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CASE REPORT

Absence of luteal phase defect and spontaneous pregnancy in IVF patients despite GnRH-agonist trigger and ''freeze all policy'' without luteal phase support: a report of four cases

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Abstract

Human chorionic gonadotropin (hCG) is commonly used for final oocyte maturation in ''*in vitro* fertilization'' (IVF)-treatment cycles, however, the main important risk is development of severe ovarian hyperstimulation syndrome (OHSS). OHSS can almost be avoided by using gonadotrophin-releasing-hormone agonist for final oocyte maturation in an antagonist protocol. However, primarily this approach lead to a very poor reproductive outcome, despite the use of a standard luteal phase support. The reason seems to be severe luteolysis. Obviously, luteolysis post-gonadotropin-releasing-hormone-agonist (post-GnRH-a) trigger is individual specific, and not all patients will develop a complete luteolysis, as expected previously. Luteolysis can been reverted by the administration of hCG. Unprotected intercourse around the time of ovulation induction and oocyte retrieval can lead to a spontaneous conception in IVF treatment and, endogenous hCG, produced by the trophoblast, will rescue the corpora lutea. Therefore, one should not rely on complete luteolysis after GnRH-a triggering and, especially patients for egg donation and pre-implantation-genetic diagnosis for single gene disorder, have to be counselled to avoid unprotected intercourse.

Keywords

GnRH-agonist-trigger, luteal deficiency, luteal phase support, ovarian hyperstimulation syndrome, spontaneous conception

History

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Introduction

Final oocyte maturation is one of the crucial steps in *in vitro* fertilization (IVF) – treatment to retrieve mature oocytes. In natural cycle, ovulation is induced by the luteinizing hormone (LH) – and follicle stimulation hormone (FSH) – surge. In the early days of IVF [1], natural LH surge had to be monitored closely to plan oocyte retrieval. Nowadays, to avoid unplanned LH surge and therefore cycle cancellation, IVF treatments involve suppression of LH through the application of gonadotropin-releasing-hormone (GnRH)-agonist (GnRH-a) or GnRH-antagonist, depending on the protocol used. For final oocyte maturation, human chorionic gonadotropin (hCG) can be used, as LH and hCG are similar in structure and function [2]. The main important risk of the use of hCG is development of severe ovarian hyperstimulation syndrome (OHSS), which is still today one of the most dangerous complications in assisted reproductive techniques.

GnRH-antagonist protocols offer the possibility of the use of GnRH-agonist (GnRH-a) for final oocyte maturation with a significant reduction of OHSS. However, the first large randomized clinical trial reported a very poor reproductive outcome, when GnRH-a was used to trigger final oocyte maturation. The reason for the poor outcome, despite a standard luteal phase support (LPS) was interpreted as a severe luteal phase insufficiency, caused by low levels of endogenous LH and progesterone [3]. After GnRH-a triggering, progesterone serum levels return to baseline after 5 days, confirming a complete luteolysis [4].

Currently, there is an ongoing debate on how best to counteract the negative impact of agonist triggering on the luteal phase. Initially, administration of low dose of hCG has been proposed to rescue the luteal phase, hence, with this approach, early and late OHSS might still occur [4–6]. Another approach would be the intensified LPS [7]. Last but not least, segmentation of the cycle with freezing of all oocytes/embryos and transfer in the subsequent cycle can be applied. However, also the approach of ''freeze all'' does not rule out completely the development of OHSS [8,9].

It has been proposed that the GnRH-a administration would cause sever luteolysis and a defective luteal phase, if not supported with high dose exogenous steroids or low dose hCG. However, the current article describes the cases of four patients, who were triggered with a GnRH-a and ''freeze all''-approach, with the absence of any kind of LPS. Nonetheless, natural conception occurred, indicating that not all patients do suffer from a complete luteolysis after GnRH-a administration for final oocyte maturation.

Material and methods

Four case reports of patients, undergoing IVF/ICSI treatment in a GnRH-antagonist protocol with the use of GnRH-a trigger, freeze-all-policy with waive of LPS. Despite this approach,

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spontaneous pregnancy occurred due to unprotected intercourse around oocyte retrieval.

Results

Case 1

About 27-year-old women with a history of 7 years of primary infertility. The infertility work-up revealed normal findings beside the ultrasound, showing ovaries with the features of the polycystic ovarian syndrome (PCO). Due to the diagnosis of unexplained infertility, the patient underwent IVF treatment.

Ovarian stimulation protocol

Antagonist protocol with the use of rec FSH and Cetrorelix 0.25 mg as GnRH-antagonist. Total stimulation duration lasted 13 days, total amount of rec FSH was 2625 IU. On the day of hCG, the concentrations of estradiol (E2) and progesterone (P4) were 7329 pg/ml and 3.71 ng/ml, respectively. Due to the risk of OHSS and the premature progesterone rise, the decision for segmentation of the cycle was taken. GnRH-a was administered for final follicular maturation. About 14 oocytes were retrieved with oocyte pick up procedure, resulting in 11 metaphase II (M II) oocytes after denudation, on which ICSI was performed. On day 3, five good-quality embryos were cryopreserved. No luteal support was given.

Eleven days after egg retrieval the patient was admitted with severe abdominal pain and dyspnoea. The ultrasound examination revealed enlarged ovaries and excessive amount of ascites. The patient stated that she had intercourse with her husband 12 h after oocyte retrieval. Her laboratory results revealed a β-hCG 183 mIU/ml. Luteal support was started and hospitalization was required for symptomatic treatment. Clinical pregnancy was confirmed; unfortunately, late spontaneous abortion occurred at 15 weeks of gestation.

Case 2

About 28-year-old patient with primary infertility for 5.5 years and a history of irregular cycles, at intervals of 30–90 days. The infertility work-up showed normal findings regarding her previous history. The patient was diagnosed with PCO, according to the Rotterdam criteria. Two intrauterine insemination (IUI) cycles were done and did not result in a pregnancy.

Ovarian stimulation protocol

Flexible GnRH-antagonist protocol with rec FSH, and start of GnRH-antagonist (Cetrorelix 0.25 mg) on day 6 of the cycle. Total stimulation duration was 9 days with a total amount of 1350 IU rFSH. On day 9 of stimulation, serum progesterone level was elevated to 2.6 ng/ml. Due to the presence of premature progesterone rise, the decision for segmentation of the cycle was taken. Final follicular maturation was triggered with GnRH-a (Triptorelin 0.2 mg), a total of 14 eggs were retrieved, 13 were M II and injected, 12 reached 2 pronucleus stages, and on day 5, 6 embryos were vitrified.

About 3 weeks later the patient came for a consultation because she did not have withdrawal bleeding. An ultrasound examination revealed a right unruptured tubal ampullary ectopic gestation. The patient underwent a laparoscopy with salpingotomy.

Case 3

About 38-year-old patient with a history of primary infertility for 12 years. Previously to IVF, laparoscopic ovarian drilling was done due to PCO and additional three cycles of IUI, however not leading to a pregnancy.

At the time of referral, transvaginal ultrasound revealed a normal uterus with polycystic ovaries and AFC of 22. Baseline hormonal investigations show an elevated Prolactin and normal levels of FSH, LH and AMH. Due to her long history of infertility and her age, IVF treatment was planned.

Ovarian stimulation protocol

Stimulation in antagonist protocol, started on day 2 with rFSH, GnRH-antagonist (Cetrorelix, 0.25 mg) was added from day 6. The stimulation duration was 8 days with a total amount of 1800 IU of rFSH. On day 8, an ultrasound revealed seven follicles on the right ovary and eight on the left, with a diameter of 16–18 mm, and the endometrial lining was 10 mm. The concentration of E2 and P4 were 7337 pg/dl and 1.8 ng/ml, respectively. GnRH-a trigger was used (Triptorelin 0.2 mg) for final oocyte maturation, due to risk of OHSS. During egg retrieval, 12 oocytes were retrieved, 8 MII, 8 were injected, 6 fertilized and 4 blastocysts were vitrified, due to the OHSS risk and high progesterone level. As the patient did not get her withdrawal bleeding, β-hCG was performed, showing a value of 11 345IU. Transvaginal ultrasound revealed single gestational sac of 11 mm. A repeat scan 1 week later showed a single live intrauterine gestation. The patient did not develop any signs of OHSS. At the time of submission of this article, the pregnancy was ongoing.

Case 4

About 31-year-old patient with a history of 2 years of unexplained infertility. Before IVF, three cycles of IUI were performed, but did not result in a pregnancy. The patient reported irregular cycles, ultrasound revealed an AFC of >15 in each ovary. Due to her 2-year history of infertility, she underwent IVF treatment, after receiving an oral contraceptive pill for 1 month for cycle regulation.

Ovarian stimulation protocol

GnRH-antagonist protocol with a stimulation dosage of 150 IU HMG/day. GnRH-a was used for ovulation induction, because the ultrasound revealed >15 follicles of >11 mm, and hormonal evaluation showed E2 level with 3.687 pg/ml. After oocyte retrieval, 19 MII oocytes were vitrified for cycle segmentation to avoid OHSS. No luteal phase medication was given. As the patient did not get her withdrawal bleeding, pregnancy test showed a positive result and pregnancy is ongoing. No signs of OHSS occurred.

Discussion

It is well established, that GnRH-a trigger in a GnRH-antagonist protocol for IVF has a major influence on the endocrine profile in the luteal phase. It induces sever luteolysis, resulting in detrimental effects on the implantation and pregnancy rates, if not supported by intensified LPS or application of hCG [3,4]. However, the presented cases demonstrate clearly that luteolysis post-GnRH-a trigger is individual-specific, and not all patients will develop a complete luteolysis.

The GnRH-a induced LH surge has been thought not to be sufficient to perpetuate corpora lutea function, however, the otherwise occurring luteolysis has been demonstrated to be reverted by the administration of hCG. This approach is implemented in the concept of modified luteal support and/or of the dual trigger, where hCG is given in a low dosage, either before oocyte retrieval or together with the GnRH-a for triggering

[10,11], leading to pregnancy rates, which are comparable with the results achieved after hCG triggering.

Withdrawal of LH support from the primate corpus luteum for at least 3 days induces luteolysis [12]. However, corpus luteum function can be rescued, if LH activity is reinitiated within 3 days [13], or by application of sufficient exogenous hCG, i.e. $\geq$1500 IU [14]. After the GnRH-a has been administered for final oocyte maturation, some patient's corpora lutea have the capability of recovering normal function even after 7 days of deprivation from LH stimulation. In the absence of any significant LH stimulation, luteal cells are able to retain both their enzymatic steroidogenic properties, and their capacity to respond to exogenous hCG up to day 7 after final oocyte maturation [15].

Notwithstanding cautious efforts of collecting all oocytes, spontaneous conception after ovarian stimulation for IVF is possible as some oocytes can be missed, especially in high responder patients [16]. Moreover, the increased serum estradiol levels due to ovarian stimulation, might also prolong the sperm survival from intercourse due to the presence of copious cervical mucus [16].

After fertilization, hCG is already produced by the preimplantation embryo [17] and hCG is detectable in maternal serum from as early as day 8 after ovulation. This hCG is able to cover the LH deficit. Therefore, the function of the corpora lutea is maintained, and implantation and development of the pregnancy is possible.

The possibility of spontaneous pregnancy despite GnRH-a trigger is of utmost importance for egg-donation patients, as well as for patients, undergoing IVF due to planned pre-implantation genetic diagnosis for single gene disorders. Consequently, it may be prudent to caution patients undergoing ovarian stimulation for IVF against unprotected intercourse after the initial days of controlled ovarian hyperstimulation. Future studies should evaluate an ''individualized LPS'' after GnRH-a triggering, based on the presence and severity of luteolysis, as measured by systemic progesterone values, and evaluate the timing of hCG during luteal phase.

Conclusions

We describe four cases of failed complete luteolysis post-GnRH-a trigger, which was sufficient to allow embryo implantation and development. Obviously, the above-mentioned pathophysiological mechanism could even explain development of severe OHSS in one of the cases. Those cases show clearly that despite the GnRH-a trigger, waive of LPS and freeze all policy, natural conception can occur.

Declaration of interest

The authors declare that they have no conflicts of interest.

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