A case of polycystic ovary syndrome conceived by intracytoplasmic sperm injection following laparoscopic ovarian drilling

S. Sugaya, R. Honma

Department of Obstetrics and Gynecology, Joetsu General Hospital, Joetsu City (Japan)

Summary

Polycystic ovary syndrome (PCOS) is a disease in which an ovulation disorder is the main cause of infertility. Clomifene citrate (CC) is the treatment of first choice for ovulation induction in PCOS. If ovulation cannot be induced by CC, then either laparoscopic ovarian drilling (LOD) or gonadotropin therapy is selected as a subsequent treatment. Assisted reproductive technology (ART) is indicated for women with PCOS, similar to other infertility patients, when pregnancy is not achieved by intrauterine insemination (IUI). In this study, we experienced a case of PCOS in which pregnancy was achieved by ART following LOD. The case pertains to a 26-year-old patient. She consulted our hospital with a chief complaint of primary infertility. IUI with administration of CC plus recombinant follicle-stimulating hormone (rFSH) was carried out; however, pregnancy was not achieved. Subsequently, ART was carried out. In the first attempt, the development of several follicles was observed under the gonadotropin releasing hormone (GnRH) agonist long protocol. However, a fertilized oocyte was not obtained. In the second attempt, an ovum could not be collected after CC-rFSH ovarian stimulation. In the third attempt, a good quality embryo could not be obtained under the GnRH antagonist protocol, and therefore pregnancy could not be achieved. We performed LOD using a harmonic scalpel for the purpose of preventing severe OHSS and improving the quality of embryos. Following the operation, ovarian stimulation was performed under the CC-rFSH-antagonist protocol. Eighteen follicles were aspirated, six oocytes were picked-up, and five oocytes were normally fertilized. As a result, four embryos from day 2 culture were cryopreserved. Cryopreserved-thawed embryo transfer was thereafter performed, and a single pregnancy was achieved. LOD is a clinically effective treatment for PCOS requiring ART.

Key words: Polycystic ovary syndrome; Assisted reproductive technology; Ovarian hyperstimulation syndrome; Laparoscopic ovarian drilling; Quality of embryos.

Introduction

Polycystic ovary syndrome (PCOS) is a disease in which an ovulation disorder is the main cause of infertility. Ovulation induction using clomifene citrate (CC) is the first-line treatment for PCOS. Laparoscopic ovarian surgery (LOS) is often carried out when ovulation cannot be induced by CC treatment. Multiple ovarian puncture using either diathermy or laser is known as ''ovarian drilling'' [1]. This treatment is a method by which an improvement in hormone abnormalities is anticipated, and has been reported to be an effective therapy for infertility from PCOS [2-5].

PCOS patients are indicated to undergo assisted reproductive technology (ART), similar to other infertility patients, when pregnancy is not achieved by intrauterine insemination (IUI). In addition, ART is indicated for cases of tubal damage and male factor infertility. Moreover, ART is selected when there is a risk of ovarian hyperstimulation syndrome (OHSS) by gonadotropin therapy. Dor *et al*. [6] reported that the fertilization rate was low in PCOS compared to patients with tubal diseases, although the pregnancy rate was equal. They mentioned that the elevated serum LH level in PCOS might affect their oocyte potential for fertilization. On the other hand, a previous report observed an improved prognosis, such as a decrease in the rate of OHSS, when LOS was performed prior to ART [7].

We herein report a case of PCOS in which pregnancy was achieved by ART following laparoscopic ovarian drilling (LOD). The patient could not conceive even after ART by means of three types of ovarian stimulation. We performed LOD with the purpose of preventing severe OHSS and improving the quality of embryos, and pregnancy was subsequently achieved by ART following LOD.

Case Report

A 26-year-old female and her 30-year-old husband visited our hospital due to primary infertility of two years duration. Her menstruation was oligomenorrhea. Her hormonal testing showed increased secretion of early follicular phase serum LH (13.6 mIU/ml), and normal secretion of serum FSH (4.7 mIU/ml). The serum testosterone level was 100.1 ng/dl. Ultrasonography showed the typical appearance of polycystic ovaries. At hysterosalpingography, her uterine cavity was normal and both tubes were patent. The semen analysis was normal (density: $40x10^6$/ml, motility: 71%). The patient underwent ovarian stimulation with 100 mg of CC on days 4-8 of her menstrual cycle plus 75 IU of recombinant follicle-stimulating hormone (rFSH) (Follistim; Organon, Osaka, Japan) on days 8 and 10 of the cycle, and IUI. The number of developing follicles were one or two in each CC-rFSH stimulation cycles. A

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total of six rounds of IUI were performed. However, the patient did not become pregnant. Thereafter, she elected to undergo *in vitro* fertilization. Soon thereafter the husband developed acute bronchitis and had a high fever. As a result, the husband's sperm count decreased. We therefore elected to perform intracytoplasmic sperm injection (ICSI).

In the first ICSI attempt, in April 2009, the patient received three weeks of oral contraceptives (planovar; ASKA Pharmaceutical Co., Ltd., Tokyo, Japan) from day 3 of the pretreatment cycle. Next, she received 900 μg of gonadotropin releasing hormone (GnRH) agonist (Suprecur; Mochida Pharmaceutical Co., Ltd., Tokyo, Japan) daily, starting on day 21 of the pretreatment cycle and ending at the time of hCG injection. The patient received 150 IU of rFSH daily from day 3 of the treatment cycle until the day before the administration of hCG (HCG Mochida; Mochida Pharmaceutical Co., Ltd., Tokyo, Japan). On day 10 of the treatment cycle (day 7 of rFSH), five follicles reached a diameter of ≥ 15 mm and more than 30 follicles reached a diameter of ≥ 11 mm. HCG administration was intended when at least two follicles reached a diameter of ≥ 18 mm. However, the administration of 5,000 IU of hCG was performed, since she was considered to be at too high a risk of OHSS to continue rFSH ovarian stimulation. Transvaginal follicular aspiration was performed approximately 34 hr after hCG injection. Only one oocyte was obtained, although more than ten follicles were aspirated. The sperm density was $8x10^6$/ml, and the sperm motility was 0.6%. Motile sperm with no obvious abnormal morphology was injected into a metaphase II oocyte using the routine ICSI procedure. However, the oocyte did not become normally fertilized.

In the second attempt, in November 2009, the patient underwent ovarian stimulation with 100 mg of CC on days 4-8 and 150 IU of rFSH injection on day 8, day 10 and day 12 of her menstrual cycle. One follicle was developed. Transvaginal follicular aspiration was performed approximately 34 hr after 5,000 IU of hCG injection. However, an oocyte could not be retrieved.

In the third attempt, in January 2010, GnRH antagonist protocol in controlled ovarian hyperstimulation (COH) was elected. From day 3 of her menstrual cycle, ovarian stimulation was commenced with 150 IU of rFSH daily for ten days. The administration of 0.25 mg of GnRH antagonist (ganirest; Schering-Plough Corp., Osaka, Japan) was performed on days 11 and 12 of her menstrual cycle. Five follicles were developed. Transvaginal follicular aspiration was performed approximately 34 hr after 5,000 IU of hCG injection. Two oocytes were retrieved. The sperm density was 101 x 10^6/ml, and the sperm motility was 67.0%. Motile sperm were injected into two metaphase II oocytes using the routine ICSI procedure. One oocyte became normally fertilized. However, the embryo transfer was cancelled due to the arrest of embryo cleavage.

We elected use of LOD in order to prevent the onset of severe OHSS, and to improve the quality of embryos. LOD was performed under general anesthesia in May 2010. We applied harmonic scalpel to LOD. The harmonic scalpel was focused on the ovary at a power level of 3 with a hook blade, and the duration of the output was 2-4 sec. We created ten punctures per ovary. The serum LH and FSH levels after surgery were 5.7 mIU/ml and 5.8 mIU/ml, respectively. The serum testosterone level was 36.6 ng/dl.

In the fourth attempt, in September 2010, ovarian stimulation was applied using the CC-rFSH-GnRH antagonist protocol. The patient underwent ovarian stimulation with 100 mg of CC on days 4-8 and 150 IU of rFSH injection on day 8, day 10 and day 12 of her menstrual cycle. On day 13 of the cycle, one follicle was reached with a diameter of 15 mm, and the administration of 0.25 mg of GnRH antagonist was started. The administration of 150 IU of rFSH and 0.25mg of GnRH antagonist were performed on day 13, day 14 and day 15 of the cycle. Eighteen follicles were developed. Transvaginal follicular aspiration was performed approximately 34 hr after 5,000 IU of hCG injection. Six oocytes were retrieved. The sperm density was 13 x 10^6/ml, and the sperm motility was 67.0%. Motile sperm were injected into six metaphase II oocytes using the routine ICSI procedure. Five oocytes became normally fertilized. Four good quality embryos were obtained in day 2 culture. All four embryos were then cryopreserved by a vitrification method [8].

Cryopreserved-thawed embryo transfer was performed with an artificial cycle using transdermal estradiol (Estrana Tape: Hisamitsu Pharmaceutical Co., Inc., Japan) and vaginal progesterone in November 2010. The patient started transdermal estradiol administration every other day from day 3 of the treatment cycle. She received transdermal estradiol at a dose of 1 mg from day 3 to day 9 of the cycle. This dose was sequentially increased from day 11, up to a maximum dose of 4.32 mg on day 15 of the treatment cycle. After adequate endometrial proliferation was documented by transvaginal ultrasonography on day 16, administration of vaginal progesterone suppository (400 mg/day) was initiated. At the same time, the dose of transdermal estradiol was decreased to 2.2 mg. After three days of progesterone administration, two embryos ($4G_1$, $4G_2$) were thawed [8], and single embryo (morula) was transferred two days later. After ten days of transfer, the patient had a positive pregnancy test. Transdermal estradiol and vaginal progesterone administration was continued until eight weeks of gestation. This pregnancy is now ongoing at 30 weeks of gestation.

Discussion

In this case, pregnancy was not achieved although ART by three types of ovarian stimulation was performed. Under the GnRH agonist long protocol, the development of several follicles was observed, accompanied by a risk of severe OHSS. On the other hand, under the CC-rFSH protocol, an oocyte could not be obtained although it was of a single follicular growth. Under the GnRH antagonist protocol, a good quality embryo could not be obtained and embryo transfer was cancelled. Subsequently, LOD was carried out, and good quality embryos were obtained by ART, which was thereafter performed, and pregnancy was achieved.

In PCOS, ART is indicated, (1) when pregnancy is not achieved even though the timing of sexual intercourse or IUI was performed following ovulation induction; (2) when male factor such as oligozoospermia or tubal disease exists; (3) when there is a high possibility of the onset of OHSS at ovarian stimulation by gonadotropin treatment; (4) when there is a high possibility of multiple pregnancy of triplets or more.

For cases in which ART is performed on PCOS as well, if several follicle growths are observed, the risk of onset of severe OHSS can be decreased by carrying out cryopreservation of all embryos. On the other hand, a reduced incidence rate of OHSS by performing LOS prior to ART has been observed [7]. Moreover, a reduction in the ART cancellation rate by LOS has been reported [9]. Even when showing onset of OHSS, there are often cases in

which long-term treatments can be avoided, although in-hospital treatment may be necessary, because embryo transfer is not performed by cryopreservation of all embryos, as mentioned previously. From this, it can be said that the necessity of LOD for patients who require ART is decreasing. However, when the psychological damage from the onset of OHSS and the psychological state of patients for whom ART was cancelled are considered, it is believed that LOD will, even then, play an important therapeutic role.

The effect of LOD on follicular growth is not apparent. However, there have been reports that serum levels of LH and testosterone were reduced after surgery [2, 4, 5, 10]. In this case, we performed LOD using a harmonic scalpel. A harmonic scalpel is a mechanical cutting and coagulating energy source causing little tissue damage, and which also obtains hemostasis at relatively low temperatures. Takeuchi *et al*. [10] performed LOD on CC-resistant PCOS using a harmonic scalpel, and reported that this procedure was safe and also clinically effective.

As mentioned above, regarding the dynamics of hormones following LOD, serum levels of LH and androgen were decreased in many cases. LH is involved in the production of androgen at theca cells, and the production of androgen increases in patients with PCOS due to the increased secretion of serum LH. It has been reported that the increased production of androgens reduces oocyte quality [11]. On the other hand, a decline in the miscarriage rate has been reported to be observed for PCOS following surgery [7]. From these facts, it can be believed that the increased secretions of LH and androgen in PCOS may thus have a negative effect on embryo quality and the subsequent course of pregnancy. Therefore, for PCOS in which an elevated serum LH level is observed, even in CC-responsive cases, it is believed that performing LOD in order to improve the quality of embryos is a clinically useful treatment modality.

ART outcome following the use of GnRH antagonist protocol in COH has been reported to be as good as that of the GnRH agonist long protocol in PCOS [12]. In our case, ART was first carried out under the GnRH agonist long protocol in COH. Several follicle developments were observed, and there was a risk of OHSS. Subsequently, ART was performed under CC-rFSH stimulation. In the third attempt, the GnRH antagonist protocol in COH was applied. As a result, no oocyte could be obtained under the CC-rFSH protocol. In the GnRH antagonist protocol, good quality embryos could not be obtained. As a result, LOD was carried out to reduce the risk of OHSS, and to improve the quality of embryos following surgery. Five fertilized ova of six were acquired at the subsequent ART, and four good quality embryos were obtained. Pregnancy was achieved by the subsequent cryopreserved-thawed embryo transfer, and the patient is progressing very well.

In conclusion, we performed LOD to achieve adequate follicullar development and also improve the quality of embryos in a case of PCOS, who could not conceive by means of three types of ovarian stimulation. Pregnancy was subsequently achieved by ART following LOD. This treatment is therefore believed to be a clinically effective treatment for PCOS requiring ART.

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Address reprint requests to:
S. SUGAYA, M.D.
Department of Obstetrics and Gynecology
Joetsu General Hospital
148-1, Daidofukuda, Joetsu City
943-8507 (Japan)
e-mail: mususu@msg.biglobe.ne.jp