Is the fertile window extended in women with polycystic ovary syndrome? Utilizing the Society for Assisted Reproductive Technology registry to assess the impact of reproductive aging on live-birth rate

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Objective: To assess whether women with polycystic ovary syndrome (PCOS) follow the same age-related decline in IVF outcomes as women with tubal factor infertility over the reproductive life span. PCOS is characterized by increased ovarian reserve as assessed by antral follicle counts and anti-Müllerian hormone levels. It is unclear whether these surrogate markers of ovarian reserve reflect a true lengthening of the reproductive window.
Design: Retrospective cohort.
Setting: Not applicable.
Patient(s): Women with PCOS and tubal factor infertility (42,286 cycles).
Intervention(s): IVF.
Main Outcome Measure(s): Pregnancy and live-birth rates.
Result(s): The mean number of oocytes retrieved was higher in women with PCOS compared with in women with tubal factor (16.4 vs. 12.8; odds ratio [OR], 1.27; 95% confidence interval [CI], 1.25–1.29). The clinical pregnancy (42.5% vs. 35.8%; OR, 1.32; 95% CI, 1.27–1.38) and live-birth rates were also increased in women with PCOS (34.8% vs. 29.1%; OR, 1.30; 95% CI, 1.24–1.35). A similar rate of decline in clinical pregnancy and live-birth rates was noted in both groups (20–44 years). The implantation, clinical pregnancy, miscarriage, and live-birth rates were not significantly different for each year after age 40 in the two groups.
Conclusion(s): Despite a higher oocyte yield in all age groups, women with PCOS over age 40 had similar clinical pregnancy and live-birth rates compared with women with tubal factor infertility. These findings suggest that the reproductive window may not be extended in PCOS and that patients with infertility should be treated in a timely manner despite indicators of high ovarian reserve. (Fertil Steril® 2013;100:208–13. ©2013 by American Society for Reproductive Medicine.)
Key Words: Polycystic ovary syndrome, fertility, IVF, outcomes

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Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 6%–8% of women of reproductive age. PCOS is typically characterized by irregular menses, hirsutism or elevated androgens, and polycystic appearing ovaries on ultrasound. Both population- and clinic-based studies have demonstrated that, although the time to fertility may be extended in PCOS, most women attempting pregnancy are successful with and without treatment (1, 2). The majority respond to oral ovulation induction agents such as clomiphene citrate, and the remaining usually respond to injectable gonadotropins

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(3). It has therefore been suggested that appropriate treatment to induce ovulation in women with PCOS typically restores normal cumulative pregnancy rates. A smaller proportion of women with PCOS are treated with IVF usually secondary to coexisting causes of infertility or to decrease the high multiple pregnancy rate associated with controlled ovarian hyperstimulation. In a meta-analysis including nine IVF studies with approximately 1,500 subjects (mean age, 31.9 years), clinical pregnancy and live-birth rates per cycle started were similar in women with PCOS compared with in age-matched controls (4).

The precise underlying etiology of PCOS is unclear, although genetic and environmental factors influence the spectrum of manifestations. Reproductive-age women with PCOS have an increased density of small preantral follicles and an increased proportion of early growing follicles (5). Ovarian cortical biopsies show a six-fold increased density of primordial and primary follicles in women with PCOS compared with in women with regular menses (6). These findings suggest that PCOS may be associated with larger ovarian reserve either due to increased numbers of germ cells at birth or a decrease in the rate of germ cell loss. Surrogate markers of ovarian reserve such as ultrasonographically measured antral follicle counts (AFC) and serum anti-Müllerian hormone (AMH) levels are also increased in women with PCOS compared with in age-matched controls (7–9). Even in the perimenopausal period, women with PCOS have increased AFC and lower serum FSH levels (1, 10). Collectively, these findings have led to the speculation that the reproductive window may be lengthened in PCOS. However, it is not clear whether these findings have implications for counseling women with PCOS regarding their fertility potential especially in the fourth decade of life.

We hypothesized that the greater number of antral follicles and higher AMH levels may confer a reproductive advantage in PCOS patients undergoing infertility treatment with IVF. We sought to assess whether this would translate into prolongation of the fertile window. To address this question, we examined the clinical outcomes after IVF in women with PCOS and compared then with those of women with tubal factor infertility using the Society for Assisted Reproductive Technology (SART) registry. The primary aim of this study was to assess whether women with PCOS follow the same age-related decline in IVF clinical pregnancy and live-birth rates as a control group of women with normo-ovulatory cycles (tubal factor infertility only). Second, we wanted to examine clinical pregnancy and live-birth rates in these two groups after the age of 40 to evaluate any possible lengthening of the reproductive window.

MATERIALS AND METHODS

The data source for this study is the SART database. Data are reported annually in a standardized manner by IVF clinics in the United States and include patient demographic characteristics, infertility diagnosis, medication, treatment methods, and outcomes for each cycle. The study proposal was submitted to the SART research committee and was approved before release of limited deidentified data fields. The 2004–2006 SART databases were then used to identify pregnancy and live-birth outcomes in fresh IVF cycles in patients with a single underlying infertility diagnosis of PCOS or tubal factor as entered by reporting clinics. Frozen cycles, donor recipient cycles, and cycles with multiple infertility diagnoses were excluded from this analysis. Comparison of treatment outcomes, including oocytes retrieved, clinical pregnancy rate, and live-birth rate, were assessed in fresh, nondonor IVF cycles by age group in patients with PCOS compared to tubal factor infertility. Institutional Review Board approval was obtained at the University of Pennsylvania.

Pregnancy Outcomes

Clinical pregnancy was defined as the presence of a gestational sac on transvaginal ultrasound and expressed per cycle start. The implantation rate reflects the number of gestational sacs divided by the number of embryos transferred. Miscarriage was defined as spontaneous pregnancy loss up to 20 weeks of gestation after detection of a gestational sac and expressed per clinical pregnancy. Live-birth rate was based on delivery after 20 weeks of gestation and expressed per IVF cycle start.

Statistical Analysis

The Wilcoxon rank-sum test was used to evaluate differences between continuous variables, and Fisher's exact test and the χ^2-test were performed for categorical variables to summarize the diagnosis groups by demographic and clinical characteristics. Generalized estimating equations (GEEs) were used to model the associations between the groups and outcomes. A Poisson distribution with log link was used to assess the number of oocytes, while a binominal distribution with logit link was used for binary outcomes. The marginal distributions were used to estimate the outcomes for each diagnosis by age, with Holm adjusted *P* values due to the multiple comparisons. All models were adjusted for age, race, number of prior assisted reproductive technology (ART) cycles, parity, reporting year, and number of embryos transferred (pregnancy outcomes only). A cubic spline model was used to assess the marginal predicted probability of outcome in each group over age continuously. All of the individual age group comparisons use a Holm adjusted *P* value for multiple comparisons. Analyses were conducted in Stata/MP 11.2.

RESULTS

A total of 368,833 IVF cycles were identified in the SART database from 2004–2006. After exclusion of cycles with donor egg cycles (n = 44,320), multiple diagnoses (n = 267,249), frozen ET (n = 12,845), and combined transfer of both fresh and frozen embryos (n = 133), a total of 44,286 IVF cycles met the inclusion criteria for analysis. Patients with a single diagnosis of tubal factor infertility contributed 27,870 cycles and were used as controls, and those with a single diagnosis of PCOS contributed 16,416 cycles and were used as the cases. Table 1 presents the demographic characteristics of women in each group. Women with PCOS were younger than women