

Analysis of 24 cases of polycystic ovary syndrome after failed controlled ovarian hyperstimulation

ABSTRACT

Some fertility patients with polycystic ovary syndrome (PCOS) undergoing controlled ovarian hyperstimulation (COH) experience ceased follicular growth during COH and fail to superovulate. In this article, 24 such PCOS patients resumed COH 15–20 days after previous COH treatment was stopped while patients were under ovarian downregulation. Seventeen cases achieved oocyte retrieval, of which 14 underwent embryo transfer and 12 resulted in clinical pregnancy. The remaining seven cases saw ceased follicular growth at 13 mm. This provides a rescue protocol for failed COH patients with PCOS.

KEYWORDS: PCOS, COH, IVF-ET

Materials and methods

Patient inclusion criteria

Included were a total of 24 patients with polycystic ovary syndrome (PCOS) who underwent *in vitro* fertilisation-embryo transfer (IVF-ET) treatments at the Reproductive Centre of Women and Children's Hospital, Hunan, China from August 2012 to May 2014. Of these, 13 patients were complicated with pelvic inflammatory disease (PID). The patients were aged between 24 and 40 years with mean age 35.5 ± 5.1 and body mass index (BMI) between 15 and 35 with mean BMI 23.5 ± 5.09 . Patients with BMI more than 25 were required to reduce their body weight more than 5 kg to be included in the study.

PCOS and PID diagnostic criteria

The PCOS diagnostic criteria are according to the standard developed by European Society for Human Reproduction (ESHRE) and the American Society for Reproductive Medicine (ASRM) revised in 2003 at the Rotterdam PCOS consensus.¹ The PID diagnostic criteria refer to the standards for diagnosis and treatment of PID made by the infectious diseases group of obstetrics and gynaecology, Chinese Medical Association.² All patients had a history of more than 2 years of infertility, and showed no signs of hydrosalpinx, ovarian cyst and adenomyosis/endometriosis under vaginal ultrasonography. Prior to their controlled ovarian hyperstimulation (COH), 13 patients had had treatment with clomiphene citrate or letrozol.

Method of treatment

After being treated with ethinylestradiol and acetate tablets (Bayer) for one to two menstrual cycles, patients were downregulated with 1.1 to 1.4 mg of leuprolide acetate (Lizhu)

at midluteal phase for 10 to 14 days, followed by COH when patients' follicle stimulating hormone to luteinising hormone (FSH/LH) measured between 1–5 IU/L, oestradiol (E2) <150 pmol/L and progesterone <2 nmol/L. Gonadotropins for COH were urine-derived follicle stimulating hormone (FSH; Lizhu) or human menopausal gonadotropins (HMG; Lizhu). The choice of using FSH and/or HMG depended on the level of patient luteinizing hormone (LH). Patients resumed COH after 15 to 20 days of failed follicle development. The criterion for resuming COH was that the ovaries were under downregulation which meant that antral follicles on both sides were under 5 mm after ceased growth follicle had been discharged or had atresia; serum FSH/LH values were less than 5 IU/L, E2 less than 150 pmol/L and progesterone less than 2 nmol/L; and endometrium was less than 5 mm in thickness. Twenty-four patients who met criteria described above were selected to resume COH. Of these, seven patients ceased follicle growth again around 13 mm with declined oestradiol and COH was cancelled without *in vitro* maturation (IVM). Seventeen patients with resumed COH met the criteria for egg retrieval when the dominant follicle was larger than 17 mm and the oestradiol value was climbing. The total and daily dose of gonadotropin (Gn) for patients in both COHs was recorded with mean and standard deviation.

Statistical analysis

The data were analysed using SPSS17.0 software with mean \pm standard deviation, and quantitative data between the two groups with the independent-samples t-test and counts data were analysed with the nonparametric χ^2 test.

Results

Statistical results of E2 and dominant follicles in both COHs

Twenty-four patients with PCOS had ceased follicular development during their IVF-ET treatment using the long protocol. If we observed that follicles stopped growing and E2 was declining, ovary stimulation was discontinued 2–4 days after. All patients had dominant follicles less than 16 mm with mean size 10.56 ± 2.744 mm and mean E2 level 785.2 ± 957.3 pmol/L when the day of stimulation stopped. After resuming COH, 17 patients successfully developed mature follicles with mean E2 $8,747 \pm 5,111.7$ on the day of HCG trigger. The remaining seven cases showed ceased follicular growth again with mean E2 level 739.3 ± 789.9 on the day that medication was discontinued (see Table 1). The different E2 levels between the 17 patients with mature follicles during the second COH and the 24 patients during the first COH were statistically significant ($p < 0.05$), but there were no differences in E2 levels between the seven patients with ceased follicle growth during the second COH and the 24 patients during the first COH ($p > 0.05$).

Table 1. Statistical analysis of the oestradiol and the dominant follicle during both controlled ovarian hyperstimulations

	24 cases in the first COH		17 cases were successful in second COH ^a		7 cases failed in second COH ^b	
	E2 (pmol/L)	F-measure (mm)	E2 (pmol/L)	F-measure (mm)	E2 (pmol/L)	F-measure (mm)
4 days prior	2,103.5±1941.3	11.2±3.0	5,623±4,455	16.2±3.7	1,879.9±1,673.2	12.0±3.1
2 days prior	1,286.3±1452.3	11.1±2.7	7,034±5,021	17.5±2.8	1,309.1±1,098.4	12.2±1.9
Drug discontinued day	510.6±674.8	10.6±2.7	8,747±5,111	19.2±3.2	639.3±589.9	11.7±3.0

E2 = oestradiol; COH = controlled ovarian hyperstimulation; F-measure = follicle size.
a = E2 for 17 cases were successful in second COH vs E2 for 24 cases with the first COH, $p < 0.05$.
b = E2 for seven cases failed again in the second COH vs E2 for 24 cases during the first COH, $p > 0.05$.

Total and daily dose of Gn, days of stimulation in both COHs

After 15–20 days of discontinuing medication for stimulation, 24 patients resumed their COH when they met the criteria for ovary under downregulation. Of these, nine patients received gonadotropin-releasing hormone antagonist (Cetrotide, Merck-Serono) to suppress elevated LH to 1–5 IU/L at the late stage of second COH. The total and daily doses of Gn used in both COHs were recorded (see Table 2). Table 2 shows that the total dose of Gn for the first COH and the second COH were 2,004±393.5 and 2,628±970.7 respectively; the daily dose of Gn for the first COH and second COH were 182.4±21.94 and 203.3±34.76 respectively. There was no statistical difference between the daily Gn dose used in the first COH and the daily Gn dose used in second COH ($p > 0.05$).

Outcome for 24 cases with resuming COH-IVF-ET cycle

Resuming the COH cycle was cancelled for seven patients without IVM when follicles showed no growth again around 13 mm with declined E2; 17 cases with resumed COH reached egg retrieval, though in one case no oocyte was retrieved. 16 cases produced embryos grading between I-III (according to the Racowsky scoring system in 2009),³ of which 14 cases underwent embryo transfer with day-3 embryos and two cases underwent embryo cryopreservation due to uterine cavity effusion. Twelve cases with embryo transfer resulted in clinical pregnancy (confirmed with intrauterine gestational sac by ultrasound 28–32

days after embryo transfer); two cases with embryo transfer resulted in no pregnancy (see Table 3). In Table 3 it shows that mean BMI for 17 patients with mature follicle and seven patients with ceased follicle growth in the second COH are 21.12±3.57 and 29.29±3.20, respectively. There is a statistically significant difference in mean BMI between the two groups of patient ($p < 0.05$).

Discussion

PCOS is a common gynaecological endocrine disorder that affects approximately 5–10% of women worldwide. Clinical characteristics include oligoovulation or anovulation, excess androgen and polycystic ovaries. It is one of the most common causes of infertility in reproductive age women.^{4–6} IVF-ET is a common treatment for PCOS patients with tubal factor, male factor, failed after multi-drugs for ovary stimulation and refractory PCOS patients. During IVF-ET treatment there are frequent cancellations due to several reasons which include abnormal follicle development due to resistance to stimulating drugs⁷ or ceased follicle growth;⁸ endometrium not synchronised with follicle growth; and ovarian hyperstimulation syndrome (OHSS) occurring during COH or after egg retrieval.⁹ At present, the long protocol with gonadotropin releasing hormone agonist (GnRHa)/FSH or HMG/HCG is the traditional treatment for PCOS patients in IVF. However, the success rate is low for PCOS patients especially for patients with high BMI because of physiopathologically complexity, such as long-term chronic anovulation resulting in polycystic ovaries

Table 2. Total dose and daily dose of gonadotropin used and days of stimulation in both controlled ovarian hyperstimulations

	Total Gn per case	Days of stimulations	Daily Gn per case ^a
First COH	2,004±393.5	11.0±1.79	182.4±21.94
Second COH	2,628±970.7	12.8±3.10	203.3±34.76

COH = controlled ovarian hyperstimulation; Gn = gonadotropin.
a = the daily Gn dose per case in first COH vs the daily Gn dose per case in second COH, $p > 0.05$.

Table 3. Outcome for 24 cases after resuming controlled ovarian hyperstimulation-*in vitro* fertilisation-embryo transfer cycle

	Success to mature follicle	Fail to mature follicle	p value
Cases, n	17	7	na
BMI, kg/m ²	21.12±3.57	29.29±3.20	0.021
Clinical pregnancy, n	12/14	na	na

BMI = body mass index; na = not applicable.

and thickening ovarian cortex or not being sensitive to ovary stimulating drugs. Furthermore because the dose of HMG/FSH for follicle development is close to the threshold of OHSS,^{10,11} COH treatment is easily induced in OHSS in patients with PCOS.¹² In recent years, IVM has been used to treat infertility caused by PCOS, and some progress has been made, but there are some problems such as low oocyte maturation rate, low fertilisation rate and low pregnancy rate.¹³ Traditionally, the 24 PCOS patients in this article experiencing ceased follicle growth around 10–14 mm with significantly declined LH and E2 during COH treatment would have been cancelled and restarted on the GnRHa/COH cycle after two to three menstrual cycles.^{14,15} We observed their ovaries and endometrium after 15–20 days of discontinuing medication. The level of FSH/LH/E2 and B ultrasounds all showed that patients were still under downregulation at the early follicle phase. We considered that the follicle was discharged or atresic after being insensitive to Gn during mid-late stage of first COH, and high levels of E2 production in COH might cause negative feedback inhibition of the hypothalamic-pituitary-gonadal-axis, causing the ovary to be under downregulation at the early follicle phase. According to what is described above, we believed that PCOS patients would be under a long period of suppression after downregulating treatment. With approval from the ethical committee, we gave the 24 patients Gn in doses of 150–225 IU daily for second round of COH. Seventeen patients developed mature follicles reaching oocyte retrieval, 16 of which had good quality of embryos. There were 14 patients with day-3 embryo transfers which resulted in good outcomes, with 12 clinical pregnancies. The remaining seven cases encountered the same problem of ceased follicle growth around 13 mm. The mean E2 level of 17 cases in the second COH on the day of HCG trigger was less than 15,000 pmol/L, even though the daily dose of Gn was numerically higher than in their first COH. In addition, no patients developed OHSS after their embryo transfers. More than half (17/24) of the patients developed mature follicles in the second COH with no statistical difference in doses of Gn in both COHs, which explains why the ovaries, after downregulating for 40 days, were more sensitive to stimulating medication. The mean BMI of the seven patients with ceased follicle development again was higher than the others, which means that the drug sensitivity of the ovary was negatively correlated with BMI. Complete weight control should be an important way to increase the sensitivity to drugs, and can obtain the ideal clinical pregnancy outcome. The result shows that resuming COH treatment for patients with PCOS as described above is a feasible and safe option. This method has not been reported in domestic or foreign articles. It provides a new path for the treatment of PCOS, though it needs a larger sample of patients to draw a further conclusion. Another factor to consider is that in the traditional long protocol of treatment, COH will be utilised after 10–14 days of downregulation. This article shows that the downregulation status of PCOS patients lasts longer than usual in IVF patients. The question is whether or not we should start COH after 1 month of downregulation for PCOS patients. ■

Conflicts of interest

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