Reproductive BioMedicine Online (2016) 32, 132–134

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SHORT COMMUNICATION

GnRH agonist trigger does not always cause luteolysis: a case report

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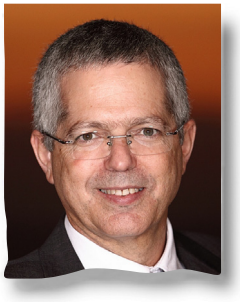

Dr Shahar Kol graduated from the Faculty of Medicine, Technion – Israel Institute of Technology, and was certified as a specialist in Obstetrics and Gynecology at the Rambam Medical Center, Haifa, Israel. Dr Kol completed a 2-year fellowship in Reproductive Endocrinology at the University of Maryland Baltimore School of Medicine, Department of Obstetrics and Gynecology, under the mentorship of Professor Eli Y Adashi. Currently, Dr Kol is the Director of the IVF Unit at Rambam Health Care Campus, Haifa, Israel.

Abstract This study reports an IVF patient with excessive ovarian response, who received gonadotrophin-releasing hormone agonist (GnRHa) triggering. Fourteen oocytes were retrieved, and one embryo transferred 2 days later. Although no further luteal support was given, close follow-up showed consistently high oestradiol and progesterone concentrations, so no exogenous luteal support was given. A clinical pregnancy was achieved without signs or symptoms of ovarian hyperstimulation syndrome. This case report highlights the importance of individual follow-up post agonist trigger.

KEYWORDS: GnRHa trigger, luteal coasting, luteal support, luteolysis, ovarian hyperstimulation syndrome

Introduction

The most important benefit of using a gonadotrophin-releasing hormone agonist (GnRHa) trigger is its ability to significantly reduce, if not eliminate, ovarian hyperstimulation syndrome (OHSS). GnRHa OHSS prevention mechanism is based on complete luteolysis (Fatemi et al., 2013; Nevo et al., 2003). Thus, it has become a viable alternative for the gold standard human chorionic gonadotrophin (HCG) trigger (Humaidan and Alsbjerg, 2014). A recent survey indicated that as many as 36% of IVF GnRH antagonist cycles in Europe are triggered with GnRHa (IVF Worldwide, 2013).

A GnRHa trigger causes a swift luteolysis if not counteracted by HCG, which is the reason why modifications of the standard luteal phase support are necessary to obtain a good reproductive outcome after fresh embryo transfer. In this line the concept of 'tailored', ovarian response-based, luteal support was suggested.

Previously, follicular phase coasting in the long GnRHa down-regulation protocol has been suggested as a strategy for OHSS prevention (Delvigne and Rozenberg, 2002). Follicular coasting seeks to induce partial atresia of the developing follicles by withholding gonadotrophin stimulation, while monitoring oestradiol concentration, considered to reflect

http://dx.doi.org/10.1016/j.rbmo.2015.09.013
1472-6483/

Table 1 Hormone concentrations from trigger day (day −2) onwards.

Day	*−2*	*0*	*+2*	*+3*	*+5*	*+6*	*+8*	*+9*	*+13*	*+15*
Oestradiol (pmol/l)	16,095	7883	5118	7624	8080	6750	5443	5598	7253	9018
Progesterone (nmol/l)	4.0	25.7	>95	>190	>190	>190	>95	>95	>190	>190
LH (IU/l)	1.8	11.5	0.8	1.7	1.1	1	1.7	<0.1	<0.1	<0.9
βHCG (IU/l)	–	–	–	–	–	–	–	2.4	65	157

βHCG = beta human chorionic gonadotropin; Day 0 = oocyte retrieval day, day +2 = embryo transfer, and so on.

theca–and granulosa cell function. Using this strategy, HCG trigger is administered when oestradiol concentratins drop below a certain cut-off point (Abdallah et al., 2010).

The luteolysis pattern after GnRHa trigger has recently been described, showing that on day 1 after trigger circulating progesterone concentrations are comparable, regardless of whether HCG or GnRHa was used for the trigger. In contrast, progesterone concentrations return to baseline five days after GnRHa trigger, reflecting complete luteolysis by this day (Fatemi et al., 2013).

To further individualize the luteal phase support in OHSS high-risk patients, having a fresh transfer after GnRHa trigger, the same principle that holds for follicular phase coasting might be valid during the luteal phase. In other words, monitoring daily progesterone concentrations from the day of oocyte retrieval onwards, and administering the luteal phase rescue bolus of HCG when progesterone concentrations drop significantly.

The following case report details post GnRHa trigger luteal phase during which intensive endogenous luteal function was maintained, leaving any additional exogenous support redundant, and resulting in ongoing pregnancy.

Materials and methods

Case report

Clinical fertility history

A 22-year-old patient was evaluated for primary infertility of 3-year duration. Medical history was significant for irregular menses (30–60 days apart). Hormonal profile was consistent with polycystic ovary syndrome with LH = 13 IU/l and FSH = 6.4 IU/l. Sperm analysis was remarkable for low concentration (volume: 2 ml, concentration: 3 million/ml, motility: 37%, pathology: 94%). Since a previous attempt of ovarian stimulation and intrauterine insemination failed, the patient was accepted for IVF treatment.

Ovarian stimulation and luteal support

Ovarian stimulation was initiated on cycle day 2 with daily injections of 112.5 units of highly purified human menopausal gonadotrophin (Menopur, Ferring, Switzerland). On the eighth stimulation day a GnRH antagonist (0.25 mg Cetrotide, Merck Serono, Germany) was added. GnRHa (0.2 mg Decapeptyl, Ferring) was given on the 11th stimulation day; oestradiol on that day was 16,085 pmol/l. Oocyte retrieval 36 h after trigger yielded 14 oocytes, of which 12 were mature (MII) oocytes, subjected to intracytoplasmic sperm injection. Eleven embryos developed normally. One embryo was transferred 48 h after retrieval, and 10 embryos were cryopreserved. Daily blood hormone concentrations were followed to ascertain luteolysis and decide when to administer a luteal support bolus of 1500 IU ("luteal coasting"). However, since *P*-value in all measurements from day +2 onwards exceeded the upper measurement range, no exogenous luteal support was deemed necessary (**Table 1**). One month post oocyte retrieval, ultrasound showed a normal gestational sac with a viable embryo.

The study was approved by the Rambam Health Care Center IRB on 11 June 2015.

Discussion

To the best of our knowledge this case is the first detailed description of failure to achieve luteolysis post GnRHa trigger, together with precise documentation of endogenous HCG production 9 days post oocyte retrieval.

While the basic principle of individualized luteal support is to closely monitor the luteolytic process after GnRHa trigger in terms of circulating progesterone concentrations, and to intervene with a rescue bolus of HCG when the process is firmly underway, the above case clearly shows that luteolysis post GnRHa trigger is patient-specific, and in certain cases does not occur at all.

Treatment segmentation and "freeze all" is certainly an option in cases of high ovarian response (Devroey et al., 2011); however, individual luteal support may be more acceptable for both patients and clinicians. Importantly, in some cases cryopreservation may not be possible due to regional, legal, economical and ethical considerations. Additionally, although the success rate after cryopreservation has increased significantly worldwide, successful cryopreservation programmes are not necessarily available in all IVF clinics.

Based on previous data, complete functional luteolysis seems to be reached within five days after GnRHa trigger (Fatemi et al., 2013). However, this case clearly indicates that there could be personal variability as to luteolysis kinetics. This phenomenon underlines the basic concept of careful individualized follow-up in deciding on HCG bolus timing.

It is well established that the corpus luteum is dependent on pituitary gonadotropin secretion throughout the luteal phase of the menstrual cycle (Hutchison and Zeleznik, 1984). In primates, it was shown that the corpus luteum can recover from a transient withdrawal of pituitary gonadotropin support (Hutchison and Zeleznik, 1985). Similarly, human corpus luteum is capable of recovering normal function after seven days of deprivation from LH stimulation (Weissman et al., 1996), or by HCG post suppression of corpus luteum

function by the gonadotropin-releasing hormone antagonist (Dubourdieu et al., 1991). We assume that in a multiple corpora lutea environment following multiple oocyte retrieval, individual rescue time varies, setting the stage to partial rescue, thereby decreasing OHSS burden.

Blind administration of a 1500 IU HCG bolus on oocyte retrieval day to the described patient would have served no purpose but increased OHSS risk. Inter-patient variability in terms of luteolysis post GnRHa trigger may explain previously described cases of OHSS, with or without HCG-based luteal support (Fatemi et al., 2014; Seyhan et al., 2013).

In summary, this study describes a case report of failed luteolysis post GnRHa trigger, leading to intensive endogenous luteal activity, more than sufficient to sustain embryo implantation and development.

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Declaration: The authors report no financial or commercial conflicts of interest.

Received 15 June 2015; refereed 26 August 2015; accepted 10 September 2015.