The Relationship between Maternal and Umbilical Cord Androgen Levels and Polycystic Ovary Syndrome in Adolescence: A Prospective Cohort Study


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Context: The prenatal antecedents of polycystic ovary syndrome (PCOS) are not known, but prenatal androgen exposure is thought to contribute. This has not previously been investigated in large prospective studies of normal human pregnancy.

Objective: The aim of the study was to establish the prospective relationship between early life androgen exposure and PCOS in adolescence.

Design and Setting: A prospective cohort study was conducted in the general community.

Patients or Other Participants: A total of 2900 pregnant women were recruited at 18 wk gestation. Prenatal androgen exposure was measured from maternal blood samples (at 18 and 34–36 wk) and umbilical cord blood. Timed (d 2–5 menstrual cycle) blood samples were collected, clinical hyperandrogenism was assessed, and transabdominal ultrasound examination of ovarian morphology was performed in 244 unselected girls from the Raine cohort aged 14–17 yr.

Main Outcome Measure(s): We examined the relationship between early life androgen exposure and PCOS in adolescence.

Results: We did not observe a statistically significant relationship between early life androgen exposure and PCOS in adolescence.

Conclusions: This is the first prospective study to evaluate the relationship between prenatal androgen exposure and PCOS in adolescence in normal pregnancy. Our findings do not support the hypothesis that maternal androgens, within the normal range for pregnancy, directly program PCOS in the offspring. ([J Clin Endocrinol Metab] 94: 3714–3720, 2009)

Puberty marks the onset of ovarian reproductive function, and there is now overwhelming evidence that factors underpinning pubertal onset can be modified by the intrauterine and early childhood environment (1). Understanding the mechanisms regulating puberty and, in particular, ovarian function is of key importance in women’s health. Abnormal ovarian function may result in common and clinically significant conditions such as subfertility and abnormal uterine bleeding. Of importance is that abnormal ovarian function in the polycystic ovary syndrome (PCOS) is closely as-

Abbreviations: A4, Androstenedione; BMI, body mass index; cFT, calculated free testosterone; DHEAS, dehydroepiandrosterone sulfate; FAI, free androgen index; PCO, polycystic ovary; PCOS, PCO syndrome; PdG, pregnanediol-3α-glucuronide; TT, total testosterone.
sociated with features of the metabolic syndrome and an adverse cardiovascular profile in adult life (2).

PCOS is the most common endocrine disorder in women, affecting approximately 7% of the adult population (3). PCOS may first present in adolescence, but the incidence in adolescence is not known, and diagnostic criteria for adult PCOS may not be appropriate for adolescence (4). The origins of PCOS are also unknown, but extensive experimental as well as clinical evidence from pathological conditions in human populations (e.g. congenital adrenal hyperplasia) suggests that excess fetal exposure to maternal androgens may induce the PCOS phenotype in offspring (5, 6).

There is little evidence substantiating a relationship between the exposure of the female fetus to maternally derived androgens and a critical developmental window of reproductive development. The hypothesis that fetal exposure to maternally derived androgens within the normal physiological range programs PCOS has not been tested in large prospective studies of unselected human populations and will be addressed in this study.

The aim of this study was to determine whether early life exposure to androgens significantly disrupts subsequent ovarian function during reproductive life. The androgen markers of interest were total testosterone (TT), free testosterone, androstenedione (A4), and dehydroepiandrosterone sulfate (DHEAS). We therefore investigated the relationship between these circulating androgen concentrations in a normal population of pregnant women at mid (18 wk) and late (34–36 wk) gestation, androgen concentrations in umbilical cord blood, and the PCOS phenotype in their adolescent daughters.

Subjects and Methods

Study design I: Raine study

The established West Australian Pregnancy Cohort (Raine) study (www.rainestudy.org.au) was designed to measure the relationships between early life events and subsequent health and behavior. The study recruited 2900 women at 18 wk gestation in Western Australia in 1989–91 who delivered 2834 singletons, 64 sets of twins, and two sets of triplets. Singleton pregnancies were randomized to an intensive investigation group (n = 1415) and a regular group (n = 1419) (7). In the intensive investigation group, maternal blood samples were collected at 18 wk (n = 1377) and 34–36 wk (n = 1228). Umbilical cord blood was collected at 870 singleton deliveries. Surveys at ages 1, 2, 3, 6, 8, 10, 14, and 16–17 yr collected detailed anthropometric, physical fitness, cardiovascular, respiratory, metabolic, endocrine, psychological, behavioral, neurocognitive, and social measurements. The current cohort includes 2358 members, of which 1800 were active at the 16-yr review. This is one of the largest and most closely followed prospective cohorts of pregnancy, childhood, and adolescence in the world. This study was approved by the Raine Executive Committee and the ethics committees of King Edward Memorial Hospital and Princess Margaret Hospital. Adolescent subjects and their accompanying parent or guardian provided written consent.

Study design II: adolescent daughters

Adolescent girls within the cohort who were postmenarche were invited to participate in the study. From the 1800 active male and female members at the 16-yr review, 723 eligible adolescent girls were invited to participate. These girls were from both the intensive and regular groups. The study visit was scheduled for d 2–5 of their menstrual cycle by asking the girls to telephone the research nurse on the first day of bleeding. This ensured that subjects with regular and irregular cycles were sampled during the early follicular phase. All visits were timed between 1530 and 1630 h. At this visit, age and personal and family medical history were recorded, and subject height, weight, waist circumference, hip circumference, and blood pressure were measured. Subjects were given a menstrual diary to record all episodes of bleeding and spotting over the next 90 d. In those girls who reported irregular periods, urinary samples were collected weekly for 12 wk for the measurement of pregnanediol-3α-glucuronide (PdG).

Collection, processing, and storage of maternal and umbilical cord blood samples

Maternal blood samples were collected at 18 and 34–36 wk gestation. Mixed arterial and venous umbilical cord blood was collected at birth. Serum was collected from the blood samples and stored at −80 °C. All samples were maintained at −80 °C (i.e. never thawed and refrozen) until the time of hormone assays. The hormone measurements from maternal serum and adolescent plasma were performed at the same time.

Assessment of clinical hyperandrogenism

Hirsutism was assessed using the Ferriman-Gallwey scoring system (8). Acne was evaluated using a validated scale and classified as mild, moderate, or severe (9).

Ultrasound

Subjects were given water to drink until a full bladder was visualized on transabdominal ultrasound. All ultrasounds were performed by one of two experienced gynecological ultrasonographers. At ultrasound, ovarian and uterine volume and the number and diameter of ovarian follicles were recorded. All images were reviewed by one expert. If any follicle larger than 10 mm was seen, the ultrasound was repeated in the early follicular phase of the next cycle.

Biochemical measurements

SHBG and androgen concentrations (TT, A4, DHEAS) were measured in the serum from mothers at 18 (n = 122) and 34–36 (n = 117) wk gestation, in cord blood (n = 84), and also in the plasma from 226 adolescent girls. TT was measured by using a double antibody RIA (DSL-4100; Beckman Coulter, Webster, TX) that was modified by Repromed Laboratory (Dulwich, South Australia) (10). The lower limit of sensitivity was 347 pmol/liter, and the interassay and interpatient coefficients were 6 and 15% at the 1 nmol/liter concentration. SHBG concentrations were determined using a noncompetitive liquid-phase im-
munoradiometric assay (68562; Orion Diagnostica, Espoo, Finland). Concentrations of DHEAS (DSL-2700; Beckman Coulter) and A4 (DSL-4200; Beckman Coulter) were determined by RIA. Concentrations of free testosterone were calculated (cFT) from the measured TT and SHBG concentrations using the Vermeulen equation (11). This calculator has been made available by one of the authors (http://www.issam.ch/freetesto.htm). Fixed values for the concentration of serum albumin were used: 43 g/liter for wk 18 maternal samples, 35 g/liter for wk 34–36 maternal samples, and 30 g/liter for cord samples (12). The free androgen index (FAI) is the TT/SHBG (in nmol/liter) × 100.

Concentrations of prolactin and TSH in the plasma from adolescent girls were determined using commercially available ELISAs from DSL labs (Beckman Coulter). Urinary concentrations of PdG were determined using an ELISA kit from Immuno- metrics (London, UK), and urinary creatinine was determined using a kit from Cayman Chemical Company (Ann Arbor, MI).

**Diagnosis of PCOS**

Diagnosis of PCOS was ascertained using the Rotterdam consensus statement (13), with the presence of two of the following criteria: polycystic ovary (PCO) morphology; clinical or biochemical hyperandrogenism; or oligoanovulation. The National Institutes of Health (NIH) criteria for PCOS (14) were considered to have been met if menstrual cycles were oligoanovulatory (as defined below), together with either clinical or biochemical hyperandrogenism (as defined below).

**PCO morphology**

Early follicular ovarian morphology was measured by transabdominal ultrasound evaluation of ovarian size and morphology performed by one of two experienced gynecological ultrasonographers, and all images were evaluated by one expert. PCO morphology was defined according to standard international criteria: one or more ovaries more than 10 cm³ or 12 or more follicles between 2 and 9 mm in diameter (15).

**Hyperandrogenism**

Clinical hyperandrogenism was defined by a Ferriman-Gallwey score of at least 8 (3, 8). Biochemical hyperandrogenism was defined as concentrations in the upper 25th centile of cFT, which was at least 24.45 pmol/liter for this data set.

**Oligoanovulation**

The presence of ovulation was assessed by initially screening with a prospective menstrual diary, collected over 3 months, to establish menstrual regularity. Irregular cycles were defined as those less than 25 or more than 35 d in duration or where the cycle length varied from month to month by more than 4 d (16). Confirmation of ovulatory status was performed by a prospective weekly collection of urine samples for the analysis of the progesterone metabolite PdG for 12 wk. Ovulation was confirmed if the ratio of PdG to creatinine was greater than three times baseline secretion in at least 2 of the 3 months assessed based on the Kassam algorithm for weekly urine collection (17). Other causes of oligo/anovulation were excluded by measuring TSH and prolactin concentrations.

**Statistical analysis**

Continuous data were summarized using means and SD values or medians and interquartile ranges according to data normality. Categorical data were summarized using frequency distributions. Univariate group comparisons were conducted using t tests or Mann-Whitney tests for continuous outcomes and χ² tests for categorical outcomes. Linear regression was used to examine associations between outcomes such as ovarian volume or total number of 2- to 9-mm follicles and androgen measurements while simultaneously adjusting for confounders (i.e. adolescent body mass index [BMI]). For all regression analyses, data were log-transformed to achieve normality, as appropriate. Nonlinear regression analyses were also performed; no significant results were concluded, and results of these analyses are not shown. All hypothesis tests were two-sided and P values < 0.05 were considered statistically significant. SPSS statistical software (version 15.0; SPSS Inc., Chicago, IL) was used for data analysis.

**Results**

From the 723 eligible adolescent girls that were invited to participate in this study, a total of 244 girls consented and were able to attend the clinic on d 2–5 of their menstrual cycle. Twelve of the adolescent girls were excluded due to hormonal contraceptive use, and 232 girls were therefore included for analysis. Fifty-three percent of the adolescent girls recruited into this study had mothers in the intensive arm of the Raine cohort. This represents 123 pregnancies with at least one blood sample.

Subject characteristics including age at assessment, time since menarche, BMI, and hip-to-waist ratio are shown in Table 1. A total of 224 (96%) girls were from singleton pregnancies. The great majority (206, or 91.6%) were Caucasian. Mean neonatal birth weight was 3278 g (SD, 601 g), corresponding to a mean z-score of 0.15 (SD, 1.0) adjusted for gestational age at delivery, nulliparity, and gender.

Mean age at menarche was 12.4 yr, which is consistent with other published studies of Caucasians in developed countries. In our sample, the proportion of girls who self-reported irregular periods at recruitment was 41% (92 of 232).

**Diagnosis of PCOS**

Data for evaluating PCOS were reviewed for 226 of 232 (97%) girls recruited, excluding six due to insufficient data. The prevalence of each diagnostic criterion is shown in Table 2. The Rotterdam diagnostic criteria for PCOS were met by 66 adolescents (28%), whereas 36 (15%) met the NIH diagnostic criteria for PCOS. The prevalence of clinical hyperandrogenism was very low in our adolescent population, with 92% of Ferriman-Gallwey scores below 5 (210 of 229). Moreover, all girls (8 of 229) who met our criteria for clinical hyperandrogenism (i.e. Ferriman-Gallwey score ≥ 8) also met our clinical criteria for biochemical hyperandrogenism.
The relationship between maternal and umbilical cord androgens and PCOS

Androgen concentrations from maternal and umbilical cord sera and from the plasma of their adolescent daughters are presented in Table 3. As expected, all indices of androgenicity (TT, DHEAS, A4, cFT, and FAI) were significantly elevated in adolescents who met the diagnostic criteria for PCOS using either the Rotterdam or NIH definition for PCOS (see Table 3 for P values). PCOS diagnosis, using either criteria, was not associated with differences in androgen concentrations of the mothers during pregnancy (wk 18, wk 34–36) or at delivery (cord).

We did not observe any significant association between maternal or umbilical cord androgens (TT, cFT, A4, DHEAS, FAI) and PCOS in adolescence using either PCOS definition (Table 3). When each diagnostic criterion was examined separately (and adjusted for current BMI), no significant associations with maternal cFT or umbilical cord cFT were found. There were no associations between irregular periods in adolescents and maternal cFT at 18 wk (P = 0.803) and 34–36 wk (P = 0.675) and at delivery (P = 0.786). There were no relationships between ovarian volume or number of ovarian follicles (size <10 mm) in adolescents and maternal cFT at 18 wk, at 34–36 wk, or at delivery. The concentration of cFT in adolescents was not related to maternal androgen concentrations.

We did not observe any significant association between maternal or umbilical cord androgens (TT, cFT, A4, DHEAS, FAI) and PCOS in adolescence using either PCOS definition (Table 3). When each diagnostic criterion was examined separately (and adjusted for current BMI), no significant associations with maternal cFT or umbilical cord cFT were found. There were no associations between irregular periods in adolescents and maternal cFT at 18 wk (P = 0.803) and 34–36 wk (P = 0.675) and at delivery (P = 0.786). There were no relationships between ovarian volume or number of ovarian follicles (size <10 mm) in adolescents and maternal cFT at 18 wk, at 34–36 wk, or at delivery. The concentration of cFT in adolescents was not related to maternal androgen concentrations.

There were no significant relationships between maternal androgens and other characteristics of the girls, including age at menarche, birth weight, and birth weight z-scores. No significant relationship was observed between birth weight and PCOS in adolescence. Similarly, no significant relationship was observed between birth weight and maternal cFT, umbilical cord cFT, menstrual irregularity in adolescence, or adolescent androgen concentrations (data not shown).

### TABLE 1. Descriptive characteristics at recruitment

<table>
<thead>
<tr>
<th></th>
<th>PCOS (Rotterdam)</th>
<th>PCOS (NIH)</th>
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<tbody>
<tr>
<td></td>
<td>All</td>
<td>No</td>
</tr>
<tr>
<td>n</td>
<td>232</td>
<td>161</td>
</tr>
<tr>
<td>Age at assessment (yr)</td>
<td>15.2 (0.48)</td>
<td>15.2 (0.44)</td>
</tr>
<tr>
<td>Age at menarche (yr)</td>
<td>12.5 (1.2)</td>
<td>12.7 (1.2)</td>
</tr>
<tr>
<td>Time since menarche (months)</td>
<td>32.2 (15.0)</td>
<td>30.2 (14.4)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.7 (3.8)</td>
<td>22.1 (3.0)</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>0.54 (0.81)</td>
<td>0.43 (0.78)</td>
</tr>
<tr>
<td>BMI categoriesa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>163 (70.3%)</td>
<td>124 (77.0%)</td>
</tr>
<tr>
<td>Overweight</td>
<td>48 (20.7%)</td>
<td>30 (18.6%)</td>
</tr>
<tr>
<td>Obese</td>
<td>19 (8.2%)</td>
<td>6 (3.7%)</td>
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<tr>
<td>Hip/waist ratio</td>
<td>0.85 (0.08)</td>
<td>0.86 (0.07)</td>
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<tr>
<td>Acne scorea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>69 (29.7%)</td>
<td>49 (30.4%)</td>
</tr>
<tr>
<td>Mild</td>
<td>109 (46.7%)</td>
<td>73 (44.3%)</td>
</tr>
<tr>
<td>Moderate-severe</td>
<td>48 (20.7%)</td>
<td>34 (21.1%)</td>
</tr>
<tr>
<td>Ferriman Gallwey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥8</td>
<td>8 (3.4%)</td>
<td>4 (2.5%)</td>
</tr>
<tr>
<td>Raw score</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
</tr>
<tr>
<td>Irregular period at recruitmenta</td>
<td>96 (41.4%)</td>
<td>54 (33.5%)</td>
</tr>
<tr>
<td>PCO morphologya</td>
<td>80 (35.4%)</td>
<td>29 (18.0%)</td>
</tr>
</tbody>
</table>

Data are shown for all study subjects and stratified by the PCOS diagnoses using both Rotterdam and NIH criteria. Continuous data are reported as: mean (SD) or median (Q1–Q3); categorical data are reported as number (%). P values are from Mann-Whitney or t tests for continuous comparisons and χ² test for categorical comparisons.

a Percentages may not add up to 100% due to missing data.

### TABLE 2. Diagnostic criteria for PCOS

<table>
<thead>
<tr>
<th></th>
<th>Menstrual irregularity</th>
<th>Clinical HA</th>
<th>Biochemical HA</th>
<th>PCO on US</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of girls (%)</td>
<td>119 (51.3%)</td>
<td>8 (3.5%)</td>
<td>60 (28.3%)</td>
<td>80 (35.4%)</td>
</tr>
<tr>
<td>Data available (n)</td>
<td>232</td>
<td>229</td>
<td>212</td>
<td>226</td>
</tr>
</tbody>
</table>
Our findings fail to support that androgen production is excessive may demonstrate a phenotype similar to PCOS (20). This is the first prospective study to examine the relation androgens in serum and plasma (10). We have accounted for this by measuring testosterone is normally bound to albumin or SHBG, and it is during pregnancy, the majority of circulating testosterone is normally bound to albumin or SHBG, and it is thought that the free fraction is the biologically active element. Circulating SHBG concentrations are increased in pregnancy due to raised estrogens, which may reduce free testosterone. We have accounted for this by measuring SHBG and TT and using these to calculate free testosterone concentrations. Although conventional testosterone assays have limited sensitivity at low concentrations, we have addressed this by employing RIA techniques that have been validated and are able to detect low concentrations androgens in serum and plasma (10).

During pregnancy, maternal circulating testosterone concentrations increase in the first trimester, with further

### Discussion

This is the first prospective study to examine the relationship between PCOS in adolescence and androgen exposure during early life, in normal pregnancy. Our study did not confirm a direct relationship between maternal circulating androgens, umbilical cord androgens, and PCOS in adolescence.

During normal pregnancy, the fetus is protected from maternal androgens by placental aromatase, which rapidly converts A4 to estrone, 16-hydroxytestosterone to estriol, and testosterone to estradiol (18). Previous animal studies indicating that raised maternal androgens program PCOS-like phenotypes have administered supraphysiological doses of testosterone in pregnancy, high enough to exceed the normal barriers of increased circulating concentrations of SHBG and the action of placental aromatase (2, 19). Human studies where maternal or fetal androgen production is excessive may demonstrate a phenotype similar to PCOS (20). Our findings fail to support the hypothesis that maternal androgens within the normal range directly program PCOS in offspring. However, this does not preclude the possibility that early life androgens may impact reproductive function through other downstream mechanisms.

During pregnancy, the majority of circulating testosterone is normally bound to albumin or SHBG, and it is thought that the free fraction is the biologically active element. Circulating SHBG concentrations are increased in pregnancy due to raised estrogens, which may reduce free testosterone. We have accounted for this by measuring SHBG and TT and using these to calculate free testosterone concentrations. Although conventional testosterone assays have limited sensitivity at low concentrations, we have addressed this by employing RIA techniques that have been validated and are able to detect low concentration androgens in serum and plasma (10).

During pregnancy, maternal circulating testosterone concentrations increase in the first trimester, with further
increments through to term (21). Maternal A4 concentrations increase in the latter part of pregnancy (22), whereas DHEAS decreases with advancing gestation (23). The androgen concentrations measured in the present study are consistent with those previously reported during normal pregnancy (24). We did not measure placental aromatase activity in our study, and it is possible that variations in the conversion of androgens to estrogens may have altered fetal androgen exposure without changing circulating maternal androgen concentrations (25). Similarly, we have no measurements of fetal androgen responsiveness or androgen receptor affinity.

It is similarly not known how closely cord blood reflects fetal androgen exposure. Sensitive periods for fetal androgen exposure likely occur early in gestation and hence may not be reflected in term cord concentrations (26). However, recent animal studies suggest that fetal androgen exposure late in gestation may still program metabolic changes in offspring (19).

Strengths of this study include the relatively large number of normal pregnancies studied and the prospective design. Furthermore, unlike other large cohort studies (27), very few girls in this study were using hormonal contraception. A potential weakness in this study is that only one third of the eligible cohort participated in the study. This was a demanding study for subjects; however, it remains the largest prospective birth cohort study from an unselected population.

Approximately 30% of the subjects were overweight or obese. Consistent with other published reports of PCOS in adolescence, overweight/obesity was increased in girls with PCOS (1). The incidence of PCOS in adolescence is not known. Using the Rotterdam criteria, we identified a high prevalence of PCOS (28%). This was primarily attributable to a high incidence of menstrual irregularity and abnormal ultrasound appearance in this population. It is possible that with time some subjects with irregular cycles might have developed regular cycles.

The diagnosis of PCOS in adolescence is problematic (4). Menstrual irregularity and multifollicular ovaries may reflect physiological maturation of the hypothalamic pituitary gonadal axis (28). When ultrasound was not a diagnostic criterion (NIH criteria), the incidence of PCOS was markedly reduced (15%), suggesting that the NIH criteria may be more appropriate in an adolescent population.

Hyperandrogenism is the principal endocrine phenotype of PCOS. Standard definitions of clinical hyperandrogenism may not be applicable in adolescents where acne is more common and hirsutism is less apparent (29). Biochemical hyperandrogenism is characteristic of adolescent PCOS (30), but there is no internationally agreed normal range for free testosterone or FAI and no clear definition for hyperandrogenism in adolescent or adult women. We chose to define hyperandrogenism as the upper 25% of free testosterone as measured in our population. This may have been overinclusive and contributed to the high incidence of PCOS seen. In addition, self-selection of subjects with menstrual disorders and/or clinical hyperandrogenism from this cohort may have increased the incidence of PCOS.

The findings from this prospective study fail to demonstrate a direct relationship between maternal or umbilical cord androgens and PCOS in adolescence. Specifically, our findings fail to support the hypothesis that maternal androgens within the normal range directly program PCOS in the offspring.

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Disclosure Summary: The authors have nothing to disclose.

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