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CASE REPORT PEER REVIEWED | OPEN ACCESS

Spontaneous dichorionic diamniotic twin pregnancy following a leuprolide acetate trigger and freeze all cycle for OHSS risk: A case report

Justin White, Jenna Gale, Aaron Jackson

ABSTRACT

Introduction: Gonadotropin-releasing hormone (GnRH) agonist triggers are increasingly used in antagonist in vitro fertilization (IVF) cycles to prevent ovarian hyperstimulation syndrome (OHSS) following a robust ovarian response. The luteolytic effects of GnRH agonists inhibit implantation or spontaneous pregnancy, warranting freezing available blastocysts for future transfer after the risk of OHSS subsides.

Case Report: A 33-year-old G1P1 with secondary infertility due to polycystic ovarian syndrome underwent IVF with a GnRH antagonist cycle. A leuprolide acetate trigger for final oocyte maturation was prescribed given her risk of OHSS. A spontaneous dichorionic/diamniotic twin pregnancy ensued.

Conclusion: This case reinforces the importance of advising abstinence during the stimulation phase of an IVF cycle and that, although rare, the endometrium may allow for spontaneous conception following a leuprolide acetate trigger, which may further potentiate the risk of late OHSS.

Keywords: In vitro fertilization, Luteal phase support, Ovarian hyperstimulation syndrome, Ovarian stimulation

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INTRODUCTION

Gonadotropin-releasing hormone agonists (GnRHa), including leuprolide acetate, trigger follicular and oocyte maturation by inducing a physiologic midcycle surge of luteinizing hormone (LH) and follicle stimulating hormone (FSH) [1]. However, this endogenous surge has a deleteriously short half-life, resulting in premature luteolysis [2]. This is in comparison to human chorionic gonadotropin (hCG), which maintains LH activity for up to ten days during which time, implantation occurs [3].

The advent of gonadotropin-releasing hormone antagonists has allowed the use of GnRHa as the "trigger shot" in IVF cycles. This is the result of competitive blockade of GnRH receptors by the antagonist, which allows for stimulation of the anterior pituitary gland with a GnRHa [4]. Using a GnRHa as opposed to the classic hCG trigger reduces the risk of ovarian hyperstimulation syndrome (OHSS) [1, 5, 6]. However, it is well documented that GnRHa trigger results in inadequate luteal phase support, low implantation rates, prompting the requirement for embryo cryopreservation precluding fresh embryo transfer. Studies also suggest that this luteal phase defect often persists whether or not the corpus luteum is abandoned or rescued with multiple

low dose hCG injections or estradiol or progesterone supplementation [1].

We present a case where a patient spontaneously conceived a dichorionic/diamniotic twin pregnancy following a leuprolide acetate trigger. Implantation occurred and the pregnancy progressed until it was lost after six weeks gestation by ultrasound.

CASE REPORT

A 33-year-old gravida 1 para 1 was referred to our fertility clinic with her 36-year-old male partner with secondary infertility due to polycystic ovarian syndrome (PCOS).

A baseline ultrasound demonstrated high ovarian reserve with an antral follicle count of 41. Hystero-salpingo contrast sonography (HyCoSy) was normal, confirming tubal patency and a normal uterine cavity. Day 3 FSH was normal at 6.1 IU/L (normal: 3.9–8.8 IU/L) [7].

The patient opted to purse in vitro fertilization (IVF) after not achieving pregnancy with ovulation induction with oral agents. A gonadotropin-releasing hormone (GnRH) antagonist protocol was prescribed to allow for the use of a GnRHa trigger for OHSS prevention. Follicular phase stimulation was initiated with follitropin alfa (137.5 IU daily, Gonal-F; EMD Serono, Canada) and lutropin alfa (75 IU daily, Luveris; EMD Serono, Canada). She began the GnRH antagonist cetrorelix (Cetrotide; EMD Serono, Canada) on the 6th day of stimulation, at which point the serum estradiol level was measured at 1029 pmol/L (280 pg/mL), which met criteria for antagonist start at our center. Given a robust ovarian response to simulation with 32 follicles measuring over 13 mm average diameter, a leuprolide acetate trigger (3 mg [0.6 mL]) was prescribed at 8 PM on the 12th day of stimulation and the patient was placed on oral cabergoline (0.5 mg every three days; Dostinex; Pfizer, Canada) for 4 doses for prevention of ovarian hyperstimulation syndrome (OHSS). Blood tests on the morning before the evening leuprolide acetate administration demonstrated a luteinizing hormone (LH) serum level of 5.6 IU/L and progesterone serum level of 3.7 nmol/L (1.2 ng/mL), both of which increased appropriately on the day after leuprolide acetate administration (12.5 hours post-leuprolide acetate injection) to 52 IU/L and 23.5 nmol/L (7.4 ng/mL), respectively. This confirmed a physiologic response to the leuprolide acetate administration. A transvaginal egg retrieval occurred 36 hours after the leuprolide acetate injection, under conscious sedation, where 13 cumulous oocyte complexes (COC) were retrieved.

The operator was unable to drain 4–5 follicles on right ovary, as the overlying bowel was obscuring visualization. The insemination method was through standard IVF. Six of 13 COCs fertilized, resulting in four day 5 blastocysts, three of which met the criteria for cryopreservation at our center (grade B3-BB or greater based on the Gardner Scoring System) [8]. The leuprolide acetate trigger was successful at preventing OHSS.

Four weeks following the retrieval, the patient called the clinic as she had not yet started a day 1 of her menses. She reported a positive home pregnancy test, admitting to intercourse during the IVF stimulation. This was confirmed with a serum beta hCG of 24 276 IU/mL.

A pelvic ultrasound confirmed a spontaneous dichorionic/diamniotic twin pregnancy with a fetal heart beat present for Twin A, with a crown-rump length of 2.2 mm (6w1d gestation). Twin B had no visible fetal pole, with a mean sac diameter of 9.5 mm (5w5d gestation) with a yolk sac.

Unfortunately, the patient experienced a spontaneous abortion shortly after her twin diagnosis, possibly unrelated to GnRHa administration, as implantation occurred and endogenous hCG production ensued. Medical management with misoprostol was prescribed.

Informed consent was obtained from the patient for publication of this case report.

DISCUSSION

To our knowledge, this is the first case of spontaneous twins following a leuprolide acetate trigger freeze all IVF cycle.

Spontaneous conception during IVF stimulation and subsequent intentional luteolysis raises the question of contraception in IVF cycles. Many patients are undergoing IVF due to infertility, with exceptionally low spontaneous pregnancy rates. However, spontaneous pregnancies have been reported in women undergoing downregulation prior to an IVF cycle with GnRH agonists [6].

The persistence of viable sperm following intercourse may be prolonged in cervical mucous in controlled ovarian stimulation cycles due to elevated estradiol levels. Therefore, it is difficult to discern if pregnancy occurred prior to the egg retrieval or shortly thereafter [9]. Furthermore, the endogenous elevation in LH from PCOS patients in addition to administration of a GnRH agonist trigger may actually rescue corpus luteal function even after the intended luteolysis of leuprolide acetate. Endogenous hCG production by the ensuing pregnancy could then further rescue and substantiate corpus luteal function [10].

Platteau et al. (2000) performed a retrospective analysis where 74 pregnancies had spontaneously occurred in women undergoing GnRHa downregulation prior to IVF. Forty-one of these pregnancies resulted in live births, with 2 cases of congenital anomalies. This study suggested that GnRHa luteal phase downregulation did not negatively impact pregnancy rate and there was minimal effect on luteal phase function. The authors suggested that luteal phase support was not required when a short-acting dose of GnRHa was administered [11].

Some studies suggest an increased risk of ectopic pregnancy in those who conceive during GnRHa administration. Westrom et al. (1981) quoted a 5.86% ectopic pregnancy risk, higher than the population risk of

1–2% [12]. Theories for this include increased progesterone secretion from the initial flare, impacting tubal motility. However, the risk may be artificially elevated as some patients may already have tubal factor infertility at baseline [12]. Another reason to encourage abstinence in a freeze all IVF cycle is in the case of pre-implantation genetic testing for monogenic conditions (PGT-M) where there could be the risk of a spontaneous unintended pregnancy affected by a single gene disorder the patient is trying to prevent [13].

Sukur et al. (2016) discussed luteal phase rescue and proceeding with fresh embryo transfer in GnRH agonist triggered antagonist cycles. Methods include high dose luteal phase support, dual trigger with hCG, or additional hCG administered the day of oocyte retrieval. Regardless, the prevention of OHSS does appear to be at the detriment of live birth rate, ongoing pregnancy rate, and increased miscarriage rate [14].

CONCLUSION

This case is an example of how spontaneous pregnancies can occur in the midst of IVF stimulation. Furthermore, the defective luteal phase following GnRHa administration may still be enough to support implantation and clinical pregnancy, as our case demonstrates. Although rare, counseling patients about the importance of abstinence is crucial in situations at high risk of OHSS as spontaneous pregnancy is possible which would further potentiate effects of hyperstimulation by endogenous hCG production.

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Author Contributions

Justin White – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Jenna Gale – Conception of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Aaron Jackson – Conception of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.