Effect of a premature luteinizing hormone surge on cumulative live birth rate during a flexible GnRH antagonist protocol: a retrospective study

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Research Article

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Abstract

Background: A premature luteinizing hormone (LH) surge refers to an endogenous LH peak that occurs before follicle maturation or human chorionic gonadotropin injection in the process of controlled ovarian hyperstimulation. Previous studies demonstrated that a premature LH surge was associated with a decline in clinical pregnancy rates in fresh embryo transfer cycles. No studies have reported the effect of a premature LH surge on the cumulative pregnancy rate (CPR) and cumulative live birth rate (CLBR). The aim of this study was to explore the effect of a premature LH surge on the CPR and CLBR of patients during a flexible GnRH antagonist protocol.

Methods: A total of 428 infertile women undergoing IVF/ICSI were recruited for this retrospective study. Only women who either delivered a live infant or had no remaining frozen embryos after a single stimulation cycle were included in the analysis. During the study period, each patient underwent a flexible GnRH antagonist protocol. Women were divided into two groups according to the presence (Group A) or absence (Group B) of a premature LH surge. The primary outcome measures were the CPR and CLBR per ovarian stimulation cycle. The secondary outcome measures were the number of oocytes retrieved, fertilization rate, clinical pregnancy rate, and implantation rate.

Results: Fifty-one women (11.92%) experienced a premature LH surge (Group A), and the other 377 (88.08%) women were assigned to Group B. There was no significant difference between Group A and Group B in the clinical pregnancy rate or live birth rate in the fresh embryo transfer cycle. The primary outcome measures, the CPR and CLBR per ovarian stimulation cycle, were not significantly different between the premature LH surge group and the control group. According to the analysis stratified by ovarian response (normal or high), there were no significant differences in pregnancy outcomes between the groups with and without a premature LH surge.

Conclusions: Our study demonstrated that a transient premature LH surge without progesterone elevation had no adverse effect on the CLBR of patients on a flexible GnRH antagonist protocol. Therefore, a transient LH surge should not be an indicator for cycle cancellation.

Background

Luteinizing hormone (LH) is a glycoprotein gonadotropin synthesized and secreted by the basophils of the anterior pituitary gland. It can act together with follicle stimulating hormone (FSH) to promote follicle maturation, and induce ovulation and luteinization. LH is secreted in a pulsatile manner and is regulated by hypothalamic gonadotropin-releasing hormone (GnRH), ovarian estrogen, progesterone and inhibin. In the natural ovulatory menstrual cycle, LH plays an important role in normal folliculogenesis and oocyte maturation[1]. During the follicular phase, LH stimulates theca cells to synthesize androgens and provide substrates for estrogen synthesis. During the ovulation phase, the LH peak promotes oocyte maturation and induces ovulation. During the luteal phase, LH promotes progesterone and estrogen synthesis and maintains luteal function. Some researchers have proposed the concept of an “LH clinical treatment

window", in which LH levels lower than the threshold or higher than the "LH ceiling" negatively affect follicular development and endometrial receptivity[2].

In the process of controlled ovarian hyperstimulation(COH), gonadotropin (Gn) can promote the development of multiple follicles and increase estrogen levels, which may trigger positive feedback to induce LH release by the pituitary gland and thus evoke an endogenous LH peak. A premature LH surge refers to an endogenous LH peak that occurs before follicle maturation or human chorionic gonadotrophin (HCG) injection. Studies have demonstrated that a premature LH surge can lead to premature follicle luteinization and a premature rise in progesterone, which affects endometrial receptivity, resulting in an increased cycle cancellation rate, decreased fertilization rate, embryo quality implantation rate and pregnancy rate[3]. At present, the criteria for a premature LH surge are vary and are controversial. A premature LH surge is defined as an LH level of 10 IU/L or higher with a progesterone level of 2ng/ml or less[3, 4], but some studies have defined a premature LH surge as an LH level greater than threefold higher than that on day 2 of the same menstrual cycle[5]. GnRH antagonists have been used to suppress pituitary activity, prevent premature LH surges and premature ovulation before follicular maturation during COH since the 1990s[6], although some women still experience this surge[3]. LH suppression with a GnRH antagonist is achieved by competitive inhibition of the GnRH receptors, endogenous estrogen-induced GnRH release was still preserved, so failure to control the LH surge occurs in a small proportion of antagonist cycles[7]. The incidence of premature LH surge reported varies greatly during GnRH antagonist protocol in different researches. Geng et al. reported 15.61%[8], while Zhang et al. reported 29.40%[9]. Studies have demonstrated that high-risk groups for a premature LH surge include patients with estradiol (E2) levels > 669 pg/ mL on the initiation day of GnRH antagonist administration on a fixed GnRH antagonist protocol[8], patients with decreased ovarian reserve[10], and obese patients[11]. Previous studies also showed that a premature LH surge was associated with a decline in the clinical pregnancy rates in fresh embryo transfer cycles[8, 9, 12]. No studies have reported the effect of a premature LH surge on the cumulative live birth rate (CLBR). A consensus has been reached that the preferred primary outcome of all infertility treatment trials is the CLBR[13], which represents live births per woman over a defined time period or number of treatment cycles. The aim of this study was to explore the effect of a premature LH surge on the CLBR of patients during a flexible GnRH antagonist protocol.

Methods

Patients

In this retrospective study, a total of 428 infertile women undergoing in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) were recruited from January to December 2019 at the Reproductive and Genetic Medical Center of Peking University First Hospital. Only women who either delivered a live infant or who had no remaining frozen embryos after a single aspiration cycle were included in the analysis. Patients were excluded if they fulfilled the following criteria: (1) age≥40 years; (2) poor ovarian response: number of oocyte retrieved ≤ 3; (3) women with hormone therapy in the past 6 months; (4) women with other endocrine diseases, including diabetes mellitus, thyroid disease, and

hyperprolactinemia. Moreover, patients with progesterone 2 ng/ml on the HCG day were excluded, in that elevated progesterone level has been proved to affect the pregnancy outcome of fresh transplantation cycle. In the study, a premature LH surge was defined as an LH level of 10 IU/L or higher with a progesterone level of 2 ng/ml or less. Women were divided into two groups according to the presence (Group A) or absence (Group B) of a premature LH surge. This study was approved by the Clinical Research Institutional Review Board of Peking University First Hospital (No. 2021 − 521).

COH protocols

During the study period, each patient underwent a flexible GnRH antagonist protocol. A daily dose of 150–300 IU FSH was started on Day 2 or 3 of the menstrual cycle, and the dose was adjusted according to follicular development and hormone levels in the patients. A daily dose of 0.25 mg GnRH antagonist was initiated when the dominant follicle was ≥ 14 mm or a premature LH surge was recognized. Recombinant HCG was administered subcutaneously when the dominant follicle was 18–20 mm in diameter. Oocytes were collected by transvaginal ultrasound-guided follicular aspiration within approximately 36 hours after the HCG trigger. Oocytes were fertilized by conventional IVF/ICSI, and embryos were transferred on Day 3 after oocyte retrieval. Luteal support was started on the day of oocyte retrieval. Fresh embryo transfer was cancelled for the following reasons: (1) to prevent the occurrence of ovarian hyperstimulation syndrome; (2) when no transferable embryos were obtained; (3) complicated with diseases unsuitable for fresh cycle transplantation, such as endometriosis or adenomyosis.

Frozen embryo transfer

Embryos were cryopreserved if they met the following criteria: day 3 embryos with at least six blastomeres and ≤ 20% fragmentation or day 5–6 blastocysts at a minimum of expansion stage 3 with an inner cell mass score of A, B or C and a trophectoderm score of A, B or C. For frozen embryo transfer cycles, endometrium preparation protocols were determined by the patient's menstrual cycle, including the natural cycle and the hormone replacement cycle. Progesterone preparation for luteal support was started 3 days before day-3-embryo transfer or 5 days before blastocyst transfer.

HCG tests were performed on day 14 after embryo transfer, and if the result was positive, luteal support was continued until 10 weeks of gestation. Clinical pregnancy was defined as the presence of an intrauterine gestational sac 4 weeks after embryo transfer. A live birth was defined as any birth event in which at least one baby was born alive after 28 weeks' gestation.

Main outcome measures

The primary outcome measures were the cumulative pregnancy rate (CPR) and CLBR per oocyte retrieval cycle. CPR was defined as pregnancy episodes in fresh and subsequent frozen-thawed embryo transfer cycles, and only the first pregnancy was included in the analysis. CLBR was defined as live birth episodes in fresh and subsequent frozen-thawed embryo transfer cycles, and only the first live birth was included in the analysis. The live birth of a singleton, twin, or other multiples is registered as one live birth[14]. The

secondary outcome measures were the number of oocytes retrieved, fertilization rate, clinical pregnancy rate, and implantation rate.

The following criteria were used to define the ovarian response according to oocyte yield[15]: normal ovarian response, oocyte yield ≥ 4 and ≤ 15; and high ovarian response, oocyte yield 15.

Statistical analysis

All analyses were performed with Software Package for Social Sciences (SPSS) version 13.0 for Windows. All normally distributed measurement data are expressed as the mean ± standard deviation (SD) after analysis with independent sample t-tests. Categorical data are presented as the number of cases and corresponding percentage after analysis by the chi-square test or Fisher's exact test. $P < 0.05$ was considered to indicate statistical significance.

Results

In this study, 51 women (11.92%) experienced a premature LH surge, and the other 377 (88.08%) women were included as controls. As shown in Table 1, there were no significant differences in age, body mass index (BMI), basal FSH or anti-Müllerian hormone (AMH) between the groups with and without a premature LH surge. Women with a premature LH surge had a higher basal LH level and antral follicle count (AFC) than those in the control group. During COH process, E2 levels on the HCG trigger day were significantly higher, the numbers of oocytes retrieved and MII oocytes were significantly greater, and endometrial thickness on the HCG trigger day was significantly thicker in the premature LH surge group than in the control group. No differences between groups were found in the total dose of Gn, progesterone level on the HCG trigger day, fertilization rate, or good-quality embryo rate. On the first day after GnRH antagonist treatment was initiated, the LH level in all patients with a premature LH surge dropped below 10 IU/L.

Table 1
Comparison of treatment-related characteristics during COH between women with or without a premature LH surge

Parameters	Group A (n = 51)	Group B (n = 377)	p value
Age (years)	31.69 ± 3.02	32.60 ± 3.54	0.081
BMI (kg/m^2)	22.81 ± 2.92	22.45 ± 3.19	0.454
Basal FSH (mIU/mL)	7.95 ± 1.90	8.36 ± 3.05	0.353
Basal LH (mIU/mL)	5.69 ± 1.91	4.30 ± 2.05	< 0.001
No. of AFCs (n)	16.12 ± 6.91	13.87 ± 7.08	0.034
AMH level (ng/ml)	3.93 ± 2.19	3.56 ± 2.88	0.411
Total Gn dose (IU)	2351.23 ± 824.11	2568.67 ± 916.77	0.109
Endometrial thickness on HCG day (mm)	11.19 ± 1.84	10.50 ± 2.24	0.035
E2 on HCG day (pg/ml)	3950.69 ± 1716.95	3209.71 ± 1578.22	0.002
Progesterone level on HCG day (pg/ml)	1.16 ± 0.93	1.09 ± 0.39	0.191
Oocytes retrieved	12.65 ± 6.28	10.40 ± 5.07	0.004
MII oocytes	10.25 ± 5.76	8.33 ± 4.60	0.007
Fertilization rate	75.35%(486/645)	71.79%(2820/3928)	0.061
Good-quality embryo rate	41.65%(187/449)	40.92%(1084/2649)	0.772
Transfer cancellation rate	56.85%(29/51)	50.93%(192/377)	0.426

Among the 428 infertility patients, 207 women underwent fresh embryo transfer. The embryo transfer cancellation rates were 56.85% for women with a premature LH surge and 50.93% for women without premature LH surge. There was no significant difference in the clinical pregnancy rate or live birth rate in the fresh embryo transfer cycle between the groups with and without a premature LH surge. In this study, 13 women had no embryos to transplant, and none of these women had premature LH surge. Among the 428 infertility patients, the primary outcome measures, the CPR and CLBR per ovarian stimulation cycle, were not significantly different between the premature LH surge group and the control group (Table 2).

Table 2
Comparison of pregnancy outcomes between women with or without a premature LH surge

Parameters	Group A (n = 51)	Group B (n = 377)	p value
Clinical pregnancy rate	63.64% (14/22)	48.65% (90/185)	0.184
Live birth rate	50% (11/22)	38.38% (71/185)	0.292
Cumulative pregnancy rate	78.43% (40/51)	66.58% (251/377)	0.089
Cumulative live birth rate	68.63% (35/51)	58.09% (219/377)	0.150

Among the 428 infertility patients, 346 had a normal ovarian response, and 82 had a high ovarian response. A premature LH surge occurred in 37 women (10.69%) in the normal ovarian response group, and 14 women (17.07%) in the high ovarian response group. According to the analysis stratified by ovarian response, whether in normal ovarian response or high ovarian response, there were no significant differences in pregnancy outcomes between women with and without a premature LH surge (Table 3).

Table 3
Comparison of pregnancy outcomes between women with or without a premature LH surge based on ovarian response

	Normal ovarian response (n = 346)			High ovarian response (n = 82)		
	Group A (n = 37)	Group B (n = 309)	P value	Group A (n = 14)	Group B (n = 68)	P value
Clinical pregnancy rate	66.67% (14/21)	47.73% (84/176)	0.101	0 (0/1)	66.67% (6/9)	0.400
Live birth rate	52.38% (11/21)	38.07% (67/176)	0.205	0 (0/1)	44.44% (4/9)	1.000
Cumulative pregnancy rate	70.27% (26/37)	61.81% (191/309)	0.315	100% (14/14)	88.24% (60/68)	0.392
Cumulative live birth rate	59.46% (22/37)	54.05% (167/309)	0.532	92.86% (13/14)	76.47% (52/68)	0.310

Discussion

In a fixed GnRH antagonist protocol, a GnRH antagonist is initiated on Day 5–6 of COH, while in a flexible GnRH antagonist protocol, a patient starts receiving an antagonist when the dominant follicle reaches ≥

14mm in size. Studies have shown that GnRH antagonists can inhibit endogenous LH peaks and avoid premature ovulation induced by LH peaks before follicular maturation. However, some women still experience a premature LH surge before GnRH antagonist administration. Researchers have identified transient premature LH surges was found in women on both the fixed and flexible GnRH antagonist protocols [8, 9]. However, studies have shown that patients on the flexible protocol were more prone to a premature LH surge than those on the fixed protocol [16]. Transient LH suppression by a GnRH antagonist is achieved by competitive inhibition of the GnRH receptor, but endogenous estrogen-induced GnRH release can still occur; thus, in a small proportion of patients, antagonist cycles fail to control the LH surge[17, 18].

Our study showed that the incidence of a premature LH surge on the flexible GnRH antagonist protocol was 11.92%. Compared with previous studies [8, 9], this study found a lower premature LH surge rate, which may be related to the different definitions of a premature LH surge and the different criteria. For example, in the study of Zhang et al., a PLHS was defined as either more than threefold of the basic LH level on day 2 of the same menstrual cycle; or the absolute value > 10IU/L[9]The underlying mechanisms of a premature LH surge are poorly identified, but are potentially related to a positive feedback loop between high E2 concentrations and the pituitary gland during ovulation stimulation [19]. In general, elevated LH levels are accompanied by elevated progesterone levels, which can lead to premature transformation of the endometrium and discordance between embryo development and the endometrium, resulting in a low pregnancy success rate after fresh cycle transfer. In addition, it has been suggested that a transient premature LH surge without a progesterone elevation during COH can lead to a reduced clinical pregnancy rate [8, 9]. Geng et al. reported that women with a premature LH rise had significantly poorer pregnancy outcomes than those without such a rise among ovarian high responders undergoing the GnRH antagonist stimulation protocol. An AFC of 22 or higher and an E2 level of 669 pg/mL or higher on the day of GnRH antagonist administration were predictive factors of a premature LH rise[8]. In a retrospective study of 405 women undergoing a fixed GnRH antagonist protocol, the results showed that a transient premature LH surge without elevated serum progesterone was associated with poor pregnancy outcomes in fresh embryo transfer cycles[9]. In contrast, our study showed no significant difference in endometrium thickness or high-quality embryo rate between women with and without a premature LH surge, and there was no decrease in the clinical pregnancy rate or live birth rate in the fresh transfer cycle among women with a premature LH surge. These results are consistent with previous findings. Kummer et al. demonstrated that a transient LH rise was not associated with a decline in fertilization, implantation, or pregnancy rate per embryo transfer [20]. Meanwhile, the main finding of our study was that the CPR and CLBR were comparable amone the women with and without a premature LH surge, with 68.63% and 58.09% of participants, respectively, achieving a live birth. According to the analysis stratified by ovarian response, a transient LH rise was not associated with a decline in pregnancy outcomes. The inconsistent findings may be due to differences in inclusion criteria, the definition of a premature LH surge and differences in protocols, such as the use of a fixed GnRH antagonist protocol in the study by Geng et al. Therefore, we concluded that a transient premature LH surge without progesterone elevation during COH had no adverse effect on oocyte development. This

result depends on the GnRH antagonist protocol and the antagonist itself, which can quickly and effectively decrease endogenous LH levels with a limited effect on endogenous FSH. At present, the most widely used GnRH antagonists are Cetrorelix and Ganirelix. Studies have shown that both GnRH antagonists effectively decrease LH levels with no significant differences in pregnancy outcomes [21, 22]. On the first day after initiating GnRH antagonist treatment, the LH level in all patients with a premature LH surge dropped below 10 IU/L. Therefore, with the flexible antagonist protocol, a premature LH surge had no adverse effect on pregnancy outcome if a GnRH antagonist was administered immediately after a premature LH surge.

Our study found that the E2 levels on the HCG trigger day, AFC, and numbers of oocytes retrieved and MII oocytes were higher in the premature LH surge group than in the control group. In addition, a stratified subgroup analysis indicated that women with a high ovarian response were more prone to a premature LH surge than those with a normal ovarian response. The incidence of a premature LH surge was higher in patients with a high ovarian response than in those with a normal ovarian response; this finding is consistent with previous findings[3]. The underlying mechanisms are incompletely understood, but it may be that compared with patients with normal ovarian response, patients with a high ovarian response have more follicles and higher estrogen levels, which increases the chance that pituitary positive feedback is induced, thus increasing the likelihood of experiencing a premature LH surge[19].

Conclusions

Our study demonstrated that a transient premature LH surge without progesterone elevation had no adverse effect on oocyte development or oocyte quality; consequently, there was no effect on the high-quality embryo rate, live birth rate in the fresh transfer cycle or CLBR of patients on a flexible GnRH antagonist protocol. In conclusion, a premature LH surge had no adverse effect on pregnancy outcomes if a GnRH antagonist was administered as soon as a premature LH surge occurred. A transient LH surge should not be an indicator for cycle cancellation.

Abbreviations

AMH, anti-Müllerian hormone

BMI, body mass index

CLBR, cumulative live birth rate

COH, controlled ovarian hyperstimulation

CPR, cumulative pregnancy rate

E2, estradiol

FSH, follicle stimulating hormone

Gn, gonadotropin

GnRH, gonadotropin-releasing hormone

HCG, human chorionic gonadotrophin

ICSI, intracytoplasmic sperm injection

IVF, in vitro fertilization

LH, luteinizing hormone

Declarations

Ethics approval

This study was approved by the Clinical Research Institutional Review Board of Peking University First Hospital (No. 2021-521). The ethics committees waived the requirement for informed consent due to the retrospective nature and anonymous data of this study.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Authors' contributions

YZ and YX conceived and coordinated the study, designed and analyzed the experiments, and wrote the paper. JY and XW verified and analyzed the data. QX, JS, XY and XS collected the data. All authors read and approved the final manuscript.

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References

1. Hillier SG. Gonadotropic control of ovarian follicular growth and development. Mol Cell Endocrinol. 2001; 179(1–2):39–46.
2. Balasch J, Fabregues F. Is luteinizing hormone needed for optimal ovulation induction? Curr Opin Obstet Gynecol. 2002; 14(3):265–74.
3. Dovey S, Mcintyre K, Jacobson D, Catov J, Wakim A. Is a premature rise in luteinizing hormone in the absence of increased progesterone levels detrimental to pregnancy outcome in GnRH antagonist in vitro fertilization cycles. Fertil Steril. 2011; 96(3):585–9.
4. Kolibianakis EM, Venetis CA, Kalogeropoulou L, Papanikolaou E, Tarlatzis BC. Fixed versus flexible gonadotropin-releasing hormone antagonist administration in in vitro fertilization: a randomized controlled trial. Fertil Steril. 2011; 95(2):558–62.
5. Barri PN, Coroleu B, Martinez F, Veiga A. Stimulation protocols for poor responders and aged women. Mol Cell Endocrinol. 2000; 166(1):15–20.
6. Hall JE, Brodie TD, Badger TM, Rivier J, Vale W, Conn PM, et al. Evidence of differential control of FSH and LH secretion by gonadotropin-releasing hormone (GnRH) from the use of a GnRH antagonist. J Clin Endocrinol Metab. 1988; 67(3):524–31.
7. Chen Q, Chai W, Wang Y, Cai R, Zhang S, Lu X, et al. Progestin vs. Gonadotropin-Releasing Hormone Antagonist for the Prevention of Premature Luteinizing Hormone Surges in Poor Responders Undergoing in vitro Fertilization Treatment: A Randomized Controlled Trial. Front Endocrinol (Lausanne). 2019; 10:796.
8. Geng Y, Lai Q, Xun Y, Jin L. The effect of premature luteinizing hormone increases among high ovarian responders undergoing a gonadotropin-releasing hormone antagonist ovarian stimulation protocol. Int J Gynaecol Obstet. 2018; 142(1):97–103.
9. Zhang D, Zhang D, Sun Z, Deng C, Yu Q, Zhen J. The effect of a transient premature luteinizing hormone surge without elevated serum progesterone on in vitro fertilization outcomes in a gonadotropin-releasing hormone antagonist flexible protocol. Gynecol Endocrinol. 2020; 36(6):550–3.
10. Reichman DE, Zakarin L, Chao K, Meyer L, Davis OK, Rosenwaks Z. Diminished ovarian reserve is the predominant risk factor for gonadotropin-releasing hormone antagonist failure resulting in breakthrough luteinizing hormone surges in in vitro fertilization cycles. Fertil Steril. 2014; 102(1):99–102.
11. Roth LW, Bradshaw-Pierce EL, Allshouse AA, Lesh J, Chosich J, Bradford AP, et al. Evidence of GnRH antagonist escape in obese women. J Clin Endocrinol Metab. 2014; 99(5):E871-E875.

12. Bosch E, Valencia I, Escudero E, Crespo J, Simon C, Remohi J, et al. Premature luteinization during gonadotropin-releasing hormone antagonist cycles and its relationship with in vitro fertilization outcome. Fertil Steril. 2003; 80(6):1444–9.
13. Maheshwari A, Mclernon D, Bhattacharya S. Cumulative live birth rate: time for a consensus? Hum Reprod. 2015; 30(12):2703–2707.
14. Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, et al. The International Glossary on Infertility and Fertility Care, 2017. Hum Reprod. 2017; 32(9):1786–801.
15. Satwik R, Kochhar M, Gupta SM, Majumdar A. Anti-mullerian hormone cut-off values for predicting poor ovarian response to exogenous ovarian stimulation in in-vitro fertilization. J Hum Reprod Sci. 2012; 5(2):206–12.
16. Kolibianakis EM, Albano C, Kahn J, Camus M, Tournaye H, Van Steirteghem AC, et al. Exposure to high levels of luteinizing hormone and estradiol in the early follicular phase of gonadotropin-releasing hormone antagonist cycles is associated with a reduced chance of pregnancy. Fertil Steril. 2003; 79(4):873–80.
17. Erb K, Klipping C, Duijkers I, Pechstein B, Schueler A, Hermann R. Pharmacodynamic effects and plasma pharmacokinetics of single doses of cetrorelix acetate in healthy premenopausal women. Fertil Steril. 2001; 75(2):316–23.
18. Inaudi P, Barra V, Vellucci FL, Regini C, Luisi S. GnRH antagonist does not prevent premature luteinization and ovulation in stimulated cycles with gonadotropins for IVF: two case reports. Gynecol Endocrinol. 2018; 34(3):189–91.
19. Martinez-Salazar J, Cerrillo M, Quea G, Pacheco A, Garcia-Velasco JA. GnRH antagonist ganirelix prevents premature luteinization in IUI cycles: rationale for its use. Reprod Biomed Online. 2009; 19(2):156–61.
20. Kummer NE, Weitzman VN, Benadiva CA, Schmidt DW, Engmann LL, Nulsen JC. In vitro fertilization outcomes in patients experiencing a premature rise in luteinizing hormone during a gonadotropin-releasing hormone antagonist cycle. Fertil Steril. 2011; 95(8):2592–4.
21. Wilcox J, Potter D, Moore M, Ferrande L, Kelly E. Prospective, randomized trial comparing cetrorelix acetate and ganirelix acetate in a programmed, flexible protocol for premature luteinizing hormone surge prevention in assisted reproductive technologies. Fertil Steril. 2005; 84(1):108–17.
22. Zhang J, Zhou X, Chen Y, Zhang Q, Li Y, Zhe J, et al. Effects of cetrorelix versus ganirelix in gonadotropin-releasing hormone antagonist cycles for preventing premature luteinizing hormone surges and on clinical outcomes of IVF-ET cycles. Nan Fang Yi Ke Da Xue Xue Bao. 2019; 39(10):1207–12.