ORIGINAL ARTICLE: REPRODUCTIVE ENDOCRINOLOGY

Differential rate in decline in ovarian reserve markers in women with polycystic ovary syndrome compared with control subjects: results of a longitudinal study

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Objective: To estimate rates of ovarian aging in polycystic ovary syndrome (PCOS) subjects versus a community control population.
Design: Longitudinal.
Setting: Tertiary academic center.
Subject(s): PCOS subjects diagnosed according to the 2004 Rotterdam criteria were systematically enrolled in a PCOS cohort study. The comparison control subjects were from the Ovarian Aging study, a prospective longitudinal study of ovarian aging in healthy women with regular menstrual cycles.
Intervention(s): Clinical data collection over two study visits.
Main Outcome Measure(s): Antral follicle count (AFC), ovarian volume (OV), and antimüllerian hormone level (AMH).
Result(s): PCOS subjects were found to have higher baseline values for all ovarian reserve markers compared with control subjects. Univariate models indicated that, compared with control subjects, PCOS patients experienced significantly faster rates of decline for both AFC and AMH. Change in OV did not differ significantly. To account for potential confounder effects, multiple analysis of covariance models were evaluated for the best fit, considering age, body mass index, and baseline ovarian reserve markers. Adjusted models demonstrated that PCOS patients do not experience a significant difference in AFC decline compared with control subjects, but they do experience a faster rate of decline in AMH ($P<.01$) and slower rate of decline in OV ($P<.01$).
Conclusion(s): Ovarian aging in PCOS is characterized by a more rapid decline in AMH and a slower decline in OV compared with control subjects. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Polycystic ovary syndrome, ovarian aging, antimüllerian hormone, antral follicle count, longitudinal

Polycystic ovary syndrome (PCOS) is a common endocrinologic disorder in women, characterized by androgen excess, oligo- or anovulation, and polycystic-appearing ovaries (PCO). There are three main diagnostic criteria: 1992 National Institutes of Health (NIH) criteria (1) 2004 Rotterdam criteria (2, 3) and the 2006 Androgen Excess Society criteria (4, 5). Depending on the diagnostic criteria used, the prevalence can range from as low as 6% (NIH) to as high as 20% (Rotterdam) (6).

Compared with healthy control women, women with PCOS demonstrate differences in reproductive function, including increased rates of subfertility due to oligo- or anovulation (7) and miscarriage (8). Furthermore, ovarian morphology varies between the two groups. Women with PCOS have ovaries with increased ovarian stroma, an increased number of follicles, and a thicker, hyperplastic theca cell layer compared with women without PCOS. Whether these

Received July 6, 2017; revised November 9, 2017; accepted November 10, 2017.
A.K.A. has nothing to disclose. C.-N.K. has nothing to disclose. M.Q. has nothing to disclose. N.L. has nothing to disclose. M.R. has nothing to disclose. M.I.C. has nothing to disclose. H.H. has nothing to disclose.
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Fertility and Sterility® Vol. ■, No. ■, ■ 2017 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2017.11.012

variations in ovarian features are also associated with differences in ovarian aging is not known. An understanding of possible differences in ovarian aging in PCOS and normal populations could shed light on determinants of this critical aspect of reproductive physiology.

It is well known that there are qualitative and quantitative changes that occur in the ovaries of women over time. Oocyte quality declines due to increasing meiotic nondisjunction and increasing mitochondrial genomic deletions (9). Morphologically, the number of primordial follicles decreases, while there is an increase in the fibrosis of stromal tissue and a decrease in ovarian volume (9). To better quantify these changes, markers of ovarian reserve exist, including: FSH, inhibin B, antimüllerian hormone (AMH), antral follicle count (AFC), and ovarian volume (OV).

Several studies have described the decline in ovarian reserve markers that occurs with age in normal women as well as in women with PCOS using cross-sectional data (10–14). However, limited longitudinal data are available. Longitudinal data provide a description of change over time in the same subject and can more accurately identify factors affecting rates of change. The objective of the present study was to use a longitudinal design to compare rates of change in markers of ovarian reserve in women with PCOS with those of community control women with regular menstrual cycles.

MATERIALS AND METHODS

The study was designed as a longitudinal follow-up study. Approval was obtained from the University of California–San Francisco Committee on Human Research.

PCOS Subjects

Subjects aged 18–50 years who originally enrolled in a cross-sectional PCOS cohort study were recruited to participate in a longitudinal follow-up study at the same institution. Institutional Review Board approval and subject consents were obtained.

The initial study visit (baseline) occurred during the years 2006–2014 at the time the patient was enrolled in the cohort study. For that visit, subjects were evaluated by a team of clinicians, including a reproductive endocrinologist, dermatologist, psychologist, genetic counselor, and nutritionist. Clinical data, including body morphometrics and ultrasound findings, were systematically collected. All subjects were premenopausal and met the Rotterdam criteria. Fasting serum samples were collected and stored at −80°C. Details of the methodology for the PCOS cohort have been previously published (15, 16).

In 2014, subjects were recruited to participate in a longitudinal follow-up study if they met the following criteria: willingness to discontinue hormonal medications for at least one month;, availability of serum samples from baseline visit; and age ≥ 18 years. A total of 206 PCOS subjects were eligible and contacted. Of these, 141 responded and 49 agreed to participate. Subjects were found to be ineligible for the ovarian reserve testing if they were pregnant or breastfeeding (n = 10), refused to discontinue oral contraceptive pills (OCPs; n = 5), or were taking other medication, such as spironolactone (n = 2). A total of 32 women were eligible and participated in the study. A total of ten subjects from the PCOS population were currently taking OCPs at the time of contact but discontinued their use for ≥ 1 month before their visit. Subjects underwent their follow-up visit in 2014–2015, regardless of the time of their baseline visit, resulting in a mean follow-up time of 3.09 ± 1.58 years.

Control Subjects

Control subjects were recruited from the community to participate in the Ovarian Aging (OVA) study, a prospective longitudinal study of healthy women with regular menstrual cycles at 22- to 35-day intervals. Exclusion criteria included chronic medical illness, oligo- or anovulation, surgically diagnosed endometriosis, premature ovarian failure, hyperandrogenism, history of uterine or ovarian surgery, oandr ovarian cysts. In addition, subjects who were taking OCPs were required to discontinue them for ≥ 3 months before enrollment in the study. Subjects were seen for their first study visit in 2007–2012 and follow-up visits in 2010–2013. Additional details regarding the design and methodology for the control population (OVA study) have been previously published (10, 17).

Transvaginal Ultrasound

The same three examiners (H.H., M.I.C., M.R.) used a Shimadzu SDU-450XL ultrasound with variable transducer frequency of 4–8 MHz for both study populations. OV was calculated as the total ovarian volume of both ovaries, using the formula for an ellipse. If a follicle or cyst >10 mm was found, the ovarian volume was excluded. AFC was calculated as the total number of antral follicles (defined as follicles measuring 2–9 mm) in both ovaries. If one ovary could not be evaluated owing to poor visualization, presence of cyst, or absence of ovary, that subject was excluded from the analysis. Control subjects underwent ultrasound examination during the follicular phase (cycle day 2–4). PCOS subjects who were ovulatory underwent ultrasound in the early follicular phase, and those who were predominantly anovulatory were scheduled according to patient convenience. To control for interobserver variation, a limited number of examiners were included in this study (n = 3), all of whom work closely together in a clinical setting with strict quality controls in place to ensure minimal interobserver variation in ultrasound measurements. In addition, two of the examiners (H.H. and M.R.) were trained in AFC and OV measurements by the third examiner (M.I.C.).

Serum Assays

For all of the study subjects, serum samples were banked at the baseline and follow-up study visits and stored at −80°C. AMH levels were measured in one batch by the Ultra-Sensitive ELISA (Ansh Labs; lower limit of detection 23 pg/mL) run at the Ligand Assay and Analysis Core Laboratory at the University of Virginia. The method uses a sandwich ELISA with functional sensitivity of 3 pg/mL. Quality control was performed by