Prevalence of polycystic ovary syndrome in young women who had idiopathic central precocious puberty

Roberto Franceschi, M.D.,[a] Rossella Gaudino, M.D.,[a] Alma Marcolongo, M.D.,[b] Maria Chiara Gallo, M.D.,[a] Luigi Rossi, M.D.,[c] Franco Antoniazzi, Ph.D.,[a] and Luciano Tatò, Ph.D.[a]

[a] Pediatrics Unit and [b] Obstetrics and Gynecology Unit, Department of Mother and Child, Biology-Genetics; and [c] Department of Clinical Biochemistry, University of Verona, Italy

Objective: To assess the prevalence of polycystic ovary syndrome (PCOS) in a cohort of young women with previous idiopathic central precocious puberty (ICPP) at least 3 years after menarche, and to look for any predictive factors of PCOS at the time ICPP was diagnosed.

Design: Longitudinal study.

Setting: Pediatrics unit, Verona, Italy.

Patient(s): Forty-six young women (18.1 ± 3.0 years) who had been treated with GnRH analogues during childhood, observed at gynecologic age of 6.23 ± 3.3 years.

Intervention(s): Semistructured interview concerning cycles, physical exam, blood sampling, and transabdominal pelvic ultrasound.

Main Outcome Measure(s): Oligomenorrhea, LH, FSH, E_2, T, DHEAS, free T, delta4-androstenedione, 17-OHP, P, polycystic ovary morphology (PCOM).

Result(s): Fifteen percent of the young women had oligomenorrhea, 28% clinical hyperandrogenism, 48% biochemical hyperandrogenism, and 37% PCOM. A total of 32% of the patients had PCOS according to the Rotterdam definition and 30% had PCOS according to the Androgen Exess Society. The prevalent phenotype of PCOS was characterized by clinical and/or biochemical hyperandrogenism and PCOM. We did not find any predictive factors for PCOS at the time ICPP was diagnosed.

Conclusion(s): Patients with ICCP are prone to developing PCOS. The prominent phenotype in this cohort was PCOM associated with clinical and/or biochemical hyperandrogenism. Further follow-ups of these young adult patients will clarify whether this phenotype persists and if it will have important long-term implications regarding increased risk of infertility or metabolic complications. (Fertil Steril® 2010;93:1185–91. ©2010 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome (PCOS), idiopathic central precocious puberty (ICPP), Rotterdam criteria, hyperandrogenism

Polycystic ovary syndrome (PCOS) is the leading cause of anovulation, hirsutism and infertility; PCOS occurs in 5%–10% of reproductive age women (1, 2). Adolescent girls with PCOS, similar to adult women with the condition, are at increased risk for development of type 2 diabetes mellitus and the metabolic syndrome (3). It is important to recognize girls and young women at risk for PCOS, because early intervention may prevent long-term sequelae and improve quality of life (4).

There has been little agreement on the criteria used to diagnose PCOS. In 2003, a consensus conference in Rotterdam, based on majority opinion rather than clinical trial evidence, proposed new criteria for the diagnosis of PCOS that included more phenotypes of PCOS and recognized that women with regular menstrual cycles and hyperandrogenism and/or polycystic ovaries could have the syndrome (5). Several researchers have argued that such criteria may be nonspecific (6, 7), and in 2006 the Androgen Excess Society (AES) Task Force on Phenotype of PCOS narrowed the Rotterdam criteria to exclude women who did not have androgen excess (8). Some authors considered these criteria to be the most useful for diagnosis of PCOS in adolescence (9).

No single factor accounts for the spectrum of abnormalities noted in PCOS, which is thought to be a complex disorder. Current data suggest that impaired hypothalamic sensitivity to progesterone feedback mediated by hyperandrogenism is a potential etiology of the LH hypersecretion observed among women with PCOS (10). Several lines of evidence suggest the role of primary hypothalamic defect in PCOS, involving pituitary hypersensitivity to GnRH and a disorder of diurnal secretion or exaggerated pulsatile release of LH (11).

Idiopathic central precocious puberty (ICPP) resembles PCOS in that it is characterized by increased LH levels and pulse frequency (12–14). Case observations have prompted speculation that an underlying neuroendocrine dysfunction

manifests first as ICPP and later as PCOS (15). PCOS occurred in 10% of one European series of ICPP (16), but it was not found in two others (17, 18). Thus, it is unclear whether the association of PCOS with ICPP is any more frequent than would be expected by chance (1), and it would be important to know whether women with ICCP are prone to develop PCOS, thereby requiring adequate follow-up after menarche.

The aims of the present study were: 1) to find the prevalence of PCOS in a cohort of young women who had ICCP; and 2) to detect any predictive factors of PCOS at the time ICPP was diagnosed.

MATERIALS AND METHODS
Subjects
Among the 170 patients treated for ICPP from 1990 to 2002 at the Pediatric Division of the Verona Hospital, 46 patients fulfilled the following criteria:

1) Their ICPP was diagnosed according to the classic definition (19): a) onset of breast development (stage B2 or above according to Tanner) before 8 years of chronologic age (CA); b) pubertal LH response (more than 7 IU/L) to GnRH stimulation test; c) increment of height velocity and advancement of bone age (BA) by at least 1 year over CA; d) uterine length >3.5 cm and ovarian volumes >1.5 cm^3 at ultrasound. No evidence of hypothalamic-pituitary organic lesions at magnetic resonance imaging (MRI) allowed the "idiopathic" classification. None of the patients had an adrenal or clinical manifestation of McCune-Albright syndrome or other causes of precocious puberty.
2) They had a postmenarche age of ≥ 3 years at the time of the study, and none were taking hormones or had other causes of ovary dysfunction.

Methods
The study protocol was in accordance with the Helsinki II declaration, and informed consent was obtained from the patients and/or the parents before each subject was enrolled in the study.

All 46 young women were studied during the early follicular phase of their menstrual cycle, i.e., during days 2–8.

All the subjects had a semistructured interview with an expert clinician concerning their cycles (e.g., interval times, duration of flow, and associated symptoms) and fertility history. To determine menstrual cycle lengths, they kept a diary for a 3-month period. The frequency of menstrual bleeding was classified as regular (menses every 25–35 days) or oligomenorrheal (menses >35 days for at least 3 consecutive months). We use the term menarche here to refer to the first menstrual period after discontinuation of GnRH agonist treatment.

All of the subjects underwent a clinical examination, and height, weight, pubertal stage, and signs of clinical hyperandrogenism were noted. Target height (TH) was calculated as midparental height adjusted for gender (-6.5) (20). Predicted adult heights (PAH) were calculated according to Bayley and Pinneau's method (21). Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2) and was expressed in standard deviation score (SDS) for CA (22). A woman was considered to be overweight at the time of the study if her BMI fell between 25 and 30, and obese if her BMI was >30. Puberty development was clinically assessed by Marshall and Tanner standards (23). Clinical hyperandrogenism was evaluated using modified Ferriman-Gallwey (mFG) scores (24). Acne was considered depending on its clinical aspect.

On the same day, patients underwent blood tests for fasting insulin, glucose, lipids, basal gonadotropins (LH, FSH), E$_2$, T, DHEAS, free T, delta4-androstenedione (A), 17-hydroxy-progesterone (17-OHP), and progesterone (P).

The LH, FSH, A, PRL, E$_2$, DHEAS, insulin, TSH, free T$_4$, P, and T were measured by immunochemiluminescence (Immulite 2000 Analyzer; Euro/DPC, Llamberis, Gwynedd, U.K.). The sensitivities were 0.05 mIU/mL for LH, 0.1 mUI/mL for FSH, 0.3 ng/mL (1.0 nmol/L) for PRL, 0.16 ng/mL (3.4 mIU/L) for A, 15 pg/mL (55 pmol/L) for E$_2$, 3 μg/dL (0.08 μmol/L) for DHEAS, 2 μIU/mL for insulin, 0.004 μIU/mL for TSH, 0.3 ng/dL for free T$_4$, 0.1 ng/mL (0.3 nmol/L) for P, and 15 ng/dL (0.5 nmol/L) for T. Free T and 17-OHP were measured by RIA (free T: Adaltis, Bologna, Italy; 17-OHP: Diagnostic Systems Laboratories, Webster, TX), and the sensitivity was 0.18 ng/mL for free T and 0.01 ng/mL for 17-OHP.

Values of 0.1 IU/L (for LH and FSH), 73.4 pmol/L (for E$_2$) and 0.63 (for P) were assigned to samples below the detection limit. All samples were stored at $-20°$C until they were assayed.

The homeostasis model assessment (HOMA) was used to estimate insulin resistance (IR) and when HOMA IR was ≥ 2.5, an oral glucose tolerance test was done, and fasting insulin ≥ 15 mcU/mL and/or a peak ≥ 150 mcU/mL was considered to be hyperinsulinemia (25).

A transabdominal uterine and ovarian scan was done using an ultrasound scanner (GE Logiq 3) with the use of a 3.5 Mhz convex transducer (GE Medical Siemens, Phoenix, AZ) when the participants had a full bladder, obtained by voluntary urine retention and oral administration of fluids. All the tests were carried out by the same ultrasonographer, and multiple images were recorded for each ovary. Uterine and ovarian volume, endometrial thickness, and number, diameter, and distribution of the follicles were recorded. The measurements for each ovary were taken separately, because there were variations between the volume and follicle diameter in each ovary. Ovarian and uterine volumes were calculated using the ellipsoid formula, calculated as length $\times$ width $\times$ height in cm multiplied by 0.5233 (26, 27). The echogenicity of ovarian stroma was scored subjectively as 0 (normal), 1 (moderately increased), or 2 (markedly increased).

Exclusion of 21-hydroxylase–deficient nonclassic adrenal hyperplasia was done using the basal morning 17-OHP level, with a cut-off value of 2 ng/mL.

Polycystic ovary syndrome was defined according to the revised 2003 Rotterdam criteria (two out of three) and exclusion of other etiologies (congenital adrenal hyperplasias, androgen-secreting tumours, Cushing syndrome):

1) Oligo- and/or anovulation;
2) Clinical and/or biochemical signs of hyperandrogenism;
3) Polycystic ovaries at the ultrasound scan.

Polycystic ovary syndrome was also defined according to the 2006 AES criteria (three of three):

1) Hyperandrogenism: hirsutism and/or hyperandrogenemia;
2) Ovarian dysfunction: oligoanovulation and/or polycystic ovaries;
3) Exclusion of other androgen excess or related disorders.

We considered the condition to be oligomenorrhea if menses were >35 days for at least 3 consecutive months and clinical hyperandrogenism if an mFG score was >9 (e.g., greater than the 95% confidence limit for a control population with regular menses and documented ovulation [23]) and/or moderate acne was present.

Biochemical hyperandrogenism (hyperandrogenemia) was defined as an androgen level greater than the 95% confidence limits in previously reported ovulatory control subjects (24), free T >12.5 pmol/L, DHEAS >400 ug/dL (11.6 μmol/L), or A >3.5 ng/mL (13.3 nmol/L) or total T >0.80 ng/mL (2.8 nmol/L). In our institution we confirmed the normal range for androgens, reported in literature for an adult population, on a control group of 20 young women attending the medical school (age range 21–25 years) in the early follicular phase of the cycle, using the same assay.

Polycystic ovarian morphology (PCOM) was defined as ≥ 1 ovary with ≥ 12 follicles 2–10 mm in diameter in a single plane and/or an ovarian volume >10 mL in the absence of a dominant follicle >10 mm, a corpus luteum, or a cyst (1, 28, 29).

We excluded multifollicular ovary morphology, defined as 6–10 follicles 4–10 mm in diameter in the maximum plane in irregular distribution without increased ovarian stroma (30, 31). We did not consider doing transvaginal ultrasound in our patients, because we visualized the uterine structure and both ovaries by transabdominal ultrasound in 100% of cases. Consensus was reached on the reading of all ultrasounds by the reviewers.

We tested the following data collected at diagnosis as variables that could be predictive or were associated with PCO or PCOS, because we wanted to test whether an earlier activation of the adrenals or of the pituitary-gonadal axis could result in an increased prevalence of PCOS and PCOM: age at diagnosis, age at telarche, age at pubarche, BA, LH-FSH-E_2 baseline and peaks, A, and 17-OHP. Furthermore, BMI SDS was tested at diagnosis, because it could determine increased BMI in adults, insulin resistance, and increased prevalence of PCOS and PCOM.

At the time of the study, we tested length of treatment with GnRH agonist and CA at menarche, to check if a longer suppression of the pituitary-gonadal axis and/or a later menarcheal age could protect from PCOM or PCOS. Furthermore, we tested GA, length of cycles, mFG score; LH-FSH-E_2, A, free T, total T, 17-OHP, mean right-left ovarian volumes, and number of follicles to find correlations and differences between groups regarding hyperandrogenism parameters. The BMI SDS, HOMA IR, and lipids were checked, because some authors have reported that in girls with PCOS the body fractions of fat and abdominal fat are high, even in the absence of obesity.

We did not test predicted and target heights, or height SDS at diagnosis and at the time of the study. These parameters are here reported only to show that our patients with ICPP, treated with GnRH agonist, reached the final height.

Statistical Analysis

Results are expressed as mean $\pm$ SD. Statistical analysis was performed with SPSS version 14.0 (SPSS, Chicago, IL). Data that were not normally distributed were log normalized for comparison. Statistical analysis of the results was assessed using the Student t test, paired and unpaired if required. Correlations between two parameters were determined by Pearson correlation coefficient analysis. The Student t test was used to compare groups and variables. A P value of $< .05$ was considered to be significant.

RESULTS

The clinical and auxologic data of the patients when diagnosed with ICPP and at the time of the study are reported in Table 1; biochemical and ultrasound data at the time of the study are reported in Table 2. None of the subjects were small for gestational age. Two young women had familial histories of polycystic ovaries but none of insulin resistance. At the time of the study, five patients (11%) were overweight and two (4%) were obese. The BMI SDS in the total study population was not statistically different from the BMI SDS for CA and for BA at start of treatment ($P=.11$ and $P=.73$, respectively). Six patients (13%) had HOMA IR >2.5, but an oral glucose tolerance test (OGTT) did not show insulin resistance. The HOMA IR was related to BMI ($P<.001$; r = 0.55). At the time of the study, none of the patients had ever been pregnant.

Figure 1 shows the prevalence of Rotterdam criteria in this cohort of patients. Fifteen percent of the women (7 out of 46) had oligomenorrhea, and at the time of being diagnosed with ICPP they did not differ in age at telarche and pubarche or in biochemical data with the girls who had normal cycles.

Clinical hyperandrogenism was found in 28% of the patients (13 out of 46), and hirsutism was the most common feature (10 patients).

TABLE 1

Clinical and auxologic data of the patients (mean ± SD).

Patient data

At diagnosis of ICPP	
Age at diagnosis (y)	7.65 ± 0.20
Age at telarche (y)	7.32 ± 0.50
Age at pubarche (y)	7.91 ± 0.80
BA at diagnosis (y)	10.15 ± 1.90
Height (cm)	137.0 ± 11.0
Height SDS for CA	0.97 ± 1.10
Height SDS for BA	−0.48 ± 0.70
TH (cm)	160.0 ± 5.0
PAH (cm)	158.0 ± 10.0
BMI SDS for CA	0.64 ± 0.82
BMI SDS for BA	0.28 ± 0.82
At time of the study	
Length of treatment with GnRH agonist (y)	2.81 ± 1.70
CA (y)	18.1 ± 3.00
CA at menarche (y)	12.22 ± 0.93
GA (y)	6.23 ± 3.30
Height (cm)	160.0 ± 6.0
Height SDS for CA	−0.33 ± 1.10
BMI (kg/m²)	22.21 ± 3.94
BMI SDS CA	0.14 ± 1.10
Ferriman-Gallwey score	9.12 ± 4.14

Note: BA = bone age; CA = chronologic age; GA = gynecologic age; ICPP = idiopathic central precocious puberty; PAH = predicted adult height; SDS = standard deviation score; TH = target height.

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TABLE 2

Hormonal and ultrasound findings in all 46 patients (mean ± SD).

Patient data

At diagnosis of ICPP	
LH baseline (μU/mL)	1.90 ± 1.85
FSH baseline (μU/mL)	6.57 ± 13.67
LH peak (μU/mL)	23.43 ± 18.78
FSH peak (μU/mL)	16.21 ± 9.29
LH/FSH ratio	1.67 ± 1.09
E_2 baseline (pg/mL)	28.94 ± 13.76
E_2 peak (pg/mL)	32.91 ± 24.50
A (ng/mL)	1.20 ± 0.47
17-OHP baseline (ng/mL)	1.17 ± 0.88
At time of study	
LH (μU/mL)	6.10 ± 3.10
FSH (μU/mL)	7.51 ± 1.90
E_2 (pg/mL)	53.95 ± 41.50
P (ng/mL)	0.54 ± 0.40
DHEAS (μg/dL)	209.80 ± 87.40
A (ng/mL)	3.50 ± 1.10
Free T (pmol/L)	7.79 ± 1.90
Total T (ng/mL)	0.46 ± 0.10
17-OHP (ng/mL)	1.30 ± 0.40
HOMA IR	1.78 ± 1.00
Mean ovarian volume (mL)	7.50 ± 3.00
Right ovary volume (mL)	7.24 ± 3.22
Left ovary volume (mL)	7.30 ± 3.45
No. of follicles	12.35 ± 3.19

Note: Data are reported as mean ± SD. To convert to SI units, multiply E_2 by 3.671 (result in pmol/L); P by 3.18 (result in nmoL/L), DHEAS by 0.02714 (result in μmol/L), A by 3.4916 (result in nmoL/L), total T by 0.035 (result in nmoL/L), and 17-OHP by 3.03 (result in nmoL/L). HOMA IR = homeostasis model assessment insulin resistance.

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Biochemical hyperandrogenism was found in 48% (22 out of the 46): All of these patients had high A, associated in two subjects with high DHEAS. Delta4-androstenedione in this cohort (3.50 ± 1.10 ng/mL) was the androgen that was significantly raised compared with values of the control group of 20 young women previously tested (2.47 ± 0.84 ng/mL; P=.008). The A levels were related to 17-OHP (P=.012; r = 0.38) and DHEAS (P=.002; r = 0.46), but not to ovary volume, number of follicles, or LH and FSH levels. At the time of the study, LH levels were only slightly high in two patients, and the LH/FSH ratio was >2 in two other patients, none of whom had hyperandrogenism.

Twenty-three out of 46 patients (50%) showed multifollicular ovaries. PCOM was found by ultrasound in 17 out of 46 patients (37%), and six patients (13%) had normal ovary morphology. Mean ovarian volume in the 46 women correlated with free T (P=.008; r = 0.65).

According to the Rotterdam criteria, 15 out of 46 patients (32%) had PCOS, and Figure 2 shows the prevalence of the different PCOS phenotypes: One patient had oligomenorrhea with clinical and/or biochemical hyperandrogenism and PCOM; four had oligomenorrhea and clinical and/or biochemical evidence of hyperandrogenism; one had oligomenorrhea and PCOM; and nine showed clinical and/or biochemical hyperandrogenism with PCOM. There were no statistically significant differences, at the time ICPP was diagnosed, in auxologic and biochemical data (LH and FSH peaks, E_2, A, and 17-OHP) between PCOS and non-PCOS subjects.

According to the AES criteria, 14 out of 46 patients (30%) had PCOS.

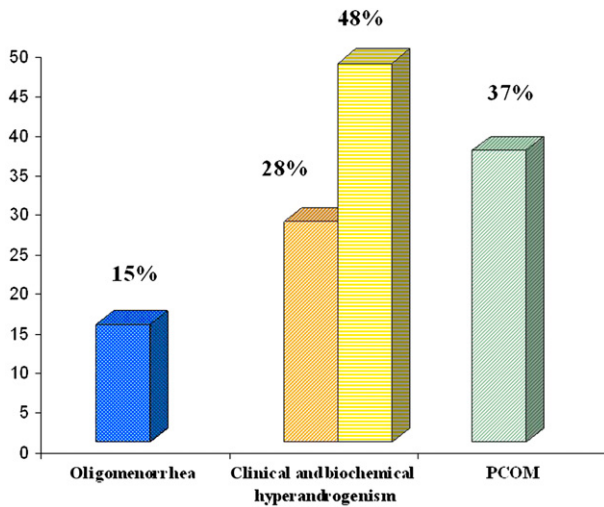## DISCUSSION

This is the first longitudinal study on the prevalence of PCOS in a homogeneous sample of 46 young women previously affected by ICPP, treated with GnRH agonist, and examined more than 3 years after menarche, at the same phase of the cycle.

FIGURE 1

Prevalence of Rotterdam criteria in the 46 women at the time of the study. PCOM = polycystic ovary morphology.

Franceschi. PCOS and ICPP. Fertil Steril 2010.

The prevalence of PCOS in these subjects was 32% using the Rotterdam 2003 criteria and 30% using the AES criteria. We found normal menstrual cycle pattern in most patients with ICPP, and the prominent phenotype of PCOS in this cohort was clinical and/or biochemical hyperandrogenism associated with PCOM.

Hyperandrogenism

Regarding clinical hyperandrogenism, the prevalence of hirsutism (23%) was similar to that reported by other authors in patients who had ICPP (14) and higher than the 12% reported for normal women (32).

Regarding biochemical hyperandrogenism, the 48% prevalence in the present patients is higher than levels reported by other authors in patients who had ICPP (33). In contrast, we found similar levels of A to Lazar et al. (34) in girls who had CPP and showed a PCO-like syndrome at 0.5–3.5 years after menarche with exaggerated adrenal response to ACTH stimulation.

Excessive secretion of androgens, prominent in the delta4-pathways in the ovaries, is reported in the literature as functional ovarian hyperandrogenism and is considered to be the prominent abnormality in women with PCOS (35). There is scarce information on A and PCOS, and the AES (8) has reported that the usefulness of also measuring this hormone is unclear, but it may help to increase the number of subjects identified as hyperandrogenemic by approximately 10%. Many authors (32, 36) have considered A to be among the androgens that define biochemical hyperandrogenism according to the Rotterdam criteria. Hyperandrogenism is the main feature of PCOS, but the pathophysiologic characteristics of this syndrome are not fully understood. We know that complex interaction between the action of gonadotropins, the ovaries, androgens, and insulin is involved (37).

In the present patients, A levels were related to 17-OHP and DHEAS. We excluded adrenal hyperplasia when ICPP was diagnosed, through an ACTH test in those who also had precocious pubarche, and through low basal morning 17-hydroxyprogesterone levels at the time of the study. Most of the women who had ICPP at the time of this study did not appear to be obese or insulin resistant. Therefore it is more likely that overproduction of ovarian androgen was caused by an early intrinsic abnormality in GnRH pulse generator pulsation that they showed at puberty. This line of

FIGURE 2

Phenotypes of patients with polycystic ovary syndrome (n = 19). H = hyperandrogenism; O = oligomenorrhea; PCOM = polycystic ovary morphology.
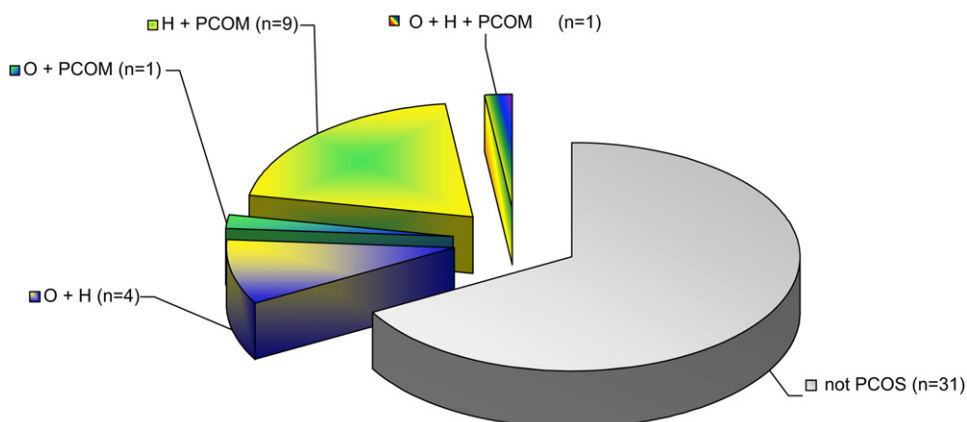
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thinking is in agreement with other authors (15), but primary thecal dysfunction, when cells are more efficient at converting androgenic precursors to A (mediated by cytochrome p450c17), cannot be excluded.

Ovary Morphology

The normal adolescent ovary is known to histologically resemble a polycystic ovary, and the perimenarchal combination of a high number of follicles and mature gonadotropin stmulation leads to a greater number of large antral follicles and a slightly greater ovarian size than at any other stage (38).

In our patients who had ICPP, examined at least 3 years after menarche, the prevalence of multifollicular ovaries was 30%, similar to ∼25% reported in healthy adolescent volunteers using the same criteria (30, 31).

In contrast, 37% of our patients had PCOM. The prevalence is higher than the 10% prevalence in the general population of regularly menstruating postmenarchal schoolchildren and also that in ICPP (10%–24%) in perimenarchal age by other studies (16, 33, 39), which used different criteria.

According to some authors, PCOM in women with regular cycles has not been considered a major risk factor for the development of PCOS (32), and over time most fail to meet the criteria for PCOM, probably because of a decrease in volume and number of antral follicles with aging. In contrast, other authors reported that PCOM with ovulatory cycles exists as a discrete entity and represents the mildest form of ovarian hyperandrogenism (40).

Relationships among ovarian histology, architecture as perceived by ultrasound, and function are not estabilished, but PCOM seems to be a marker for excessive thecal androgen production, even if in some patients with PCOM thecal androgen excess is not manifest as hyperandrogenemia, the reason for which is not known (38).

The prevalence of PCOS in our subjects was 32% using the Rotterdam 2003 criteria and 30% using the AES criteria, higher than the prevalence reported by other authors in patients who had ICPP (16–18), but older criteria for PCOS were used in those studies.

Abnormal gonadotropin dynamics with excess ovarian production of androgens and PCOM may occur despite the treatment with GnRH agonist in patients who had ICPP. It would be interesting if later studies could enroll as control subjects a group of girls with ICPP who had not been treated with GnRH agonist to evaluate whether GnRH therapy per se could modify the prevalence of PCOS. What we know from a randomized study (33) in treated and nontreated girls with ICPP is only that adverse effects of treatment on the reproductive function can be excluded.

Unfortunately, we did not find any risk or predictive factors of PCOM or clinical and/or biochemical hyperandrogenism at the time ICPP was diagnosed. The birth weight, age at telarche or pubarche, BMI SDS, or gonadotropin and andro-

gen levels could not predict the risk of developing PCOM or PCOS in these women with ICCP.

Nevertheless, we can conclude that patients who had ICCP are prone to developing PCOS. The prominent phenotype in the present cohort wasPCOM associated with clinical and/or biochemical hyperandrogenism. Further follow-ups of these patients will verify whether this phenotype persists and if it has important long-term implications regarding increased risk of infertility or metabolic complications.

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