Does premature luteinization or early surge of LH impair cycle outcome? Report of two successful outcomes

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Abstract

Purpose To report two successful antagonist IVF cycles; one ending up with pregnancy despite premature luteinization (case 1, aged 35 years), and the other with the retrieval of high quality oocytes despite premature ovulation (case 2, aged 39 years).

Methods Serum LH was 36 and 47 IU/L on cycle day 7 before antagonist administration, which was then brought to 6.94 and 3.92 IU/L by antagonist administration, and kept below these levels throughout the remaining stimulation in case 1 and 2 respectively. Serum progesterone was 1.42 and 5.5 ng/mL on the day of hCG respectively. Ten metaphase II (MII) oocytes were harvested wherein 3 grade A embryos were transferred in case 1, and seven good quality MII oocytes were retrieved wherein six embryos were cryopreserved in case 2.

Capsule Management of premature luteinization in controlled hyperstimulation with GnRH antagonist, regarding the decision to cancel the cycle, is still controversial.

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Conclusions More precise cut thresholds for both LH and progesterone are necessary for accurate prediction of the cycle outcomes.

Keywords Premature luteinization · Progesterone · Oocyte quality · Embryo quality · Implantation

Introduction

It has been consistently reported that the occurrence of premature LH surge during ovarian stimulation is associated with reduced pregnancy rates [1]. Conventionally, premature LH surge is defined as an LH level of ≥ 10 mIU/mL, and a progesterone level of ≥ 1.0 ng/mL occurring before the criteria of hCG administration is met. [2–6]. It is not an uncommon problem in GnRH antagonist cycles especially before the administration of the drug. The first successful application of GnRH antagonists to prevent LH surge during ovarian stimulation for IVF was reported by Cassadenti and Frydman [7, 8]. Even though using a flexible GnRH antagonist protocol instead of a fixed GnRH antagonist protocol may avoid the untimely occurrence of premature LH surge to some extent, when an unexpected high ovarian response occurs, LH may prematurely elevate before administration of the drug.

It is not clear when to cancel an IVF cycle if LH rises prematurely before antagonist administration or whether there is a threshold for LH surge to continue the ovarian stimulation safely, provided that the LH is brought to a safe range with daily antagonist injections. The accompanying rise in progesterone levels may guide the physician; however, no definitive cut off value exists for follicular phase progesterone level that may have a negative effect on implantation. However, despite blockage of LH surge by

GnRH agonists, elevated serum progesterone levels can also be seen in up to 30% of GnRH agonist down-regulated IVF cycles [9]. Here we report two successful antagonist IVF cycles: one achieving pregnancy despite premature luteinization, and the other with the production of good quality oocytes despite premature ovulation.

Patients

Case 1

A 35-year-old woman with a diagnosis of unexplained infertility was scheduled for IVF in our clinic. On baseline evaluation, serum FSH, LH and estradiol levels were 5.9 IU/L, 10.3 IU/L and 27 pg/mL, respectively, and 12 antral follicles were observed on ultrasound. An antagonist protocol was selected and ovulation induction (OI) was started on cycle day 2 using a combination of hMG (Menogon®, Ferring, Italy) 150 IU/day and rFSH (Gonal F®, Merck Serono, Geneva, Switzerland) 150 IU/day. On the 6th day of OI and 7th day of the cycle, transvaginal sonography revealed several antral follicles in each ovary, the largest of which measured 12 mm in diameter. Serum estradiol level was 918 pg/mL and LH was 36 IU/L on the same day. Since premature LH surge prior to administration of GnRH antagonist occurred, cycle cancellation was discussed with the patient due to reported low success rates; however, she elected to continue the cycle. The patient continued to receive hMG at the same dose, although rFSH was decreased to 112 IU/L and Cetrotide acetate (Cetrotide®, Merck Serono, Geneva, Switzerland) was started. Serum LH level decreased to 6.94 IU/L the day after and serum progesterone was measured 1.2 ng/mL. On the 9th day of the cycle LH was 4.77 IU/mL and estradiol was 1,178 pg/mL. On the 10th day of the cycle, serum estradiol, LH and progesterone were 1,987 pg/mL, 3.52 IU/L and 1.34 ng/mL, respectively (Fig. 1). The ovarian stimulation was maintained with the same gonadotropin doses, and on cycle day 12 ovulation was triggered by 10,000 IU hCG. Ten mature and two immature oocytes were retrieved and three grade A embryos were replaced on day 3 using a Swemed intrauterine catheter (Vitrolife, Kungsbacka, Sweden). Serum β hCG was 134 IU on the 12th day of the embryo transfer, and twin pregnancy with heart beats were demonstrated on the 6th gestational week. Currently the pregnancy is ongoing healthy at the 20th gestational week.

Case 2

A 39-year-old woman was scheduled to undergo IVF for unexplained infertility in our IVF unit. Day 3 FSH and estradiol levels were 8.0 IU/L and 86 pg/mL, respectively and ultrasound revealed 11 antral follicles. Ovarian stimu-

lation was performed using rFSH 375 IU/day (Gonal F®, Merck Serono, Geneva, Switzerland) on the 3rd day of the cycle. On the 5th day of the stimulation (cycle day 7) when the leading follicle was 13 mm in diameter, serum estradiol was 971 pg/mL and LH was 47 IU/L. Daily antagonist administration was started (Cetrotide®, Merck Serono, Geneva, Switzerland) and the stimulation was carried out with rFSH 150 IU/day and hMG 150 IU/day (Menogon®, Ferring, Italy). The day after antagonist administration (cycle day 8) serum progesterone was 1.36 ng/mL and LH was 3.92 IU/L. On the 11th day of the cycle, serum estradiol, LH and progesterone levels were 1,375 pg/mL, 1.08 IU/L and 5.5 ng/mL; respectively, which clearly demonstrated ovulation (Fig. 2). The patient elected not to cancel the cycle due to regulations of the insurance policy which does not cover IVF in patients aged ≥ 40 , and 10,000 IU hCG was administered on the 11th day of the cycle. Oocyte retrieval was performed after 35.5 h and seven good quality metaphase II oocytes were retrieved. Six fertilizations were achieved; however, since ovulation had already occurred, embryo transfer was cancelled, and six grade A embryos were cryopreserved on day 3 for future use.

Institutional review board approval was not provided for the cases, since both patients received one of the treatment protocols routinely practiced in our institution.

Discussion

The original concept of the existence of a therapeutic window for LH during ovarian stimulation was first put forward by Hillier [10]. According to this, there is not only a threshold requirement for LH to guarantee an optimal cycle but also a ceiling level beyond which LH might be deleterious to ovarian stimulation. During ovarian stimulation no clear-cut threshold was defined to cancel an IVF cycle when premature LH surge occurs. Gordon and associates reported that a physiological LH range has to be set between 0.5 and 10 mIU/mL in ovarian stimulation protocols [11]. The criteria for premature luteinization also vary among studies. Even though decreased cycle outcome has been reported when LH is >10 IU/L and $P > 1.0$ ng/L, some groups accepted the criteria for LH surge as LH >12.4 IU/L and P level as >2 ng/mL [12], and others elected to choose a cut-off value of >1.2 ng/mL for progesterone to define premature luteinization [9, 13]. As has been highly debated, one of the hypothesis to explain the pregnancies despite the occurrence of premature LH surge may be that the premature increase in progesterone before hCG administration, may be related to mature granulosa cells' response to high FSH rather than to LH activity [14].

Clinically, endometrial hyperechogenicity has been associated with endometrial exposure to progesterone

Fig. 1 LH, estradiol and progesterone levels before and after GnRH antagonist administration in case 1

Fig. 2 LH, estradiol and progesterone levels before and after GnRH antagonist administration in case 2. The increase in progesterone showed ovulation; embryo transfer was cancelled and the embryos were cryopreserved

during the follicular phase which is closely linked to poor IVF outcome [15]. Fanchin et al also suggested that even minor elevations in progesterone at the end of stimulation negatively affect implantation and ongoing pregnancy rates [16]. This could be attributed to either a negative impact of progesterone on oocyte/embryo quality or on the endometrium. In another study by Allegro and co-workers, no pregnancy was observed when the LH serum level on the day of hCG administration was >10 mIU/mL. [17]. Likewise, in stimulated intrauterine cycles, none of the 17 subjects with both an LH level >10 IU/L and a progesterone level >1.0 ng/mL became pregnant [4]. Among the 73 patients undergoing IVF stimulated with recombinant FSH, none of the seven patients with progesterone values >4 ng/mL became pregnant; however, five women with LH rises >10 IU/L without accompanying increase in progesterone became pregnant [18]. In donor oocyte cycles, where endometrium is spared from the negative effects of high progesterone, premature luteinization did not have a negative impact on oocyte and embryo quality [9]. Besides, in donors who had premature luteinization, a significantly higher number of total and mature oocytes were noted. In the stimulated cycles of PCOS patients who had premature luteinization, retrieved and mature oocyte numbers were higher when compared to the cycles of PCOS patients who did not have premature luteinization, but the pregnancy rates were similar for the two groups. Likewise, Legro et al analyzed oocyte-donation cycles, and found significantly higher pregnancy rates in patients who received oocytes from donors with premature luteinization [13]. They asserted that premature luteinization as defined by serum progesterone concentration >1.2 ng/mL on the day of hCG administration reflects healthy follicular development, and is associated with increased pregnancy rates. Moreover, the authors affirmed that the term premature luteinization may even be an “*inaccurate designation*.”

In our clinic, we prefer to start ovarian stimulation with a combination of hMG and recombinant FSH in patients aged ≥ 35 years, despite the fact that it is still a highly debated issue. Even though we do not routinely assay serum LH concentration during ovarian stimulation, since unexpected responses occurred in the presented cases we assessed serum LH to rule out premature luteinization. Achievement of a twin clinical pregnancy or generation of high quality oocytes and grade A embryos, despite documentation of a prematurely occurred LH surge and resultant increase in serum progesterone may encourage us to re-discuss or redefine the criteria for premature LH surge and premature luteinization. However, in presented case 1 the increase in serum levels of LH and progesterone were maintained low and the LH surge appeared prior to GnRH antagonist administration in early follicular, but from leading follicle growth phase to hCG day. In addition, the

outcomes were not affected negatively due to not severe alterations of progesterone level accompanying the LH surge. Therefore this situation should be addressed as early surge of LH, but not a premature luteinization.

It is also important to observe that immediately after GnRH antagonist administration, LH surge decreased from very high concentrations of 36 and 47 IU/mL to a safe range of <10 IU/L in case 1 and 2 respectively. It is possible that in case 1 administration of GnRH antagonist might have rescued the cycle by reversing the already occurred LH surge and then keeping the LH levels in a safe range throughout the remaining cycle despite “moderately” increased progesterone levels. In other words, a detrimental effect on endometrium is not likely if a higher follicular progesterone threshold, that is, >2 ng/mL, is not exceeded during the early follicular phase. Nevertheless, it could be presumed that detrimental cycle outcomes did not result in case 1 because of the possible inadequate response of follicles (<12 mm) to LH presurge regarding maturation due to their small size and fewer LH receptors status.

The LH levels after antagonist administration until the time of hCG in both cases reported here, both of which were their first IVF cycle, were below 10 IU/L but the difference in these cases was progesterone levels. In the first case progesterone levels was kept in a steady state after antagonist until hCG administration not exceeding 1.5 ng/mL and the cycle resulted in a twin pregnancy. In contrast, in the second case, progesterone levels began to increase after antagonist administration reaching a level of 5.5 ng/mL at the time of hCG injection confirming premature luteinization. We thought that the implantation window might have closed and all embryos were cryopreserved. Therefore, the question here is whether we have to define a more clear-cut threshold for progesterone when LH level is brought <10 IU/L after GnRH antagonist, which predicts good quality oocytes, successful implantation and pregnancy. If we know that we could end up with good quality oocytes despite high progesterone (>2 ng/mL) albeit with a likelihood of compromised implantation, then instead of canceling the cycle we could go forward with cryopreservation of available embryos for future use. On the other hand, if follicular phase progesterone levels do not exceed 2 ng/mL, then we can give the patient a chance to proceed with cycle and embryo transfer.

One critical point is the selection of the most appropriate GnRH antagonist regimen in COH cycles. Today, two current GnRH antagonist regimens are flexible and fixed regimens, wherein GnRH antagonists are initiated due to dominant follicle size (as soon as >12 – 14 mm) or serum levels of estrogen (as soon as >350 pg/mL), and fixed on the 6th day of ovarian hyper stimulation, respectively. However, given the existence of a positive feedback

between LH and the increasing levels of E2 during follicular development, it appears that a considerable number of patients showed an abrupt increase of LH prior to the fixed regimens of standard day6 of antagonist administration. Furthermore, there still remains the 10% of the women who have elevated E2 levels when follicle diameter is not yet 14 mm. Therefore, flexible GnRH antagonist regimen seems to be more appropriate to normo-responders. In addition, especially for women with a more rapid follicular growth, or women with low ovarian reserve, earlier administration of the antagonist with a more flexible antagonist regimen initiated particularly regarding high serum levels of estrogen >350 pg/mL may improve IVF outcome by limiting LH surges.

Although pregnancies were reported despite the occurrence of “premature luteinization,” there is a lack of knowledge on how to manage GnRH antagonist cycles when premature LH surge occurs with or without ovulation after GnRH antagonist administration. Therefore, with present cases reported here with LH presurge (case 1) and with (case 2) premature luteinization we aimed to discuss our managements and results of cycle outcome in these cases, and emphasize the need to find more clear-cut threshold values for serum progesterone and LH to redefine the concept of premature luteinization.

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