ORIGINAL ARTICLE: REPRODUCTIVE ENDOCRINOLOGY

Association of testosterone and antimüllerian hormone with time to pregnancy and pregnancy loss in fecund women attempting pregnancy

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Objective: To examine whether higher T and/or antimüllerian hormone (AMH) was associated with anovulation, time to pregnancy (TTP), or pregnancy loss risk among healthy, fecund women without diagnosed polycystic ovary syndrome.
Design: Prospective cohort study conducted as a secondary analysis from the Effects of Aspirin in Gestation and Reproduction randomized trial.
Setting: University medical centers.
Patient(s): A total of 1,198 healthy, eumenorrheic women aged 18–40 years attempting spontaneous pregnancy with one to two prior pregnancy losses were included. Women were categorized by baseline antimüllerian hormone (AMH), as a surrogate marker of antral follicle count, and T concentrations; the highest quartile for each was "high," and below the top quartile (i.e., lower 75% of values) was "norm," forming four groups: norm T/norm AMH (n = 742), norm T/high AMH (n = 156), high T/norm AMH (n = 157), and high T/high AMH (n = 143).
Intervention(s): Not applicable.
Main Outcome Measure(s): Anovulation, pregnancy incidence, TTP, and pregnancy loss incidence.
Result(s): Women with high T/high AMH had a greater anovulation risk (risk ratio 1.58, 95% confidence interval 1.13–2.22) compared with women with norm T/norm AMH, but with imprecise differences in incidence of pregnancy, TTP, or pregnancy loss.
Conclusion(s): Women with higher T and AMH had more frequent anovulatory cycles but with marginal impacts on TTP or pregnancy loss. A continuum of mild inefficiency in reproductive function may be related to higher T and AMH, including in fecund women with normal menstrual cycles and no clinical diagnosis of polycystic ovary syndrome, but with unclear effects on fecundability and pregnancy loss.
Clinical Trial Registration Number: NCT00467363. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)

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Polycystic ovary syndrome (PCOS) is a collection of abnormalities including elevated androgens, irregular or absent menstrual cycles, and/or polycystic ovarian morphology, and is the most common cause of infertility in women (1). Furthermore, mechanisms similar to those leading to ovulatory infertility in PCOS may impact women not meeting the varying criteria for a clinical diagnosis, because these symptoms occur along a continuum, with relatively higher T alone linked to more frequent anovulatory menstrual cycles among healthy, premenopausal women without any PCOS or infertility diagnoses (2). In addition, current understanding of reproductive dysfunction related to PCOS characteristics is almost exclusively based on clinical populations. Yet women from a population sample meeting criteria for PCOS demonstrated lesser adiposity, different racial makeup, and milder perturbations in endocrine parameters compared with a clinical sample, suggesting that our current understanding and characterization of PCOS may be biased (3). Given the importance of identifying endocrinologic perturbations that may predispose toward reproductive dysfunction across the spectrum of PCOS-related characteristics and characterizing the extent of that dysfunction, the present investigation aimed to examine associations of PCOS-related endocrine features among women without a known PCOS diagnosis with incidence of pregnancy, time to pregnancy, and incidence of pregnancy loss. Therefore, the specific aims of the present study were to examine the incidence and time to pregnancy and incidence of pregnancy loss, as well as sporadic anovulation and metabolic, endocrine, and menstrual cycle characteristics in relation to higher levels of total T and/or antimüllerian hormone (AMH, as a marker of antral follicle count) among regularly menstruating fecund women with no known diagnosis of PCOS or infertility attempting spontaneous pregnancy.

MATERIALS AND METHODS

The Effects of Aspirin in Gestation and Reproduction (EAGeR) trial was a multicenter, block-randomized, double-blind, placebo-controlled trial of low dose aspirin (81 mg) in 1,228 women recruited from four university medical centers in the United States from 2007 to 2011. Institutional review board approval was obtained at each study site and the data coordinating center. All participants provided written informed consent. A data safety and monitoring board optimized patient safety (4). The trial was registered with ClinicalTrials.gov (NCT00467363). Full details of the study design, methods, and participant characteristics have been previously described (5).

Study Design and Population

Women trying to conceive aged 18–40 years with regular menstrual cycles of 21–42 days in length, no known history of infertility, confirmation of one to two prior pregnancy losses, and up to two prior live births were eligible for the EAGeR trial. In the parent trial, participants were randomized to receive either 81 mg low-dose aspirin (n = 615) or placebo (n = 613), taken daily until completion of six menstrual cycles or until week 36 of gestation among those who became pregnant (5). Exclusion criteria for all women included, but were not limited to, the following: clinical indication for use of anticoagulant therapy or chronic use of nonsteroidal anti-inflammatory drugs; major medical disorders (e.g., diabetes, hypertension); and any prior diagnosis of infertility or subfertility, including related conditions such as PCOS (5).

Furthermore, all women must have not taken long-acting hormonal contraceptive medication (e.g., Depo-provera, intrauterine device) for at least 12 months and/or not taken oral contraceptive pills or other hormone supplements (i.e., patch, ring) within 3 months before enrollment. The effects of low-dose aspirin on live birth, pregnancy loss, and fecundability have been previously reported (6–8).

Study Procedures

Participants attended a baseline study visit timed to occur at approximately day 2–4 of their menstrual cycle (i.e., study entry, immediately before randomization). During this baseline visit, participants completed questionnaires related to reproductive health, demographic, and lifestyle factors. In addition, anthropometric measures (weight, height, and bicep, tricep, subscapular, and suprailiac skinfolds) were measured by trained study staff. The averages of triplicate measures of skinfolds were used to calculate the central to peripheral skinfold ratio as (subscapular + suprailiac)/(bicep + tricep) (9), and the sum of skinfolds was calculated as the sum of all four skinfold locations. Blood samples were also collected at the same visit, centrifuged, and serum/plasma aliquoted and frozen within 90 minutes and stored at −80°C until analysis. Fertility monitors were provided to assist with timing of intercourse and scheduling study visits by menstrual cycle phase (Clearblue Easy Fertility Monitor; Inverness Medical).

During the first two menstrual cycles of study participation, women collected daily first morning urine samples, which were stored in provided labeled vials and freezer boxes in their home freezer and provided frozen to study staff at clinic visits. Urine samples then remained frozen at −80°C until analysis.

Cycle length was defined as the number of days between the first day of bleeding of each menstrual cycle. Duration of the follicular phase was the first day of menstrual bleeding through the day of expected ovulation according to the LH peak on the fertility monitor; luteal length was the day after expected ovulation through the last day before the next