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Premature Adrenarche Followed to Adolescence: PCOS Risk and Phenotype

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ABSTRACT

Objective: To evaluate the development of polycystic ovary syndrome (PCOS) during adolescence in girls with a history of premature adrenarche (PA) and to identify clinical, biochemical, and familial factors associated with subsequent PCOS.

Materials and Methods: This retrospective longitudinal cohort study included 88 girls diagnosed with PA in childhood who were followed until adolescence. PCOS was evaluated during adolescence in clinically indicated participants according to contemporary guideline-based diagnostic criteria.

Results: During follow-up, 15 of 88 girls developed PCOS (cumulative incidence, 17.0%). At PA diagnosis, age, birth weight SDS, and body mass index (BMI)-SDS were similar between the PCOS and non-PCOS groups, and baseline androgen measures did not differ (dehydroepiandrosterone sulfate [DHEA-S], p=0.35; DHEA-S SDS, p=0.80; total testosterone, p=0.87; Δ4-androstenedione, p=0.69). At adolescent/final evaluation, BMI-SDS and ΔBMI-SDS were comparable between the groups (p=0.84 and p=0.58, respectively). Girls who developed PCOS also had menstrual irregularity and clinical hyperandrogenism, with a median modified Ferriman-Gallwey score of 15 (IQR, 11–21). Maternal history of PCOS was more frequent among girls who developed PCOS than among those who did not (7/15 [46.7%] vs. 13/65 [20.0%], p=0.047; OR, 3.50). Total testosterone levels were significantly higher in the PCOS group (p=0.005), whereas DHEA-S and Δ4-androstenedione levels did not differ significantly between the groups.

Conclusion: In girls with PA, adrenal androgen levels at diagnosis did not predict subsequent PCOS. Familial susceptibility was associated with later PCOS development. At adolescent evaluation, total testosterone distinguished girls with PCOS from those without PCOS better than DHEA-S or Δ4-androstenedione. These findings support the continued follow-up of girls with PA through adolescence, with particular attention to familial predisposition, menstrual regularity, and clinical or biochemical hyperandrogenism.

Keywords: Adolescent, Adrenarche, Hyperandrogenism, Polycystic Ovary Syndrome, Risk Factors

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INTRODUCTION

Premature adrenarche (PA) is characterized by early clinical signs of androgen action (pubic/axillary hair, acne, and body odor) before 8 years of age in girls and before 9 years of age in boys, after the exclusion of congenital adrenal hyperplasia, androgen-producing tumors, and other rare causes of androgen excess.[1] PA accounts for most isolated premature pubarche (PP) presentations and is usually considered a developmental variant but has been linked to later hyperandrogenic and metabolic risk in selected phenotypes.[1]

Polycystic ovary syndrome (PCOS) is among the most common endocrine disorders and carries a substantial reproductive and metabolic burden; guideline data estimate a global prevalence of ~10–13% and highlight persistent under-recognition.[2] In adolescents, diagnosis requires caution because physiological puberty may mimic PCOS; thus, recommendations require persistent menstrual irregularity (by years since menarche) and clinical or biochemical hyperandrogenism after the exclusion of mimicking disorders, while pelvic ultrasonography and AMH are not recommended for diagnosis in this age group.[3]

A biologically plausible link between PA and the later development of PCOS has long been proposed. Early follow-up studies suggested increased postpubertal hyperandrogenic ovarian phenotypes after premature pubarche.[4,5] However, more recent longitudinal cohorts have reported heterogeneous outcomes, with some showing limited ovarian dysfunction and others reporting a higher PCOS risk and highlighting maternal PCOS history and adiposity as correlates.[6,7] Accordingly, whether PA represents a benign variant or an early marker of future PCOS in specific subgroups remains clinically important. Therefore, we aimed to evaluate adolescent PCOS outcomes after PA and to identify clinical and biochemical predictors at presentation and during follow-up that may improve risk stratification.

MATERIALS AND METHODS

This retrospective longitudinal cohort study included girls diagnosed with premature adrenarche (PA) in childhood and followed through adolescence at a tertiary pediatric endocrinology center. At presentation, alternative causes of androgen excess were excluded, including classic/non-classic congenital adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome, and central precocious puberty, using appropriate clinical, biochemical, and imaging assessments.[1,8]

Clinical history and follow-up data included age at symptom onset, birth weight, gestational age, maternal PCOS history, and maternal age at menarche. These data were obtained from medical records. Missing maternal history data were verified by telephone interview with the mother when possible.

Physical examination and anthropometric assessment were performed at 3–6-month intervals. Height and weight were measured using standardized methods; BMI was calculated as kg/m^2 and converted to age- and sex-specific SDS using Turkish reference data.[9] Auxologic and skeletal assessment included BMI-SDS change, bone age, and birth weight SDS. ΔBMI-SDS was defined as BMI-SDS at outcome evaluation minus BMI-SDS at PA diagnosis. Birth weight was expressed as SDS for gestational age; small for gestational age (SGA) was defined as birth weight <−2.0 SDS.[10]

Bone age (BA) and chronological age (CA) were recorded at PA diagnosis, and BA was assessed using the Greulich–Pyle method.[11]

Adolescent PCOS evaluation followed the 2023 International Evidence-based Guideline and adolescent-specific recommendations.[2,3] PCOS diagnosis required both ovulatory dysfunction, based on years-since-menarche criteria, and clinical and/or biochemical hyperandrogenism after the exclusion of mimicking disorders. Physical examination findings related to androgen action, including pubic/axillary hair, acne, body odor, and hirsutism during adolescence, were reviewed. Clinical hyperandrogenism was assessed by the presence of hirsutism and/or severe acne; hirsutism was quantified using the modified Ferriman–Gallwey (mFG) score.[12]

Laboratory assessment at PA diagnosis included serum DHEA-S, androstenedione, total testosterone, and 17-hydroxyprogesterone (17-OHP). At the adolescent/final evaluation, biochemical assessment for comparison between the PCOS and non-PCOS groups included total testosterone, DHEA-S, and androstenedione. DHEA-S was measured using an automated chemiluminescence immunoassay (ADVIA Centaur, Siemens Diagnostics, Erlangen, Germany). DHEA-S concentrations >1084 nmol/L (40 µg/dL) were considered indicative of adrenal activation, and age- and sex-adjusted DHEA-S SDS values were calculated.[13] Total testosterone and androstenedione were measured using automated immunoassays on a Beckman Coulter platform (Beckman Coulter, Brea, CA, USA).

Imaging and metabolic assessments were performed during the PCOS work-up when clinically indicated. Metabolic testing included fasting glucose, fasting insulin, HOMA-IR, and HbA1c when available. HOMA-IR was calculated according to the homeostasis model assessment described by Matthews et al.[14] using the following formula: fasting insulin (µU/mL)×fasting plasma glucose (mg/dL)/405. Pelvic ultrasonography was used to assess ovarian morphology and ovarian volume. Ovarian volumes were calculated using the ellipsoid formula: volume=length×width×thickness×0.523.[15]

Statistical Analysis

Statistical analyses were performed using GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA, USA). Normality was assessed using the Shapiro–Wilk test. Continuous variables are presented as mean±SD or median (IQR), as appropriate, and categorical variables as n (%). Between-group comparisons were performed using Student's t-test for normally distributed data, the Mann–Whitney U test for non-normally distributed data, and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Two-sided p values <0.05 were considered statistically significant.

Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Marmara University Institutional Ethics Committee (Approval No.: 09.2009.1020; Date: December 06, 2019), and written informed consent was obtained from the legal guardians.

RESULTS

A total of 88 girls were followed for PA diagnosed at a mean age of 6.6±1.1 years. The mean BMI SDS at presentation was 0.7±1.1. Most patients (81.9%) were born at term, and 8.0% were born SGA. The mean maternal age at menarche was 12.6±1.4 years; the corresponding mean age at menarche in the girls was 11.8±0.9 years. The mean BA/CA ratio was 1.0±0.2, and the mean DHEA-S concentration was 82.8±45.7 mcg/dL. The mean follow-up duration was 8.0±2.6 years, and PCOS was diagnosed in 15/88 girls (17.0%). Age at PA diagnosis was similar in the PCOS and non-PCOS groups (6.6±1.1 vs. 6.6±1.0 years; p=0.97). BMI-SDS at PA diagnosis did not differ between the PCOS and non-PCOS groups (0.9±1.2 vs. 0.6±1.1; p=0.47). Birth weight SDS did not differ between the groups (−0.57±1.10 vs. −0.54±0.96; p=0.93). SGA was observed in 2/15 (13.3%) girls in the PCOS group and 4/73 (5.5%) in the non-PCOS group (p=0.27). ΔBMI-SDS was similar between the groups (−0.08±1.3 vs. 0.09±1.0; p=0.58). In girls who developed PCOS, the mean age at menarche was 12.0±0.6 years, and the mean time from menarche to adolescent/final evaluation was approximately 5 years. Menarcheal age did not differ between girls who later developed PCOS and those who did not (p=0.70). At adolescent/final evaluation, age was 17.0±2.0 years in the PCOS group and 15.9±1.8 years in the non-PCOS group (p=0.057), while BMI-SDS was similar between the groups (0.70±2.3 vs. 0.8±1.6; p=0.84). At PCOS evaluation, all girls in the PCOS group reported menstrual irregularity, and clinical hyperandrogenism was evident, with a median Ferriman–Gallwey score of 15 (IQR, 11–21). Maternal history of PCOS was more frequent in girls who developed PCOS than in those who did not (7/15 [46.7%] vs. 13/65 [20.0%]; p=0.047; OR, 3.50; 95% CI, 1.07–11.42).

Maternal age at menarche did not differ between the PCOS and non-PCOS groups (13.0±0.8 vs. 12.6±1.4 years; p=0.40). In the non-PCOS group, daughters' age at menarche did not differ from maternal age at menarche (p=0.72). In contrast, in the PCOS group, daughters reached menarche significantly earlier than their mothers (p=0.001).

At PA diagnosis, neither DHEA-S concentration nor DHEA-S SDS differed between girls who later developed PCOS and those who did not (DHEA-S: 72.3±47.1 vs. 84.9±45.5, p=0.35; DHEA-S-SDS: 0.9±2.5 vs. 1.0±2.0, p=0.80); similarly, total testosterone and Δ4-androstenedione were comparable between the groups (p=0.87 and p=0.69, respectively) (Table 1).

Consistent with this clinical hyperandrogenic phenotype, total testosterone was significantly higher in the PCOS group than in the non-PCOS group (60.6±11.3 vs. 39.0±17.6, p=0.005), whereas Δ4-androstenedione (3.0±0.7 vs. 2.6±0.8, p=0.17) and DHEA-S (252±112 vs. 219±97.1, p=0.26) did not differ significantly between the groups. In the PCOS group, mean LH and FSH levels were 11.7±3.8 and 6.1±1.9, respectively. Metabolic assessment revealed a mean HOMA-IR of 3.7±2.2 and a mean HbA1c of 5.4±0.2%. Pelvic ultrasonography demonstrated mean ovarian volumes of 12.0±8.5 mL and 12.3±10.5 mL for the right and left ovaries, respectively, while peripheral follicular distribution was present in 40% of cases.

DISCUSSION

In this longitudinal cohort of girls with PA, 16.9% developed PCOS during adolescent follow-up. The main findings were that baseline clinical and biochemical characteristics at PA diagnosis, including age at presentation, birth weight, BMI-SDS, DHEA-S, DHEA-S SDS, total testosterone, and Δ4-androstenedione, did not differ between girls who subsequently developed PCOS and those who did not. In contrast, maternal history of PCOS was more frequent among girls who developed PCOS, and total testosterone at adolescent/final evaluation was the biochemical parameter that best differentiated PCOS status.

In the general adolescent population, the prevalence of PCOS is substantially lower than that observed after premature adrenarche, with recent meta-analytic data estimating a pooled prevalence of 6.3% using guideline-consistent adolescent criteria and 9.8% using the original Rotterdam criteria.[16] Our study found that 16.9% of girls with a history of PA developed PCOS during follow-up. This estimate falls within the range reported in longitudinal studies from Spain (15–40%).[17,18] Taken together, these findings support the view that premature adrenarche is associated with an increased risk of subsequent PCOS. Rather than representing only a benign variation in pubertal timing, PA may serve as an early clinical marker of susceptibility to later hyperandrogenism and PCOS development.

Table 1. Baseline and adolescent/final characteristics according to subsequent PCOS outcome

Variable	PCOS	Non-PCOS	p
Birth weight SDS	−0.57±1.10	−0.54±0.96	0.93
At PA diagnosis			
Age at PA diagnosis, years	6.6±1.1	6.6±1.0	0.97
BMI SDS	0.9±1.2	0.6±1.1	0.47
DHEA-S, mcg/dL	72.3±47.1	84.9±45.5	0.35
DHEA-S SDS	0.9±2.5	1.0±2.0	0.80
Total testosterone, ng/ml	0.09±0.06	0.09±0.08	0.87
Δ4-androstenedione, µg/L	0.6±0.4	0.6±0.4	0.69
17-hydroxyprogesterone (17-OHP), µg/L	1.1±0.9	0.8±0.5	0.10
At adolescent/final evaluation			
Age at adolescent/final evaluation, years	17.0±2.0	15.9±1.8	0.057
Age at menarche, years	12.0±0.6	11.7±1.0	0.70
BMI SDS	0.70±2.3	0.8±1.6	0.84
ΔBMI SDS	−0.08±1.3	0.09±1.0	0.58
Total testosterone, ng/dl	60.6±11.3	39.0±17.6	**0.005**
Δ4-androstenedione, µg/L	3.0±0.7	2.6±0.8	0.17
DHEA-S, mcg/dL	252±112	219±97.1	0.26

PCOS: Polycystic Ovary Syndrome; PA: Premature Adrenarche; SDS: Standard Deviation Score; BMI: Body Mass Index; DHEA-S: Dehydroepiandrosterone Sulfate.

In our cohort of girls with premature adrenarche, birth weight SDS did not differ between those who developed PCOS and those who did not (p=0.93), and although SGA was numerically more frequent in the PCOS group than in the non-PCOS group, this pattern was not statistically robust. These findings are consistent with the heterogeneous literature on prenatal growth and later PCOS risk. A prospective birth cohort study reported that women born SGA had approximately double the prevalence of PCOS compared with AGA peers (adjusted RR, 2.44; 95% CI, 1.39–4.28), supporting a developmental contribution of fetal growth restraint.[19]

However, more recent long-term follow-up data in premature adrenarche did not confirm SGA as an independent predictor (univariate OR, 0.94; p=0.92), with baseline BMI z-score and maternal PCOS history emerging as more relevant predictors.[7]

In our cohort, a maternal history of PCOS was present in 20/80 participants (25.0%) with available data and was more frequent among girls who developed PCOS than among those who did not (7/15 [46.7%] vs. 13/65 [20.0%]; OR, 3.50). This finding is consistent with the established familial aggregation of PCOS in first-degree relatives.[20] Maternal PCOS history has also been highlighted in PA/PP cohorts. Olgun et al.[21] reported maternal PCOS in ~15% of girls with premature pubarche. Efthymiadou et al.[22] found maternal PCOS in 33/89 (37.1%) girls with premature adrenarche. Differences across studies may reflect variation in the definition of family history, under-recognition of PCOS in mothers, and differences in outcome ascertainment.

Moreover, in the long-term follow-up of girls with premature adrenarche, Saroufim et al.[7] identified maternal PCOS history as the strongest risk factor for subsequent self-reported PCOS (OR, 4.1). Differences across studies likely reflect variation in the definition of family history, under-recognition of PCOS in mothers, and outcome ascertainment.

At the adolescent/final evaluation (mean age, 17.0±2.0 years in the PCOS group and 15.9±1.8 years in the non-PCOS group; p=0.057), the PCOS work-up in the PCOS group was performed approximately 5 years after menarche (mean age at menarche, 12.0±0.6 years), reducing the likelihood of misclassification due to normal pubertal maturation. With respect to pubertal tempo, age at menarche did not differ by later PCOS status in our cohort. While Guarnotta et al.[23] reported earlier menarche in girls with precocious pubarche who later developed PCOS (p=0.015). Menarche timing appears to be an inconsistent standalone predictor of PCOS risk and may be shaped by genetic background and adiposity.[24]

Maternal age at menarche was similar between girls who developed PCOS and those who did not (13.0±0.8 vs. 12.6±1.4 years; p=0.40). Although maternal PCOS has been associated with earlier pubertal development in daughters, this effect appears to be driven predominantly by adrenarche-related milestones rather than menarche.[25] In our cohort, an intergenerational shift toward earlier menarche was observed only among daughters who later developed PCOS. Nevertheless, Mendelian randomization data suggest that the inverse association between age at menarche and PCOS risk is modest, limiting the usefulness of menarcheal timing as a clinical discriminator.[26]

Girls diagnosed with PCOS in our cohort had a median mFG score of 15 (11–21), which is clearly above the recommended ethnicity-specific threshold (4–6) for detecting hirsutism.[2,3] This indicates that hirsutism was a major clinical feature at PCOS evaluation. As self-treatment is common and may reduce visible terminal hair growth, the recorded mFG values may underestimate the true severity of hirsutism.[2,3]

The laboratory findings showed that adrenal androgen levels at PA diagnosis had limited prognostic value. DHEA-S and DHEA-S SDS measured at the time of PA diagnosis did not differ between girls who later developed PCOS and those who did not (p=0.35 and p=0.80, respectively). Similarly, baseline total testosterone and Δ4-androstenedione were comparable between the groups. This aligns closely with Guarnotta et al.,[23] who evaluated girls with precocious pubarche both at diagnosis and again 10 years after menarche and reported similar DHEA-S values in those who later developed PCOS versus those who did not at both time points.

Likewise, in a long-term PA follow-up cohort, baseline androgen levels were not associated with later self-reported PCOS.[7] Taken together, these data suggest that the degree of adrenal androgen excess at PA presentation alone is insufficient to predict later PCOS.

In contrast, the adolescent biochemical profile was more informative. Importantly, most adolescents reach adult-range androgen concentrations by 12–15 years of age.[2] This supports the interpretability of biochemical hyperandrogenism assessed in our cohort at these ages. Total testosterone was significantly higher in the PCOS group, whereas DHEA-S and Δ4-androstenedione did not differ significantly between the groups. This pattern is clinically plausible and consistent with contemporary international recommendations, which prioritize total and free testosterone as the main biochemical markers of hyperandrogenism in adolescent PCOS, while DHEA-S and androstenedione are considered secondary markers with lower specificity.[2,3] Our findings are also consistent with longitudinal PA/PP literature suggesting that adrenal androgen markers, particularly DHEA-S, may reflect adrenarchal activation but do not reliably distinguish later PCOS phenotype on their own.[6,23] Accordingly, biochemical assessment in girls with a history of premature adrenarche should be interpreted together with menstrual pattern and persistent clinical hyperandrogenism rather than isolated adrenal androgen values.[2,3]

The hormonal profile in the PCOS group, characterized by higher LH relative to FSH (mean LH/FSH ratio ≈1.9), is consistent with the relative LH predominance described in PCOS. This pattern is thought to reflect altered hypothalamic-pituitary-ovarian regulation, with increased GnRH pulse frequency favoring LH secretion, thereby enhancing ovarian theca-cell androgen production and contributing to follicular arrest. However, as LH and the LH/FSH ratio are not recommended diagnostic criteria in adolescents, these findings should be interpreted as supportive of the underlying neuroendocrine phenotype rather than diagnostically specific.[27,28] The mean HOMA-IR of 3.7±2.2 in the PCOS group is consistent with increased insulin resistance in late/postpubertal adolescence, although interpretation should remain cautious given the known effects of pubertal stage and adiposity on HOMA-IR and the absence of a universally accepted adolescent threshold. Published pediatric cutoffs have ranged from 3.82 in pubertal girls to 2.91 in postpubertal adolescents.[29,30]

Hyperinsulinemia is pathophysiologically relevant in PCOS, as it may enhance ovarian androgen production and suppress hepatic SHBG synthesis, thereby aggravating the hyperandrogenic milieu; accordingly, the normal mean HbA1c in our cohort does not exclude early metabolic dysfunction.[2]

Pelvic ultrasonographic findings were described in girls with PCOS; however, ovarian morphology is not recommended as a diagnostic criterion for adolescent PCOS, particularly within 8 years after menarche.[2,3] Therefore, ultrasonographic findings in this cohort should be considered supportive descriptive data rather than diagnostic evidence.

This study has certain limitations. First, its retrospective single-center design may have led to missing data and variability in the timing of adolescent/final assessments. Second, adolescent PCOS evaluation was performed in clinically indicated participants rather than systematically in the entire cohort. Third, maternal PCOS history was unavailable for a subset of participants and was partly verified by telephone interview. Finally, metabolic parameters such as HOMA-IR and HbA1c were not systematically available for the non-PCOS group, limiting direct comparison of metabolic profiles between the groups.

Nonetheless, the long-term follow-up and the application of contemporary adolescent-specific diagnostic criteria provide clinically meaningful insight into the relationship between premature adrenarche and the later development of PCOS.

CONCLUSION

Our findings indicate that premature adrenarche is not uniformly benign and may represent an early clinical marker of the later development of PCOS in a susceptible subgroup. Early adrenal androgen levels at presentation were not predictive, whereas maternal PCOS history emerged as a more informative risk marker. These data support a longitudinal surveillance approach in girls with PA that extends beyond childhood and focuses on familial background, menstrual pattern, and evolving hyperandrogenic features during adolescence.

DECLARATIONS

Ethics Committee Approval: The study protocol was approved by Marmara University Institutional Ethics Committee (Approval No: 09.2009.1020; Date: December 06, 2019).

Informed Consent: Written informed consent was obtained from the legal guardians of the participants.

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