality and pregnancy in humans [15, 16].

Administering myoinositol in women before starting the process of hormonal stimulation in IVF cycles can increase the quality of eggs and embryos and reduce the amount of FSH administration and the duration of treatment needed to stimulate ovulation. These are among the parameters that directly cause a significant increase in the chance of pregnancy. At the ovarian level, it seems that myoinositol is involved in various mechanisms and signaling pathways that cause eggs to mature and reach metaphase II. The role of myoinositol is related to the effects of InsP3 (Inositol trisphosphate) in the regulation of intracellular calcium ion concentration in response to the FSH and LH. In the eggs, this mechanism occurs through interaction and connection with specific receptors (InsP3-R1), which play an essential and necessary role in the maturation process [17].

In line with the results of the current study, other studies have also reported and confirmed the positive effects of inositol treatment in infertile patients [18-20]. Different cellular and molecular mechanisms are involved in creating this therapeutic effect. The following can be mentioned to explain these mechanisms and related processes. Myoinositol isomers are involved explicitly in activating the insulin receptor, and these compounds can also activate the intracellular metabolic processes of glycolysis. Myoinositol can play an important role in cell morphogenesis and cytogenesis, lipid synthesis, cell membrane production, reproduction, and development. Myoinositol is a precursor of phospholipids, which is responsible for producing important intracellular signals in mammals' eggs and guides oocyte maturation and meiotic development [17]. Cell signals through inositol and its phosphates, including myoinositol, are involved in the regulation of various cell signaling pathways, including insulin signal transmission, calcium ion flow, cellular skeleton protein accumulation, lipid metabolism, serotonergic pathway regulation, the process of cell growth and differentiation, egg maturation, and they control and direct fertility. Myoinositol is involved in various processes and cycles of human reproduction. Studies show that increasing the concentration of myoinositol in the human follicular fluid has a positive functional role in follicular maturation and is considered an indicator of good follicle and egg quality [21].

Facchinetti et al., in their studies, focused on the administration of myoinositol in patients with polycystic ovary syndrome and found strong evidence regarding the greater efficacy of myoinositol (at a dose of 2-4 grams per day for 12-16 weeks) compared to treatment methods based on the use of D-chiroIns [17]. Regidor and Schindler (2016), in a study entitled "Myoinositol, an alternative and safe approach to the treatment of infertile women with polycystic ovary syndrome," reported the effect of 2000 x 2 mg of myoinositol plus 2 x 200 mcg of folic acid per day for three months as a promising and safe medication for the effective treatment of syndrome symptoms and reducing infertility in patients with polycystic ovary syndrome. An ovulation improvement was observed in 70% of the studied women, and the pregnancy rate increased by 15.1%.

In this study, testosterone levels decreased while progesterone levels increased. These researchers stated that no side effects were observed in the studied patients following myoinositol administration and suggested using myoinositol to treat infertility in these patients [22]. Gerli et al. (2007) also reported administering myoinositol and folic acid-induced ovulation in 82% of patients. While in this report, ovulation occurred in 63% of patients receiving a placebo (control group), which was significantly less than in the treatment (case) group [23]. Also, Raffone et al. reported a higher number of pregnancies in the group receiving myoinositol compared to the group receiving metformin .In another study, it has been reported that treatment with myoinositol and folic acid in patients with polycystic ovaries causes a significant decrease in the number of GV stage and degenerate eggs in aspired follicles. In contrast, the treatment did not significantly affect the total number of recovered eggs [15].
Enrichment of the culture medium with myoinositol increases the meiotic maturation of mouse oocytes and finally causes the production of fertilized embryos. In contrast, the depletion and exhaustion of the intracellular reserves of myoinositol reduce the sensitivity of inositol-dependent transmission pathways, which leads to a decrease in InsP3 level and proper release of

calcium, and ultimately delays the process of follicle and egg maturation [21]. When the oocytes are matured in the presence of myoinositol, fertilized in the laboratory environment, and transferred to foster mothers, the rate of implantation and survival of the resulting embryos increases significantly. Also, studies conducted on the role of myoinositol in increasing the primary implantation rate of mammals have shown that the enrichment of the culture medium with myoinositol significantly improves the rate of blastocyte formation in rabbits and cows, which leads to the development and birth of a healthy baby [24,25]. The membrane transporters' activity allows myoinositol absorption into mammalian cells, including newly transferred eggs and embryos (before implantation). In mice, the activity of at least two different membrane transporters causes a progressive and active increase in the absorption of myoinositol in the early stages of development (between the single-cell zygote stage and the blastocyst stage). Then, myoinositol is quickly combined with phosphoinositides. In the zygote, calcium ion concentration fluctuations caused by PLC-dependent InsP3 production play an important role in zygote activation and blastomere production in the embryo. Studies show that using myoinositol in the embryo culture medium significantly increases the number of good-quality embryos and ultimately improves IVF cycles in humans [26].

Conclusion

In the current study, the therapeutic effects of myoinositol on all fertility parameters, improving the number and quality of mature eggs and improving the fertilization rate in patients with polycystic ovary syndrome have been shown. This drug can be a suitable alternative to common infertility treatments in patients with polycystic ovary syndrome. To further investigate the therapeutic effect of myoinositol on sperm biological parameters (sperm number, motility, and quality) as well as all specialized indexes of sperm fertility, it is recommended to increase the fertility rate of infertile or low-fertility men.It should be noted that the Ethics Committee approved this study of Shahrekord University of Medical Sciences.

Conflicts of interest

This article was derived from the MD thesis of dr. Shadrooz Moazzam whose protocol was approved by the Deputy of Research and Technology of Shahrekord
University of Medical Sciences.
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The ethics code of this research was
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