Mildly Stimulated Cycle with Letrozole Compared with Natural Cycle and HRT Cycle in Patients undergoing FET with Normal Ovulation

liqun lou
Shanghai General Hospital, Shanghai Jiao Tong University
Yisong Xu
Xiamen University
Mu Lv
Shanghai General Hospital, Shanghai Jiao Tong University
Juanjuan Yu
Shanghai General Hospital, Shanghai Jiao Tong University
Qimeng Xiao
Shanghai General Hospital, Shanghai Jiao Tong University
Peiqin Chen
Shanghai General Hospital, Shanghai Jiao Tong University
Mingzhu Bai
Maternal and Child Health Hospital in Xuzhou
zhenbo zhang (zhangzhenbozzb@aliyun.com)
Shanghai General Hospital, Shanghai Jiao Tong University

Research Article

Keywords: Frozen embryo transfer, pregnancy outcomes, letrozole, live birth rate, HRT cycle, natural cycle

Posted Date: April 13th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1528522/v1

Abstract

Background: The number of frozen embryo transfer (FET) is increasing, however, an optimal protocol for FET is undetermined. Our study was to evaluate the letrozole use on the patients with normal menstrual cycles (MC) compared with HRT cycle and natural cycle.

Methods: It is a large retrospective study involved 2932 patients. Inverse probability of treatment weighting (IPTW) approach aimed to equate each group with respect to measured baseline covariates to achieve a comparison with reduced selection bias. Patients matched by algorithm were divided into 3 groups: hormone replacement therapy (HRT) cycle (n=2877), letrozole cycle (n=2637) and natural cycle (NC) (n=2475). The primary outcome measure was live birth rate, the secondary outcome measures were positive hCG rate, biochemical pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate, early miscarriage rate, late miscarriage rate, preterm delivery rate and full-term pregnancy rate.

Results: In our crude analysis, letrozole group had a higher live birth rate compared with HRT cycle (OR 1.2, 95% CI 1.07–1.35) and natural cycle (OR 1.31, 95% CI 1.16–1.47) and after adjusting for confounding factors, live birth rate was consistently higher in letrozole group. Moreover, the biochemical pregnancy, clinical pregnancy, ongoing pregnancy and full-term delivery rate were higher in letrozole group.

Conclusion: For infertile women with normal menstrual cycle undergoing frozen-thawed embryo transfers, mildly stimulated cycle with letrozole present relatively large advantage compared with HRT cycle and natural cycle with higher live birth pregnancy indicating that letrozole use could improve pregnancy outcomes in patients with normal ovulation during FET.

Trial registration: Retrospectively registered.

1 Background

Infertility is a reproductive disease affecting birth rate and aged tendency of population. Infertility is defined as failure to enable clinical pregnancy after regular unprotected sexual intercourses for 12 month or more(1). Increasing assisted reproductive technology such as in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and frozen embryo transfer (FET) relieves the situation.

Frozen embryo transfer has increased in the past decades with the improvements in embryo cryopreservation methods. Slow-freeze methods were gradually replaced by vitrification which allowed cells and extracellular environments to be glass-like status and avoided cellular ice formation(2, 3). Compared with fresh embryo transfer, FET could reduce ovarian hyperstimulation syndrome (OHSS), improve pregnancy outcomes, maintain fertility preservation and allow time for preimplantation genetic testing and receptive endometrial preparation(4–6). It was reported that newborns conceived from frozen embryo enable decreased risk of preterm delivery, low birth weight and small for gestational age which enable better maternal and neonatal outcomes even if it was associated with a higher risk of pre-

eclampsia(7, 8). Among regular endometrial preparation protocol, some clinical observation revealed that letrozole could produce superior pregnancy outcomes in patients undergoing single embryo transfer cycles leading to singleton pregnancies compared with a natural or HRT cycles (9). However, the evidence is poor for the superior protocol for patients with normal ovulation undergoing FET. Therefore, our study focused on the effect of letrozole on the pregnancy outcomes and provided a new sight to choose optimal endometrial preparation.

2 Methods

Data collection and patient populations

The retrospective study was performed at Reproductive Medicine Center of Shanghai General Hospital of Shanghai Jiao Tong University School of Medicine between November 2015 and December 2020. Inclusion criteria are as follows: (1) sterile women with regular menstrual cycle (21–35 days); (2) females under 40 years of age at oocyte retrieval and embryo transfer. Exclusive criteria are as follows: (1) patients with uterine malformations, endometrial polyps, adenomyosis, leiomyomas and some congenital uterine anomalies; (2) women diagnosed with PCOS according to the 2003 Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop. (3) women with acute and chronic systemic diseases. Patients who met the criterion were included in our study.

A total of 2932 infertile patients undergoing FET cycles met the inclusion criteria. Patients were divided into 3 groups: HRT cycle group, a letrozole cycle group and natural cycle group.

Endometrial preparation before FET

The application of endometrial preparation was based on physician preference.

In natural cycles, when the diameter of the dominant follicle was 15–16 mm, serum estradiol and LH were monitored. When the diameter of the dominant follicle was 18-20mm, endometrial thickness was at least 8mm and serum estradiol was greater than 150pg/ml, 250ug of recombinat human chorionic gonadotropin (Merck Serono S.p.A. Italy) was delivered by subcutaneous injection to trigger ovulation.

In HRT cycles, on the second day of the menstrual cycles, 6mg of estradiol tablets (Abbott Biologicals B.V. Netherlands) were taken orally daily until embryo transfer. 7 days after administration the endometrial thickness was monitored by vaginal ultrasound, additional 2mg of estradiol tablets can be given and the administration time prolonged for another week if necessary. If endometrial thickness was at least 8mmand serum progesterone level was not higher than 8nmol/l, Crinone 8% vaginal progesterone gel (Merck Co. Germany) was given. Insufficient endometrial thickness or elevated progesterone level can result in cycle cancellation.

In letrozole group, 2.5 mg of letrozole tablet (HengRui Co. China) was taken orally daily for constitute 5 days on MC2. HMG (Lizhu Pharmaceutical Trading Co. Zhuhai, China) 75 IU was administered based on the follicle development on MC6 and HMG was delivered until the diameter of the dominant follicle was

18-20mm. When the diameter of the dominant follicle was greater than 18mm, the thickness of the endometrium was more than 8mm and E2 serum level was suitable(> 150pg/ml), 250ug of recombinational human chorionic gonadotropin (Merck Serono S.p.A. Italy) was administrated. For all groups, endometrial progesterone preparation time depends on embryo transferred. Endometrial transformation time for cleavage-stage embryo is 3 days and for blastocyst-stage embryo is 5 days.

Outcome definition

The primary outcome measure was live birth. The secondary outcome measures were positive hCG rate, biochemical pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate, early miscarriage rate, late miscarriage rate, preterm delivery rate, full-term delivery rate. Live birth was defined as live newborns born after 28 weeks. Biochemical pregnancy was defined as hCG > 5 IU/L at 14 days after embryo transfer. Clinical pregnancy was defined as the presence of at least one gestational sac in uterine cavity at 4 weeks after embryo transfer. Ongoing pregnancy was defined in this study as greater than 12 gestational weeks. Early miscarriage was defined as loss of pregnancy before 12 gestational weeks and late miscarriage was defined as loss of pregnancy between 12–28 weeks. Preterm delivery was defined as childbirth occurs before 37 gestational weeks. Full-term delivery rate was defined as birth occurring after 37 gestational weeks and before 42 gestational weeks.

Statistical analysis

R statistical programming language (version 4.1.2; R Foundation for Statistical Computing, Austria) were used for data analysis. P-value < 0.05 was considered significant statistically. Normally distributed data was expressed as the mean ± standard deviation (SD), non-normal data was expressed as median (25th quartiles – 75th quartiles). Categorical variables were described as absolute numbers and percentage. In order to eliminate the influence of potential selection bias and confounding factors on the comparison of outcomes, we performed weighted propensity score analysis to control for differences in baseline characteristics between groups. A propensity score for each patient was calculated as the predicted probability of each group from multivariable logistic regression that included major confounding factors associated with pregnancy outcomes: maternal age, body mass index, duration of infertility, type of infertility, and type and number of transferred embryos. Using the inverse probability of treatment weighting (IPTW) approach the propensity model was generated. Each patient was weighted by the inverse probability of being in a different group. The balance in baseline characteristics between groups were assessed by standardized mean differences (SMD) and SMD < 0.1 was considered as reaching balance(10). Univariate logistic regression models were used to estimate the relationship between grouping and reproductive outcomes. Multivariate logistic regression was performed to adjusted for confounding factors. IPTW was conducted via “Twang” R package(11). SMD and P-value of baseline condition were calculated via “TableOne” and “Survey” R package(12, 13). Code can be provided if needed.

3 Results

Baseline condition

Table 1 and Table 2 list the patients' baseline characteristics. After performing IPTW, no significant difference was observed among the three groups in maternal age, body mass index, endometrial thickness, duration of infertility, type of infertility and type and number of embryos.

Table 1
Unweighted study population basic characteristics at transfer level.

Unweighted study population				
Characteristics	HRT group (n = 2190)	Letrozole group (n = 537)	Natural group (n = 205)	SMD
Maternal age	30.7 (4.54)	29.9 (3.97)	31.4 (4.14)	0.248
Body mass index	21.5 (3.15)	21.6 (2.98)	21.1 (2.54)	0.117
Endometrial thickness	9.10 (1.05)	8.88 (1.13)	9.03 (1.36)	0.128
Duration of infertility	3.56 (2.62)	3.26 (2.29)	3.50 (2.50)	0.08
Type of infertility, n (%)				0.158
Primary infertility	1480 (67.6%)	375 (69.8%)	17 (8.3%)	
Secondary infertility	710 (32.4%)	162 (30.2%)	85 (41.5%)	
Type and No. of embryos, n (%)				0.241
Blastocysts and double embryos	126 (5.8%)	48 (8.9%)	17 (8.3%)	
Blastocysts and single embryo	231 (10.5%)	59 (11.0%)	15 (7.3%)	
Cleavage – stage embryos and blastocysts	8 (0.4%)	5 (0.9%)	6 (2.9%)	
Cleavage – stage embryos and double embryos	1391 (63.5%)	316 (58.8%)	139 (67.8%)	
Cleavage – stage embryos and single embryos	434 (19.8%)	109 (20.3%)	28 (13.7%)	
Note: Data are presented as mean ± SD for continuous variables and n (%) for categorical variables. SMD < 0.1 was considered as reaching balance.				

Table 2
Weighted study population basic characteristics at transfer level.

Weighted study population				
Characteristics	HRT group (n = 2877)	Letrozole group (n = 2637)	Natural group (n = 2475)	SMD
Maternal age	30.58 (4.43)	30.41 (4.26)	30.73 (3.92)	0.051
Body mass index	21.51 (3.08)	21.50 (2.89)	21.41 (2.72)	0.024
Endometrial thickness	9.05 (1.07)	9.03 (1.05)	9.01 (1.02)	0.029
Duration of infertility	3.50 (2.55)	3.40 (2.42)	3.33 (2.34)	0.046
Type of infertility, n (%)				0.069
Primary infertility	1934 (67.2%)	1781 (67.5%)	1550 (62.6%)	
Secondary infertility	943 (32.8%)	856(32.5%)	925 (37.4%)	
Type and No. of embryos, n (%)				0.075
Blastocysts and double embryos	184 (6.4%)	180 (6.8%)	194 (7.9%)	
Blastocysts and single embryo	299 (10.4%)	260 (9.8%)	249 (10.1%)	
Cleavage – stage embryos and blastocysts	17 (0.6%)	21 (0.8%)	19 (0.8%)	
Cleavage – stage embryos and double embryos	1818 (63.2%)	1673 (63.5%)	1615 (65.2%)	
Cleavage – stage embryos and single embryos	559 (19.4%)	503 (19.1%)	399 (16.1%)	
Note: Data are presented as mean ± SD for continuous variables and n (%) for categorical variables. SMD < 0.1 was considered as reaching balance. Non-integer value in the number of people and embryos was rounded to nearest whole number.				

Reproductive outcomes

Crude analysis results shown in Table 3 between Letrozole group and HRT group showed great statistically significant difference upon live birth (OR 1.2, 95% CI 1.07–1.35). Secondary pregnancy outcomes: positive hCG rate (OR 1.35, 95% CI 1.21–1.5), clinical pregnancy rate (OR 1.22, 95% CI 1.1–1.36), ongoing pregnancy rate (OR 1.22, 95% CI 1.1–1.36) and full-term delivery rate (OR 1.2, 95% CI 1.06 – 1.35) have statistical significance (P < 0.01). Compared with HRT group, Letrozole group have decreased early miscarriage rate (OR 0.72, 95% CI 0.56–0.91) and late miscarriage rate was similar between groups.

Table 3
Reproductive outcomes between Letrozole cycles and HRT cycles.

Unadjusted and adjusted odds ratios (ORs) of reproductive outcomes following Letrozole cycles versus HRT cycles.				
Outcome	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Positive hCG test rate	1.35 (1.21,1.5)	< 0.001*	1.35 (1.21, 1.51)	< 0.001*
Biochemical pregnancy rate	1.49 (1.23,1.81)	< 0.001*	1.37 (1.23, 1.53)	< 0.001*
Clinical pregnancy rate	1.22 (1.1,1.36)	< 0.001*	1.21 (1.09, 1.36)	< 0.001*
Ongoing pregnancy rate	1.21 (1.09,1.35)	< 0.001*	1.21 (1.08, 1.34)	< 0.001*
Early miscarriage rate	0.72 (0.56,0.91)	0.006*	0.73 (0.57,0.93)	0.017*
Late miscarriage rate	1.63 (0.96,2.75)	0.071	1.63 (0.95, 2.77)	0.071
Pre-term delivery rate	1.1 (0.87,1.4)	0.432	1.09 (0.85, 1.39)	0.467
Full-term delivery rate	1.2 (1.06,1.35)	0.003*	1.20 (1.05,1.35)	0.004*
Live birth rate	1.2 (1.07,1.35)	0.001*	1.20 (1.07, 1.35)	0.002*
Note: CI = confidence interval. A P-value < 0.05 was considered to be statistically significance.				

In crude analysis shown in Table 4, the live birth in letrozole group was significantly higher than natural cycle group (OR 1.31, 95% CI 1.16–1.47). Positive hCG rate (OR 1.18, 95% CI 1.05–1.31), clinical pregnancy rates (OR 1.16, 95% CI 1.04–1.3), ongoing pregnancy rate (OR 1.15, 95% CI 1.03–1.28) and full-term delivery rate (OR 1.51, 95% CI 1.33–1.72) in letrozole group remained consistently higher than natural cycle group (P < 0.05). The pre-term delivery rate was lower in letrozole group (OR0.72, 95% CI 0.57–0.9), however, the rate of late miscarriage rate was higher in letrozole group for unknown reason (OR 2.29, 95% CI 1.06–4.93).

Table 4
Reproductive outcomes between Letrozole cycles and natural cycles.

Unadjusted and adjusted odds ratios (ORs) of reproductive outcomes following Letrozole cycle versus natural cycle.				
Outcome	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Positive hCG test rate	1.18 (1.05, 1.31)	0.004*	1.22 (1.09, 1.37)	< 0.001*
Biochemical pregnancy rate	1.03 (0.85, 1.24)	0.764	1.22 (1.09, 1.37)	< 0.001*
Clinical pregnancy rate	1.16 (1.04, 1.3)	0.009*	1.19 (1.06, 1.33)	0.003*
Ongoing pregnancy rate	1.15 (1.03, 1.28)	0.015*	1.17 (1.05, 1.32)	0.005*
Early miscarriage rate	1.01 (0.74,1.38)	0.931	1.01 (0.73,1.38)	0.960
Late miscarriage rate	2.29 (1.06, 4.93)	0.034*	2.20 (1.01, 4.79)	0.047*
Pre-term delivery rate	0.72 (0.57, 0.9)	0.005*	0.69 (0.55, 0.87)	0.001*
Full-term delivery rate	1.51 (1.33, 1.72)	< 0.001*	1.55 (1.36, 1.76)	< 0.001*
Live birth rate	1.31 (1.16, 1.47)	< 0.001*	1.32 (1.17, 1.49)	< 0.001*
Note: CI = confidence interval. A P-value < 0.05 was considered to be statistically significance.				

After adjusting for confounding factors, the live birth rate in letrozole group was still higher than HRT group (OR 1.20, 95% CI 1.07–1.35) and natural group (OR 1.32, 95% CI 1.17–1.49). Furthermore, the secondary pregnancy outcomes were consistent with precious results.

4 Discussion

Our study showed that infertile women with normal menstrual cycle undergoing frozen-thawed embryo transfers, mildly stimulated cycle with letrozole presented relatively large advantage over HRT cycles and natural cycles with higher live birth rate. Positive hCG rate, clinical pregnancy rate, ongoing pregnancy rate and full-term delivery rate were all higher than HRT and natural cycles. Letrozole could reduce miscarriage and preterm-delivery rate which was consistent with previous studies. Previous evidence showed that mild stimulation with letrozole could produce better pregnancy outcomes in patients with abnormal ovulation(14–17). Consistently, S.C. Jwa et al. performed a large retrospective study, which demonstrated that letrozole cycles had higher clinical pregnancy rate and lower miscarriage rate compared with HRT cycles and natural cycles(9).

Letrozole is a third-generation aromatase inhibitor and blocks the function of the enzyme aromatase and prevents body from estrogen transformation(18). We speculated that letrozole may enhance the

susceptibility to estrogen by increasing the expression of estrogen receptor (19). Similarly, evidence showed that letrozole could increase integrin αvβ3 and pinopode expression in endometrium, thereby promoting endometrial receptivity in the general population(20, 21). However, evidence was poor for infertile patients with regular menstrual cycles. Our study adds to the evidence of endometrial preparation protocol selection for FET in this population.

We acknowledge that our study had inadequacies. Although IPTW was performed to balance the baseline condition and multivariate logistic regression was performed to adjust for potential confounds, other unknown confounders such as the quality of embryos and ovarian response which might as well influence the results. We could not eliminate all the confounders completely. The retrospective study was conducted at one reproductive center, the endometrial preparation protocol selection might produce bias because the therapeutic regimens depended on the preference of physicians. Large-scale and multi-center clinical trials need to be conducted for more accurate study results. In addition, multi-center prospective cohort study needs to be carried out as well with more rigorous grouping criteria.

Based on the large samples' quantity, there's reason to believe our study results are reliable. Besides, native data exhibited slight difference and IPTW was performed to enable the groups to be comparable. Our study based on infertile women with normal menstrual cycles undergoing FET, which might be helpful to the treatment according to such populations.

5 Conclusions

We suggest that letrozole use in infertile patients with normal ovulation contributes to pregnancy outcomes with a higher live birth rate. The result was reliable because of the fact that it is a large-scaled study, however, multi-center and larger randomized controlled studies needed to be conducted for more solid evidence.

Declarations

Acknowledgements

The authors thank Reproductive Medicine Center, Department of Obstetrics and Gynecology, Shanghai General Hospital, Shanghai Jiao Tong University, Shanghai; National Institute for Data Science in Health and Medicine, School of Medicine, Xiamen University, Xiamen; Reproductive Medicine Center, Maternal and Child Health Hospital in Xuzhou, Jiangsu; Shanghai Key Laboratory for Assisted Reproduction and Reproductive Genetics, Renji hospital, Shanghai Jiao Tong University, Shanghai.

Author contributions

LL wrote the manuscript. All authors participated, contributed to data collection, statistical analysis, edited the report and approved the final version of the manuscript for publication.

Funding

This work was supported by grants from the National Key Technology R&D Program of China (2019YFC1005200 and 2019YFC1005201), National Natural Science Foundation of China (grants81902630, 81872111 and 81672562), Shanghai Municipal Science and Technology Committee of Shanghai outstanding academic leaders plan (19XD1423100), the project of Outstanding Medical Doctor for ZZ.

Availability of data and materials

The raw data analyzed in the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Patients involved in this study were collected with the informed consent and approval from the ethics committee approved by Shanghai General Hospital Research and Ethics Committee (2018KY078).

Consent for publication

Not applicable.

References

1. Szamatowicz M, Szamatowicz J. Proven and unproven methods for diagnosis and treatment of infertility. Adv Med Sci. 2020;65(1):93–6.
2. Rienzi L, Gracia C, Maggiulli R, LaBarbera AR, Kaser DJ, Ubaldi FM, et al. Oocyte, embryo and blastocyst cryopreservation in ART: systematic review and meta-analysis comparing slow-freezing versus vitrification to produce evidence for the development of global guidance. Hum Reprod Update. 2017;23(2):139–55.
3. Singh B, Reschke L, Segars J, Baker VL. Frozen-thawed embryo transfer: the potential importance of the corpus luteum in preventing obstetrical complications. Fertil Steril. 2020;113(2):252–7.
4. Donnez J, Dolmans MM. Fertility Preservation in Women. N Engl J Med. 2017;377(17):1657–65.
5. Ginstrom Ernstad E, Wennerholm UB, Khatibi A, Petzold M, Bergh C. Neonatal and maternal outcome after frozen embryo transfer: Increased risks in programmed cycles. Am J Obstet Gynecol. 2019;221(2):126 e1- e18.
6. Sha T, Yin X, Cheng W, Massey IY. Pregnancy-related complications and perinatal outcomes resulting from transfer of cryopreserved versus fresh embryos in vitro fertilization: a meta-analysis. Fertil Steril. 2018;109(2):330–42 e9.

7. Maheshwari A, Pandey S, Raja EA, Shetty A, Hamilton M, Bhattacharya S. Is frozen embryo transfer better for mothers and babies? Can cumulative meta-analysis provide a definitive answer? Human Reproduction Update. 2018;24(1):35–58.
8. Wei D, Liu JY, Sun Y, Shi Y, Zhang B, Liu JQ, et al. Frozen versus fresh single blastocyst transfer in ovulatory women: a multicentre, randomised controlled trial. Lancet. 2019;393(10178):1310–8.
9. Tatsumi T, Jwa SC, Kuwahara A, Irahara M, Kubota T, Saito H. Pregnancy and neonatal outcomes following letrozole use in frozen-thawed single embryo transfer cycles. Human Reproduction. 2017;32(6):1244–8.
10. Vuvan V, Vicenzino B, Mellor R, Heales LJ, Coombes BK. Unsupervised Isometric Exercise versus Wait-and-See for Lateral Elbow Tendinopathy. Med Sci Sports Exerc. 2020;52(2):287–95.
11. Ridgeway G, McCaffrey DF, Morral AR, Burgette LF, Griffin BA. Toolkit for Weighting and Analysis of Nonequivalent Groups: A Tutorial for the R TWANG Package. Santa Monica, CA: RAND Corporation; 2014.
12. Lumley T. Analysis of Complex Survey Samples. Journal of Statistical Software. 2004;9(8):1–19.
13. Yoshida K BA. Create 'Table 1'to Describe Baseline Characteristics with or without Propensity Score Weights. 2021.
14. Hu YJ, Chen YZ, Zhu YM, Huang HF. Letrozole stimulation in endometrial preparation for cryopreserved-thawed embryo transfer in women with polycystic ovarian syndrome: a pilot study. Clin Endocrinol (Oxf). 2014;80(2):283–9.
15. Zhang J, Li Z, Sun L, Guan Y, Du M. Comparison of Pregnancy and Neonatal Outcomes of Single Frozen Blastocyst Transfer Between Letrozole-Induction and HRT Cycles in Patients With Abnormal Ovulation. Front Endocrinol (Lausanne). 2021;12:664072.
16. Sharon-Weiner M, Farladansky-Gershnabel S, Schreiber H, Shavit T, Levitas E, Berkovitz A. Clinical pregnancy rates among anovulatory and oligoovulatory women after letrozole versus hormone replacement therapy in frozen-thawed embryo transfer cycles. Hum Fertil (Camb). 2021:1–8.
17. Li SJ, Zhang YJ, Chai XS, Nie MF, Zhou YY, Chen JL, et al. Letrozole ovulation induction: an effective option in endometrial preparation for frozen-thawed embryo transfer. Arch Gynecol Obstet. 2014;289(3):687–93.
18. Kharb R, Haider K, Neha K, Yar MS. Aromatase inhibitors: Role in postmenopausal breast cancer. Arch Pharm (Weinheim). 2020;353(8):e2000081.
19. Colon-Otero G, Zanfagnin V, Hou X, Foster NR, Asmus EJ, Wahner Hendrickson A, et al. Phase II trial of ribociclib and letrozole in patients with relapsed oestrogen receptor-positive ovarian or endometrial cancers. ESMO Open. 2020;5(5):e000926.
20. Badawy A, Aal IA, Abulatta M. RETRACTED: Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. Fertil Steril. 2020;114(3):669.
21. Bao SH, Sheng SL, Peng YF, Lin QD. Effects of letrozole and clomiphene citrate on the expression of HOXA10 and integrin alpha v beta 3 in uterine epithelium of rats. Fertil Steril. 2009;91(1):244–8.