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CASE REPORT

Live births from *in vitro* fertilization-embryo transfer following the administration of gonadotropin-releasing hormone agonist without gonadotropins: Two case reports

Mai Li, Ping Su, Li-Ming Zhou

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Abstract

BACKGROUND

The prevalence of female infertility between the ages of 25 and 44 is 3.5% to 16.7% in developed countries and 6.9% to 9.3% in developing countries. This means that infertility affects one in six couples and is recognized by the World Health Organization as the fifth most serious global disability. The International Committee for Monitoring Assisted Reproductive Technology reported that the global total of babies born as a result of assisted reproductive technology procedures and other advanced fertility treatments is more than 8 million. Advancements in controlled ovarian hyperstimulation procedures led to crucial accomplishments in human fertility treatments. The European Society for Human Reproduction and Embryology guideline on ovarian stimulation gave us valuable evidence-based recommendations to optimize ovarian stimulation in assisted reproductive technology. Conventional ovarian stimulation protocols for *in vitro* fertilization (IVF)–embryo transfer are based upon the administration of gonadotropins combined with gonadotropin-releasing hormone (GnRH) analogues, either GnRH agonists (GnRHa) or antagonists. The development of ovarian cysts requires the combination of GnRHa and gonadotropins for controlled ovarian hyperstimulation. However, in rare cases patients may develop an ovarian hyper response after administration of GnRHa alone.

CASE SUMMARY

Here, two case studies were conducted. In the first case, a 33-year-old female diagnosed with polycystic ovary syndrome presented for her first IVF cycle at our reproductive center. Fourteen days after triptorelin acetate was administrated (day 18 of her menstrual cycle), bilateral ovaries presented polycystic manifest-

ations. The patient was given 5000 IU of human chorionic gonadotropin. Twenty-two oocytes were obtained, and eight embryos formed. Two blastospheres were transferred in the frozen-thawed embryo transfer cycle, and the patient was impregnated. In the second case, a 37-year-old woman presented to the reproductive center for her first donor IVF cycle. Fourteen days after GnRHa administration, the transvaginal ultrasound revealed six follicles measuring 17-26 mm in the bilateral ovaries. The patient was given 10000 IU of human chorionic gonadotropin. Three oocytes were obtained, and three embryos formed. Two high-grade embryos were transferred in the frozen-thawed embryo transfer cycle, and the patient was impregnated.

CONCLUSION

These two special cases provide valuable knowledge through our experience. We hypothesize that oocyte retrieval can be an alternative to cycle cancellation in these conditions. Considering the high progesterone level in most cases of this situation, we advocate freezing embryos after oocyte retrieval rather than fresh embryo transfer.

Key Words: Gonadotropin-releasing hormone agonist; Ovarian hyperstimulation; *In vitro* fertilization; Live birth; Infertility; Frozen-thawed embryo transfer; Human chorionic gonadotropin; Case report

Core Tip: Gonadotropin-releasing hormone agonist (GnRHa) is administered in the 'long protocol' regimen for pituitary downregulation *in vitro* fertilization-embryo transfer. The development of ovarian cysts requires gonadotropin administration after pituitary downregulation in the long protocol. However, our cases presented an extremely special condition that a very small group of patients can develop called ovarian hyperstimulation receiving GnRHa alone. It is extremely rare that both patients had a successful egg retrieval during their first *in vitro* fertilization cycle and were impregnated. These cases provide some experience for clinical judgment and a new insight into the possible mechanisms of GnRHa action without gonadotropins.

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INTRODUCTION

Gonadotropin-releasing hormone agonist (GnRHa) has been widely administered since the 1980s in the "long protocol" regimen for pituitary downregulation[1-5]. It manifests pulsatile secretion in the physiological state and has a self-priming effect. If it is given persistently, the pituitary will be inhibited. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estrogen levels decrease in a response similar to menopause, and this occurrence is called "pituitary downregulation." After 6-8 wk, the effects of inhibition recover. The use of GnRHa in the long protocol effectively inhibits the preovulatory LH surge[6], which reportedly occurs in 20%-25% of *in vitro* fertilization (IVF) cycles[7]. Thus, GnRHa can significantly reduce the preovulatory rate to 2%[8].

Generally, the development of ovarian cysts requires the administration of gonadotropins (Gn) after pituitary downregulation in the long protocol. However, several case reports have presented an extremely special condition where a patient developed ovarian hyperstimulation after receiving GnRHa alone[9-12]. Only a small number of these cases underwent oocyte aspiration from the follicles in the first cycle of IVF and had a successful pregnancy; our two cases were similar. However, our cases were extremely rare because the eggs from both patients were retrieved during their first IVF cycle. The patients both had successful pregnancies and delivered healthy babies. The results provided knowledge based upon clinical experience that will inform clinical judgment and impart new insight into the possible mechanisms of GnRHa action without Gn.

CASE PRESENTATION

Chief complaints

Case 1: A 33-year-old female in our reproductive center was first referred to IVF because of polycystic ovary syndrome (PCOS).

Case 2: A 37-year-old female presented to the reproductive center for her first donor IVF cycle.

History of present illness

Case 1: The patient had a 3-year history of secondary infertility. Her menstrual cycles were irregular, and she was diagnosed with PCOS.

Case 2: The patient had an 8-year history of primary infertility. Her husband suffered from severe hepatic disease, diabetes, and hypertension and was unable to discontinue the drugs affecting the reproductive system. The patient's menstrual cycles were irregular.

History of past illness

Case 1: The patient underwent many cycles of ovulation induction with different ovulation-stimulating drugs but without conception.

Case 2: The patient underwent three ovulation induction cycles with donor intrauterine insemination without conception.

Personal and family history

The patient's family in both cases had no related diseases.

Physical examination

Case 1: The patient's body mass index was 18.4 kg/m^2. No abnormalities were found.

Case 2: The patient's body mass index was 21.9 kg/m^2. No abnormalities were found.

Laboratory examinations

Case 1: The patient's husband's seminal sample analysis finding was within the normal limits. The patient's basic hormonal profile was as follows: FSH of 8.17 mIU/mL (normal range: 4.00-15.00 mIU/mL); LH of 5.12 mIU/mL (normal range: 4.00-30.00 mIU/mL); estradiol of 90.00 pg/mL (normal range: 15.16-127.81 pg/mL); progesterone of 0.67 ng/mL (normal range: 0-1.00 ng/mL); and testosterone of 40.88 ng/mL (normal range: 6.00-86.00 ng/mL).

Case 2: The seminal sample was from a donor. The patient's basic hormonal profile was as follows: FSH of 6.72 mIU/mL (normal range: 3.85-8.78 mIU/mL); LH of 4.04 mIU/mL (normal range: 2.12-10.89 mIU/mL); estradiol of 33.00 pg/mL (normal range: 95.00-433.00 pg/mL); and progesterone of 0.620 ng/mL (normal range: 0.057-0.893 ng/mL).

Imaging examinations

Case 1: The ultrasound showed polycystic manifestations.

Case 2: The ultrasound showed that her antral follicle count was 12.

FINAL DIAGNOSIS

Case 1: Secondary infertility and PCOS.

Case 2: Primary infertility.

TREATMENT

Case 1: On day 18 of the patient's menstrual cycle, daily treatment was started with 0.1 mg triptorelin acetate (Decapeptyl; Ferring, Kiel, Germany). Fourteen days later, the patient complained of mild abdominal distension. Her bilateral ovaries were surprisingly enlarged under ultrasonography and contained approximately 15 follicles with a diameter of 18-22 mm and endometrial thickness of 10 mm. The laboratory investigations showed estradiol levels of 5110.00 pg/mL and progesterone levels of 4.47 ng/mL. The patient received 5000 IU of human chorionic gonadotropin (HCG; Livzon, Guangzhou, China). Oocyte retrieval was performed 36 h later, and 22 oocytes were obtained. Twenty oocytes were

fertilized, and eight high-quality embryos were formed. All embryos were frozen because of the elevated progesterone. Two blastospheres were transferred in the subsequent frozen-thawed embryo transfer cycle (Tables 1 and 2).

Case 2: The patient was given 0.1 mg of triptorelin acetate (Decapeptyl; Ferring) daily from the mid-luteal phase (day 20 of her menstrual cycle) for 14 d. The progesterone level increased to 7.13 ng/mL. Fourteen days after GnRHa administration, the transvaginal ultrasound revealed six follicles measuring 17-26 mm in the bilateral ovaries. The endometrial thickness was 8 mm. Laboratory investigations revealed an estradiol level of 2664.00 pg/mL, FSH of 2.29 U/L, LH of 1.38 U/L, and progesterone of 3.36 ng/mL. The patient did not feel abnormal. She decided to continue the IVF treatment after communicating with her attending doctor. Then, she was given 10000 IU HCG (Livzon), and oocyte retrieval was performed 36 h later. A total of three oocytes were retrieved and fertilized by IVF, which underwent subsequent cleavage. The three embryos were frozen because of the high progesterone levels. Two months later, the patient underwent a frozen-thawed embryo transfer cycle with estradiol valerate tablets (Progynova; Schering, Berlin, Germany). After the endometrial thickness exceeded 8 mm and serum estradiol concentration reached 268.00 pg/mL, two high-grade embryos were transferred (Tables 3 and 4).

OUTCOME AND FOLLOW-UP

Case 1: The patient was impregnated. Her b-HCG concentration was 8897 mIU/mL 14 d after embryo transfer. Two gestational sacs and fetal pulses were detected on ultrasound 14 d later. She gave birth to two healthy babies weighing 1950 g and 3100 g at 37 wk of gestational age.

Case 2: The patient's b-HCG concentration was 473.3 mIU/mL 14 d after embryo transfer. A single gestational sac and fetal pulse were detected upon ultrasound at 7 wk. She gave birth to a full-term baby at 39 wk of gestational age.

DISCUSSION

The conventional long protocol of ovarian stimulation for IVF-embryo transfer is based upon the administration of exogenous Gn combined with GnRHa. The aim of using GnRHa is to prevent the premature rise of LH due to positive feedback by the high serum concentration of estradiol[13-15]. The use of GnRHa is associated with an increased incidence of functional ovarian cysts; this may be the effect of the "flare-up" phenomenon of GnRHa. GnRHa can stimulate the pituitary gland and cause a temporary increase in FSH, LH, and other sex hormones secreted by the ovaries[9]. This may cause the formation of sporadic cysts (generally one or two). The cysts can be aspirated or ignored if the serum hormones are normal.

However, a few reports have observed that ovarian hyperstimulation occurred following the use of GnRHa alone in the long protocol[9-12]. These reports documented evidence of hyperstimulation and extremely high estradiol levels after the administration of GnRHa. Park *et al*[16] reported a case of depot preparation (3.75 mg) of tryptorelin without Gns induced ovarian multifollicular enlargement with a high estradiol level and was followed by HCG administration and oocyte retrieval. Then, three embryos were transferred to the recipient, but none resulted in pregnancy. For instance, Parinaud *et al*[17] demonstrated that GnRHa-related cysts could be used to retrieve oocytes after HCG administration. Subsequently, oocyte retrieval has been reported instead of cycle cancellation, and several cases of high-quality embryo transfers and pregnancies were confirmed[11,18].

Ovarian hyperstimulation following the use of GnRHa without Gn is extremely rare. The pathogenesis of this phenomenon remains controversial. Some reports have suggested that the incidence is higher in older patients in which GnRHa was started in the follicular phase instead of the mid-luteal phase[19]. Nevertheless, this phenomenon can also happen in younger patients[20].

Some researchers proposed that GnRHa may result in a transient "flare-up effect" on the pituitary, and this surge triggers the development of primordial follicles. GnRHa are typically administered during the mid-luteal phase in the conventional long protocol, which occurs approximately 1 wk after ovulation. At this phase, the endogenous Gn levels are lowest, and the "flare-up" is least likely to stimulate a new wave of follicular development. We hypothesized that some patient subgroups begin follicular recruitment earlier than normal. Instead of inhibiting follicular development, they stimulate waves of follicular development, which leads to a hyperstimulation state.

Furthermore, it appears that some follicles may become highly sensitive to short-term stimulation of Gn caused by GnRHa. However, this hypothesis cannot explain why these "cysts" continue growing without exogenous Gn stimulation for a prolonged period. An increase in serum FSH and LH concentrations within the first 48 h of GnRHa administration was demonstrated. A transient increase in estradiol levels is also observed. However, continuous administration of GnRHa for 4 d results in

Table 1 Protocol timeline for Case 1

Date	Protocol
June 9, 2015	Triptorelin acetate 0.1 mg/d for 14 d
June 23, 2015	HCG 5000 IU im
June 25, 2015	Oocyte retrieval
June 28, 2015	D3 embryos frozen
June 30, 2015	D5 embryos frozen
August 31, 2015	Two blastospheres were transferred

HCG: Human chorionic gonadotropin.

Table 2 Hormone concentrations before and after treatment for Case 1

	Hormone concentrations before treatment	Hormone concentrations after treatment
FSH in mIU/mL	8.17	8.68
LH in mIU/mL	5.15	5.17
E2 in pg/mL	90.00	5110.00
Progesterone in ng/mL	0.67	4.47

E2: Estradiol; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone.

Table 3 Protocol timeline for Case 2

Date	Protocol
March 28, 2015	Triptorelin acetate 0.1 mg/d for 14 d
March 12, 2015	HCG 10000 IU im
March 14, 2015	Oocyte retrieval
March 17, 2015	D3 embryos frozen
June 14, 2015	Two D3 embryos were transferred

HCG: Human chorionic gonadotropin.

Table 4 Hormone concentrations before and after treatment for Case 2

	Hormone concentrations before treatment	Hormone concentrations after treatment
FSH in mIU/mL	6.72	2.29
LH in mIU/mL	4.04	1.38
E2 in pg/mL	33.00	2664.00
Progesterone in ng/mL	0.62	3.36

E2: Estradiol; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone.

decreased serum estradiol levels. Nevertheless, estradiol production by these "cysts" continues, and their growth persists. It may be possible that these cysts exert the "flare-up effect" at a later time and can stimulate ovarian hyperstimulation from the initial Gn concentration. It may also result from the increased sensitivity of ovarian follicles to circulating Gn.

Another possibility is that pituitary desensitization takes longer than 14 d in some women following the long protocol. Therefore, the circulating sex hormone concentrations may not have decreased to

"hypophysectomized" levels. We have observed the presence of "functional cysts" and continuously increased levels of FSH, LH, or estradiol in some patients during GnRHa administration. It is likely that the circulating Gn levels do not decrease. Instead, circulating Gn levels increase and generate self-feedback, which results in ovarian hyperstimulation.

It has also been hypothesized that GnRHa may directly affect the ovaries and steroidogenesis. This theory is based on the observations of GnRHa receptors on the ovary and GnRHa-induced steroidogenesis in cultured human granulosa cells[17]. However, there is no definitive evidence of direct action of GnRHa on the ovary.

The procedure presented in our report suggests that ovarian hyperstimulation following the administration of GnRHa without Gn may tend to occur in patients with PCOS. A previous study analyzed the nucleotide mutations of the *LH* and *LHR* genes in PCOS patients and found that *LHβ* TC and CC genotypes were closely related to the risk of PCOS, indicating that variants of these genes may affect the metabolic pathways of PCOS[21]. These variant genotypes likely cause abnormal responses to GnRHa. Both patients began downregulation in the mid-luteal phase without receiving an oral contraceptive pill pretreatment. GnRHa administration during the luteal phase may have the advantage of yielding more follicles because LH-stimulated androgen production and circulating androgen levels are more effectively suppressed throughout folliculogenesis[22].

Most previous reports are of cases that resulted in no pregnancies. Researchers have hypothesized that the aberrant rise in serum estradiol after GnRHa administration may cause imperfect pituitary suppression, with subsequent effects on oocyte and embryo quality[23]. However, there are reports of live births following administration of GnRHa without Gn, like in our cases. Therefore, it is possible that these patients can achieve a positive outcome after optimal management. Instead of cycle cancellation, oocyte retrieval can be an acceptable choice for these patients. Our two cases successfully underwent oocyte retrieval, and high-quality embryos were obtained after administration of HCG at the proper time. It was appropriate to undertake embryo cryopreservation, considering the presence of high progesterone and impaired endometrial receptivity.

CONCLUSION

Ovarian hyperstimulation following the administration of GnRHa without Gn can occur, though the mechanism is still unclear. This report may provide new insights into the possible mechanisms of GnRHa and indicated that oocyte retrieval can be an alternative to cycle cancellation in the appropriate conditions. The optimal and standard management of this condition is still unclear because of the paucity of data. Considering the high progesterone level in most cases of this situation, we advocate freezing embryos after oocyte retrieval rather than fresh embryo transfer.

FOOTNOTES

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