Sonographic markers of ovarian morphology, but not hirsutism indices, predict serum total testosterone in women with regular menstrual cycles

Heidi Vanden Brink, M.Sc.,[a] Amy D. Willis, M.Sc.,[b] Brittany Y. Jarrett, B.S.,[a] Annie W. Lin, M.Sc.,[a] Steven Soler, B.S.,[a] Siân Best, B.A.,[a] Erica L. Bender, M.S.N.,[a] Andrew K. Peppin, M.D.,[a] Kathleen M. Hoeger, M.D.,[c] and Marla E. Lujan, M.Sc., Ph.D.[a]

[a] Human Metabolic Research Unit, Division of Nutritional Sciences, Cornell University, Ithaca; [b] Department of Statistical Sciences, Cornell University, Ithaca; and [c] Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Rochester Medical Center, Rochester, New York

Objective: To determine whether sonographic markers of ovarian morphology or male pattern hair growth scores predict androgen levels in women with regular or irregular menstrual cycles.
Design: Cross-sectional observational study.
Setting: Clinical research unit.
Patient(s): Seventy-six women of reproductive age (18–39 years) were evaluated for male-pattern hair growth (using a modified Ferriman-Gallwey scoring system), ovarian morphology (by transvaginal ultrasonography), and total serum testosterone (T) (by liquid chromatography tandem mass spectrometry).
Intervention(s): Not applicable.
Main Outcome Measure(s): Regional and total modified Ferriman-Gallwey scores, number of follicles per follicle size category, follicle number per ovary, ovarian volume, ovarian area, stromal to ovarian area ratio, stromal echogenicity index, total testosterone (total T), and menstrual cycle length.
Result(s): Neither regional nor total modified Ferriman-Gallwey scores correlated with total T concentrations in women with regular or irregular menstrual cycles, as judged by the Least Absolute Shrinkage and Selection Operator technique. By contrast, a sonographic marker (follicle number per ovary 6–9 mm) significantly predicted total T concentrations in women with regular menstrual cycles but not in women with irregular menstrual cycles.
Conclusion(s): Sonographic markers of ovarian morphology, but not hirsutism scores, predicted total T levels. However, the predictive value of ovarian morphology for total T differed by menstrual cycle status. That sonographic markers did not predict androgen levels in a diverse cohort of women with cycle irregularity suggests the potential for distinct variations in ovarian morphology for androgenic and nonandrogenic types of cycle irregularity. Overall, our findings support that an assessment of ovarian morphology may be helpful in reflecting total T levels. (Fertil Steril® 2016;105: 1322–9. ©2016 by American Society for Reproductive Medicine.)
Key Words: Hirsutism, oligoamenorrhea, ovaries, testosterone, ultrasonography

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/brinkh-ovarian-morphology-androgen-levels/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Received June 5, 2015; revised December 24, 2015; accepted December 28, 2015; published online January 27, 2016.
H.V.B. has nothing to disclose. A.D.W. has nothing to disclose. B.Y.J. has nothing to disclose. A.W.L. has nothing to disclose. S.S. has nothing to disclose. S.B. has nothing to disclose. E.L.B. has nothing to disclose. A.K.P. has nothing to disclose. K.M.H. has nothing to disclose. M.E.L. has nothing to disclose.
Supported by Cornell University's Division of Nutritional Sciences, the President's Council of Cornell Women, the United States Department of Agriculture (#34324-20769), and the National Institutes of Health (T32-DK007158). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Diabetes and Digestive and Kidney Diseases or the National Institutes of Health.
Portions of this work were presented at the annual meetings of the Canadian Fertility and Andrology Society (September 11–14, 2014, Quebec City, Quebec, Canada) and the Androgen Excess and PCOS Society (October 22–23, 2014, Lihue, Hawaii).
Reprint requests: Marla E. Lujan, M.Sc., Ph.D., Division of Nutritional Sciences, Cornell University, 216 Savage Hall, Ithaca, New York 14853 (E-mail: MEL245@cornell.edu).

Fertility and Sterility® Vol. 105, No. 5, May 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.12.136

Biochemical assessments of androgens in women are controversial (1). Commercial assays for serum testosterone (T) yield inconsistent results (2, 3), whereas direct measurements of free T are technically challenging (3, 4) and influenced by metabolic status (5, 6). Overall, mass spectrometry assay performance is improved compared with commercially available products—albeit modest interlaboratory differences in estimates have been reported (7, 8). To that end, a national effort to standardize androgen measurements across centers is underway and promises to have significant impact on future estimates of androgens in women (1, 3). Given these challenges in biochemical assessments of androgens in women, additional measures to evaluate androgen status are also needed.

Male-pattern hair growth is the most commonly accepted clinical indicator of androgen status (9). Atypical hair growth is commonly quantified using the modified Ferriman-Gallwey (mFG) scoring system, which rates hair growth on nine androgen-sensitive regions of the body using a 0–4 scale (10). The utility of all nine regions in the prediction of androgen excess remains a topic of debate (11–15). This notion has merit because a more focused approach involving a subset of regions with the greatest sensitivity to androgen levels could help to obviate some of the subjectivity associated with hirsutism scoring (11, 13, 16). Uncertainty in the utility of hirsutism scores stems from findings of poor interrater agreement in hirsutism scores (6, 17, 18), as well as the known influence of age (15), race and ethnicity (19–22), and adiposity (6, 17, 18) on male-pattern hair growth. Although hirsutism has shown better sensitivity for biochemical hyperandrogenism compared with acne or alopecia (23, 24), its specificity is low because idiopathic hirsutism occurs in 5%–15% of the general population (22) and in up to 50% of all mild hirsutism cases studied (25). The advent of more standardized approaches to measure serum androgens provides an opportunity to revisit the utility of hirsutism scores to reflect androgen levels.

In view of the improved resolution afforded by the latest imaging systems (26–28), there is growing evidence supporting an expanded role for ovarian ultrasonography in the clinical evaluation of androgen excess. We (29), using mass spectrometry, and others (30–32), using commercially available assays, have shown that ovarian markers, such as antral follicle count, ovarian size, and stromal characteristics, are significantly associated with total testosterone (total T) concentrations. In the case of antral follicle count, this is consistent with the concept that small antral follicles are a significant source of androgen production by the ovaries (33). Whether the relationship between ovarian morphology and androgen production is conserved between women with and without regular menstrual cycles is uncertain. Studies to date have been limited primarily to women with hyperandrogenic causes of anovulation (31) and those undergoing assisted reproduction (34, 35). Given that androgen excess can manifest in women with regular menstrual cycles and is associated with increased risk for cardiometabolic disease (36–38), there is relevance in identifying clinical markers of androgen excess in women with both regular and irregular menstrual cyclicity.

The primary objective of this research was to assess the ability of mFG scores and sonographic markers of ovarian morphology to predict total T levels in women. To this end, we enrolled women with regular and irregular cycles, to assess any impact of menstrual cycle status on these relationships. We hypothesized that a sonographic marker from the ovary, the main site of androgen production, would significantly predict total T concentrations, whereas a marker reflecting a consequence of androgen action, such as a hirsutism index, would have limited ability to predict total T. In this way, ultrasonography could represent an additional tool to predict androgen status.

MATERIALS AND METHODS

Study Subjects

Seventy-six women from the general population (Tompkins County, New York and surrounding area) were recruited to the study between 2009 and 2014. Participants were recruited using targeted advertisements seeking both healthy women of reproductive age with regular menstrual cycles (every 21–35 days) and women with a history of irregular or absent menstrual cycles (>35 days), with the goal of recruiting equal numbers of women in each group. Women who were 18–39 years of age with clear visualization of at least one ovary on ultrasonography were eligible to participate. Exclusion criteria included evidence of reproductive aging as gauged by the Stages of Reproductive Aging (39) and/or premature ovarian insufficiency, use of hormonal therapy, insulin sensitizers, and/or statins in the previous 2 months, participation in a drug trial within the last 30 days, pregnancy, lactation, hyperprolactinemia, diabetes, or uncontrolled thyroid disorders. Written, informed consent was obtained from all participants. This study was approved by the institutional review board at Cornell University (Ithaca, NY).

Study Procedures

Participants were evaluated at Cornell University's Human Metabolic Research Unit for the following: [1] an assessment of self-reported menstrual cycle history to determine the extent of any menstrual cycle disturbance; [2] a physical examination to assess height, weight, vital signs, and male-pattern terminal hair growth; [3] a transvaginal ultrasound scan to characterize ovarian morphology; and [4] fasting blood tests. Menstrual cycle history was taken at the time of enrollment as part of establishing eligibility to participate in the study. A baseline ultrasound scan was also conducted at this initial visit to corroborate visualization of ovaries and stage of cycle. A physical examination, repeat ultrasound scan, and blood draw were then conducted on the same day during a follow-up early morning study visit to the research unit. In the case of women with regular menstrual cycles, biochemical and sonographic evaluations occurred during a follow-up visit scheduled between days 2 and 7 of their cycle. In women with irregular cycles, none demonstrated a dominant follicle or corpus luteum at the initial ultrasound scan or during the follow-up study visit (approximately 1 to 2 days later). In this way, all measures for this group were