Long-term follow-up of patients with polycystic ovary syndrome: reproductive outcome and ovarian reserve

M. Hudecova¹, J. Holte, M. Olovsson, and I. Sundström Poromaa
Department of Women's and Children's Health, Uppsala University 751 85 Uppsala, Sweden
¹Correspondence address. Tel: +46 18 611 57 87; E-mail: miriam.hudecova@kbh.uu.se

BACKGROUND: The purpose of the present study was to examine long-term reproductive outcome and ovarian reserve in an unselected population of women with polycystic ovary syndrome (PCOS).

METHODS: A total of 91 patients with confirmed PCOS and 87 healthy controls were included in the study. Patients had been diagnosed between 1987 and 1995 and at the time of the follow-up, subjects were 35 years of age or older.

RESULTS: Among women who had attempted a pregnancy, 86.7% of PCOS patients and 91.6% of controls had given birth to at least one child. Among PCOS patients who had given birth, 73.6% had done so following a spontaneous conception. Mean ovarian volume and the number of antral follicles in PCOS patients were significantly greater than in control women (P<0.001, respectively). PCOS patients also had higher serum concentrations of anti-Müllerian hormone and lower follicle-stimulating hormone levels.

CONCLUSIONS: Most women with PCOS had given birth, and the rate of spontaneous pregnancies was relatively high. Together with the ultrasound findings and the hormonal analyses, this finding could imply that PCOS patients have a good fecundity, and an ovarian reserve possibly superior to women with normal ovaries.

Key words: polycystic ovary syndrome / long-term follow-up / ovarian reserve / fecundity / anti-Müllerian hormone

Introduction

Polycystic ovary syndrome (PCOS) is a complex and heterogeneous clinical condition characterized by hyperandrogenism and chronic oligo/anovulation. It is estimated that ~6.5% of fertile women have PCOS, although no precise determinations have been possible to obtain (Diamanti-Kandarakis et al., 1999; Asuncion et al., 2000; Azziz et al., 2004). There are only a few long-term follow-up studies, based on modern PCOS diagnostic criteria and with sample sizes sufficiently large for detailed reproductive and metabolic analyses (Dahlgren et al., 1992; Cibula et al., 2000; Wild et al., 2000).

Decreased rates of ovulation and metabolic alterations in women with PCOS are both associated with subfertility in this population (Diejomaoh et al., 2003). Miscarriage rates among women with PCOS are believed to be increased compared with normal fertile women, although supporting evidence is limited (Wang et al., 2001; Legro, 2007; Boomsma et al., 2008).

Very few studies assessing the long-term reproductive outcome and ovarian reserve in older women with previously confirmed PCOS have been conducted. The typical ultrasound features of PCOS appear to diminish with increasing age. In a Finnish population-based study, polycystic ovaries were prevalent in 6% of healthy women of 34 years of age and in 10% of women of similar age who fulfilled the criteria for the metabolic syndrome. In women of 44 years of age, the prevalence of polycystic ovaries was 2 and 5% in healthy controls and patients with metabolic syndrome, respectively (Korhonen et al., 2003).

Although studies on reproductive performance in older PCOS patients are few, some studies have indicated that menstrual cycles become normalized with increasing age, at least in some of the patients (Dahlgren et al., 1992; Elting et al., 2000). This also holds true for subjects who have not undergone ovarian wedge resection (Dahlgren et al., 1992).

Measurements of factors thought to reflect ovarian reserve are used as an important means to predict the outcome of assisted reproduction techniques. Variables used to estimate the ovarian reserve include basal or stimulated levels of follicle-stimulating hormone (FSH), anti-Müllerian hormone (AMH), inhibin B and the number of antral follicles and ovarian volume, assessed by means of transvaginal ultrasound

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Long-term follow-up of PCOS patients

Patients and Methods

Patients

Eligible patients were identified by the out-patient register at Uppsala University Hospital. Inclusion criteria for the study were diagnosis of PCOS between 1987 and 1995 and age at the follow-up >35 years. As the emphasis in this study was to follow patients with a PCOS diagnosis made by transvaginal ultrasound, the medical records at the time of diagnosis were scanned to confirm the diagnosis and to verify the use of transvaginal ultrasound for the diagnosis. Only subjects with a diagnosis of PCOS according to the Rotterdam criteria (2004) were included and one of the features had to be polycystic ovaries on ultrasound examination (Adams et al., 1986; Holte et al., 1994). In addition to the ultrasound criterion, one of the following two features had to be present for the PCOS diagnosis: (i) oligomenorrhea, with eight or fewer menstruations in the previous 12 months, or amenorrhea, or (ii) clinical and/or biochemical signs of hyperandrogenism such as testosterone >2.7 nmol/l, elevated dehydroepiandrosterone sulfate, free androgen index (FAI) ≥5.0 or hirsutism (>7 on the Ferriman and Galloway scale). The PCOS diagnosis also implied that no evidence of thyroid disease (normal s-TSH), adrenocortical dysfunction (normal 17-hydroxyprogesterone) or hyperprolactinaemia (prolactin<30 μg/l) was present at diagnosis. Subjects with a PCOS diagnosis based on clinical history and laboratory findings but without transvaginal ultrasound examination were not included.

Healthy controls were selected from population registries. For each PCOS patient, three healthy controls residing in Uppsala County and born during the same month as the index patients were selected. The control women were invited by letter, and in case the first control did not respond to the invitation, the second (and third) control subject was subsequently invited. Healthy control status was assured by the absence of polycystic ovaries on transvaginal ultrasound. Furthermore, all control subjects denied a prior history of oligomenorrhea or amenorrhea (last ing more than 3 months).

Information on the PCOS patients who did not wish to participate was retrieved from the Swedish Medical Birth Registrar, where data on almost all Swedish births have been collected since 1973. From this register, it was possible to determine the number of subjects who had had at least one delivery. Data on pre-pregnancy height and weight could be obtained for parous women, along with the reports about the duration of infertility and previous miscarriages. At the time of the study, the Swedish Medical Birth Registrar comprised data on all births between 1973 and 2005. Data from the Swedish Medical Birth Register was retrieved only at a group level. Data from individual non-participating woman were not available.

The patients and controls gave written informed consent and the Independent Ethical Review Board at Uppsala University, Sweden approved the study.

Methods

All subjects consenting to participate attended a health examination at the department of Women’s and Children’s Health, Uppsala University Hospital. As the reproductive status was variable among subjects (premenopausal with or without hormonal contraception, post-menopausal with or without hormone therapy (HT), the visit was not scheduled according to menstrual cycle phase. However, records were kept on the last menstrual period, and transvaginal ultrasound examination together with assays of estradiol, FSH and luteinizing hormone (LH) confirmed the cycle phase in subjects without hormonal contraception.

The ultrasound examination was performed with a 7 MHz transvaginal probe by either of two physicians (M.H. or I.S.P.). The ultrasound measurements were obtained in real-time according to a standardized protocol, with examination of the ovaries made under the highest possible magnification. After the longest medial axis of the ovary had been determined, the second dimension was measured, and then the vaginal probe was rotated 90° to obtain the third dimension. Ovarian volume was calculated in the largest ovary according to a simplified formula for an ellipsoid (0.523 × length × width × thickness (Adams et al., 1986)). The ovary was scanned in both longitudinal and transverse cross-section from the inner to the outer margins to count the total number of follicles. All follicles, antral and growing, were counted.

All blood samples for the endocrine measurements were obtained in a standardized manner between 08:00 and 09:00 h during rest in the supine position and after an overnight fast. The FAI was calculated from testosterone/sex hormone-binding globulin (SHBG) × 100.

The participants filled out a questionnaire on reproductive health, including obstetric history (previous pregnancies and previous live births), infertility history (duration of infertility, infertility treatments and infertility treatment in relation to each live birth), menstrual cycle history (menstrual frequency during the last 12 months), treatment and ongoing hormonal treatment (any treatment with ovarian steroids such as oral contraceptives, progestagens, hormonal IUD and post-menopausal HT).

Assays

Serum concentrations of testosterone, SHBG, FSH, LH were analysed by solid-phase chemiluminescent immunometric assays and estradiol was measured by competitive immunoassay, using commercial kits obtained from Siemens Medical Solutions, Germany. Detection limits for the estradiol essays was 73.0 pmol/l and for testosterone 0.5 nmol/l. Total coefficients of variation varied between 5.7 and 10.6% for these analyses.

The serum concentrations of AMH were determined using enzyme-linked immunaoassay kits, from Immunotech Beckman Coulter Company, France. The detection limit for AMH was 0.07 pmol/l and levels below this limit were considered undetectable. Total coefficient of variation was 12.3% for the AMH analyses.

Statistical methods

All values in the text and tables are displayed as mean ± SD, unless otherwise stated. For comparison between groups, independent t-tests or Mann–Whitney U-tests were performed, depending on whether the variable was normally distributed or not. Frequencies were compared between groups by the χ² test. To protect against multiple testing, the false discovery rate was used, where the cut-off for significant P-values is established by the following formula [(number of tests + 1) × P-value]/(2 × number of tests). Correlations between different measures of ovarian reserve were obtained by Pearson’s correlation coefficient. Multiple linear regression models were used to assess the relationship between the group and age in terms of ovarian reserve. For the regression analyses, log-transformed variables were used. To evaluate if the time-course by which the ovarian reserve declined was different in PCOS patients, age by group interactions were tested with ANOVA analyses. The SPSS statistical package was used for all analyses (SPSS Inc., Chicago, IL, USA). A P-value of <0.025 was considered significant.
Results

In all, 174 PCOS patients had been previously identified with a PCOS diagnosis. Of these, 3 patients (1.7%) were dead, 12 patients had emigrated (6.9%) and 14 patients (8.0%) were living too far from Uppsala to be invited. Hence, 145 patients (83.3% of the identified patients) were invited to participate in the study (Fig. 1).

Among the 145 invited PCOS patients, 84 women (57.9%) attended the clinical examination and 7 women (4.8%) filled out the questionnaires but were unable to visit the clinic. Among PCOS patients still living in the Uppsala area, 61 women (66.3%) attended the clinical examination, whereas the corresponding figures for PCOS patients living outside the Uppsala area were 23 (43.4%) and 4 (7.5%), respectively (Fig. 1). At the time of the original diagnosis, 58 (40.0%) of invited PCOS patients had PCO and oligomenorrhea only, 8 (5.5%) had PCO and hirsutism only, and 79 (54.5%) had PCO, oligomenorrhea and hirsutism. There were 87 age-matched control women who participated in the study.

Demographic data and physical characteristics for the PCOS patients and control subjects are given in Table I. PCOS patients had higher BMI and were more often unemployed than control subjects.

Data on PCOS patients not consenting to participate in the study are given in Table II. There were no differences in parity between participating and non-participating PCOS patients.

Reproductive outcome

Among PCOS patients, 83 had attempted a pregnancy, 79 had become pregnant and 72 had given birth at least once. There was no difference between PCOS patients and controls in number of women who had given birth. Among women who had attempted a pregnancy, 72 (86.7%) PCOS patients and 76 (91.6%) control subjects had given birth to at least one child. The overall rate of subjectively defined spontaneous conception was also high among PCOS patients. Among the 83 PCOS patients who had attempted a pregnancy, 56 (67.5%) became spontaneously pregnant at least once. Among the PCOS patients who had given birth to a child, 53 (73.6%) did so at least once following a spontaneous conception.

The rate of miscarriages was not increased in PCOS patients (PCOS patients 0.6 ± 1.1 miscarriages versus 0.6 ± 0.9 miscarriages in control subjects). Among women who conceived at least once, 36 (45.6%) of PCOS patients and 41 (49.4%) of control women had at least one miscarriage.

The majority of subjects were still premenopausal, Table I. Premenopausal PCOS patients without hormonal contraception reported 8.8 ± 3.9 menstruations during the last year, whereas control women reported 11.4 ± 2.2 menstrual periods during the last year, P < 0.01. The number of premenopausal PCOS patients without hormonal contraception who had had eight or more menstrual bleedings during the last year was 38 (73.1%).

Ovarian reserve

Mean ovarian volume and number of antral follicles in premenopausal PCOS patients without hormonal treatment were significantly higher than in corresponding control subjects, 9.5 ± 6.6 ml compared with 6.6 ± 4.1 ml (P = 0.001) and 11.7 ± 12.4 compared with 5.0 ± 2.4.
Table I: Demographic data and physical characteristics for the PCOS patients and control subjects in the study

<table>
<thead>
<tr>
<th></th>
<th>PCOS patients (n = 91)</th>
<th>Control subjects (n = 87)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>43.2 ± 6.0</td>
<td>43.6 ± 6.4</td>
<td>ns</td>
</tr>
<tr>
<td>Premenopausal (n)</td>
<td>80 (87.9%)</td>
<td>70 (80.5%)</td>
<td>ns</td>
</tr>
<tr>
<td>Nordic ethnicity (n)</td>
<td>89 (97.8%)</td>
<td>86 (98.8%)</td>
<td>ns</td>
</tr>
<tr>
<td>Married/partner (n)</td>
<td>68 (74.7%)</td>
<td>66 (75.9%)</td>
<td>ns</td>
</tr>
<tr>
<td>Employed (n)</td>
<td>65 (71.4%)</td>
<td>81 (93.1%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.5 ± 2.9</td>
<td>14.6 ± 3.1</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.4 ± 6.0</td>
<td>25.7 ± 4.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoker (n)</td>
<td>19 (20.9%)</td>
<td>12 (13.7%)</td>
<td>ns</td>
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</table>

Data given as mean ± SD.

Discussion

The main findings of the present study were that reproductive outcome did not differ between this unslected population of women with a previous diagnosis of PCOS and healthy control subjects, and that ovarian reserve seemed better preserved in the women with PCOS. The live birth rate and the rate of miscarriages were similar in PCOS patients and control women. Mean ovarian volume and the number of antral follicles, measures of ovarian reserve, were significantly higher in PCOS patients. Likewise, PCOS patients had markedly higher serum concentrations of AMH.

In our study, almost all PCOS patients who attempted a pregnancy were successful. The cumulative delivery rate in our subjects was almost 90%, which is in line with a population-based study of PCOS patients (Koivunen et al., 2008) and a previous long-term follow-up study of infertile women with ovulatory disorders, where a cumulative delivery rate of 82% was reported (Sundstrom et al., 1997). More than two-thirds of the PCOS patients in the present study reported at least one spontaneous pregnancy.

The menstrual frequency among PCOS patients who were premenopausal and without hormonal contraception was lower than in control subjects, but PCOS patients reported on average almost nine menstrual cycles per year. Some clinical observations suggest improved fertility in ageing women with PCOS. A positive impact of ageing on cycle regularization in PCOS has recently been claimed, but the fertility outcome was not evaluated (Elting et al., 2000). The authors concluded that the follicle loss through the process of ovarian ageing could explain the occurrence of more regular cycles in older patients with PCOS (Elting et al., 2000). In women overall, ageing is associated with a subtle shortening of menstrual cycles of a mean of 2–3 days from the age of 20 to the early 40s (Small et al., 2006; Brodin et al., 2007). Most likely, the mechanism is associated with a reduction in antral follicle numbers, and consequently a more rapid follicular growth and selection, thus a shortening of the follicular phase. Careful monitoring has suggested that basal FSH levels are lower in young women with PCOS than in the early follicular phase of women with normal ovaries (Holte et al., 1994). The mechanism behind these low FSH levels, which may partly explain a lack of follicular growth, is probably increased production of inhibin B from the increased number of antral follicles in polycystic ovaries (Lockwood et al., 1998). Ovarian ageing results in diminution of the follicular cohort in both normal women and PCOS patients, and is associated with decreased inhibin B and AMH levels (Nikolaou and Gilling-Smith, 2007).
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Miscarriages in PCOS patients (Wang et al., 2004; Macklon and Fauser, 2005). Ageing may thus be followed by lower inhibin B levels, which will permit FSH enhancement and lead to full follicle maturation, more regular menstrual cycles and the appearance of ovulatory cycles in polycystic ovaries. A similar mechanism may be responsible for the increased number of ovulatory cycles after ovarian wedge resection or ovarian drilling, when the cohort of resting follicles is dramatically reduced (Farquhar et al., 2004; Macklon and Fauser, 2005). Ageing may thus be followed by a gradual decline in the pool of resting follicles and a catch-up of fecundity.

The number of subjects who had at least one miscarriage throughout their fertile life did not differ in comparison with the control subjects. These findings are at odds with previous reports of increased rates of miscarriages in PCOS patients (Wang et al., 2001; Legro, 2007; Boomsma et al., 2008). The discrepancy is most likely due to the fact that previous studies have merely included infertile PCOS patients undergoing assisted reproduction, whereas the present study included an unselected population, i.e. PCOS patients seeking help for various symptoms such as oligomenorrhea, hirsutism or infertility. However, more than half of our PCOS patients had at some point been treated for infertility. Our findings suggest that factors other than the PCOS diagnosis might contribute to the increased risk of miscarriage reported in prior studies, such as obesity, fertility treatment (Wang et al., 2001) or smoking (George et al., 2006). Indeed, in women with polycystic ovaries, but not a full syndrome, miscarriage rates have been reported to be normal (Koivunen et al., 2000).

There are several means of assessing ovarian reserve. The most established variables include basal FSH, AMH, inhibin B, ovarian volume and number of antral follicles. A number of previous reports about young women with PCOS lend support for an increased

<table>
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<th>Table III</th>
<th>Mean ± SEM serum concentrations of ovarian volume, number of antral follicles, ovarian steroids and gonadotropins in 52 premenopausal PCOS patients and 56 premenopausal controls without hormone treatment</th>
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<tr>
<td></td>
<td>Premenopausal women without hormone treatment</td>
</tr>
<tr>
<td></td>
<td>PCOS (n = 52)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>42.4 ± 4.5</td>
</tr>
<tr>
<td><strong>Ovarian volume (ml)</strong></td>
<td>9.5 ± 0.9**</td>
</tr>
<tr>
<td><strong>Antral follicles (n)</strong></td>
<td>11.7 ± 1.7***</td>
</tr>
<tr>
<td><strong>Estradiol (pmol/l)</strong></td>
<td>514 ± 79*</td>
</tr>
<tr>
<td><strong>Testosterone (nmol/l)</strong></td>
<td>1.5 ± 0.1***</td>
</tr>
<tr>
<td><strong>SHBG (nmol/l)</strong></td>
<td>50.4 ± 4.5*</td>
</tr>
<tr>
<td><strong>FAI</strong></td>
<td>5.1 ± 0.8**</td>
</tr>
<tr>
<td><strong>FSH (IU/l)</strong></td>
<td>6.2 ± 1.1*</td>
</tr>
<tr>
<td><strong>LH (IU/l)</strong></td>
<td>7.1 ± 0.7</td>
</tr>
<tr>
<td><strong>AMH (pmol/l)</strong></td>
<td>39.9 ± 6.1***</td>
</tr>
</tbody>
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*P < 0.025 in comparison with the respective control group, Mann–Whitney U-test.
**P < 0.01 in comparison with the respective control group, Mann–Whitney U-test.
***P < 0.001 in comparison with the respective control group, Mann–Whitney U-test.

<table>
<thead>
<tr>
<th>Table IV</th>
<th>Correlation between ovarian volume and follicle count and reproductive hormones in 52 premenopausal PCOS patients and 56 premenopausal control subjects without hormone treatment</th>
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<tbody>
<tr>
<td><strong>Follicles count</strong></td>
<td>Estradiol</td>
</tr>
<tr>
<td>Ovarian volume (ml)</td>
<td>0.62**</td>
</tr>
<tr>
<td>Antral follicles (n)</td>
<td>−0.10</td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.04</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.22*</td>
</tr>
<tr>
<td>SHBG</td>
<td>−0.53***</td>
</tr>
<tr>
<td>FAI</td>
<td>−0.17</td>
</tr>
<tr>
<td>FSH</td>
<td>0.52***</td>
</tr>
<tr>
<td>LH</td>
<td>0.00</td>
</tr>
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</table>

*P < 0.025 Pearson’s correlation coefficient.
**P < 0.01 Pearson’s correlation coefficient.
***P < 0.001 Pearson’s correlation coefficient.
ovarian reserve in these women compared with age-matched controls (Nikolaou and Gilling-Smith, 2004). Thus, polycystic ovaries are larger and contain more antral follicles as assessed by ovarian ultrasound (Adams et al., 1986; Balen and Michelmore, 2002). An important biopsy-study showed a much increased density of follicles at primary stages in polycystic ovaries compared with normal ovaries, suggesting that women with polycystic ovaries may actually be endowed with a larger ovarian reserve at birth (Webber et al., 2003). Several studies have reported higher levels of AMH in women with PCOS than in controls (Pigny et al., 2003; La Marca and Volpe, 2006; Catteau-Jonard et al., 2008), although findings on inhibin B are more discrepant (Chu et al., 2005; Tsigkou et al., 2008). Our findings for older women with PCOS are in accordance with these results, suggesting a retained greater ovarian reserve in these women in their 40s. Results for basal levels of FSH in PCOS have been less conclusive (Franks et al., 2008), which may to some extent be due to the high variability of this hormone and the necessity to restrict the comparisons to strictly cycle-matched samples (Holte et al., 1994). Interestingly though, Dahlgren et al. (1992) found lower levels of FSH in 50-year-old women with a previous PCOS diagnosis compared with controls, in spite of the fact that the women with PCOS had been wedge-resected, which is in line with our findings. Recently, it was proposed that serum FSH assessments are inferior to measuring AMH in identifying women with reduced ovarian reserve, largely because AMH is cycle-independent (Tremellen et al., 2005). This assumption is substantiated in the present study, where AMH levels correlated strongly both with ovarian volume and follicle counts. Recent results show AMH to be a strong predictor for success rates at assisted reproduction, i.e. ovarian reserve (La Marca and Volpe, 2006; Gnoth et al., 2008; Singer et al., 2008), underlining the importance of the vast differences in AMH levels that we found between women with PCOS and the controls.

The menstrual cycle length has also been reported to be an age-independent marker of female fertility. Recently, it was shown that the mean menstrual cycle length correlated linearly with pregnancy and delivery rates after in vitro fertilization (IVF)/intra cytoplasmic sperm injection (ICSI), even after age adjustment (Brodin et al., 2007). Although women with anovulatory PCOS were not included in that study, the authors found an association between mean menstrual cycle length and antral follicle counts, as many of the patients with cycles >28 days were women with multifollicular or ovulating polycystic ovaries. In line with those findings, others (Child et al., 2001; Tan and Child, 2002) have reported on higher pregnancy rates after IVF in women with PCOS than in women with normal ovaries.

The PCOS patients in our study had increased FAI compared with controls. Clearly, although their menstrual frequency might be normalized across time, the androgen levels remain increased in comparison with controls. In cross-sectional studies of PCOS patients, it appears as though older patients have 40–60% lower levels of total testosterone compared with younger patients. However, older PCOS patients continue to have increased testosterone levels in comparison with their age-matched controls (Winters et al., 2000).

The major limitation of the present study was the low overall response rate among PCOS patients, especially among subjects residing outside the Uppsala area. However, according to data from the Swedish Medical Birth Registrar, which comprises almost all births in Sweden.

Figure 2. The relationship between ovarian volume, number of antral follicles, AMH serum concentrations, PCOS status and age in 57 pre- and post-menopausal PCOS patients and 64 pre- and post-menopausal controls without hormonal treatment. Data are displayed with log-transformed variables as regression lines fit better with the statistical findings. The ovarian reserve declined at a similar rate with age in both groups ($P < 0.001$, respectively), and PCOS patients had a better ovarian reserve across ages compared with controls ($P < 0.001$ for each ovarian reserve variable). No group by age interactions were evident.
since 1973, no major selection bias has occurred, as birth rates were similar between participating and non-participating patients.

In conclusion, the present study indicates that most women with PCOS have given birth and that the rate of spontaneous pregnancies was relatively high. Together with the ultrasound findings and the increased levels of AMH, these findings could imply that PCOS patients have a good fecundity, and an ovarian reserve possibly superior to women with normal ovaries.

**Acknowledgements**

This study could not have been done without the excellent help from our research nurse Lena Moby.

**Funding**

The study was supported by grants from the Family Planning Foundation.

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Submitted on October 15, 2008; resubmitted on November 29, 2008; accepted on December 3, 2008.