MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 4248-4253
DOI: 10.12659/MSM.910743

Received: 2018.04.22
Accepted: 2018.05.21
Published: 2018.06.20

# A Retrospective Study of Letrozole Treatment Prior to Human Chorionic Gonadotropin in Women with Polycystic Ovary Syndrome Undergoing *In Vitro* Fertilization at Risk of Ovarian Hyperstimulation Syndrome

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**Source of support:** This study was supported by grants from YanTai Union Foundation of China (ZR2015HL017), and ZheJiang Clinical Medicine Foundation of China LKFJ039)

**Background:** Women with polycystic ovary syndrome (PCOS) undergoing *in vitro* fertilization (IVF) are given letrozole before a trigger injection of human chorionic gonadotropin (hCG) to lower estrogen ($E_2$) levels, but can experience ovarian hyperstimulation syndrome (OHSS). The aim of this study was to evaluate the effect of oral letrozole, prior to administration of hCG, on the outcome of IVF and development of OHSS.

**Material/Methods:** Retrospective clinical review included 181 cases of women with PCOS who underwent IVF cycles with intracytoplasmic sperm injection (ICSI) and embryo transfer (ET) (IVF/ICSI-ET). The day before the use of hCG, cases were divided into a letrozole-treated group (N=78) and a non-letrozole group (N=103). An oral dose of 2.5 mg qd of letrozole was given when the peak level of $E_2$ was ≥4000 pg/ml during ovarian stimulation and ceased before the day of egg retrieval.

**Results:** The letrozole-treated group had a significant increase in the number of retrieved oocytes, viable embryos, and fresh ET rate (P>0.05); peak levels of $E_2$, and $E_2$ levels on the day of the egg retrieval, were significantly higher, and the fertilization rate was significantly lower (P<0.001). No significant differences were found in the rates of pregnancy, abortion, or ectopic pregnancy between the two groups (P>0.05). The incidence OHSS was lower in the letrozole-treated group, but this difference did not reach statistical significance (P>0.05).

**Conclusions:** Women with PCOS who underwent IVF, oral treatment with letrozole a day prior to treatment with hCG lowered $E_2$ levels, but did not significantly reduce the incidence of OHSS.

**MeSH Keywords:** **Fertilization *in Vitro*** • **Ovarian Hyperstimulation Syndrome** • **Polycystic Ovary Syndrome**

**Full-text PDF:** https://www.medscimonit.com/abstract/index/idArt/910743







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## Background

The current 2016 American Society for Reproductive Medicine (ASRM) guidelines include recommendations for the prevention and treatment of moderate and severe ovarian hyperstimulation syndrome (OHSS), which can be associated with polycystic ovary syndrome (PCOS) [1]. The current ASRM guidelines include the advice for the management of women with PCOS who are being treated for infertility with *in vitro* fertilization (IVF), who can have higher peak levels of estrogen ($E_2$), resulting in more retrieved oocytes, but which can also increase the risk of ovarian hyperstimulation syndrome (OHSS) [1].

Assisted reproductive therapy can include IVF cycles with intracytoplasmic sperm injection (ICSI) and embryo transfer (ET) (IVF/ICSI-ET). OHSS is an uncommon but potentially severe complication of IVF, and although it is a self-limiting condition and the symptoms may resolve by the next menstrual cycle, if the patient fails to become pregnant. However, the symptoms of OHSS can persist in the first three months in pregnant patients, because of the continuous rise in levels of endogenous human chorionic gonadotropin (hCG), which has a stimulatory effect on the ovaries.

According to the clinical manifestations of OHSS, this condition can be graded as mild, moderate, or severe. Severe OHSS can lead to severe complications that include pleural effusion, acute renal insufficiency, venous thrombosis, and thromboembolism. OHSS can also be classified according to the time of onset, as early-onset OHSS and late-onset OHSS. Early-onset OHSS usually occurs between 3–7 days following injection of hCG, and could be related to the dose of exogenous hCG [2]. Late-onset OHSS is often associated with endogenous hCG during pregnancy [2].

Therefore, it is advisable to determine the probability of OHSS before selecting an appropriate ovarian stimulation protocol in women with PCOS who are undergoing IVF. Also, choosing the correct dose of gonadotropin, treating any abnormal conditions promptly, are important considerations for the fertility doctor.

Recent studies have shown that patients with PCOS who underwent IVF with high-risk factors for OHSS and who were treated with letrozole after egg retrieval had significantly lower E2 levels and a lower incidence of OHSS [3,4].

Therefore, this study aimed to evaluate the effect of oral letrozole, before administration of hCG, on the outcome of IVF and development of OHSS in women with PCOS.

## Material and Methods

### Study design and patients

The study was undertaken at a single center, the In Vitro Fertilization (IVF) Center of The Second Hospital Affiliated to WenZhou Medical University, China. The retrospective clinical review included 181 cases of women with polycystic ovary syndrome (PCOS) who underwent IVF cycles with intracytoplasmic sperm injection (ICSI) and embryo transfer (ET) (IVF/ICSI-ET). The day before the use of human chorionic gonadotropin (hCG), cases were divided into a letrozole-treated group (N=78) and a non-letrozole group (N=103). A long gonadotropin-releasing hormone agonist protocol in the early follicular phase was used for ovarian stimulation.

In the letrozole-treated group, patients were given letrozole 2.5mg qd when the peak level of estrogen ($E_2$) was ≥4000 pg/ml during ovarian stimulation and stopped before the day of egg retrieval. Inclusion criteria for this retrospective study included women with PCOS, who were treated with a gonadotropin-releasing hormone agonist protocol in the early follicular phase used for ovarian stimulation, and a peak level of $E_2$ ≥4000 pg/ml during ovarian stimulation.

### Ovulation induction protocol

In the ovulation induction protocol, all the patients were given a subcutaneous injection of 3.75 mg of a gonadotropin-releasing hormone (GnRH) agonist during the follicular phase of the menstruation cycle. After between 33–35 days, patients were monitored to see whether pituitary down-regulation was achieved, with $E_2$ <25 pg/ml, luteinizing hormone (LH) <5 U/L, the diameter of the ovarian follicles, using beta-ultrasound, measuring <5mm, and an endometrial thickness <5 mm. Patients who met these inclusion criteria commenced ovarian stimulation with gonadotropin of 150–225 IU daily. The starting dose of gonadotropin was determined according to the body mass index (BMI), ovarian antral follicle count (AFC), ovarian reserve, and ovarian response in the past IVF/ICSI cycles. The dose could be adjusted in accordance with hormonal level changes and the size of the oocytes. Triggering of final follicular maturation was performed with a 4,000/5,000 IU injection of hCG, as a trigger, when at least one dominant follicle reached 18 mm in diameter or three follicles reached diameters of 17 mm. Oocytes were retrieved at between 36–38 hours after triggering of final follicular maturation.

### Statistical analysis

Data statistical analysis was performed using SPSS version 23.0 software. Results were presented as the mean ± standard deviation (SD) or as a percentage (%). Measured data were





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**Table 1.** The comparison of general information (x±s)

| | Non-LE group (103) | LE group (78) | P value |
|---|---|---|---|
| Maternal age (y) | 30.87±3.91 | 30.25±3.61 | 0.276 |
| Duration of infertility (y) | 3.21±2.62 | 3.36±1.78 | 0.762 |
| BMI | 20.15±2.68 | 20.58±3.05 | 0.319 |
| AFC | 18.54±4.76 | 19.56±5.51 | 0.192 |
| AMH (ng/ml) | 5.88±3.65 | 4.90±2.95 | 0.453 |
| Basal hormone levels | | | |
| LH (U/L) | 6.05±4.18 | 5.80±3.21 | 0.672 |
| $E_2$ (pg/ml) | 51.60±22.88 | 58.61±36.86 | 0.152 |
| P (ng/ml) | 0.84±1.70 | 0.52±0.26 | 0.184 |
| FSH (U/L) | 6.90±1.74 | 6.55±1.74 | 0.202 |
| Endometrial thickness (mm) | 5.60±1.75 | 5.60±1.86 | 0.990 |

compared with analysis of variance. A chi-squared ($\chi^2$) test was used. P<0.05 was considered to be statistically significant.

## Results

### Comparison between the letrozole-treated group and the non-letrozole group

Comparison of the women with polycystic ovary syndrome (PCOS) undergoing *in vitro* fertilization (IVF) in the letrozole-treated group (N=78) and a non-letrozole group (N=103), included patient age, body mass index (BMI), the ovarian antral follicle count (AFC), serum anti-Müllerian hormone (AMH) levels, including luteinizing hormone (LH), $E_2$, progesterone, and follicle-stimulating hormone (FSH), and the duration of infertility were comparable between the two groups (P>0.05) (Table 1).

### Ovulation induction

There were no significant differences between two groups in the hormone levels and endometrial thickness on gonadotropin starting day (P>0.05). Also, the hormonal levels and endometrial thickness on the hCG trigger day did not differ significantly (P>0.05). On the day of retrieval, although the progesterone level, gonadotropin duration, and gonadotropin dose were similar in the two groups, there was a significant difference in $E_2$ levels (P<0.001) (Table 2).

### Retrieved oocytes and embryos

The number of oocytes, mature oocytes, fertilized oocytes, high-quality embryos, cryopreserved embryos, and fresh embryo transfer (ET) rates were comparable between the two groups (P>0.05). In the letrozole-treated group, the fertilization rate was significantly lower than in non-letrozole-treated group (P<0.05) (Table 3).

### Clinical outcome

There were no significant differences in clinical outcome between two groups (P>0.05). However, the clinical pregnancy rate in the letrozole-treated group was higher than in non-letrozole-treated group, and the incidence of moderate-to-severe OHSS was lower in the letrozole-treated group, but this difference did not reach statistical significance (P>0.05). The pregnancy rate was lower in the letrozole-treated group (Table 4).

## Discussion

This retrospective clinical study included women with polycystic ovary syndrome (PCOS) undergoing *in vitro* fertilization (IVF) who were given a trigger injection of human chorionic gonadotropin (hCG) to lower estrogen ($E_2$) levels, but who were at risk of ovarian hyperstimulation syndrome (OHSS). The aim of this study was to evaluate the effect of oral letrozole, prior to administration of hCG, on the outcome of IVF and development of OHSS.

During assisted reproductive therapy or IVF, OHSS could occur in all patients with PCOS treated with hCG during IVF treatment. However, as this study has shown, the incidence of OHSS is higher in some groups of patients.





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**Table 2.** The comparison of ovarian stimulation (x±s).

| | Non-LE group (103) | LE group (78) | P value |
|---|---|---|---|
| Hormonal levels on Gn starting day | | | |
| LH (U/L) | 0.56±0.33 | 0.57±0.60 | 0.913 |
| $E_2$ (pg/ml) | 23.17±13.04 | 25.22±15.65 | 0.351 |
| P (ng/ml) | 0.55±0.49 | 0.47±0.21 | 0.205 |
| FSH(U/L) | 3.15±1.61 | 2.89±1.16 | 0.474 |
| Endometrial thickness (mm) | 2.89±1.06 | 2.95±1.38 | 0.776 |
| LH levels on trigger day (U/L) | 0.96±1.01 | 0.82±1.52 | 0.465 |
| $E_2$ levels on trigger day (pg/ml) | 4610.19±697.92 | 4430.52±1521.98 | 0.289 |
| Peak levels of $E_2$ (pg/ml) | 4681.52±656.04 | 5206.28±919.09 | <0.001 |
| P levels on trigger day (ng/ml) | 1.05±0.51 | 0.97±0.58 | 0.342 |
| Endometrial thickness on trigger day (mm) | 11.12±2.35 | 11.15±2.74 | 0.910 |
| $E_2$ levels on the day of retrieval (pg/ml) | 1690.65±827.47 | 1001.60±489.30 | <0.001 |
| P levels on the day of retrieval (ng/ml) | 16.05±9.30 | 17.90±11.07 | 0.340 |
| Gn duration (d) | 11.19±2.01 | 11.39±1.63 | 0.624 |
| Gn dose (iu) | 2191.49±748.94 | 2113.58±624.90 | 0.604 |

**Table 3.** The comparison of Laboratory Information (x±s, %).

| | Non-LE group (103) | LE group (78) | P value |
|---|---|---|---|
| No. of oocytes retrieved | 18.93±6.42 | 19.91±6.22 | 0.307 |
| No. of mature oocytes | 16.64±6.05 | 17.82±6.19 | 0.242 |
| No. of fertilized oocytes | 13.28±5.77 | 13.48±5.17 | 0.808 |
| No. of cleaved embryos | 12.86±5.89 | 13.12±5.16 | 0.756 |
| No. of high-quality embryos on D3 | 6.84±3.98 | 6.76±3.83 | 0.901 |
| No. of embryo transferred | 0.73±0.80 | 0.73±1.21 | 0.981 |
| No. of cryopreserved embryos | 6.84±4.57 | 6.75±4.32 | 0.901 |
| Mature oocyte rate (%) | 88.84 (1725/1953) | 89.62 (1390/1551) | 0.226 |
| Fertilization rate (%) | 79.19 (1366/1725) | 75.54 (1050/1390) | 0.015 |
| Cleavage rate (%) | 96.93 (1324/1366) | 96.19 (1010/1050) | 0.323 |
| High-quality embryonic rate on D3 (%) | 53.40 (707/1324) | 51.88 (524/1010) | 0.467 |
| Fresh embryo transfer rate (%) | 55.34 (57/103) | 48.72 (38/78) | 0.377 |

**Table 4.** The comparison of clinical outcome (%).

| | Non-LE group (103) | LE group (78) | P value |
|---|---|---|---|
| Incidence rate of OHSS (%) | 7.77 (8/103) | 2.56 (2/78) | 0.191 |
| Clinical pregnancy rate(%) | 47.37 (27/57) | 60.53 (23/38) | 0.208 |
| Abortion or ectopic pregnancy rate (%) | 1.75 (1/57) | 2.63 (1/38) | 0.999 |
| Biochemical pregnancy rate(%) | 12.28 (7/57) | 5.26 (2/38) | 0.735 |





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The current 2016 American Society for Reproductive Medicine (ASRM) guidelines include recommendations for the prevention and treatment of moderate and severe OHSS, which can be associated with PCOS [1]. The ASRM concluded that when the serum anti-Müllerian hormone (AMH) levels were ≥3.4 ng/ml, the ovarian antral follicle count (AFC) was ≥24, the number of developed follicle was ≥25, the $E_2$ level was ≥3,500 pg/ml, or the number of eggs retrieved was ≥24, patients were at an increased risk of OHSS [1].

Pathophysiological characteristics of OHSS encompass vascular hyperpermeability and the resulting shift of fluid within the ovarian tissue, and the role of vascular endothelial growth factor (VEGF) are two key components in the development of OHSS, as VEGF induces vascular hyperpermeability. Although hCG has no vascular activity itself, it stimulates granulosa-lutein cells to produce VEGF and vascular endothelial growth factor receptor 2 (VEGFR2) mRNA to increase hyperpermeability and become symptomatic. Some studies have shown a positive correlation between the level of VEGF and the degree of OHSS [5,6].

Currently, there are several clinical approaches to prevent OHSS in clinical practice during IVF [1,8,9], including reducing the dose of hCG on the trigger day, which is shown to be effective without negative clinical outcomes[10]. Therefore, in this present study, the dose of hCG was reduced to half the dose used in routine use. Kovács et al. found that gonadotropins should be stopped when the E2 level was too high and the administration of HCG was not recommended until the E2 level decreased to a safe range [11,12]. However, there are no standard recommendations regarding the time os withdrawal of gonadotropin. A previously published study showed that although pregnancy outcome would not be affected, the transplant rate could decrease when gonadotropin was stopped for more than four days [13]. Also, low-dose aspirin during ovulation induction has been shown to be effective prevention against some severe and life-threatening conditions associated with OHSS [14].

Because of its complex and varied pathogenesis, the level of E2 is unlikely to be the only important clinical factor when assessing the severity of OHSS [7]. However, the level of E2 is still an important clinical marker to evaluate the risk of OHSS, which means that the significantly increased E2 level on the hCG trigger day is positively correlated with the incidence of OHSS [8]. Letrozole is an aromatase inhibitor, that prevents aromatase from producing estrogens, and lowers the level of $E_2$, as letrozole does not affect the central nervous system, the process of follicular growth and ovulation continues normally. It has been previously reported that letrozole treatment was more applicable for patients with breast cancer, as reduced E2 levels reduced the recurrence of breast cancer and also was associated with improved long-term safety following gonadotropin stimulation to preserve fertility in women with breast cancer [15,16].

In normal responders, co-treatment with letrozole has been shown to improve the outcome of IVF treatment in terms of increased number of mature oocytes and blastocysts obtained, without increasing the risk of OHSS [17]. In an IVF cycle, the advantage of letrozole could include an increase in the number of oocytes, a lower risk of OHSS, an increased embryo transfer rate, and a lower risk of thromboembolism. Also, a study by Sain et al. showed that in a rat model of OHSS, treatment with letrozole could effectively reduce the level of VEGF and increased pigment epithelium-derived factor (PEDF) [18]. VEGF has been identified as one of the key pathogenic factors of OHSS, while PEDF has antiangiogenic activity. The combination of these two factors might result in a lower incidence of OHSS. Previously published studies have shown that oral administration of letrozole after egg retrieval could significantly lower the level of $E_2$, decreasing the risk of OHSS [2,3,19]. Mai et al. compared treatment with letrozole and aspirin in the prevention of early-onset OHSS [20]. The results showed that letrozole had a more significant preventive effect against moderate and severe OHSS, which could be ascribed to luteolysis rather than the effects of VEFG [20]. Luteolysis could lower the level of $E_2$ and terminate the progression of early OHSS [20]. In this study, 2.5 mg of oral letrozole was administrated before or on the hCG trigger day, and the duration of drug use was determined according to $E_2$ level and was between 1–3 days [20]. The initial time of drug use was compared with previous studies and the results showed that letrozole could decrease the level of $E_2$ both effectively and rapidly [20].

Allaway et al. found that a single dose of 20 mg of letrozole could lower the $E_2$ levels while increasing the levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) level when the diameter of dominant ovarian follicles reached 12 mm or 18 mm after ovulation [21]. However, the changing levels of hormones did not result in the disappearance of dominant follicles, and in this study, the use of letrozole at $E_2$ peak levels could quickly lower $E_2$ levels to effectively prevent OHSS [21]. However, the development of the dominant ovarian follicle was not be affected and the lowered $E_2$ level was beneficial for embryo transfer [21]. Another study also indicated that the co-administration of letrozole and gonadotropin in the IVF cycle could increase the expression of integrin in the endometrium and increased endometrial receptivity [22]. In this study, endometrial thickness was not affected by letrozole but there was an increased trend of clinical pregnancy rates [22].

Tatsumi et al. compared the cycle using letrozole for ovarian stimulation with the natural cycle, and showed that the use of letrozole did not increase the rate of birth defects or increase





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the risk of adverse pregnancy outcomes [23]. Instead, the risk of abortion decreased in letrozole-treated group in this study [23]. Therefore, the findings of previous studies support those of the present study, that letrozole is a safe component of the IVF protocol. In this study, although the biochemical pregnancy rate in the letrozole-treated group showed a tendency to reduce, at this time, the majority of patients are pregnant, which means that no obstetric outcomes have yet to be compared.

## Conclusions

In this retrospective clinical study, women with polycystic ovary syndrome (PCOS) who underwent *in vitro* fertilization (IVF), oral treatment with letrozole a day prior to treatment with human chorionic gonadotropin (hCG) lowered estrogen ($E_2$) levels, but did not significantly reduce the incidence of ovarian hyperstimulation syndrome (OHSS). Oral administration of letrozole before the hCG trigger day could effectively lower $E_2$ levels ($P<0.05$) for patients with PCOS whose peak levels of $E_2$ were ≥4000 pg/ml. Although the incidence rate of OHSS in the letrozole-treated group was lower than in control group, the differences were not significant ($P>0.05$) possibly because of the small study sample size.

### Conflict of interest

None.

## References:

1. Practice Committee of the American Society for Reproductive Medicine: Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: A guideline. Fertil Steril, 2016; 106(7): 1634–47
2. Orvieto R: Ovarian hyperstimulation syndrome – an optimal solution for an unresolved enigma. J Ovarian Res 2013; 6(1): 77
3. Papanikolaou EG, Polyzos NP, Humaidan P et al: Aromatase inhibitors in stimulated IVF cycles. Reprod Biol Endocrinol, 2011; 9: 85
4. Garcia-Velasco JA, Quea G, Piró M et al: Letrozole administration during the luteal phase after ovarian stimulation impacts corpus luteum function: A randomized, placebo-controlled trial. Fertil Steril, 2009; 92(1): 222–25
5. McClure N, Healy DL, Rogers PA et al: Vascular endothelial growth factor as capillary permeability agent in ovarian hyperstimulation syndrome. Lancet, 1994; 344(8917): 235–36
6. Soares SR, Gómez R, Simón C et al: Targeting the vascular endothelial growth factor system to prevent ovarian hyperstimulation syndrome. Hum Reprod Update, 2008; 14(4): 321–33
7. Delvigne A: Symposium: Update on prediction and management of OHSS. Epidemiology of OHSS. Reprod Biomed Online, 2009; 19(1): 8–13
8. Kasum M, Orešković S, Franulić D et al: Current medical strategies in the prevention of ovarian hyperstimulation syndrome. Acta Clin Croat, 2017; 56(1): 133–42
9. Engmann L, Diluigi A, Schmidt D et al: The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing *in vitro* fertilization prevents the risk of ovarian hyperstimulation syndrome: A prospective randomized controlled study. Fertil Steril, 2008; 89(1): 84–91
10. Lin H, Wang W, Li Y et al: Triggering final oocyte maturation with reduced doses of hCG in IVF/ICSI: A prospective, randomized and controlled study. Eur J Obstet Gynecol Reprod Biol, 2011; 159(1): 143–47
11. Toftager M, Bogstad J, Bryndorf T et al: Risk of severe ovarian hyperstimulation syndrome in GnRH antagonist versus GnRH agonist protocol: RCT including 1050 first IVF/ICSI cycles. Hum Reprod, 2016; 31(6): 1253–64
12. Rollene N, Amols M, Hudson S et al: Treatment of ovarian hyperstimulation syndrome using a dopamine agonist and gonadotropin-releasing hormone antagonist: a case series. Fertil Steril, 2009; 92(3): 1169.e1115–67
13. Nardo LG, Cheema P, Gelbaya TA et al: The optimal length of 'coasting protocol' in women at risk of ovarian hyperstimulation syndrome undergoing *in vitro* fertilization. Hum Fertil, 2006; 9(3): 175–80
14. Várnagy A, Bódis J, Mánfai Z et al: Low-dose aspirin therapy to prevent ovarian hyperstimulation syndrome. Fertil Steril, 2010; 93(7): 2281–84
15. Kim J, Turan V, Oktay K: Long-term safety of letrozole and gonadotropin stimulation for fertility preservation in women with breast cancer. J Clin Endocrinol Metabol, 2016; 101(4): 1364–71
16. Rodgers RJ, Reid GD, Koch J et al: The safety and efficacy of controlled ovarian hyperstimulation for fertility preservation in women with early breast cancer: A systematic review. Hum Reprod, 2017; 32(5): 1033–45
17. Haas J, Bassil R, Meriano J et al: Does daily co-administration of letrozole and gonadotropins during ovarian stimulation improve IVF outcome? Reprod Biol Endocrinol, 2017; 15(1): 70
18. Sahin N, Apaydin N, Toz E et al: Comparison of the effects of letrozole and cabergoline on vascular permeability, ovarian diameter, ovarian tissue VEGF levels, and blood PEDF levels, in a rat model of ovarian hyperstimulation syndrome. Arch Gynecol Obstet, 2016; 293(5): 1101–6
19. Wang Y, Yang J, Xu W et al: [Luteal letrozole administration decreases serum estrogen level but not the risk of ovarian hyperstimulation syndrome]. Beijing Da Xue Xue Bao Yi Xue Ban, 2013; 45(6): 869–72 [in Chinese]
20. Mai Q, Hu X, Yang G et al: Effect of letrozole on moderate and severe early-onset ovarian hyperstimulation syndrome in high-risk women: A prospective randomized trial. Am J Obstet Gynecol, 2017; 216(1): 42.e1–10
21. Allaway HC, Chizen DR, Adams GP, Pierson RA: Effects of a single 20 mg dose of letrozole on ovarian function post dominant follicle selection: An exploratory randomized controlled trial. J Ovarian Res, 2017; 10(1): 6
22. Haas J, Casper R: *In vitro* fertilization treatments with the use of clomiphene citrate or letrozole. Fertil Steril, 2017; 108(4): 568–71
23. Tatsumi T, Jwa SC, Kuwahara A et al: No increased risk of major congenital anomalies or adverse pregnancy or neonatal outcomes following letrozole use in assisted reproductive technology. Hum Reprod, 2017; 32(1): 125–32





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