Case Report

Crossing the Hurdle of a Low Oocyte Yield in an *in vitro* Fertilization Cycle to Obtain Mature Oocytes

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Abstract

The complex process of oocyte maturation involves a coordinated set of events to take place so that an adequate number of oocytes can be obtained during an oocyte pickup procedure following controlled ovarian stimulation. A weak link in any of the steps can yield a sparse number of oocytes which can be a setback in the process.

Keywords: *Gonadotropin-releasing hormone analogue, gonadotrophin-releasing hormone antagonist, human chorionic gonadotrophin, immature, in vitro fertilisation, low yield oocytes*

Introduction

The maturation of oocyte is a complex process and requires multipronged coordination of events to take place to be able to produce a competent oocyte which goes through the process of embryo development, implantation and pregnancy successfully. In humans, meiosis begins in the developing ovaries at 11–12 weeks of gestation.[1] After entering into meiosis in the foetal ovary, oocytes pass through leptotene, zygotene and pachytene stages before arresting in the last stage of meiotic prophase I, the diplotene or dictyate stage at about the time of birth.[2]

It is widely accepted that in mammals, a female is born with a fixed number of oocytes or primordial follicles within the ovaries, which over the years progressively decreases without the possibility for renewal. The oocytes arrested in prophase 1 undergo resumption of meiosis (an event which occurs decades later) only after the beginning of the luteinising hormone (LH) surge.[3] In response to the LH surge, the cumulus cells display almost complete expansion by 20 h, thereby, detaching from the follicular wall before ovulation.[4] Although nuclear maturation and cumulus expansion are intricately linked, it is unclear if different LH levels are needed to regulate the two processes.

In this report, we describe a two case reports of patients who underwent controlled ovarian stimulation and who received a gonadotropin-releasing hormone analogue (GnRHa) trigger which resulted in zero number of retrieved oocytes during the first procedure of oocyte pickup; both patients received a human chorionic gonadotropin (HCG) trigger 35 h before the second oocyte pickup. Repeat procedure yielded mature metaphase II (MII) oocytes.

Case Report

1. A 33-year-old nulligravida, diagnosed with primary infertility was stimulated with gonadotropins as per antagonist protocol. After the baseline ultrasound and blood investigations, she was stimulated with injection Folisurge (follicle-stimulating hormone [FSH] [Intas Pharmaceuticals Ltd.]) for 9 days, and the total dose of FSH was 1575 IU. The starting dose of FSH was 225 IU, however, it was titrated depending on her response to FSH determined by the size, number of follicles as monitored by transvaginal ultrasound and the oestradiol level. She received a trigger of gonadotropin-releasing hormone analogue (injection leuprolide acetate 1 mg [Lupin]) in view of multiple follicles observed on trans-vaginal ultrasound TVS on Day 9 of stimulation. The initial procedure of oocyte pickup was carried out

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35 h later, but it was suspended in view of no oocytes retrieved after aspiration of follicles from the first ovary. In view of zero number of oocytes, she received a second trigger of (HCG (Inj. Ovitrelle (Merck)) 6500 IU and oocyte retrieval was again attempted 35 hrs later which yielded eight mature (MII) oocytes, of which six embryos were fertilised and cryopreserved for future use. She has undergone two frozen embryo transfer until now which were not successful and has one further attempt of transfer with two day 3 embryos.

2. A 26-year-old nulligravida, diagnosed with primary infertility underwent controlled ovarian stimulation using antagonist protocol. She was stimulated for 9 days. The initial dose of FSH (injection Gonal F [Merck]) received was 225 IU based on the initial cycle Day 2 antral follicle count and the antimullerian hormone level. It was then titrated according to the response monitored by transvaginal ultrasound and accordingly human menopausal gonadotrophin (HMG) 150 IU (injection Persinal [Serum Institute of India]) was added. The total dose of FSH received was 1800 IU and the total dose of HMG received was 450 IU. She received a dual trigger of injection leuprolide 1 mg and injection HCG 2000 IU and the procedure of oocyte pickup was carried out 35 h later. During the initial procedure, there was zero number of oocytes retrieved during the procedure of oocyte pickup. However, after receiving a second trigger of HCG 6500 IU, a second oocyte aspiration was done 35 hours after the trigger which yielded eight mature (MII) oocytes were retrieved. All were inseminated by intracytoplasmic sperm injection procedure which resulted in two Day 3 embryos and are currently frozen for future use.

Discussion

In this case report, we have discussed two cases in which MII oocytes were obtained only after the second trigger with HCG.

The incidence of empty follicle syndrome (EFS) after a GnRHa trigger is 3.1%.[5] Our case report clearly suggests that the follicles have a LH threshold for oocyte maturation. In further support of this, we found that despite obtaining an adequate number of follicles and corresponding oestradiol levels, the low LH level may be the cause for obtaining no oocytes during the first oocyte retrieval. The second retrieval after HCG administration resulted in an adequate number of oocytes retrieved which further proves our assumption that an adequate level of LH should be there for optimum oocyte maturation.

The injection of GnRHa results in an acute release of LH and FSH. The levels rise for 4–12 h, respectively, and remain elevated for 24–36 h.[6] The nature of the LH surge induced by GnRHa is different from that seen in the normal menstrual cycle. The endogenous LH surge has three phases, i.e., a rapidly ascending limb – 14 h, a plateau – 14 h, and a descending phase – 20 h.[7] In comparison to the LH surge induced by GnRHa, which consists of only two phases, i.e., a short ascending limb (>4 h) and a long descending limb (>20 h).[6,8] As a result of which, corpus luteum deficiency and luteal phase defect may occur.[9] HCG, on the other hand, has a longer half-life when compared to LH (>24 h vs. 60 min), thereby having a prolonged luteotropic effect.[10,11] Therefore, the shorter and lower amount of LH released after a GnRHa trigger, may not be sufficient for oocyte maturation.

There could be numerous explanations such as faulty administration of GnRHA trigger, poor quality or underdosing especially in obese individuals and prior admnistration of GnRH agonist deport for causes of poor oocyte retreival following GnRH agonist trigger. However, in our case series report, we did not find these to be the causes of poor oocyte retrieval. Another explanation could be a dyssynchronous follicular growth, but this may not be the cause since the follicular growth observed in these patients was optimal and expected to be seen in an (IVF) *in-vitro* fertilization cycle.

The second and rare explanation is the response obtained to GnRHa trigger was insufficient for oocyte maturation in all follicles. However, the same dose of GnRHa has proven to be sufficient to induce a LH surge and cause maturation.[12,13] Unfortunately, in our case, we did not repeat the LH level post-trigger, and the level of 4mIU/mL was obtained 36 h pre-trigger. This would be the only possible explanation for the reason for low oocyte yield in the second case. Chen *et al* in their study demonstrated that LH levels <15.0mIU/ml 12 hours post-trigger were inadequate for oocyte yeild.[12] Similar to this, Shapiro et al. also demonstrated that LH levels at 12 hours post-trigger < 52.0mIU/ml was suboptimal with the risk of submaximal oocyte yield and maturity.[13] A similar case was reported by Honnma *et al*. where a GnRHa trigger resulted in no oocytes being recovered in two patients with polycystic ovaries.[14] EFS is a condition in which no oocytes are retrieved from the mature follicle after ovulation induction in IVF cycles. This syndrome was first reported by Coulam *et al*. in 1986.[15] The incidence of this syndrome has been estimated at 0.6%–7.0%.[16]

The main reason for insufficient LH levels would be the administration of GnRH antagonists, wherein they have a higher affinity to the GnRH receptor, and when administering the agonist, only a small portion of the antagonist is displaced by the GnRHa.[17] Administering

4 mg of leuprolide acetate has proved to be effective for optimal oocyte yield and maturation.[18] A few other studies have suggested to combine low-dose HCG (1000-2500IU) with GnRHa known as 'dual trigger.[19] However, there is a lack of robust evidence to suggest the appropriate dose of GnRH agonists required for an optimal LH surge.

Conclusion

The cases presented here suggest either of the two causes of the different responses obtained. There may be the possibility that different follicles may exhibit different LH thresholds for oocyte maturation which could be the reason for inadequate response in the second case and in the first case, the low LH levels may be the prime reason for suboptimal response for the low oocyte yield. The clinical importance of these case series is that if a sparse number of oocytes are recovered following a GnRHa trigger, then, it is advisable for another trigger with HCG.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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