The Pregnancy in Polycystic Ovary Syndrome II study: baseline characteristics and effects of obesity from a multicenter randomized clinical trial

Richard S. Legro, M.D.,[a] Robert G. Brzyski, M.D., Ph.D.,[b] Michael P. Diamond, M.D.,[f] Christos Coutifaris, M.D., Ph.D.,[e] William D. Schlaff, M.D.,[c] Ruben Alvero, M.D.,[c] Peter Casson, M.D.,[g] Gregory M. Christman, M.D.,[d] Hao Huang, M.D., M.P.H.,[o] Qingshang Yan, Ph.D.,[o] Daniel J. Haisenleder, Ph.D.,[h] Kurt T. Barnhart, M.D.,[e] G. Wright Bates, M.D.,[l] Rebecca Usadi, M.D.,[k] Richard Lucidi, M.D.,[i] Valerie Baker, M.D.,[j] J. C. Trussell, M.D.,[m] Stephen A. Krawetz, Ph.D.,[f] Peter Snyder, M.D.,[e] Dana Ohl, M.D.,[d] Nanette Santoro, M.D.,[c] Esther Eisenberg, M.D., M.P.H.,[n] and Heping Zhang, Ph.D.,[o] for the National Institute of Child Health and Human Development Reproductive Medicine Network

[a] Department of Obstetrics and Gynecology, Pennsylvania State University, Hershey, Pennsylvania; [b] Department of Obstetrics and Gynecology, University of Texas Health Science Center at San Antonio, Texas; [c] Department of Obstetrics and Gynecology, University of Colorado, Denver, Colorado; [d] Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, Michigan; [e] Department of Obstetrics and Gynecology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; [f] Department of Obstetrics and Gynecology, Wayne State University, Detroit, Michigan; [g] Department of Obstetrics and Gynecology, University of Vermont, Burlington, Vermont; [h] Ligand Core Laboratory University of Virginia Center for Research in Reproduction, Charlottesville, Virginia; [i] Department of Obstetrics and Gynecology, Virginia Commonwealth University, Richmond, Virginia; [j] Department of Obstetrics and Gynecology, Stanford Hospital, Palo Alto, California; [k] Department of Obstetrics and Gynecology, Carolinas HealthCare Center for Reproductive Medicine, Charlotte, North Carolina; [l] Department of Obstetrics and Gynecology, University of Alabama, Birmingham, Alabama; [m] Urology, SUNY Upstate Medical University, Syracuse, New York; [n] Fertility and Infertility Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Rockville, Maryland; and [o] Department of Biostatistics, Yale University School of Medicine, New Haven, Connecticut

Objective: To summarize baseline characteristics from a large multicenter infertility clinical trial.
Design: Cross-sectional baseline data from a double-blind randomized trial of two treatment regimens (letrozole vs. clomiphene).
Setting: Academic Health Centers throughout the United States.
Patient(s): Seven hundred fifty women with polycystic ovary syndrome (PCOS) and their male partners took part in the study.
Intervention(s): None.
Main Outcome Measure(s): Historic, biometric, biochemical, and questionnaire parameters.
Result(s): Females averaged 30 years and were obese (body mass index [BMI] 35) with ~20% from a racial/ethnic minority. Most (87%) were hirsute and nulligravid (63%). Most of the women had an elevated antral follicle count and enlarged ovarian volume on

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Reprint requests: Richard S. Legro, M.D., Department of Obstetrics and Gynecology, Penn State College of Medicine, M.S. Hershey Medical Center, 500 University Drive, H103, Hershey, Pennsylvania 17033 (E-mail: RSL1@PSU.EDU).

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ultrasound. Women had elevated mean circulating androgens, LH-to-FSH ratio (~2), and antimüllerian hormone levels (8.0 ng/mL). In addition, women had evidence for metabolic dysfunction with elevated mean fasting insulin and dyslipidemia. Increasing obesity was associated with decreased LH-to-FSH levels, antimüllerian hormone levels, and antral follicle counts but increasing cardiovascular risk factors, including prevalence of the metabolic syndrome. Men were obese (BMI 30) and had normal mean semen parameters.
Conclusion(s): The treatment groups were well matched at baseline. Obesity exacerbates select female reproductive and most metabolic parameters. We have also established a database and sample repository that will eventually be accessible to investigators.
Clinical Trial Registration Number: NCT00719186. (Fertil Steril® 2014;101:258–69. ©2014 by American Society for Reproductive Medicine.)
Key Words: Insulin resistance, hirsutism, infertility, ovulation induction, metabolic syndrome

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The Pregnancy in Polycystic Ovary Syndrome II (PPCOS II) study is a randomized, double-blinded clinical trial sponsored by the National Institutes of Health/Eunice Kennedy Shriver National Institute of Child Health and Human Development, conducted at 11 clinical sites in the United States. Briefly, the purpose of the trial is to determine which method of first-line ovulation induction with oral agents, clomiphene citrate (CC) or letrozole, is more likely to result in live birth in infertile women with polycystic ovary syndrome (PCOS). The trial rationale, summary of the protocol, and statistical analysis plan have been described previously (1). The PPCOS II trial builds on methodology that we developed during our PPCOS I trial (2), which tested CC, metformin, or the combination of both for ovulation induction, with live birth as the primary outcome (3). That trial led to the choice of CC as the primary comparator for the PPCOS II trial.

This report summarizes the baseline demographic and biomedical characteristics of the randomized subjects with PCOS, both by treatment arm and as a cohort in the PPCOS II trial. Furthermore, because we systematically examined and characterized the female subjects with PCOS, the baseline data provide insight into the infertility and medical history, biometric, ultrasonographic, biochemical, and psychosocial aspects of the syndrome. We also consented and collected data on male partners relating to their sperm parameters, sexual function, and quality of life (QoL) in the study, thus putting forward the concept of a couple, rather than an individual, as participants in an infertility trial. Because obesity coexists in many women with PCOS, we also examined key phenotypic parameters in these women with PCOS by established body mass index (BMI) categories.

MATERIALS AND METHODS

Study Design and Overview

The PPCOS II study is a multicenter, double-blind clinical trial of CC versus letrozole for five cycles of ovulation induction (24 weeks). Enrollment began in February 2009 and was completed in January 2012. After progestin withdrawal, 750 women were equally randomized to two different treatment arms: [1] CC 50 mg every day for 5 days (days 3–7 of cycle), or [2] letrozole 2.5 mg every day for 5 days (days 3–7 of cycle), for up to five cycles. Because both drugs were prescribed in a similar fashion (i.e., giving for 5 days to initiate follicular development and increasing stepwise by one additional pill if anovulatory [50 mg for CC and 2.5 mg for letrozole]), we used a study drug that was overencapsulated and identical in appearance. Dose was increased in subsequent cycles in both treatment groups for nonresponse or poor ovulatory response up to a maximum of 150 mg/d (3 pills) of CC (×5 days) or 7.5 mg/d (3 pills) of letrozole (×5 days). All subjects who conceived were followed for the outcome of pregnancy, including live birth. The protocol was approved by the local Institutional Review Board at all sites and participants (men and women) all gave written informed consent. The study was overseen by a National Institute of Child Health and Human Development appointed Data and Safety Monitoring Board.

Participants

We report on the 750 women and their male partners who were randomized into the study. Inclusion/exclusion criteria were applied both to women with PCOS and couples to identify other infertility factors.

Inclusion criteria for female subjects. Women diagnosed with PCOS based on a modified form of the Rotterdam criteria (4, 5) were enrolled. All women were required to have ovulatory dysfunction combined with either hyperandrogenism and/or polycystic ovaries (PCO).

Chronic anovulation or oligomenorrhea was defined as spontaneous intermenstrual intervals of $\geq$45 days or a total of $\leq$8 menses per year, or for women with more regular menses but suspected anovulatory bleeding, a midluteal (~21 days from last bleeding episode) serum P level <3 ng/mL, which was considered to be indicative of chronic anovulation.

Hyperandrogenism was defined as either hirsutism or hyperandrogenemia. Hirsutism was determined by a modified Ferriman-Gallwey score >8 at screening examination (6). Hyperandrogenemia was determined from serum measurements performed at local laboratories (using predetermined local cutoffs within the year prior to participation).

We used the revised Rotterdam criteria for diagnosing PCO (7).The PCO on ultrasound were defined as either an ovary that contains 12 or more follicles measuring 2–9 mm in diameter, or an increased ovarian volume (>10 cm^3 without concomitant cysts) on at least one ovary, for entry into the study.