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CLINICAL REVIEW: Identifying Children at Risk for Polycystic Ovary Syndrome

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Context: Polycystic ovary syndrome (PCOS) appears to arise as a complex trait with contributions from both heritable and nonheritable factors. Polygenic influences appear to account for about 70% of the variance in pathogenesis. In view of this evidence for congenital contributions to the syndrome, childhood manifestations may be expected.

Objective: The objective has been to review the evidence that risk factors for PCOS can be recognized in childhood.

Design: This study consisted of screening of the PCOS literature for articles pertaining to potential childhood and adolescent antecedents.

Results: Congenital virilizing disorders; above average or low birth weight for gestational age; premature adrenarche, particularly exaggerated adrenarche; atypical sexual precocity; or intractable obesity with acanthosis nigricans, metabolic syndrome, and pseudo-Cushing syndrome or pseudo-acromegaly in early childhood have been identified as independent prepubertal risk factors for the development of PCOS. During adolescence, PCOS may masquerade as physiological adolescent anovulation. Asymptomatic adolescents with a polycystic ovary occasionally (8%) have subclinical PCOS but often (42%) have a subclinical PCOS type of ovarian dysfunction, the prognosis for which is unclear.

Conclusion: Identifying children at risk for PCOS offers the prospect of eventually preventing some of the long-term complications associated with this syndrome once our understanding of the basis of the disorder improves. **(*J Clin Endocrinol Metab* 92: 787–796, 2007)**

POLYCYSTIC OVARY SYNDROME (PCOS) becomes symptomatic during adolescence and affects at least 5% of reproductive-age women (1). PCOS is a heterogeneous syndrome of unexplained chronic hyperandrogenism and oligo-anovulation (2), with a polycystic ovary being an alternative diagnostic criterion (3). About half of cases lack some of the classic Stein-Leventhal syndrome features of menstrual irregularity, hirsutism, obesity, and polycystic ovaries. Whether the syndrome can be diagnosed in the absence of hyperandrogenism is controversial (4, 5), and the documentation of hyperandrogenemia can be problematic (5). The broad spectrum of the disorder seems to encompass atypical cases of hyperandrogenemia with central obesity and features of insulin resistance instead of hirsutism or anovulation (6).

Functional ovarian hyperandrogenism (FOH) is usually the source of the androgen excess (7, 8). It is characterized by 17-hydroxyprogesterone (17PROG) hyperresponsiveness to the gonadotropin stimulation of GnRH agonist or human chorionic gonadotropin testing and subnormal suppressibility of plasma testosterone upon adrenal suppression by glucocorticoid. It is often accompanied by functional adrenal hyperandrogenism, characterized by 17-hydroxypregnenolone or dehydroepiandrosterone (DHEA) hyperresponsiveness to ACTH; in atypical PCOS, the sole source of androgen excess may be functional adrenal hyperandrogenism. The underlying defect seems to be a constitutive dysreglulaton of steroidogenic cells (9). Intrinsic granulosa cell dysfunction is also present (8, 10, 11). LH excess appears to contribute to 50–75% of cases (12, 13). Evidence is accumulating that it arises from androgen interfering with the progesterone negative-feedback effect on LH secretion (14, 15). However, the possibility of primary central mechanisms for LH excess remains, particularly in adolescent PCOS (16–18).

Increasing evidence suggests that PCOS arises as a complex trait with contributions from both heritable and nonheritable factors (19–21). Polygenic influences appear to account for about 70% of the variance in pathogenesis. Nearly half of sisters of women with PCOS have an elevated plasma testosterone level, although only half of them are symptomatic. Polycystic ovaries appear to be transmitted as a dominant trait, usually asymptomatic but often accompanied by a subclinical PCOS type of ovarian dysfunction (22). Central obesity and insulin resistance seem to play important roles in PCOS (23, 24), perhaps by accentuating steroidogenic dysregulation (7, 8) but perhaps more fundamentally because PCOS is closely related to these features in parents (25). Gestational factors have also been incriminated; the syndrome has been associated with high birth weight in heavy mothers (26) and can arise from fetal programming by androgen excess (27). In view of these indications for congenital origins of the syndrome, it is not surprising that there is increasing recognition of risk factors for PCOS in childhood (Fig. 1), the evidence for which is reviewed here.

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Abbreviations: CAH, Congenital adrenal hyperplasia; CPP, central precocious puberty; DHEA, dehydroepiandrosterone; DHEA-S, DHEA sulfate; FOH, functional ovarian hyperandrogenism; LBW, low birth weight for gestational age; PAA, physiological adolescent anovulation; PCOS, polycystic ovary syndrome; 17PROG, 17-hydroxyprogesterone; SGA, subnormal birth weight for gestational age.

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Congenital Virilization Programs PCOS Neuroendocrine and Metabolic Features

PCOS is common in females with congenital virilizing disorders (17, 18). Congenital adrenal hyperplasia (CAH) is the most frequent, but not exclusive, cause of this outcome. The diagnosis of PCOS is established in CAH by finding persistent elevation of testosterone when anovulatory symptoms persist in women in whom the adrenal dysfunction of CAH is well controlled on glucocorticoid therapy. It seems to be present in about half of women with classic CAH but occurs in only perhaps one fifth of women with nonclassic CAH. The PCOS of CAH is associated with a higher degree of LH hyperresponsiveness to GnRH agonist testing than found in ordinary PCOS. It has been suggested that the LH hyperresponsiveness to GnRH may distinguish this secondary PCOS from the LH-dependent adrenal rests that rarely occur in CAH (17, 28). Insulin resistance has been reported in nonobese females with nonclassic CAH before initiating glucocorticoid therapy (29).

The ascertainment of ovarian hyperandrogenism may be difficult. On one hand, undertreatment of virilizing CAH mimics PCOS by causing polycystic ovaries (30–32), elevated LH levels (33, 34), and infertility (33, 35). On the other hand, glucocorticoid overtreatment also causes amenorrhea (36). The diagnosis may require ovarian function testing.

Congenital androgenization has recently been recognized in mice, sheep, and monkeys as interfering with the negative-feedback inhibition of LH release by progesterone (27, 37, 38). Studies in the rhesus monkey exposed to androgen excess early in gestation have been particularly informative, showing classic PCOS features (27, 39); these animals have ovarian and adrenal hyperandrogenism, oligomenorrhea, polyfollicular ovaries, and elevated LH levels. They also have abdominal obesity, insulin resistance, impaired glucose tolerance, and dyslipidemia. Embryogenesis is impaired. Although low birth weight is not found in these monkeys, it is found in prenatally androgenized sheep (38). Androgen exposure later in gestation causes a similar picture except for LH and insulin disturbances. These considerations would seem to predict that prenatal treatment of affected female fetuses would not only improve genital anatomy but would also improve adult reproductive function.

An intriguing implication of these studies is that excessive testosterone secretion from the ovary of a fetus destined to develop PCOS may program many facets of the syndrome. PCOS theca cells are known to constitutively overproduce androgen (9). Theca-interstitial cells of the fetal primordial follicle begin forming androstenedione and DHEA as early as 3 months in humans, well before antral follicle development begins (40). An alternate possibility that the fetus is exposed to increased maternal testosterone during PCOS pregnancy (41) remains to be confirmed using a testosterone assay appropriately specific for pregnancy serum (42). Thus, although the fetal PCOS ovary potentially overproduces androgen, the question remains whether the quantity would be sufficient to contribute substantially to the fetal endocrine milieu.

Premature Adrenarche and Premature Pubarche

Definitions and background

Adrenarche, the adrenal puberty, is the maturational increase in adrenal androgen production. It reflects the development of the adrenocortical zona reticularis, which becomes continuous at about 6 yr of age and enlarges steadily over the subsequent decade (43, 44).

DHEA sulfate (DHEA-S), is the predominant marker for adrenarche (45–48). Adrenarche represents a change in the pattern of adrenocortical secretory response to ACTH, characterized by disproportionately increasing responsiveness of Δ5-steroid intermediates (17-hydroxypregnenolone and DHEA) compared with Δ^4-steroids (*e.g.* 17PROG and androstenedione) in the presence of stable responses of cortisol (46, 49). This pattern of adrenal secretion results from a unique enzyme expression profile in the zona reticularis, the cells of which express low 3β-hydroxysteroid dehydrogenase type 2 but high cytochrome b5 (an enhancer of the 17,20-lyase activity of cytochrome P450c17) and steroid sulfotransferase (SULT2A1) activities (44) (Fig. 2).

Zona reticularis development requires ACTH, but its determinants are otherwise poorly understood. Another unidentified specific pituitary factor is likely to be involved (50). Adrenarche is not directly related to the pubertal maturation of the neuroendocrine-gonadotropin-gonadal axis. Adiposity may play a role in its development (51, 52). Leptin, insulin, and IGF-I are candidate mediators of this effect (44, 53, 54).

Pubarche, the appearance of sexual hair, requires adren-

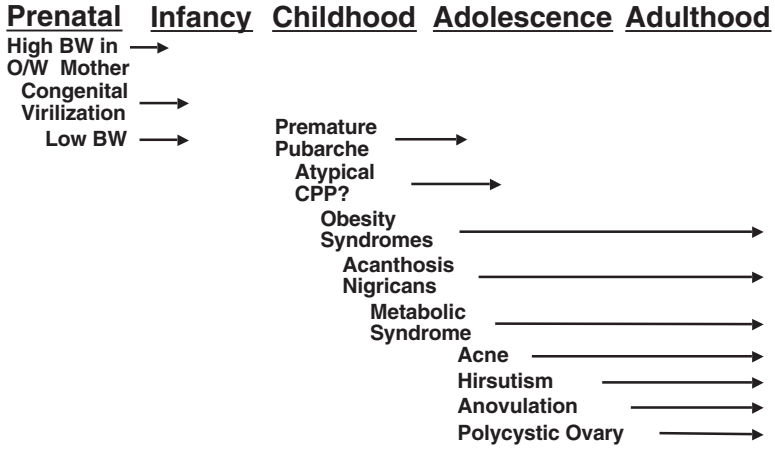

FIG. 1. Childhood risk factors for PCOS. The clinical presentations are listed below the developmental stages in which they first appear, and the *arrows* indicate duration of the symptoms. BW, Birth weight; O/W, over-average weight. Modified with permission from Buggs and Rosenfield (6).

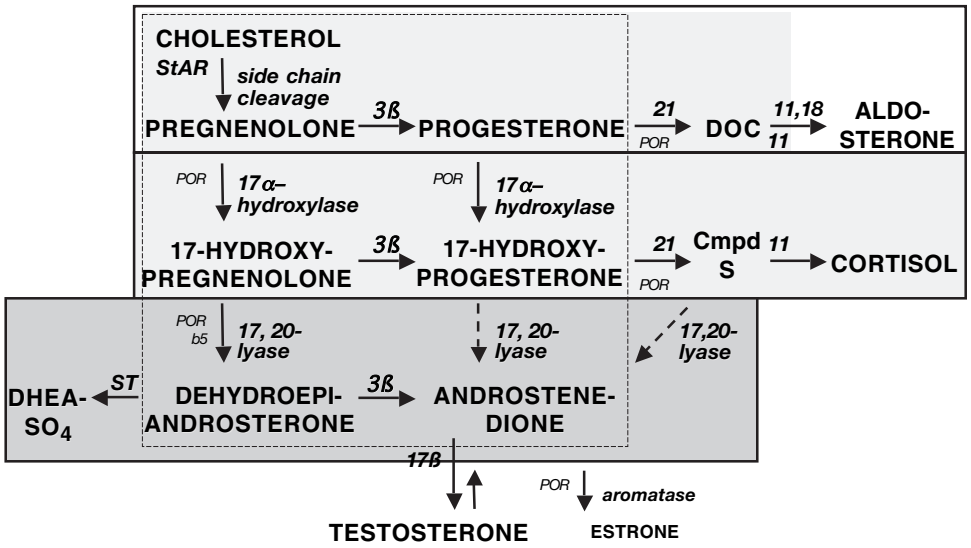

FIG. 2. Outline of the organization of the major steroid biosynthetic pathways in the adrenal cortex. The area within the *dotted square* contains the core steroidogenic pathways, of which the *left* column shows the Δ^5-pathway and the *right* column the Δ^4-pathway, also used by ovarian theca cells. The *top row* shows the pathway to aldosterone; the *middle row* shows the zona fasciculata pathway to cortisol. The *lower*, *darkly shaded row* shows the zona reticularis steps to DHEA-S (SO_4) and other 17-ketosteroids. *Dotted pathways* are considered to be relatively minor. Compound (Cmpd) S is 11-deoxycortisol; the 11-deoxy intermediate to aldosterone (deoxycorticosterone) is not shown. The steroidogenic enzymes are *italicized*. Cytochrome P450 enzyme steps are side chain cleavage (*scc*), 17α-hydroxylase/17,20-lyase, 21-hydroxylase (*21*), 11β-hydroxylase/18-hydroxylase-dehydrogenase (*11*, *18*), and aromatase. Non-P450 enzyme steps are steroidogenic acute regulatory protein (*StAR*), Δ^5-isomerase-3β-hydroxysteroid dehydrogenase (*3*β), 17β-hydroxysteroid dehydrogenase (*17*β), and sulfotransferase (*ST*). Clinically relevant electron transfer enzymes are P450 oxidoreductase (*POR*) and cytochrome b5 (*b5*).

archeal levels of androgen but typically does not occur until shortly after the estrogen rise of true puberty (55). Premature pubarche refers to isolated pubarche before the age of 8 yr in girls (before 9 yr of age in boys) and traditionally has been considered an extreme variation of normal (56). It is ordinarily not accompanied by any other signs of puberty, other than possibly an increase in axillary body odor and microcomedonal acne. Sexual hair development increases slowly, and the bone age increases in proportion to linear growth. Because the pilosebaceous unit sensitivity to androgen is highly variable (57, 58), pubarche may occur at androgen levels that range from those of a young child (idiopathic premature pubarche) to elevated.

Premature adrenarche is the term applied to otherwise unexplained premature pubarche with a plasma steroid pattern indicative of adrenarche (Table 1) (www.esoterix.com) (43, 47, 57, 59, 60). This is traditionally indicated by a DHEA-S level above 40 μg/dl, which is above normal for 1- to 5-yr-olds and above average for 6- to 8-yr-olds although within normal limits for early puberty (57). It is accompanied by an above-average DHEA level and minimal if any elevation of other androgens. The plasma steroid responses to ACTH parallel these changes, with rises of 17-hydroxypregnenolone and DHEA predominating. Corresponding to the trend of androgen levels, children who have premature adrenarche tend to have an above-average but normal growth rate and bone age. It is unclear whether premature adrenarche is simply due to advanced onset of normal zona reticularis development or an early manifestation of the zona reticularis overactivity that is the first manifestation of persistent functional adrenal hyperandrogenism.

Exaggerated adrenarche is a clinically extreme type of premature adrenarche that seems to place children at increased risk for PCOS and its associated features (56, 61, 62). The term originated as a hypothesis for the functional adrenal hyperandrogenism of adults with PCOS (59, 63) that now appears to be due to the dysregulational hyperandrogenism that involves the ovaries as well (64). Thus, the exaggerated adrenarche of childhood may be the first manifestation of steroidogenic dysregulation, rather than simply being an extreme variant of normal adrenarche.

The term exaggerated adrenarche has been variously applied when the baseline DHEA-S or androstenedione level is over a critical level (61) or elevated for age (65) or when baseline plasma androgens (62) or the response to ACTH of 17-hydroxypregnenolone (66) is above that of early pubertal girls. We suspect this diagnosis in children with premature adrenarche who have clinical features that suggest an atypical degree of androgen excess (*e.g.* significant bone age advancement) or insulin resistance (*e.g.* central adiposity or acanthosis nigricans). Such children generally have a slightly advanced onset of true puberty; compromised height potential is uncommon unless there is a congenital or hereditary reason for short stature (67).

Evidence for a relationship of premature adrenarche to PCOS

A change in the traditional benign view of premature pubarche occurred with the 1993 report by Ibañez *et al.* (61) that many girls with premature adrenarche went on to develop PCOS during adolescence. Thirty-five postmenarcheal girls with a history of premature pubarche were recalled at an average age of 15–16 yr. Sixteen fulfilled criteria for PCOS, with oligomenorrhea, hirsutism, and elevated androgen lev-

TABLE 1. Typical ranges expected for serum androgens and steroid precursors in normal females and premature adrenarche

	17PREG (ng/dl)	17PROG (ng/dl)	11-Deoxycortisol (ng/dl)	Cortisol (μg/dl)	DHEA-S (μg/dl)	DHEA (ng/dl)	Androstenedione (ng/dl)	Testosterone (ng/dl)
Before ACTH (0800 h)								
Children, 1–5 yr old	10–105	5–115	20–160	3–20	5–35	20–130	10–50	<20
Children, 6–10 yr old	10–200	5–115	20–160	3–20	10–115	20–345	10–75	<20
Premature adrenarche	20–350	5–115	20–160	3–20	40–130	50–600	20–75	10–35
Early pubertal girls	35–350	15–220	20–160	3–20	35–130	40–600	40–175	10–35
Adult females, follicular phase	55–360	15–150[a]	20–160	3–20	75–255	100–850	60–200	20–60
After $ACTH_{1–24}$ (30–60 min after ≥10 μg/m^2 iv)								
Children, 1–5 yr old	45–350	50–270	95–300	17–45	5–35	25–100	15–70	<20
Children, 6–10 yr old	60–650	85–300	95–300	17–45	10–115	70–320	25–100	<20
Premature adrenarche	80–750	85–400	95–300	17–45	40–130	80–725	25–230	10–35
Early pubertal girls	150–750	90–400	95–300	17–45	35–130	70–725	55–230	10–35
Adult females, follicular phase	150–1070	35–160[a]	95–300	17–45	75–255	250–1470	60–250	20–60
Conversion multipliers to SI units	0.0316 (nmol/liter)	0.0303 (nmol/liter)	0.0289 (nmol/liter)	0.0276 (μmol/liter)	0.0271 (μmol/liter)	0.0347 (nmol/liter)	0.0349 (nmol/liter)	0.0347 (nmol/liter)

Ranges are for RIA after preparatory chromatography, except for cortisol and DHEA-S. Values differ slightly among laboratories. 17PREG, 17-hydroxypregnenolone. Data are from Esoterix Laboratory Services, Inc. (www.esoterix.com and Steroid Response to ACTH Handbook, 1991) and Refs. 43, 47, 57, 59, and 60.

[a] 17PROG early and midfollicular phase baseline levels greater than 140 ng/dl are found in normal women who are heterozygous for 21-hydroxylase deficiency, and they often have responses to ACTH greater than those shown. 17PROG begins rising in the preovulatory phase and peaks as high as 400 ng/dl in the luteal phase of the cycle.

els; half had a polycystic ovary. The other nineteen were regularly menstruating; one third of these had mild hirsutism, and one sixth had a polycystic ovary. Twelve normal volunteers were studied for comparison. None were obese. A GnRH agonist test showed FOH in all of the PCOS group, with significant LH hyperresponsiveness, but there was no evidence of FOH in the other group of former premature pubarche patients. A retrospective analysis showed significant correlations between their mid-childhood DHEA-S and androstenedione levels and their postpubertal 17PROG responses to GnRH agonist testing (Fig. 3). A DHEA-S level over 185 μg/dl (5 μmol/liter) at pubarche onset appeared to have both a positive and negative predictive value for PCOS of about two thirds. An androstenedione level over 99 ng/dl (3 nmol/liter), in an assay that did not use preparatory chromatography, appeared to have a positive predictive value over 90% and a negative predictive value of about two thirds. These levels approximate the upper quartile of their overall premature pubarche population (43) and are atypically high for premature adrenarche (Table 1).

This correlation between androgen levels at the time of presentation with premature pubarche and the development of the PCOS type of ovarian dysfunction during adolescence is compatible with the concept that the ovarian and adrenal dysfunction of PCOS represent an inborn dysregulation of steroidogenesis. Two children had 17PROG responses to ACTH upon presentation for premature pubarche that were similar to those sometimes seen in the functional adrenal hyperandrogenism of adult PCOS (7). These data further suggest that children with the exaggerated adrenarche type of premature adrenarche are those at greatest risk of PCOS.

This investigative team subsequently carried out a series of studies in their Catalan (Northern Spanish) population. Ovarian function testing was performed on 76 premature adrenarche girls when they became pubertal (68). In premenarcheal girls averaging 12 yr and postmenarcheal girls averaging 15.4 yr of age, 17-hydroxypregnenolone responses to GnRH agonist tests were strikingly higher than 17PROG responses. Indeed, this postmenarcheal group did not have FOH. The investigators interpreted the data to indicate that

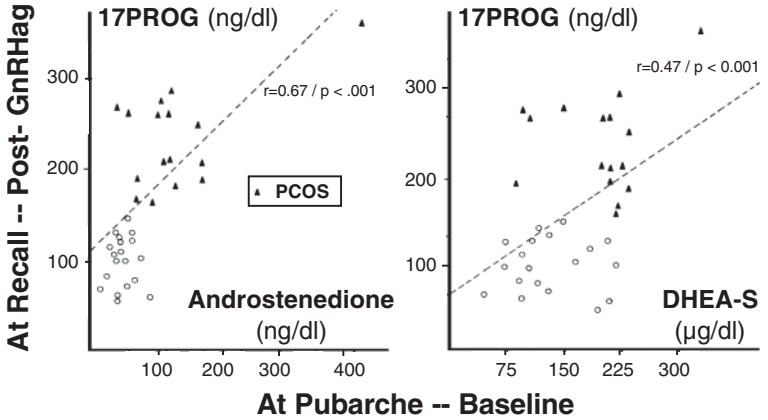

FIG. 3. Relationship of androstenedione and DHEA-S blood levels at presentation with premature pubarche to the 17PROG response to GnRH agonist (GnRHag) testing of the same girls when postmenarcheal. PCOS subjects were hyperandrogenic and oligomenorrheic. Modified with permission from Ibañez *et al.* (61).

pubertal girls with a history of premature pubarche show a distinct pattern of ovarian maturation that is initially characterized by abnormalities in the Δ^5 pathway (17-hydroxypregnenolone) and only later by abnormalities in the Δ^4 pathway (17PROG). Such an unprecedented shift in steroidogenic pathway seems more likely, however, to be attributable to the coexistent functional adrenal hyperandrogenic responses to a stressful research protocol.

In another set of studies, Ibañez *et al.* (69, 70) reported that, as in PCOS, premature pubarche girls were excessively insulin resistant from mid-childhood through puberty. This was associated with central adiposity and dyslipidemia but not obesity (71). Other populations of premature pubarche girls have been reported to be insulin resistant and obese, with a correlation between insulin resistance and androgen levels (72).

The type of longitudinal studies reported by the Ibañez team is very difficult to carry out. As yet, only one report of an attempt to replicate these findings has appeared. A Parisian collaborative group identified Caucasian former premature pubarche patients with no hormone abnormality who were postpubertal (73). One third could be studied, and at an average age of 17.4 yr, these 27 patients had a higher free androgen index and lower SHBG than 25 population controls. On the other hand, they did not differ from controls in hirsutism score, acne, prevalence of menstrual irregularity, BMI, or glucose and insulin during an oral glucose tolerance test. The investigators concluded that only 15–20% of their premature pubarche population developed hyperandrogenism. Their study did not clarify whether the subgroup of girls with exaggerated adrenarche is at increased risk of developing PCOS.

Low-birth-weight risk for premature adrenarche and PCOS

A low birth weight for gestational age (LBW) was meanwhile recognized to predispose to premature pubarche and, in turn, PCOS by Ibañez *et al.* in their Catalan population (65). Girls with premature pubarche associated with elevated DHEA-S or androstenedione levels (averaging 120 μg/dl and 141 ng/dl, respectively) had lower birth weights for gestational age than clinic controls according to a retrospective comparison; the respective birth weights of these groups were 0.81 and 0.38 SD below average compared with Flemish standards. Twenty-seven percent of such exaggerated adrenarche girls had subnormal birth weights for gestational age (SGA) (67). One French group obtained confirmatory results, finding birth weights of unselected girls with premature pubarche to be significantly lower than expected (74). However, no association between birth weight and premature pubarche was found in the above smaller Parisian cohort (73).

Healthy postmenarcheal Catalan girls without premature pubarche who were born SGA had DHEA-S levels twice as high as those with normal birth size (averaging 282 *vs.* 136 μg/dl) (75). A smaller group of Italian SGA girls evaluated at 6.0–7.5 yr of age were found to have 30% higher DHEA-S levels than matched controls, although pubarche had not occurred (76). However, their SGA group evaluated at 17.5–18.5 yr of age showed no significant DHEA-S elevation or clinical evidence of PCOS. A Dutch study showed significantly increased DHEA-S levels in SGA children before puberty but loss of significance during puberty (77). A United Kingdom study revealed an inverse relationship between the birth size at term and mid-childhood DHEA-S level (78). Thus, these data confirm an association of early adrenarche with SGA but indicate that it may not be symptomatic or a harbinger of persistent adrenal hyperandrogenism in all populations.

Postmenarcheal follow-up of the Catalan exaggerated-adrenarche girls revealed that 52% were not hyperandrogenic, whereas 25% had the PCOS type of FOH without hyperinsulinemia during an oral glucose tolerance test and 23% had both FOH and hyperinsulinemia (65). The birth weights of these successive groups averaged 0.25, 1.0, and 2.0 SD below average. Thus, increasing degrees of intrauterine growth restriction seemed to be associated with successively increasing risk for premature adrenarche, PCOS, and hyperinsulinemia. Notably, LBW seemed to protect those who acquired PCOS from developing polycystic ovaries (79). The data were interpreted as consistent with the fetal-origins hypothesis that intrauterine growth restriction predisposes to postnatal insulin resistance, an association that is well established (80). In addition, the investigators postulated that premature pubarche and PCOS were likewise consequences of LBW-related insulin resistance and were, indeed, more sensitive markers of insulin resistance than diabetes.

However, follow-up of birth cohorts in other populations has not found a relationship of LBW to PCOS. Follow-up of a large 1950s British birth group to an average age of 27 yr showed no relationship of LBW to PCOS (26). Indeed, heavy babies whose mothers' weights were above average developed PCOS. Birth weight may also be a correlated with the development of polycystic ovaries (26, 81). Study of a similar Finnish population showed no relationship of low birth weight to PCOS symptoms (82). The above Parisian investigators, who had found no relationship of LBW to premature pubarche, ascertained no relationship to late-pubertal hyperandrogenism (73) and found that young adult women born SGA did not have an increased prevalence of menstrual irregularity or higher androgen levels, although they were significantly insulin resistant, a predisposition that was independent of adiposity (83). Thus, although SGA predisposes to insulin resistance, it seems to pose less risk for premature pubarche or PCOS in most populations studied to date.

Exaggerated adrenarche coexistent with central precocious puberty

Lazar *et al.* (84) found an unexpectedly high (55%) prevalence of exaggerated adrenarche in Israeli girls with central precocious puberty (CPP), detected as 17-hydroxypregnenolone hyperresponsiveness (>750 ng/dl) to ACTH, at the start of puberty. The only clinical clue may have been the coincident onset of pubic hair with breast development because DHEA-S elevation was found in only a minority. They also found that about 40% of an older cohort of their CPP girls developed PCOS in the early postmenarcheal years and that this occurred exclusively in those who similarly had 17-hydroxypregnenolone and DHEA-S hyperresponsiveness to ACTH, *i.e.* functional adrenal hyperandrogenism (66). These data suggest a previously unrecognized relationship of a subtle form of exaggerated adrenarche, not detected by

DHEA-S, to PCOS. If confirmed longitudinally, the data would suggest that atypical CPP can be but the first manifestation of a disturbance that will eventually culminate in PCOS.

Conclusions: relationship of premature pubarche and premature adrenarche to PCOS

Premature pubarche is quite heterogeneous. That associated with exaggerated adrenarche appears to carry increased risk for PCOS. However, the extent of risk is unclear and may vary with the clinical and hormonal characteristics of the particular study population.

Is Abnormal Hypothalamic-Pituitary-Ovarian Function Detectable in Early Childhood?

Activation of the hypothalamic-pituitary-gonadal axis, a process distinct from adrenarche, underlies true puberty, the first sign of which is breast development in girls. Abnormality of pituitary-ovarian function has been sought at presentation in girls with premature adrenarche, and none was found (85). There has been no follow-up of the predictive value of ovarian morphology for PCOS.

Premature (precocious) puberty, *i.e.* before 8 yr of age in girls (86–88), is due to early activation of the normal axis and is usually of unknown etiology, which is termed idiopathic CPP. It has been a prime candidate disorder because it resembles PCOS in being characterized by a disproportionate rise in LH relative to FSH. Case observations have prompted speculation that an underlying neuroendocrine dysfunction may be manifest first as CPP and later as PCOS (89). This possibility has been specifically addressed in three series of idiopathic CPP cases. PCOS occurred in about 10% of one European series (90), but it was not found in two others (52, 91). Thus, it is unclear whether the association with typical CPP is any more than would be expected by chance. Isolated reports suggest that PCOS may be associated with atypical CPP, however (66, 92).

Recently, spontaneous pituitary-ovarian function was studied in young daughters of PCOS patients at 2–3 months (during the mini-puberty of the newborn) and 4–7 yr of age (11). Significant elevation of anti-Müllerian hormone, a marker of granulosa cell function, was reported. However, only 18% had elevated levels, which is substantially less frequent than the prevalence of testosterone elevation (nearly 50%) in adult daughters of PCOS women (93). Pursuit of this line of investigation will be of interest.

Prepubertal and Peripubertal Obesity

We recently recognized that intractable prepubertal obesity preceded severe insulin resistance syndromes that heralded adolescent PCOS in four cases (92). In two cases, the manifestation of insulin-resistant hyperinsulinism was pseudo-Cushing syndrome, diagnosed at 7.8 and 10.3 yr of age; in two, pseudo-acromegalic gigantism was recognized on presentation with tall stature at puberty. Notably, one of the pseudo-Cushing patients had developed CPP at 5.8 yr of age; this was atypical in being poorly suppressible by chronic GnRH agonist treatment. Three had an elevated basal index of insulin resistance, and insulin rose to extremely high levels (1000–1800 μU/ml) during oral glucose tolerance testing (normal maximum, 500 μU/ml). The other was asymptomatically diabetic in early puberty with peak insulin levels of 600–800 μU/ml post glucose load. Acanthosis nigricans and metabolic syndrome were present in all. Polycystic ovaries were found in one case 2.5 yr before menarche. However, androgen excess could not be documented until menstrual irregularity developed after menarche at 10.8–12.8 yr of age. Three had a type 2 diabetic parent, one of whom had PCOS; ethnicity was diverse.

We suspect that these syndromic cases represent the tip of an iceberg that relates inborn insulin resistance to a predisposition to childhood obesity and PCOS. It remains to be determined to what extent more ordinary manifestations of insulin resistance, such as metabolic syndrome, a variably expressed cluster of central obesity, hyperglycemia, hypertension, and dyslipidemia that is the result of insulin resistance interacting with obesity and age, for which various childhood criteria have been proposed (25, 94, 95), are risk factors for PCOS.

Ordinary peripubertal obesity has been proposed to predispose to PCOS. Pre- and early-pubertal obese girls have been reported to have a subtle, subclinical increase in testosterone that normalizes with substantial weight loss (96, 97). Adipose tissue is known to be a major site for the formation of testosterone from circulating precursors (98). Because androgen excess inhibits progestin negative feedback in adults, it has been speculated that the hyperandrogenemia of peripubertal obesity may result in increased LH secretion to enhance ovarian androgen production and progression to PCOS in susceptible girls (97).

An attempt to alter the outcome of girls at risk for PCOS by reversing their metabolic abnormalities has been undertaken by Ibañez *et al.* (99, 100). Insulin-lowering treatment with metformin was administered for 1 yr before or during puberty to LBW subgroups of Catalan premature pubarche girls. Metformin improved insulin resistance, adiposity, and features related to them as well as androgen levels, but the effects subsided promptly when treatment was discontinued.

Physiological Adolescent Anovulation (PAA)

Half of menstrual cycles are anovulatory in the first two postmenarcheal years (101). PCOS is often overlooked because it masquerades as this PAA. About half of PAA girls have a PCOS-like increase in LH levels and LH pulse frequency; this group has significantly higher plasma testosterone than controls (102). Testosterone levels are elevated in most such cases, and once testosterone levels become elevated, they seldom normalize (103, 104). Most girls whose anovulatory symptoms persist more than 2 yr will have ongoing menstrual irregularity (105), so PCOS will account for a substantial proportion of these cases. Although elevation of plasma total or free testosterone provides firm supporting evidence for the hyperandrogenism of PCOS (6), their documentation may be difficult, often requiring determination by a specialty laboratory (5, 106).

PAA resembles PCOS in other ways as well. Normal puberty is characterized by insulin resistance and compensa-

tory hyperinsulinemia that seem to result from the transient pubertal increase in GH production (107–109). The insulin resistance of puberty is like that of PCOS in its degree and in its tissue selectivity (110). Although insulin is synergistic with gonadotropins in promoting ovarian androgen excess (7, 111), it may contribute to anovulation independently of androgen hypersecretion to some extent (112). For example, all maneuvers that lower insulin levels, from weight loss to drug treatment, have about a 50% probability of improving menstrual cyclicity and ovulatory status (113–116). Because plasma testosterone falls only modestly with these therapies, ovulation seems partly independent of normalization of androgen levels and directly attributable to lowered insulin resistance. The possibility that this physiological insulin resistance accounts for PAA is untested.

In addition, PAA resembles PCOS in ovarian anatomy. The normal adolescent ovary is known to histologically resemble a polycystic ovary (117, 118). The perimenarcheal combination of a high number of follicles and mature gonadotropin stimulation leads to a greater number of large antral follicles and a slightly greater ovarian size than at any other stage (22). Ultrasound imaging has shown that about one quarter of healthy adolescent volunteers develop multifollicular ovaries, defined as six to 10 follicles of 4–10 mm diameter in the maximum plane without increased ovarian stroma (119, 120). The distinction of these from polycystic ovaries is often difficult (104).

The prevalence of a polycystic ovary appears to be about 10% in the general population of regularly menstruating postmenarcheal schoolchildren (121). The presence of a polycystic ovary appears to have multiple congenital determinants; there is evidence for autosomal dominant transmission (22), linkage to paternal metabolic syndrome (25), and correlations with birth weight and length of gestation (26, 81). About 8% of asymptomatic adolescent volunteers with a polycystic-size ovary were found to have subclinical PCOS (22) and nearly half (42%) to have a subclinical PCOS type of ovarian dysfunction, secreting excessive 17PROG in response to GnRH agonist stimulation without having hyperandrogenemia (22). It is presently unclear whether the latter subgroup is heterozygous for a polycystic ovary gene or is at risk for developing symptomatic PCOS later.

Summary and Conclusions

Identifying girls at risk for PCOS appears to be possible in some situations and offers the potential of eventually preventing some of the long-term complications associated with this syndrome. Nevertheless, more research is needed to increase the prepubertal ascertainment of risk.

CAH and other congenital virilizing disorders appear to be strong risk factors. Failure to correct hyperandrogenemia and normalize menses with glucocorticoid replacement therapy of CAH suggests the diagnosis of PCOS. Prenatal treatment of female fetuses with CAH may prove to prevent the complication of PCOS as well as improve genital anatomy.

SGA seems to pose increased risk for early adrenarche and insulin resistance but to pose less risk for postmenarcheal hyperandrogenism in most populations. In contrast, birth size or gestational age may be related to the development of polycystic ovaries.

Premature pubarche patients appear to carry about a 15–20% risk of developing PCOS. It seems likely that the risk is relatively high in those with exaggerated adrenarche (indicated by, for example, DHEA-S 130–185 μg/dl, androstenedione $>$ 75–99 ng/dl, or post-ACTH 17-hydroxypregnenolone $>$ 750 ng/dl) and relatively low in those with ordinary premature adrenarche (DHEA-S = 40–130 μg/dl) or idiopathic premature pubarche (DHEA-S $<$ 40 μg/dl).

Atypical CPP may pose a risk for PCOS, although ordinary CPP does not appear to do so.

Insulin-resistant obesity in early childhood seems to be a PCOS risk factor. Extreme degrees of insulin resistance are indicated by pseudo-Cushing syndrome or pseudo-acromegaly. Whether ordinary peripubertal obesity predisposes to PCOS remains to be determined, but those with insulin resistance, manifested as acanthosis nigricans or metabolic syndrome or predisposed by family history, may be at particular risk.

Nearly half of adolescents in whom a polycystic ovary is incidentally discovered have a subclinical PCOS type of ovarian dysfunction. Assessment for hyperandrogenism seems reasonable, although most will not have PCOS, and the prognosis for most is unclear. A polycystic ovary is uncommon before menarche and so may be a high-risk factor.

During adolescence, PCOS may masquerade as PAA. There is a high probability of PCOS as the cause if anovulatory symptoms persist for more than 2 yr.

PCOS is a complex trait with a large hereditary component. Therefore, the presence of PCOS, polycystic ovaries, or central obesity, diabetes, or other insulin-resistant features in a parent should heighten the concern about risk for PCOS if the child presents other risk factors.

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