

Multifollicular ovaries in female adolescents with cystic fibrosis

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Objective: To assess hormonal status and morphology of ovaries in cystic fibrosis (CF) adolescents.

Design: Prospective study.

Setting: University teaching hospital.

Patient(s): Female adolescents: 18 with CF and 18 normal.

Intervention(s): Transabdominal pelvic ultrasonography and venipuncture.

Main Outcome Measure(s): Hormone profile and ultrasound examination of ovaries and uterus.

Result(s): Levels of LH, LH/FSH, androstenedione, and PRL were significantly higher in the CF adolescents. Levels of sex hormone-binding globulin (SHBG) were significantly lower and had negative correlation with percentage of body fat. Percentage of body fat and body mass index were significantly lower in CF and had significant correlation. Levels of E₂, FSH, T, and DHEAS were comparable in the two groups. Ultrasound revealed cysts in eight (44%) of the CF subjects; six of these had LH/FSH >3, and three had been operated for ovarian torsion. Nine out of all of the CF subjects (50%) had DM. No obesity, hirsutism, or acne was observed. The Shwachman score was 87.44 ± 4.83 and correlated significantly with the percentage of body fat.

Conclusion(s): Multifollicular ovaries were frequent in CF adolescents. Hormone changes characteristic of polycystic ovary syndrome were detected. The low T levels, despite low SHBG, and the absence of hirsutism or acne may be a result of a lower percentage of body fat, disturbances at the pilosebaceous-adipocyte endocrine unit, or mechanical or other causes. (Fertil Steril® 2006;85:1484–7. ©2006 by American Society for Reproductive Medicine.)

Key Words: Cystic fibrosis, hormones, ovaries, cysts, and multifollicles

Cystic fibrosis (CF) is an autosomal recessive disease arising from the mutation of a gene located on the long arm of chromosome 7. Cystic fibrosis transmembrane conductance regulator (CFTR) is the protein coded by the CF gene; it is an apical chloride channel responsible for ion transport through epithelial cells. The absence or dysfunction of CFTR results in thickened and desiccated secretions throughout the respiratory airways, exocrine pancreas, hepatobiliary ducts, sweat ducts, and the reproductive organs (1).

The CFTR gene and protein expression in the reproductive system may be responsible for infertility in male individuals with CF. In 95% of male adults with CF, congenital bilateral absence of the vas deferens is associated with ob-

structive azoospermia and infertility (2, 3). The effect of CFTR gene and protein expression on the fertility of women is less clear. Johannesson et al. (4) have demonstrated in rats that the CFTR messenger RNA is expressed within the cerebral cortex and medial preoptic area, which regulate the visceral and endocrine functions associated with sexual differentiation. The exact nature of the pathogenesis of infertility and delayed sexual maturation could relate to changes in GnRH secretion.

The aim of this prospective study was to investigate the hormonal status (gonadotropins and gonadal steroids) in female adolescents with CF and to correlate these findings with their fat measures, their menses, and the ultrasonographic morphology of their ovaries.

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MATERIALS AND METHODS

Eighteen female adolescents, age range 12 to 23 years, who attended the CF clinic were included in the study. The control group consisted of 18 healthy female adolescents matched for age and stage of puberty. The clinical status was

evaluated with Shwachman score, pulmonary function, and the presence of diabetes mellitus. Body mass index (BMI) and percentage of body fat (BF%) were used as parameters of growth and nutrition. Serum E₂, FSH, LH, androstenedione (A), T, DHEAS, sex hormone-binding globulin (SHBG), and PRL were measured during the follicular phase. Ultrasound examination of ovaries and uterus were also performed at this time. Age of menarche of all the participants was noted. Patients with thyroid gland disease were excluded.

Assessment of BMI

The nutritional status was estimated calculating the BMI as kg of body weight divided by the height value (in m) squared (Quetelet's Index).

Assessment of Fat Percentage

Body composition analysis was performed using the hand-foot bioelectrical impedance analysis (Maltron 906; Maltron International Ltd., Rayleigh, Essex, UK), and the following parameters were measured: total body fat (TBF), percentage fat (BF%), lean mass (LM), percentage lean mass (LM%), and percentage body water (BW%).

Assessment of Shwachman Score

This clinical score was estimated according to the Shwachman-Kulczycki criteria (5).

Assessment of Hirsutism and Acne

Body hair grading was performed according to the modified Ferriman and Gallwey score grades on 11 body areas (upper lip, chin, chest, upper and lower abdomen, thighs, upper and lower back, arm, forearm, and buttocks) from 0 (no hair) to 4 (frankly virile) (6). A total score of 8 or more was considered abnormal for an adult caucasian woman. A score of 44 was the most severe. Acne was assessed according to the Plewing and Kligman score (7). Acne was defined as a score ≥ 1 and serious acne as a score ≥ 2 .

Assessment of Hormones

Serum E₂, FSH, LH, A, T, DHEAS, SHBG, and PRL were measured during the follicular phase. Serum LH and FSH concentrations were determined by immunofluorometric assay (Amerlite, Amersham, UK). For the LH assay, the lower limit of detection was 0.3 IU/L, and the intraassay and interassay coefficients of variation (CV) were 5% and 10%, respectively. For the FSH assay, the lower limit of detection was 0.5 IU/L, and the intraassay and interassay CV were 6% and 9%, respectively. Prolactin concentrations were measured by an immunoradiometric-assay (Medgenix Diagnostics, Fleurus, Belgium) with a lower limit of detection of 0.05 IU/L, an intraassay CV of 4%, and an interassay CV of 9%. Estradiol concentrations were measured by means of a radioimmunoassay (Oestradiol-2; Sorin Biomedica, Salug-

gia, Italy). The detection limit was 37 pmol/L, the intraassay CV was 4%, and the interassay CV was 11%. Serum A and DHEAS were determined by a radioimmunoassay (Coat a Count; DPC, Los Angeles, CA). For the A assay, the lower limit of detection was 0.4 nmol/L, the intraassay CV was 5%, and the interassay CV was 11%. For DHEAS, the detection limit was 0.2 μ mol/L, the intraassay CV was 4%, and the interassay CV was 8%. Testosterone concentrations were determined using a double antibody radioimmunoassay (Coat-A-Count; DPC). The lower limit of detection was 0.3 nmol/L; the intraassay CV was 4%–12%, and the interassay CV was 12%. Serum SHBG levels were measured using an enzyme immunoassay method (Rasim, Liege, Belgium) with an intraassay CV of 5% and an interassay CV of 9.5%.

Assessment of Cystic Fibrosis-Related Diabetes Mellitus

Nine of the 18 CF patients had cystic fibrosis-related diabetes mellitus (CFRDM); two had uncontrolled CFRDM, and eight were well controlled using insulin (short and intermediate) injections twice daily and having a glycosylated hemoglobin of 5.5%–7.0% (DCA 2000; Bayer Diagnostics, Chemical Analyzers, Germany).

Assessment of Pelvic Ultrasonography

Ovarian and uterine morphology and volume were studied by transabdominal ultrasonography in all patients and healthy controls. Two-dimensional ultrasound was applied to determine follicle size as well as calculate ovarian volume. Three-dimensional ultrasound was applied to count the number of follicles measuring 2–10 mm in diameter in the largest single sonographic plan.

Committee of Bioethics

The study was approved by the Medical School Committee of Bioethics.

Statistical Analysis

Independent Student *t* test was used for the statistical analysis. Values of $P < .05$ were considered statistically significant.

RESULTS

In eight (40%) of the CF adolescents, a multifollicular ovarian structure was observed by pelvic ultrasonography. All eight had irregular menses. The multifollicular ovaries (MFO) were normal or slightly enlarged in size and filled with six or more cysts 4–10 mm in diameter. The ovarian stroma was normal. Six of these eight patients had an LH/FSH ratio > 3 , and four were operated on because of ovarian torsion. Nine (50%) CF patients, all of them older, had CFRDM, uncontrolled in two of them. No obesity, hirsutism, or acne was observed, and menarche occurred within the normal time range for Greek girls.

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