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Case Report

Successful Pregnancy in Infertile Elderly Woman with Polycystic Ovarian Syndrome after Multiple Attempts of Ovarian Stimulation: A Case Report

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ABSTRACT

Ovarian stimulation (OS) in infertile elderly women with polycystic ovary syndrome (PCOS) is challenging because of the high risk of ovarian hyperstimulation syndrome (OHSS) and the possibility of age-related poor response.

We present a case of an elderly woman with anovulation due to PCOS who achieved pregnancy in the sixth intrauterine insemination (IUI) combined with letrozole plus gonadotropin without any adverse effects since OS using the clomiphene citrate (CC) or gonadotropin was not effective. In the clinical course of this case, adequate follicular development was not achieved by OS using CC only, and severe OHSS arose using FSH only. The regular and adequate follicular development by using OS combined with letrozole plus gonadotropin could be conceived by repeated IUI.

The OS method combined with letrozole plus gonadotropin was effective for elderly women with anovulation due to PCOS.

Introduction

Ovarian stimulation (OS) is required for treating infertility in women with the polycystic ovarian syndrome (PCOS). However, OS is challenging in the elderly patients as the follicles have a poor response with clomiphene citrate (CC) or a small amount of gonadotropin; and it may lead to ovarian hyperstimulation syndrome (OHSS) due to PCOS when using a lot of gonadotropins.

We present the case of an elderly woman with anovulation due to PCOS who achieved pregnancy in the sixth intrauterine insemination (IUI) combined with letrozole plus gonadotropin as OS without any adverse effect since OS by the CC or gonadotropin was not effective every time. Here, we have shown the successful OS by the co-administration of letrozole.

Case Presentation

A 44-year-old woman who has been oligomenorrhea due to polycystic ovary syndrome (PCOS) visited the clinic for primary infertility of 4 years. Her laboratory data revealed the follicle-stimulating hormone (FSH) of 8.01 mIU/ml, luteinizing hormone (LH) of 12.3 mIU/ml, estradiol (E2) of 52 pg/ml, and anti-müllerian hormone (AMH) of 3.80 ng/ml. Hysterosalpingography showed the normal shape of the uterus and good passage of the bilateral oviducts. Moreover, her husband's sperm was normal.

As the first line protocol, she received clomiphene citrate (CC) 100 mg/day for 5 days to induce ovulation. On the fifth day after withdrawal bleeding (WBD5), one follicle growth was observed. Then, the HCG 5000 IU was administered at WBD16 when the diameter of the leading follicle reached 18 mm. Afterward, no follicular growth was observed even after increasing the dosage of the CC up to 150 mg/day.

After that, FSH 150 IU/day for seven days from WBD3 was administered. This time, a total of 5-6 follicles were developed with a maximum follicular size of 18-19 mm and E2 was 3430 pg/ml at WBD14. Then, HCG 5000IU was administered as a trigger, following timed intercourse. After one week, she complained of lower abdominal distension and appetite loss. The ultrasonic examination revealed the

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ascites and the swollen bilateral ovaries that were approximately 8-10 cm. Laboratory data indicated that circular red blood counts were evaluated: red blood cell count, 480 million/ml; haemoglobin, 14.5 g/ml; and hematocrit, 43%. Blood electrolyte analysis revealed the following findings: sodium, 142 mEq/ml; potassium, 4.7 mEq/ml; serum chloride, 108 mEq/ml; uric acid, 4.2 mg/ml; creatinine, 0.5 mg/ml; and d-dimer, 1.5 μg/ml. Due to elevated levels of d-dimer, heparin 3000 IU/day was administered for five days to prevent embolism by blood condensation and dissolved thrombosis.

Table 1: Clinical course of the patient.

No. of attempt	OS methods	Pre-ovulatory follicle development	Trigger	Kinds of treatment	Pregnancy	Adverse effect
1	CC 100 mg/day for 5 days	Right side, 18 mm	HCG 5000IU	TSI[a)] at WDB16	no	mild OHSS***
2	CC 100 mg/day for 5 days	Follicular growth (-)	non	non	no	no
3	CC 150 mg/day for 5 days	Follicular growth (-)	non	non	no	no
4	FSH 150 IU/day for 11days	Total of 7-8 development follicles Both sides, 19-18 mm size at WDB13	HCG 5000IU	TSI[a)] at WDB15	no	Severe OHSS***
5	FSH 75 IU/day for 8 days, FSH 150 IU/day for 8 days, and FSH 300 IU/day for 8 days	Follicular growth (-)	non	non	no	no
6	Letrozole 25 mg/day for 10 days	Left side, 19 mm	HCG 5000IU	TSI* at WDB21	no	no
7~11	Letrozole 25 mg/day plus FSH 150 IU/day for 7-8days	Development follicles (1–2) Right or Left 20–19 mm size	Gn-RH agonist	IUI** at D14-15	no	no
11	Letrozole 25 mg/day plus FSH 150 IU/day for 7 days	Right side, 21 mm	Gn-RH agonist	IUI** at D14	yes	no

a)Timed sexual intercourse. b) Intrauterine insemination. c) Ovarian hyperstimulation syndrome.
1) Ovarian stimulation was started from WDB 5 until third attempt and started from WDB 3 after fourth attempt.
2) CC, FSH, and letrozole were administered every day.

The symptoms of ovarian hyperstimulation syndrome (OHSS) reduced gradually after five days when her menstruation started and the symptoms disappeared after three weeks. After ultrasonic and blood examinations confirmed the disappearance of OHSS, treatment with OS combined with FSH once again started. Initially, FSH 75 IU/day was administered and, the dosage was increased to 150 IU/day and 300 IU/day for eight days each. However, no follicular growth was observed. Since follicular growth was not recognized with the administration of CC or FSH, letrozole 25 mg/day was administered from WDB 5 to 10 and two mature follicles grew. Despite the administration of the HCG at WDB17 following timed sexual intercourse, no conceive was received.

Thereafter, letrozole combined with FSH 150 IU/day was administered until follicle maturation. Once the letrozole with FSH as OS had been established, she was treated with the same OS protocol and she got pregnant during the sixth intrauterine insemination (IUI).

Discussion

In this case, CC was used for OS as the first-line protocol to prevent OHSS, so a high risk of one was considered by the hormone examinations despite old age. However, because CC was not effective in spite of increase in dose, FSH was used as the second step. Administration of the usual dose of FSH (150IU daily) resulted in severe OHSS, and follicular growth was not recognized when OS was started with a low-dose of FSH (75IU daily). As the second step, letrozole 2.5 mg/day was used. As this may lead to slow follicular growth, OS protocol combined with letrozole with FSH. In this case, she got regular follicular growth by this OS protocol and achieved pregnancy after repeated IUI.

Letrozole is an aromatase inhibitor used for treating breast cancer. For the past two decades, aromatase inhibitors have often been used in ovarian stimulation as effective alternative agents [1]. Generally, letrozole is often used as OS in the patient with anovulation due to PCOS, as it is effective to avoid OHSS by preventing excessive elevation of estradiol and vessel epidermal growth factor [2]. Furthermore, aromatase inhibitors are associated with one or two follicular developments [3]. However, multiple follicular growth increases the chances of pregnancy in IUI, the risk of multiple pregnancies, and OHSS.

Many studies have also shown the effectiveness of OS by the co-administration of aromatase inhibitors in IVF or IUI for poor responders and old infertile women with ovulation disorders [4]. The combined treatment with letrozole plus FSH for 7-8 days has led to 1-2 follicular growth. However, some suggested that the administration of CC plus FSH or the increased dose of letrozole enables suitable follicular growth. Many regimens for OS in IUI have been accessed by comparing the following parameters: pregnancy rate, live birth rate, multiple pregnancy rates, etc. [5].

However, the optimal OS protocol for IUI should achieve regular 1-2 follicular growths by the same OS protocol without any adverse effect until successfully conceived. Aromatase inhibitor plus FSH elevates the possibility of the risk of OHSS and multiple pregnancies by multiple follicular growths. However, in this case, the number of growing follicles was 2-3 and OHSS did not occur even after adding FSH. Thus, the adjustment of the FSH dosage was important.

In conclusion, the best OS for old women who have anovulation due to PCOS in IUI was supposed the OS combined with letrozole plus adjustment of the FSH dosage.

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