Ovarian volume in normal and hyperandrogenic adolescent women

Franca Fruzzetti, M.D.,[a] Anna Maria Campagna, M.D.,[b] Daria Perini, M.D.,[a] and Enrico Carmina, M.D.[b]

[a] Department of Obstetrics and Gynecology, University of Pisa, Pisa; and [b] Endocrinology and Metabolism, University of Palermo, Palermo, Italy

Objective: To study the threshold for increased ovarian size during different periods of adolescence.
Design: Cross sectional study with retrospective analysis.
Setting: University center.
Patient(s): A total of 146 hyperandrogenic adolescent women and 72 healthy adolescent controls.
Intervention(s): Intravaginal or transabdominal ovarian sonography.
Main Outcome Measure(s): Determination of normal ovarian size during the different phases of adolescence calculated using the ellipsoid formula; calculation of threshold for increased ovarian size during different adolescent gynecologic ages and prevalence of increased ovarian size for hyperandrogenic girls at different gynecologic ages.
Result(s): In adolescent women, the threshold for increased ovarian size was 11.5 cm^3 during first 2 years from menarche, 10.5 cm^3 during the third year from menarche, and 10 cm^3 during the fourth and fifth years from menarche. The prevalence of increased ovarian size in hyperandrogenic adolescents was around 50% from the third to fifth years from menarche and 35% during the first 2 years from menarche.
Conclusion(s): After the first 2 years from menarche, the thresholds for increased ovarian size are similar to those used among adults. During first 2 years from menarche, ovarian size is larger, and differentiation between normal or increased ovarian sizes may be more difficult. In hyperandrogenic adolescent patients, the prevalence of increased ovarian size is relatively low (ranging from 35% to 50% during the different periods of adolescence). In these patients, increased ovarian size may have low sensitivity as a criterion for the diagnosis of possible polycystic ovary syndrome. (Fertil Steril® 2015;104:196–9. ©2015 by American Society for Reproductive Medicine.)
Key Words: Adolescence, adolescent ovarian size, adolescent PCOS, hyperandrogenism, increased ovarian size, PCOS

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The possibility making a diagnosis of polycystic ovary syndrome (PCOS) in adolescents remains controversial (1). In fact, the same criteria—anovulation, hyperandrogenism, and polycystic ovaries—that are used for diagnosis in adults may be transitory or in evolution, in adolescents (2–4). In our literature review several years ago we suggested that the diagnosis of PCOS during adolescence may be reasonably suspected if the same three criteria are contemporaneously present in girls who are at least 2 years past menarche (1). However, the definition of polycystic ovaries can be difficult at this age.

In adult women, follicular count seems to be a more useful measure than increased ovarian size for defining polycystic ovaries (5), but during adolescence the number of follicles is particularly high (6), so the threshold for defining increased follicular count used in adult women may be incorrect. In addition, a precise follicular count may require transvaginal ovarian sonography, a methodology that is often not possible in young girls. Thus, it has been suggested that increased ovarian size may be of more use in the diagnosis of polycystic ovaries in adolescent girls (7). However, ovarian size is larger during adolescence than adulthood (8), and its progressive reduction with gynecologic age (9, 10) complicates its use for diagnosing polycystic ovaries. Our previous review suggested using the same cutoff of 10 cm^3 in adolescents and adults (1), but the available data to support this cutoff are few (11) and are mainly based on a magnetic resonance imaging (MRI) study of adolescent ovaries (9).

In this study, we assessed ovarian size in a group of healthy adolescent

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Reprint requests: Enrico Carmina, M.D., Endocrinology and Metabolism, University of Palermo, Via delle Croci, 47, 90139 Palermo, Italy (E-mail: enricocarmina@libero.it).

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girls and for comparison in a large group of hyperandrogenic adolescent girls. Because the available data show that ovarian size decreases with the progression of adolescence, we divided our controls and patients according their gynecologic age and determined the ovarian size cutoffs during the different phases of adolescence.

MATERIALS AND METHODS

This study was conducted in two Italian university centers between 2011 and 2013. The healthy adolescent women (controls) were students in two local schools who volunteered for the study. The young hyperandrogenic women were consecutive patients at the two participating institutions being treated as outpatients for clinical or biochemical signs of hyperandrogenism.

We enrolled 72 healthy, menstruating, nonhyperandrogenic women, aged 11 to 17 years (mean age 13.7 ± 1 years) of gynecologic age (time in years elapsed since menarche) of 1 to 5 years. The patients were 146 hyperandrogenic adolescents aged 11–17 years (mean age 14.1 ± 1 years) of gynecologic ages 1 to 5 years who were retrospectively evaluated. The large majority of the young hyperandrogenic women studied (138 out of 146) had irregular menses. The two groups were not matched for age or body weight.

The project design included a medical examination, biochemical analyses, and ovarian sonography. The procedures we adopted were in agreement with the Helsinki Declaration of 1975 as revised in 1983, and the study was approved by the local ethics councils. All participants in the study gave their informed consent. Because of the age of the controls and patients, legal informed consent was also obtained from authorized representatives (parents), who also were present during all stages of the medical examination, including the laboratory analyses and ovarian ultrasounds.

At admission all participants underwent a medical examination and answered a questionnaire on their personal and medical information, including age, past medical history, and use of medications. All controls were studied in a single institution (Endocrinology and Metabolism, University of Palermo). None of patients or controls were taking medication from at least 3 months before entering the study. Menstrual cycles were recorded for ≥3 months, and normal menses were defined as a menstrual cycle interval of 24 to 35 days.

Laboratory Analyses

In all patients and controls the serum levels of total testosterone (T) and dehydroepiandrosterone sulfate (DHEAS) were determined on days 3–5 of the cycle. In non-menstruating women the blood samples were drawn after the menstrual cycle had been induced by progesterone administration.

Serum hormone levels were quantified by well-established methods that had been validated previously in our laboratories. The total T concentrations were determined by use of a competitive immunoassay (Johnson & Johnson/Ortho Clinical). The DHEAS concentrations were determined by use of radioimmunoassay (Orion Diagnostics). In all assays, the intra-assay and interassay coefficients of variation did not exceed 6% and 15%, respectively.

Biochemical hyperandrogenism was defined as serum T >60 ng/dL (≥2.08 nmol/L) and/or serum DHEAS 3 μg/mL (≥7.8 mmol/L). These values for hyperandrogenism had been previously validated in adult women with the use of the previously described assays.

Ovarian Ultrasound

In all patients and controls, on days 3 to 6 of the cycle the ovarian morphology was assessed by intravaginal or transabdominal ultrasound using a transducer frequency of 6–10 MHz. In both centers, the same machine (MyLab 50 Xvision, Esaote) was used.

Ovarian volume was calculated by the formula $\pi/6$ ($DB_1 \times DB_2 \times DB_3$), where the dimensions (D) of length, width, and thickness were used. The size of both ovaries was assessed, and the mean ovarian size was calculated. In no instance did the ovarian ultrasound have to be repeated because of the finding of a dominant follicle. Both data obtained by transabdominal and intravaginal ultrasound were considered useful for the diagnosis. However, in all controls and in the large majority of hyperandrogenic adolescent patients (n = 117, 80%) a transabdominal ultrasound scan was performed.

Statistical Analyses

Statistical analyses were performed using Statview 5.0 (SAS Institute). Univariate analyses were performed using an unpaired *t* test for the numeric variables. Bonferroni correction for multiple comparisons was applied. Thresholds for increased ovarian size were calculated as mean ± 2 standard deviation (SD) of the values of the healthy controls. The results are expressed as mean ± SD.

RESULTS

Table 1 shows the clinical data, hormone levels, and mean ovarian size of the healthy and hyperandrogenic girls. Although the two groups were not matched for age or body weight, their mean ages were similar; the hyperandrogenic adolescent girls had statistically significantly ($P<.01$) higher body mass index (BMI), hirsutism scores, total testosterone levels, DHEAS levels, and ovarian size compared with the healthy adolescent girls. All controls had normal menses whereas the large majority of hyperandrogenic patients had irregular menses (n = 134, 92%).

Table 2 reports the ovarian sizes of the healthy and the hyperandrogenic girls, divided according their gynecologic age. Because there were fewer healthy girls of gynecologic age 1, the patients of gynecologic ages 1 and 2 were regrouped. It may be observed that the younger girls (1–2 years after the menarche) had a higher threshold (95 percentile of values of ovarian size) for increased ovarian size (11.5 cm^3), but then the threshold was around 10 cm^3. At any gynecologic age, the hyperandrogenic adolescents had larger ovarian sizes ($P<.01$) than the healthy adolescent controls (Table 2). According to these thresholds, 66 (45.2%) hyperandrogenic adolescents had increased ovarian size.