Case report

First live birth following IVF–embryo transfer and use of GnRHa alone for ovarian stimulation

Foad Azem studied medicine at the Hebrew University in Jerusalem, Israel, where he received the faculty prize. He finished his internship in Obstetrics and Gynecology (with distinction) at Hakerya hospital in Tel-Aviv. In 1993 he received the Fulbright award, and from 1993–1994 he served as post-doctoral fellow in reproductive endocrinology at Yale University. Currently he is a senior physician at the Racine IVF unit, and practices IVF, reproductive and endoscopic surgery. He is also in charge of the fertility preservation service.

Dr Foad Azem

Foad Azem1, Beni Almog, Dalit Ben-Yosef, Rita Kapustiansky, Israel Wagman, Ami Amit
The Sara Racine IVF Unit, Lis Maternity Hospital and the Tel Aviv Sourasky Medical Centre, affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Israel
1Correspondence: e-mail: azemf@tasmc.health.gov.il

Abstract

Several case reports have shown that some patients may develop ovarian cysts or ovarian hyperstimulation syndrome following the administration of gonadotrophin-releasing hormone agonist (GnRHa). This is the first report of a live birth following ovarian stimulation and IVF–embryo transfer using sole administration of GnRHa as part of the short protocol. The 31-year-old woman was referred to IVF because of severe male factor. Following spontaneous menses, ovulation induction was started by administering a conventional flare-up regimen (triptorelin 0.1 mg) on day 1 of the cycle. On day 3, the oestradiol concentration was 444 pg/ml and the progesterone concentration was 0.3 ng/ml. On day 4, about 10 follicles, 8–10 mm in size, were detected in each ovary, and the oestradiol concentration rose to 704 pg/ml (progesterone was unchanged). Surprisingly, on day 9, the follicles were 18–19 mm in diameter, oestradiol had increased to 3678 pg/ml and progesterone was now 2.88 ng/ml. Informed consent was obtained for administering human chorionic gonadotrophin and for performing ovum retrieval 36 h later. Nineteen MII oocytes were retrieved, and all were fertilized, yielding high-quality embryos. Two embryos were transferred, and the patient conceived and recently gave birth to a healthy singleton.

Keywords: embryo transfer, GnRHa, IVF, live birth, ovarian stimulation

Introduction

Conventional ovarian stimulation protocols for IVF–embryo transfer are based upon the administration of exogenous gonadotrophins combined with gonadotrophin-releasing hormone (GnRH) analogues, either agonists (GnRHa) or antagonists (Macklon et al., 2006). The rationale for using GnRH analogues is to prevent premature rise of LH due to positive feedback by high serum concentrations of oestradiol, and thereby to prevent premature luteinization and maturation (Manna et al., 2005). The premature LH surge reportedly occurs in 20–25% of IVF cycles, deleteriously affecting IVF–embryo transfer outcome. The co-treatment of GnRHa significantly improves the IVF–embryo transfer outcome and facilitated programming and timing of ovum retrieval (Healy et al., 1986). Several case reports have shown that some patients may develop ovarian cysts or ovarian hyperstimulation following the administration of GnRHa, but no pregnancy has been reported following administration of only GnRHa (Weissman et al., 1998).

This is the first report of a live birth following ovarian stimulation and IVF–embryo transfer in a patient who was treated by daily injections of only GnRHa, starting at the follicular phase, without subsequent administration of gonadotrophins. This report may provide new insights into the possible mechanisms of GnRHa action.

Case report

A 31-year-old nulliparous woman presented for her second IVF and intracytoplasmic sperm injection (ICSI) cycle. She had a 2-year history of primary infertility related to severe male
factor. She reported regular menstrual cycles, and there were no observable signs of acne or hirsutism. Her day-3 baseline hormonal profile was as follows: FSH 8.1 mIU/ml, LH 6.8 mIU/ml, oestradiol 29 pg/ml, thyroid-stimulating hormone (TSH) 0.9 mIU/l, dihydroepiandrosterone sulphate 0.8 µg/ml, testosterone 0.1 ng/ml, cortisol 8.2 µg/ml, and insulin 16.0 µIU/ml.

The first cycle was cancelled because of a developing hyperstimulation of the ovaries following the administration of a conventional flare-up regimen on day 1 of the cycle (triptorelin [Decapeptyl 0.1 mg; Ferring, Kiel, Germany]) and daily injections on day 3 of follitrophin alpha 150 IU (Gonal F; Serono, Geneva, Switzerland). The second cycle was scheduled for 2 months later, following spontaneous menses. Ovulation induction was started by administering triptorelin 0.1 mg on day 1 of the cycle, and 75 IU follitrophin alpha was scheduled for administration daily from day 3 of the cycle. Surprisingly, on day 4 of the cycle, about 10 follicles that were 8–10 mm in size were detected in each ovary, her oestradiol concentration had risen to 444 pg/ml and her progesterone concentration was 0.3 ng/ml. The patient was advised to continue injecting Decapeptyl and was scheduled to undergo a vaginal ultrasound on the next day to rule out cyst formation. On day 4 of the cycle, about 10 follicles that were 8–10 mm in size were detected in each ovary, her oestradiol concentration had risen to 704 pg/ml while progesterone concentration remained at 0.3 ng/ml. Although the oestradiol concentration on day 4 was in accordance with follicles of that size, the patient was asked to continue injecting Decapeptyl only until day 8 of the cycle in order to achieve complete down-regulation before the start of gonadotrophin administration. Again unexpectedly, there were 18 follicles, 16–18 mm in size, in both ovaries on day 8, her oestradiol concentration had increased to 2800 pg/ml, and her progesterone concentration was 2.31 ng/ml. On day 9, the follicles were 18–19 mm in diameter, the oestradiol concentration had risen to 3678 pg/ml and the progesterone concentration was 2.88 ng/ml (Figure 1). Serum concentrations of endogenous gonadotrophins that had initially risen subsequently declined (Figure 2).

![Figure 1](image1.png)  
Figure 1. Serum oestradiol concentration (pg/ml) during GnRHa administration.

![Figure 2](image2.png)  
Figure 2. Serum gonadotrophins FSH and LH (mIU/ml), throughout a cycle.

The patient now gave her informed consent for the administration of human chorionic gonadotrophin and the performance of ovum retrieval 36 h later. A total of 19 oocytes were retrieved and, because of severe male factor, all were fertilized by ICSI. A total of 19 zygotes were obtained, and two embryos were transferred. Seventeen embryos were frozen: all were given the highest scores according to their morphology and the symmetry of the blastomeres. The patient’s β-human chorionic gonadotrophin was positive 10 days following embryo transfer. A gestational sac and a fetal pulse were detected on ultrasound at 7 weeks. The course of the pregnancy was uneventful, and she recently gave birth at term to a healthy baby weighing 3130 g.

Discussion

Several reports have demonstrated that ovarian hyperstimulation as well as formation of ovarian cysts may occur following use of GnRHa in the long protocol (Yeh et al. 1989, Ron-El et al. 1989). These reports have documented evidence of hyperstimulation at least 14 days after the first administration of GnRHa. Oocyte retrieval was performed in some of these reports, but there has been no reported pregnancy following the sole use of GnRHa without gonadotrophins. Weissman et al. (1998) postulated several explanations for the ovarian hyperstimulation and cyst formation that had been observed in their study: they suggested transient stimulatory phase, increased sensitivity of the ovarian follicles to circulating gonadotrophins, and/or a direct effect of GnRHa at the ovarian level.

As far as is known, this is the first reported successful pregnancy and birth achieved after IVF–embryo transfer and ovarian stimulation using GnRHa alone in a scheduled flare-up protocol in a patient with regular menses.

As expected, there was an early rise of serum concentrations of both FSH and LH that were followed by suppression, although the inhibitory effect was greater on FSH than on LH. The progesterone concentrations during the follicular phase were nearly 0.3 ng/ml, consistent with the findings of Bständig et al.
(2000), who reported progesterone values below 0.9 ng/ml and no significant rise following triptorelin administration whatever the dose of GnRHa used.

The ovarian response in this case may be partly explained by a direct effect of GnRHa at the ovarian level. By exposure to higher doses of GnRHa and a longer duration of treatment, it is reasonable to suggest that a significant amount of GnRHa may reach the follicular fluid and directly affect the follicles. Endogenous GnRH or GnRH-like peptides may have autocrine, paracrine effects following binding to their receptors in the ovarian tissue (Metallinou et al., 2007). Insulin-like growth factor-II and epidermal growth factor, which were found to affect ovarian cell proliferation, are potential modulators of this activity (Zeleznik et al., 2002; Metallinou et al., 2007).

The ovarian follicle development and the oestradiol elevation in the serum combined with the decline in the concentrations of serum FSH and LH may be somewhat compatible with the FSH threshold and window concept (Zeleznik, 2004). According to that model, ovarian stimulation following exogenous gonadotrophin administration is achieved by increasing the duration (window) that serum FSH concentrations are maintained above threshold levels, either by direct administration of exogenous FSH or by interfering with the negative feedback action of oestrogen on FSH secretion by the administration of anti-oestrogens or aromatase inhibitors (Zeleznik, 2004). Maintenance for a longer duration above the FSH threshold stimulates the growth of small follicles, thus increasing the number of follicles that will grow until the preovulatory stage (Vegetti and Alagna, 2006). By having increased sensitivity to FSH, the follicles continue to mature and develop despite a decline in FSH concentrations. It should be emphasized, however, that no exogenous gonadotrophins were administered to the patient. Nevertheless, it is possible that the initial flare-up following GnRHa administration stimulated the release of gonadotrophins which induced the growth of follicles. These follicles achieved autonomous growth dynamics, independently of the subsequent down-regulation of gonadotrophins, which finally led to the growth of preantral follicles with mature oocytes. As noted earlier, there was a smaller decline in LH than in FSH (Figure 2): at this stage, LH acts on its receptors and activates adenylate cyclase, giving further additive response to FSH.

Nineteen mature oocytes were retrieved, all of which were fertilized and given the highest morphological scores. The high oocyte and embryo quality and the high fertilization rate may be attributed to the fact that these oocytes were completely synchronous (Zeleznik, 2004). This synchrony may be explained by some hypothetical mechanisms, which suggest that the number of follicles that are recruitable by FSH may be explained by some hypothetical mechanisms, which were suggested to play a role in this process, but in-vivo studies have not provided proof for any of them (Zeleznik et al., 2002).

In summary, the successful ovarian response that was shown in this case may be attributed to a synergism of several mechanisms related to GnRHa: (i) a flare-up effect of GnRHa that caused the elevation of FSH and LH above the threshold for allowing the recruitment of many follicles; (ii) desensitization of the hypothalamic pituitary GnRH receptors that blocked the effect of an elevated oestradiol and augmented the effect of FSH and LH on the ovary; (iii) autonomous growth of preantral follicles that followed the initial flare-up; and (iv) the possibility of GnRHa having anti-apoptotic effects upon the ovary, resulting in high synchrony of the maturing follicles.

As far as is known, this is the first report of a live birth following the sole administration of GnRHAs. Its mechanism of action, as may be learned from this case, provides insights into a possible direct effect of GnRHa on the ovary and, or autonomous maturation of follicles following a flare-up protocol.

References


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