Original Article

Diminished Ovarian Reserve Predisposes to Premature Luteinizing Hormone Surges in Gonadotropin-Releasing Hormone Antagonist Cycles in *In vitro* Fertilization

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Abstract

Context/Background: A premature luteinizing hormone (LH) surge, in *in vitro* fertilization (IVF) cycles with gonadotropin-releasing hormone (GnRH)-antagonist downregulation, leads to cycle cancellation. Currently, risk factors for the development of premature LH surge remain unknown. **Objective:** The aim of the study was to determine the incidence and identify the contributing factors for premature LH surge in IVF cycles with GnRH antagonist suppression. **Design:** This was a retrospective cohort study. **Setting:** IVF-embryo transfer program at a fertility and research center. **Materials and Methods:** The study included all patients undergoing IVF from December 1, 2014, to November 30, 2018, in whom GnRH-antagonist (cetrorelix 0.25 mg/d) flexible protocol was used. The primary outcome measure was the identification of premature LH surges (documented by a 2.5-fold increase in LH from the baseline above a threshold of 17 mIU/mL) with or without a decrease in E_2 and appearance of free fluid on ultrasound. **Results:** Premature LH surges occurred in 15 (2.16%) of 692 patients undergoing IVF with GnRH-antagonist suppression. Patients with premature surges had significantly lower ovarian reserve as compared to the controls (as seen from their higher age group, higher day 2 follicle-stimulating hormone (FSH), lower antral follicle counts, and lower anti-Müllerian hormone). **Conclusions:** Premature LH surge in a GnRH-antagonist cycle can lead to cycle cancellation and disappointment. Although this is a rare event, the incidence is higher in patients with diminished ovarian reserve. Further studies are needed to determine if giving the human chorionic gonadotropin trigger a day earlier or giving higher doses of GnRH-antagonist can benefit such cases.

Keywords: *Cycle cancelation, gonadotropin-releasing hormone antagonist, in vitro fertilization, premature luteinization, premature luteinizing hormone surge*

Introduction

Conventionally, gonadotropin-releasing hormone (GnRH) agonists were used to attain downregulation in *in vitro* fertilization (IVF) cycles. Over the past two decades, GnRH antagonists have replaced GnRH agonists as the drug of choice for pituitary suppression in most IVF clinics worldwide. The reason for this shift can be attributed to the benefits of GnRH antagonists including fewer days of injections, higher patient satisfaction, lower gonadotropin dose requirement, lower risk of ovarian hyperstimulation syndrome, the ability to use GnRH agonist as a trigger for oocyte maturation, and comparable clinical pregnancy rates.[1,2] GnRH antagonists (cetrorelix or ganirelix) have been found to

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be equally efficacious when used in the fixed and flexible protocols.[3,4] The most commonly used dose for GnRH antagonists is 0.25 mg given daily as a subcutaneous injection, as this has been found to be associated with the highest clinical pregnancy rates and lowest rates of premature luteinizing hormone (LH) surge.

However, despite stringent control with the above regimen, a premature LH surge can sometimes occur in IVF where antagonist cycles are used. This leads to cycle cancellation and is extremely disappointing for both patients and clinicians. So far, it has not been possible to identify patients at risk of developing premature LH surge. Thus, this study was done to retrospectively analyze all women who underwent IVF with GnRH antagonists and had a premature LH surge over a period of 4 years. We aimed to determine the incidence of antagonist failure and to identify any predisposing factors that might help in identifying such cases.

Materials and Methods

This was a retrospective cohort study carried out at a fertility and research center after approval by the institutional ethical committee. All IVF cycles carried out from December 1, 2014, to November 30, 2018, using GnRH antagonists for downregulation, were studied. During this period, a total of 692 antagonist cycles were carried out. Among these, cycles in which premature LH surges occurred were identified. These included cycles canceled before or on the day of oocyte retrieval, with increase in serum LH levels above a threshold of 17 mIU/mL, decrease in serum E_2 levels, free fluid on ultrasound, and regression or disappearance of follicles. An LH of 17 mIU/mL was used as it is the lower limit of the central 95% range for ovulatory LH.[5] Disappearance of follicles with appearance of free fluid on transvaginal ultrasound along with a decrease in serum E_2 levels was assumed to indicate ovulation. Demographic characteristics were compared between these index cycles and all other antagonist cycles.

Controlled ovarian hyperstimulation (COH) was carried out with recombinant follicle-stimulating hormone (FSH) or HMG (Foligraf: Bharat serum; Folisurge: Intas Pharmaceutical; or Menopur: Ferring). Stimulation was started on day 2 or 3 of the menstrual cycle with or without pretreatment with oral contraceptives (OCs). The ovarian response to stimulation was monitored through the ultrasonographic size of the follicles and serum E_2 levels. The FSH dose was adjusted according to the patient's response to stimulation. Subsequently, flexible GnRH antagonist, ganirelix acetate 0.25 mg (Orgalutran, Organon), or cetrorelix acetate 0.25 mg (cetrolix, Intas) administration was initiated subcutaneously once daily, when either the lead follicle reached 13 mm or serum E_2 exceeded 400 pg/mL, whichever occurred earlier and continued until the day of human chorionic gonadotropin (hCG) administration. Serum E_2 and LH were measured on alternate days thereafter till the day of hCG trigger. Serum progesterone was measured on the day of hCG trigger. hCG (Koragon: Ferring Pharmaceuticals; or Ovitrelle: Merck-serono) was administered to trigger follicular maturation when ≥2 follicles reached ≥17 mm. Patients underwent oocyte retrieval under local or general anesthesia 35–36 h after hCG administration. Cycles in which LH levels increased above 17 mIU/mL were considered at risk for premature ovulation and were planned for oocyte retrieval at exactly 34–35 h post hCG trigger. The appearance of free fluid on ultrasound with disappearance or reduction in the size of sonolucent follicles was interpreted to indicate ovulation.

For each cycle studied, we recorded the age of the woman, parity, body mass index (BMI), number of prior IVF cycles, diagnosis, use of OCs; antral follicle count, day 2 FSH, anti-Müllerian hormone (AMH) level, starting dose and total dose of gonadotropins used, type of GnRH antagonist used (ganirelix or cetrorelix), day of initiation of GnRH antagonist, days of antagonist use, number of stimulation days up to surge or up to trigger, peak E_2 concentration, and P and LH concentrations on the day of hCG administration.

All statistical analysis were performed using STATA Statistical Software Version 11 (StataCorp, Texas, USA). $P < 0.05$ was considered to be statistically significant.

Results

Among the 692 antagonist cycles studied, 2.16% had premature ovulation leading to cycle cancelation. These 15 patients (who had premature ovulation despite antagonist administration) were significantly older and had a lower ovarian reserve, as compared to the remaining cohort. The demographic and cycle characteristics of the index patients compared with the controls are listed in Table 1.

Both the groups were similar in terms of parity, BMI, number of prior IVF cycles, and use of oral contraceptive pill before stimulation. However, patients who had premature ovulation had significantly lower antral follicle counts ($P = 0.0008$), higher day 2 FSH levels ($P = 0.0002$), lower AMH levels ($P = 0.02$) and higher starting doses of gonadotropins ($P = 0.03$), as compared to the controls. Thus, significantly, more of the index patients (with premature ovulation) had diminished ovarian reserve, as compared to the controls. In most cases, women with premature LH

Table 1: Comparison of patients experiencing premature ovulation versus controls

	Index cases (*n*=15)	Control (*n*=677)	*P*
Mean age (years)	39.1±2.2	34.4±3.3	0.01
Parity	0	0	0.46
BMI	25.7±4.6	24.4±4.3	0.11
Preceeding OCP use (%)	26.6±3.8	22.1±5.3	0.81
Day 2 FSH (mIU/mL)	10.8±4.7	7.9±4.6	0.0002
Antral follicle count	4.3±2.8	9.1±3.4	0.0008
AMH (ng/mL)	0.5±0.2	2.3±1.4	0.02
Starting dose of gonadotropins (units/day)	375±75	262.5±112.5	0.03
Total gonadotropins (IU)	4125.5±1100.0	2362.5±1252.0	0.0001
Basal LH (mIU/mL)	3.1±1.4	3.7±1.9	0.80
LH before surge/trigger (mIU/mL)	9.8±2.1	2.9±1.9	0.0001
Peak E2 before surge/trigger (pg/mL)	486.5±196.1	1875.4±683.2	0.0001
Number of days of antagonist administered	4.4±1.5	4.7±1.8	0.41
Number of days of gonadotropins	11.1±2.4	8.8±2.6	0.0001

AMH=Anti-Müllerian hormone, BMI=Body mass index, OCP=Oral contraceptive pill, FSH=Follicle-stimulating hormone, LH=Luteinizing hormone

surge had 2.3 days longer stimulation compared to controls (11.1 vs. 8.8 days, $P = 0.0001$).

In all but two patients, a transvaginal ultrasound 35 h after LH elevation (before the planned oocyte retrieval) confirmed free fluid on ultrasound with the disappearance of sonolucent follicles. The remaining two patients underwent oocyte retrieval, with only two oocytes being retrieved in the first patient. IVF was done as per our standard protocol, and 2 cleavage-staged embryos were frozen on day 3 and transferred in the next cycle, resulting in a positive pregnancy test. The patient, however, had an anembryonic gestation, which required termination. The second patient had three oocytes retrieved and two fertilized after IVF and were frozen at the cleavage stage. A frozen embryo transfer in the subsequent month resulted in a negative pregnancy test.

Discussion

LH is synthesized in the anterior pituitary gland. In females, a steep rise in LH (LH surge) triggers ovulation and corpus luteum formation. Premature LH surges occurring during ovarian stimulation in IVF cycles lead to reduced pregnancy rates.[6] To prevent premature LH surge, protocols of COH in IVF include administration of either GnRH agonist or GnRH antagonist to suppress the endogenous gonadotropins. However, despite routine suppression of endogenous gonadotropins, cases of elevated LH have been reported. The mechanism leading to these cases of premature luteinization is not clear yet.

According to the concept of a therapeutic window for LH, proposed by Hillier, there is not only a threshold requirement for LH for an optimal cycle outcome but also a ceiling level beyond which LH can be detrimental to ovarian stimulation.[7] Most researchers have reported a physiological LH range between 0.5 and 10 mIU/mL.[8] However, the criterion for premature luteinization varies among different studies. Conventionally, premature LH surge is defined as an LH level of ≥10 mIU/mL and a progesterone level of ≥1.0 ng/mL occurring before the criteria of hCG administration are met.[9] Some other studies have defined LH surge as LH >12.4 IU/L and P level as >2 ng/mL.[10] No clear threshold criterion has been defined for cancelling an IVF cycle when a premature LH surge does occur.

The present study was conducted to determine the incidence of GnRH-antagonist failure in IVF cycles and to identify any predisposing factors that might help in identifying such cases. Premature LH surge was found to occur in 2.16% of the patients undergoing IVF with GnRH-antagonist suppression. Most patients with premature surges were those who had significantly lower ovarian reserve as compared to the controls (i. e, they had higher day 2 FSH, lower antral follicle counts, and lower AMH). Two other independent previous studies have found a similar correlation between low ovarian reserve or older age group patients (who required higher doses of gonadotropins) and premature LH elevation.[5,11]

Keeping consistent with our results, Bosch concluded that in patients with premature luteinization, the number of stimulation days and total FSH dose used were significantly higher.[12] Other previous studies have also shown that the initial high FSH dose administered during the first 6 days of stimulation (as is required in most protocols for poor responders) increases granulosa cell steroidogenetic activity and could be responsible for premature luteinization.[13,14]

In an attempt to prevent premature LH surges in antagonist cycles in women where premature ovulation has occurred, Reichman *et al*. doubled the dose of antagonist in subsequent cycles to twice-daily dosing.[5] With a higher dosing of the drug, they eliminated premature LH increases in few patients. Higher doses than 0.5 mg are inadvisable due to lower pregnancy rates noted in the dose finding studies when higher doses of ganirelix were used.[15] Alternatively, patients who undergo premature LH surge can use conventional GnRH-agonist suppression in subsequent stimulation cycles. It is unlikely that earlier administration would prevent premature LH surges, as the index patients in this study had been given the GnRH antagonist for an average of 4.4 days before the surge occurred.

Another attempt to salvage cycles with premature LH surges was made by Choi *et al*. by doing an earlier ovum pick up (OPU).[16] However, if the observed surge represented an ascending limb, an earlier OPU will not provide sufficient time for the oocytes to mature. On the other hand, if this surge represents the descending limb, an earlier OPU may be more effective for retrieving oocytes and avoiding cycle cancellation. However, earlier OPU was not found to be effective for reducing the risk of cycle cancellation in patients with a premature LH surge on hCG day. Incidentally, the earlier OPU group showed high basal FSH levels and low E_2 levels on hCG day (consistent with poor ovarian reserve). This group also had low maturation rates, statistically significantly low fertilization rates, and higher OPU failure rates.

Conclusions

The relationship between diminished ovarian reserve and responsiveness to GnRH antagonist remains unclear. Although using GnRH antagonists is a highly efficacious and reliable form of pituitary suppression, they may be more likely to fail in patients who already have a poor prognosis (those with increased age and diminished ovarian reserve). The weakness of our study is that it is a retrospective study with a small number of patients. A larger prospective study is warranted to confirm these preliminary results.

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Conflicts of interest

There are no conflicts of interest.

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