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CASE REPORT

Natural IVF cycles may be desirable for women with repeated failures by stimulated IVF cycles

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Abstract

Purpose Although many reports support stimulated in vitro fertilization, several patients do not respond to it well. Furthermore, stimulated treatment could be associated with reduced ovarian response. We describe three successful cases involving patients of advanced age from whom dominant follicles were retrieved during the natural cycle.

Materials and methods All patients had failed to bear children through stimulated in vitro fertilization. In case 1, a follicle was retrieved after a gonadotropin-releasing hormone agonist was used to induce luteinizing hormone surge. In cases 2 and 3, pregnancy was achieved via completely natural cycles.

Results One embryo was transferred every 16 cycles. Ongoing pregnancy—defined as pregnancy progressing beyond gestation week 9—was established in three cycles. The patients successfully delivered and had uneventful neonatal courses.

Conclusion Mature oocyte retrieval followed by natural rather than stimulated in vitro fertilization might be a potential treatment for patients of advanced age when stimulated in vitro fertilization has been repeatedly unsuccessful.

Keywords Advanced age · GnRH agonist · LH surge · Natural IVF cycle · Stimulated IVF cycle

Capsule We describe three successful pregnancies and deliveries achieved via natural IVF cycles: the patients were older than 37 years with repeated failures by stimulated IVF.

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Introduction

The first successful pregnancy and live birth resulting from in vitro fertilization (IVF) were achieved during an unstimulated natural cycle [1]. Soon thereafter, natural IVF was replaced by stimulated IVF because of the very high cancellation rate of natural cycles, and stimulated treatment became the standard in IVF [2]. The side effects of ovarian stimulation with gonadotropins, including ovarian hyperstimulation syndrome (OHSS), have been well described. The long-term side effects however remain largely unknown. Although these problems are not encountered in natural IVF, several other problems occur, including an increased risk of oocyte not being retrieved during oocyte retrieval and embryos not being available for transfer.

Ovarian stimulation is of paramount importance for IVF. Therefore, analysis of the ovarian reserve is mandatory in order to identify the best ovarian stimulation protocol. When the ovarian reserve is reduced, induction of follicular growth is difficult.

Various tests have been suggested for analysis of the ovarian reserve, but no sufficiently accurate predictive test is currently available. Many different stimulation protocols have been suggested, but the lack of large-scale, prospective, randomized, controlled trials for these protocols makes it difficult for any definitive conclusions to be reached.

No controlled, prospective, randomized studies are available to compare natural IVF with stimulated IVF in infertile patients of advanced age after repeatedly unsuccessful stimulated IVF. However, the efficacy of natural IVF is hampered by high cancellation rates mainly due to an untimely luteinizing hormone (LH) surge and empty follicles.

In this paper, we describe three successful pregnancies and deliveries achieved via natural IVF cycles for patients of advanced age when stimulated IVF cycles had repeatedly failed. Our results indicate that mature oocyte retrieval followed by a natural IVF cycle might be a potential treatment for such patients.

Materials and methods

The ethics committee of Kato Ladies Clinic approved the study design. In our natural IVF program, all the patients had failed stimulated IVF treatment several times. All of them were over 37 years old; their average age was 40.9± 3.5 years. Advanced age was defined as that over 37 years [3]. After informed consent was obtained, 33 infertile patients were enrolled in a natural IVF program. In patients with regular menstrual patterns, natural ovulation was confirmed via a transvaginal ultrasound and the measurement of basal body temperature and serum E_2, LH, and P_4 levels. The serum hormone levels were measured by using an enzyme immunoassay (AIA-1800, TOSO, Tokyo, Japan). In patients who had a dominant follicle ≥ approximately 17 to 18 mm [1], LH surge was not observed or initiated (LH≥20 mIU/ml or LH levels/LH basal levels >1.5 [4]), GnRH agonist was administered to induce endogeneous LH surge [2]. In case, E_2 levels was lower than previous data and P_4 levels was higher, or LH levels was going to decrease, we considered that the LH surge was triggered spontaneously [5]. At 20 cycles, we retrieved a single oocyte for each patients. At 16 cycles, a single embryo was transferred. In three cycles, the patients became pregnant and delivered. In case 1, a GnRH agonist (Suprecur®; Mochida Pharmaceutical Co., Tokyo, Japan) was administered at 1,200 μg. In all cases, fertilization was performed by conventional IVF or intracytoplasmic sperm injection (ICSI), following standard techniques. Commercial medium was used for embryo cultivation.

Case reports

Case 1

A 37-year-old woman with a 5-year history of infertility presented with regular menstruation cycles with a 34-day interval. Analysis of her husband's semen revealed oligospermia. Previous treatments include three unsuccessful cycles of intrauterine insemination (IUI) and five of stimulated IVF–ICSI with the transfer of a few embryos each time. The patient had also received a few cryopreserved embryos three times in a natural cycle. After all these approaches failed, she came to our clinic. Since she had never conceived with repeated stimulated IVF cycles, she consented and enrolled into the natural IVF cycle program. In her first natural cycle, no significant signs were observed in both ovaries from a day 1 baseline ultrasound scan.

The serum E_2, FSH, and LH levels were 59 pg/ml, 5.7 mIU/ml, and 3.8 mIU/ml, respectively. On day 13, a dominant follicle (diameter: 15 mm) was detected via an ultrasound scan. The serum E_2 and LH levels were 154 pg/ml and 4.0 mIU/ml, respectively. On day 15, the dominant follicle was 17.5 mm in diameter. The serum E_2 and LH levels were 310 pg/ml and 4.0 mIU/ml, respectively (Table 1). The patient was administered a GnRH agonist on the same day. After 33 h, oocyte retrieval was performed. One mature oocyte (M-II stage) was retrieved. This oocyte was inseminated via ICSI at 3 h after retrieval, and fertilization was confirmed after 18 h. On day 2 after oocyte retrieval, embryo transfer (ET) was performed. On the day of the ET, the endometrial thickness was 8 mm, and the condition of the embryo was good. Twelve days after the ET, the serum HCG level was 183.6 mIU/ml, and at 4 weeks after the ET, an intrauterine singleton pregnancy with a fetal heartbeat was observed via transvaginal ultrasonography. At 7 weeks after the ET, the fetus was in good condition, and at 40 weeks' gestation, the patient delivered a 2,958 g male via spontaneous vaginal delivery.

Case 2

A 41-year-old woman with a 1-year history of infertility presented with regular menstruation cycles with 28- to 30-day intervals. Previous treatments included five cycles of IUI and two cycles of stimulated IVF. After the first stimulated IVF, no ET was performed. At the second instance, three embryos were transferred. After all these attempts failed, the patient visited our clinic. Since she did not want to undergo a repeated stimulated IVF cycle, she attempted the

Table 1 Case 1: follicle size and serum FSH, LH, and E_2 levels

Day	1	13	15
Follicle size (mm)	None	15	17.5
FSH (mIU/ml)	5.7	–	–
LH (mIU/ml)	3.8	4.0	4.0
E2 (pg/ml)	59	154	310

Follicle size represents a dominant follicle. The serum FSH, LH, and E_2 levels were measured. "Day" represents the number of days from the first day of menstruation.

natural IVF cycle. On day 3, an ultrasound scan revealed no significant signs in the right ovary. Minor endometriosis was detected in the left ovary. The serum E2, FSH, and LH levels were 57 pg/ml, 11.4 mIU/ml, and 3.2 mIU/ml, respectively. On day 11, the dominant follicle was 11 mm in diameter. The serum E_2 and LH levels were 167 pg/ml and 5.3 mIU/ml. On day 15, a dominant follicle (diameter: 16.5 mm) was observed via a transvaginal ultrasound scan. The serum E_2, LH, and P_4 levels were 228 pg/ml, 29.3 mIU/ml, and 1.1 ng/ml, respectively (Table 2). We diagnosed the patient's condition as the descent of the LH surge just before ovulation. On the same day, she underwent needle aspiration for oocyte retrieval and one mature oocyte (M-II stage) was obtained. This oocyte was inseminated by the ICSI method. Fertilization occurred after 18 h. On day 2 after oocyte retrieval, the embryo was transferred. On the day of the ET, the endometrial thickness was 10 mm, and the condition of the embryo was good. Twelve days after the ET, the serum HCG level was 152.6 IU/l, and at 3 weeks after the ET, an intrauterine singleton pregnancy with a fetal heartbeat was observed by using transvaginal ultrasonography. At the 18th week of pregnancy, the baby was in good condition. At 39 weeks, the patients delivered a 2,900 g female, and the neonatal course was uneventful.

Case 3

A 38-year-old woman presented with regular, 26-day menstrual cycles. Previous treatments include five cycles of IUI and two cycles of stimulated IVF. During the first treatment, two embryos were transferred. During the second treatment, three embryos were transferred by ZIFT. Although this attempt resulted in pregnancy, she unfortunately miscarried at 5 weeks after the ET. Her first medical examination at our clinic was on the 11th day of her menstrual cycle. On the same day, a dominant follicle (diameter: 18 mm) was observed via a transvaginal ultrasound scan. At 11:35, the E_2, LH, and P_4 levels were 151 pg/ml, 73.2 mIU/ml, and 1.0 ng/ml, respectively. At 14:30, the E_2 and LH levels were 113 pg/ml, and 54.7 mIU/ml, respectively (Table 3). We diagnosed the patient's condition as the descent of the LH surge just before ovulation. She wanted to try the complete natural IVF in this cycle. At 16:00, she underwent needle aspiration for oocyte retrieval, and one mature oocyte (M-II stage) was obtained. This oocyte was inseminated by the conventional IVF method. Fertilization occurred after 18 h and one cleavage embryo was transferred 2 days later. The endometrial thickness was 10 mm on the day of the ET. Twelve days after the ET, the serum HCG level was 533.6 IU/l, and at 7 weeks after the ET, an intrauterine singleton pregnancy with a fetal heartbeat was observed by transvaginal ultrasonography. At 13 weeks of gestation, the baby was in good condition. At 40 weeks, the patient delivered a 3,838 g female.

Table 2 Case 2: follicle size and FSH, LH, E_2, and P_4 levels

Day	3	11	15
Follicle size (mm)	Small	11	16.5
FSH (mIU/ml)	11.4	–	–
LH (mIU/ml)	3.2	5.3	29.3
E2 (pg/ml)	57	167	228
P4 (ng/ml)	–	–	1.1

Follicle size represents a dominant follicle. The serum FSH, LH, E_2, and P_4 levels were measured. "Day" represents the number of days from the first day of menstruation.

Table 3 Case 3: follicle size and serum LH, E_2, and P_4 levels

Day	11 (11:35)	11 (14:30)
Follicle size (mm)	18	18
LH (mIU/ml)	73.2	54.7
E2 (pg/ml)	151	113
P4 (ng/ml)	1.0	–

Follicle size represents a dominant follicle. The serum LH, E_2, and P_4 levels were measured. "Day" represents the number of days from the first day of menstruation.

Discussion

We describe three successful pregnancies and deliveries on treatment via natural IVF cycles. Our results indicate that mature oocyte retrieval followed by a natural cycle might be a potential treatment for patients of advanced age when stimulated IVF has failed.

Problem related to natural IVF cycles include an increased risk of untimely LH surge and the possibility that no oocyte is retrieved and no embryo is available for transfer. Nevertheless, the interest in natural IVF cycle treatment has been renewed in recent years because of the increased efficiency of IVF technology. In this report, we focused on patients for whom treatment in stimulated IVF cycles failed to produce embryos that developed to term and were delivered.

In case 1, we retrieved a single oocyte by using the flare-up effect of a GnRH agonist. However, several studies have reported that HCG is better than GnRH agonists in triggering final oocyte maturation, although these studies involved stimulated IVF cycles and GnRH antagonists [6, 7]. Thus, HCG may not always improve the flare-up effect of GnRH agonists on egg maturation in natural IVF cycles. It has been reported that the administration of GnRH agonists and not HCG can stimulate a midcycle LH surge,

leading to follicular maturation and pregnancy [8]. Although the dominant follicle would suppress the development of other follicles and would induce follicular and oocyte atresia, some follicles that remain after HCG administration produce irregular menstrual cycles and possibly cause luteal dysfunction: this could occur because of the long half-life of HCG and the closing insufficiency of small follicles [9, 10]. However, although HCG administration appears to be the most reliable standard for triggering ovulation, the patient in case 1 did not become pregnant when this standard protocol was used. Further, Troukoudes et al. [11] reported that the treatment of using GnRH antagonist and HCG in the natural cycles, the induction of an LH surge using not HCG, but GnRH agonist might be an effective treatment methods.

As observed from cases 2 and 3, there is an increasing interest in treatment of infertile patients via natural IVF cycles because it is simple and rapid and because the side effects associated with ovarian stimulation are eliminated. However, natural IVF cycles are also associated with a relatively high incidence of failed of oocyte retrieval, because of which the pregnancy rate per started cycle is relatively low. Natural IVF cycles resulted in an ongoing pregnancy rate of approximately 7% per started cycle and approximately 16% per ET [12]. Nevertheless, because natural cycle treatments can be compressed over consecutive cycles, the cumulative pregnancy and live birth rates might be as high as 46% and 32%, respectively [13]. In addition, problems related to ovulation treatment such as OHSS, multiple pregnancies, and the need for expensive drugs can be eliminated if natural IVF cycles are used. Some patients might prefer several successive natural IVF cycles instead of stimulated IVF cycles, which can only be repeated once a month. It has been reported that the clinical pregnancy rate with stimulated IVF has reached approximately 25–30% [14, 15]. However, repeated stimulated cycles should span over several months to allow for the ovaries to recover. Further, if stimulated IVF cycles are repeated, the pregnancy rate will obviously decrease [14, 16, 17]. If repeated stimulated IVF cycles are unsuccessful, patients of advanced age are considered to have a low chance of pregnancy, and they are often advised to stop undergoing treatment. In case of our patients, although we have not confirmed that the oocyte obtained from natural cycles is superior in quality to that obtained from stimulated IVF cycles, previous treatments may have failed due to chromosomal abnormalities in the oocytes, which were retrieved after stimulated IVF treatment [18]. Therefore, natural IVF cycles might be more efficient for obtaining ideal embryos. Treatment via natural IVF cycles is inexpensive, has low associated risks, is easy to perform, and is comfortable for the patient. It can be repeated on a monthly basis, and the overall chances of success are therefore higher. Scheduling of oocyte retrieval based on the LH surge requires intensive monitoring and an almost round-the-clock service. Furthermore, timely retrieval of the mature oocyte is a critical factor for the success of the procedure. A timely LH surge may also be achieved by using the flare-up effect of GnRH agonists. Edward RG reported that the IVF methods used now require reconsideration [19].

In conclusion, treatment via natural IVF cycles may assist patients of advanced age who have failed to become pregnant after treatment via stimulated IVF cycles and who have regular ovulatory cycles. To determine whether treatment via natural IVF cycles should be used as one of the standard treatment measure for patients of advanced age, a prospective, randomized study that compares natural and stimulated IVF is required.

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