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CLINICAL ARTICLE

Fertility of patients with polycystic ovary syndrome undergoing in vitro fertilization by age☆

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ABSTRACT

Objective: To evaluate outcomes of in vitro fertilization (IVF) among patients with polycystic ovary syndrome (PCOS) by age. *Methods:* In a retrospective study, data were retrieved for patients with PCOS (Rotterdam 2003 criteria) and individuals with tubal factor infertility who underwent IVF at a center in Seoul, South Korea, between January 2003 and August 2012. IVF outcomes were compared by age group (A: 30–32 years; B: 33–35 years; C: 36–38 years; D: 39–41 years). *Results:* The analysis included 307 women with PCOS and 364 with tubal factor infertility. There was a significant difference between women with PCOS and those with tubal infertility factor in the live birth rate in group B (41.3% vs 28.6%, $P=0.038$) and in group C (40.4% vs 15.1%, $P=0.002$). Among women with PCOS, no significant differences in number of retrieved oocytes were observed between the age groups (18.8 ± 9.6, 19.1 ± 10.0, 17.7 ± 7.5, and 17.0 ± 13.8). However, the clinical pregnancy rate was significantly lower in group D than in group C (47.2% vs 18.8%, $P=0.042$). *Conclusion:* Fertility in patients with PCOS was maintained until age 38 years using IVF. Thereafter, the pregnancy rate decreased, although the number of oocytes retrieved by IVF remained stable.

1. Introduction

Polycystic ovary syndrome (PCOS) is a fairly common endocrine disorder among women of reproductive age. This disorder is characterized by oligo-ovulation or anovulation, polycystic ovarian morphology on ultrasonography, and androgen excess [1]. The clinical manifestations of PCOS include irregular menstruation related to ovarian dysfunction, hirsutism, and obesity. Affected patients also have an increased risk of type 2 diabetes [1]. Moreover, ovulatory dysfunction in patients with PCOS often leads to subfertility [1].

Among women without ovulation abnormalities, fertility throughout reproductive life is largely determined by age [2]. Age-related female infertility is primarily a result of decreasing ovarian reserve [2]. After the age of 35 years, the serum level of follicle-stimulating hormone (FSH) begins to increase, the serum level of inhibin B decreases slightly, and the serum estradiol (E_2) level remains unchanged [3]. The serum levels of FSH and inhibin B are known endocrine markers of ovarian aging [4]. The serum anti-Müllerian hormone (AMH) concentration also demonstrates age-related decreases in women without ovulation abnormalities [5]. Furthermore, the serum AMH level is correlated with the ovarian response in patients with a normal FSH level undergoing in vitro fertilization (IVF) [6,7]. As a woman ages, the ovarian follicles are depleted and the ovary develops a poorer response to exogenous gonadotropin [8].

However, the number of oocytes in patients with PCOS does not seem to decrease with age. On the basis of the rate of AMH decline, Tehrani et al. [9] estimated that the onset of menopause is delayed by approximately 2 years among women with PCOS when compared with women without ovulation abnormalities. Even during the premenopausal period, women with PCOS have an increased antral follicle count and a lower serum FSH level than do women without PCOS [10]. Furthermore, women with PCOS can achieve normal menstruation, reflecting appropriately balanced hormones, at late reproductive ages [11,12].

In the past, it was thought that patients with PCOS and women without ovulation abnormalities have similar rates of pregnancy and live birth per IVF cycle [13]. However, a study by Mellembakken et al. [14] showed that women of advanced reproductive age with PCOS actually had better fertility than did control women. Therefore, the

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primary objective of the present study was to evaluate IVF outcomes among patients with PCOS according to age. The secondary aims were to assess the decrease in fertility with age and to compare pregnancy rates at advanced reproductive age between patients with and without PCOS undergoing IVF.

2. Materials and methods

In a retrospective study, data for patients with PCOS or tubal factor infertility undergoing IVF were retrieved from the IVF database of Cheil General Hospital and Women's Healthcare Center, Dankook University College of Medicine, Seoul, South Korea. All patients had been treated between January 1, 2003, and August 30, 2012. Patients with PCOS (diagnosed according to the Rotterdam 2003 criteria [1]) had undergone IVF after attempting natural pregnancy or using ovulation induction for at least 2 years. Women without PCOS but with tubal factor infertility were included as controls. The exclusion criteria included age of less than 30 years or 42 years or more, male factor infertility, in vitro maturation cycles, and presence of another endocrine disorder (thyroid disorder, diabetes mellitus, Cushing syndrome, 21-hydroxylase deficiency, androgen-secreting tumor, and hyperprolactinemia). The study was approved by the institutional research ethics committee of Dankook University College of Medicine and was designed and performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [15] and Committee on Publication Ethics (COPE) guidelines. Because the present study analyzed medical records that dated back up to 10 years, informed consent could not be obtained.

Several characteristics were recorded: age; body mass index; cycle number; basal serum E_2, FSH, luteinizing hormone (LH), and AMH levels on menstrual day 2 or 3; total number of gonadotropin units used; serum E_2 level and endometrial thickness on the day of human chorionic gonadotropin (hCG) administration; and numbers of retrieved oocytes, matured oocytes, fertilized embryos, and transferred embryos. Patients were treated with one of three IVF protocols: a flexible multidose gonadotropin-releasing hormone (GnRH) antagonist protocol, a long GnRH agonist protocol, or a short flare-up GnRH agonist protocol. On the second or third day of the menstrual cycle, the serum levels of FSH, LH, and E_2 were measured. Transvaginal ultrasonography was used to evaluate the pelvic cavity.

In the flexible multidose GnRH antagonist protocol, stimulation with gonadotropin (FSH [Gonal-F, Merck Serono, ModugnoBA, Italy; or Puregon, Organon, Barcelona, Spain]; step-up protocol, 75–150 IU/day) was initiated on menstrual day 3 or 4 on the basis of the serum E_2 level. On menstrual day 5 or 6, the serum E_2 level was measured again and transvaginal ultrasonography was performed. Once the leading follicles were more than 12 mm in size or the serum E_2 concentration was 200–400 pg/mL, a GnRH antagonist (0.25 mg/day cetrorelix acetate [Cetrotide; Merck Serono, Geneva, Switzerland] or 0.25 mg/day ganirelix acetate [Orgalutran; Merck Sharp and Dohme Limited, Munich, Germany]) was added until the day of hCG administration.

In the long GnRH agonist protocol, pituitary suppression was initiated with a GnRH agonist (0.1 mg/day leuprolide acetate [Lucrin; Abbott Laboratories, North Chicago, IL, USA]) from the midluteal phase of the previous cycle to the day of hCG administration. Ovarian stimulation began on menstrual day 3 or 4 and was continued until the day of hCG administration. The stimulation dose was determined by the patient's age and the ovarian response during the previous cycle.

In the short flare-up protocol, pituitary suppression was initiated with the same GnRH agonist (0.1 mg/day leuprolide acetate [Lucrin]) from menstrual day 2 or 3. The gonadotropin (75–150 IU/day FSH [Gonal-F or Puregon]) was started on menstrual day 3 or 4 and was continued until the day of hCG administration.

All patients were monitored for follicle size and serum E_2 concentration. Once a leading follicle reached more than 17–18 mm in diameter, hCG (250 μg choriogonadotropin α [Ovidrel; Merck Serono, Rome, Italy]) was added. Ovum retrieval was performed through transvaginal ultrasonography 36 hours after hCG injection. The embryos were transferred into the uterine cavity via transvaginal ultrasonography 3–5 days after oocyte retrieval. Twelve days after oocyte retrieval, the pregnancy status was assessed through a test of the serum levels of the beta subunit of hCG (β-hCG).

The main outcomes were: the oocyte maturation, fertilization, and implantation rates; a positive hCG test result; and pregnancy. A positive hCG result was defined as a serial serum level of the beta subunit (β-hCG) of more than 5 IU/L. Pregnancy was defined as the presence of a gestational sac as detected by transvaginal ultrasonography, and the implantation rate was calculated as the number of gestational sacs divided by the number of transferred embryos. Spontaneous abortion was defined as absence of a fetal heartbeat before the 20th week of pregnancy.

All statistical analyses were performed using SPSS version 21.0 (IBM, Amonk, NY, USA). The patients were divided into four age groups: group A contained women aged 30–32 years, group B contained women aged 33–35 years, group C women aged 36–38 years, and group D women aged 38–41 years. The Kolmogorov–Smirnov test was used to evaluate the normality of the data. Independent-sample *t* tests were used to compare basal characteristics if the data were normally distributed. Categorical variables were compared using the χ^2 test or the Fisher exact test. The IVF outcomes were analyzed according to age using one-way analysis of variance. Post-hoc analysis was performed using the Bonferroni method. $P<0.05$ was considered statistically significant.

3. Results

A total of 307 women with PCOS and 364 women with tubal factor infertility who did not have PCOS were included in the present analysis. No significant differences in age, number of IVF cycles, or number of transferred embryos were observed between women with PCOS and those with tubal factor infertility (Table 1). The IVF stimulation protocols used also did not differ significantly (GnRH antagonist protocol: 172 [56.0%] with PCOS vs 220 [60.4%] with tubal factor infertility; long GnRH agonist protocol: 81 [26.4%] vs 72 [19.8%]; short flare-up GnRH agonist protocol: 54 [17.6%] vs 72 [19.8%]). By contrast, there were significant differences between the two groups with respect to body mass index, serum AMH level, total gonadotropin dose, endometrial thickness and serum E_2 level on the day of hCG administration, and

Table 1
Baseline characteristics and pregnancy outcomes.[a]

Characteristic/outcome	Polycystic ovary syndrome (n = 307)	Tubal factor infertility (n = 364)	*P* value
Age, y	33.5 ± 2.7	33.8 ± 2.7	0.286
Body mass index[b]	22.1 ± 3.7	21.3 ± 2.7	0.001
IVF cycles	1.7 ± 1.0	1.6 ± 0.9	0.150
Serum anti-Müllerian hormone, ng/mL	9.2 ± 4.1	2.8 ± 2.0	<0.001
Total gonadotropin dose, IU	1977.5 ± 1016.4	2584 ± 942.7	<0.001
Endometrial thickness, mm	11.1 ± 2.5	10.6 ± 2.1	0.03
Serum estradiol at hCG administration, ng/L	2979.6 ± 2151.3	2222.9 ± 1730.9	<0.001
Retrieved oocytes	18.6 ± 9.6	12.7 ± 8.3	<0.001
Matured oocytes	13.8 ± 8.1	9.6 ± 6.9	<0.001
Fertilized oocytes	11.5 ± 6.6	8.2 ± 5.8	0.002
Transferred embryos	3.0 ± 0.8	3.0 ± 0.9	0.188
Implantation rate, %	28.1 ± 32.0	24.0 ± 32.5	0.091
Positive hCG test	193/307 (62.9)	185/364 (50.8)	0.002
Clinical pregnancy	161/307 (52.4)	158/364 (43.4)	0.020
Spontaneous abortion	21/161 (13.0)	13/158 (8.2)	0.204
Loss to follow-up	7/161 (4.3)	9/158 (5.7)	0.799
Live births per cycle	128/300 (42.7)	125/355 (35.2)	0.878

Abbreviations: IVF, in vitro fertilization; hCG, human chorionic gonadotropin.
[a] Values are given as mean ± SD or number/total number (percentage), unless indicated otherwise.
[b] Calculated as weight in kilograms divided by the square of height in meters.

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