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Polycystic Ovary Syndrome: Ontogeny in Adolescence

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Introduction: the Challenge of Studying Nascent PCOS

Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (PCOM); it is also associated with metabolic comorbidities such as obesity and insulin resistance [1]. PCOS is a complex, multigenic disorder with important environmental determinants, but its etiology remains poorly understood [2–4].

The pathophysiology of symptomatic PCOS generally unfolds across puberty—the developmental stage during which increases in pulsatile GnRH release and gonadotropin secretion drive both ovarian sex steroid production and follicular development, with the eventual establishment of highly-complex feedback relationships that govern cyclic ovulation. However, the pubertal ontogeny of PCOS has been difficult to study because PCOS cannot be diagnosed prior to puberty, and diagnostic criteria appropriate for pubertal girls remain elusive [4, 5]. For example, pubertal hyperandrogenemia has not been clearly defined; hirsutism takes time to develop; oligomenorrhea in the 1–2 years after menarche is not by itself considered abnormal; and there are no validated criteria for PCOM in adolescent girls.

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By the time a diagnosis of adolescent PCOS can be substantiated, the pathophysiology of PCOS appears to be largely, if not fully, entrenched. However, several groups appear to be at higher risk for developing adolescent PCOS—daughters of women with PCOS, girls with premature pubarche, and girls with obesity—and the study of such groups can offer important insights into the pubertal ontogeny of PCOS.

Etiology of PCOS: a Brief Overview

Some of the most carefully studied aspects of PCOS pathophysiology relate to abnormal ovarian function, insulin resistance and hyperinsulinemia, neuroendocrine dysfunction, and genetics. Additional factors include epigenetic modifications, adipose tissue dysfunction, inflammation, increased sympathetic nerve activity, environmental exposures, the microbiome, etc. [2–4]. The multitude of contributing factors likely play different relative roles in different subsets of patients with PCOS.

Abnormal Ovarian Steroidogenesis and Folliculogenesis

Adolescents and adults with PCOS exhibit abnormal patterns of sex steroid secretion (e.g., exaggerated 17-hydroxyprogesterone and androstenedione secretion) in response to acute GnRH agonist or human chorionic gonadotropin administration [3]. Abnormal steroidogenesis appears to be a stable property of ovarian theca cells in PCOS, partly reflecting increased expression of a splice variant of the *DENND1A* gene [3]. Similar abnormalities of adrenal sex steroid secretion are observed after exogenous ACTH administration, suggesting a more global dysregulation of steroidogenesis in PCOS [3]. Such abnormalities are exacerbated by factors such as hyperinsulinemia and disordered gonadotropin secretion [2].

PCOS is also characterized by abnormal follicular dynamics (enhanced follicular recruitment and later follicular arrest), which partly accounts for PCOM and likely involves, among other factors, abnormal gonadotropin action, intraovarian androgen excess, and hyperinsulinemia [2, 3, 6]. Moreover, anti-Müllerian hormone (AMH) concentrations—derived from granulosa cells in pre- and small antral ovarian follicles (2–9 mm)—are approximately 2- to 4-fold elevated in PCOS [7].

Insulin Resistance and Hyperinsulinemia

Women and adolescents with PCOS demonstrate metabolic insulin resistance that is exacerbated by, but partly independent of, obesity [8]. Insulin resistance may be further exacerbated during puberty, in part related to activation of the growth hormone axis [4]. The resulting compensatory hyperinsulinemia augments ovarian and adrenal androgen production, reduces hepatic SHBG production (increasing androgen bioavailability), and disrupts ovarian follicular dynamics and function [8]. Genetic studies implicate a number of metabolism-related genes including *INSR* (insulin receptor), *INS-VNTR* (insulin gene variable number of tandem repeats) and *IRS1* (Insulin Receptor Substrate-1) [9]; and a recent Mendelian randomization study suggested that a genetic risk score for fasting insulin is associated with an increased risk of PCOS [10].

Reproductive Neuroendocrine Dysfunction

PCOS is associated with relative LH excess and FSH deficiency, both of which promote ovarian hyperandrogenism and impair follicular development [11]. Genetic studies support the relevance of genes related to gonadotropin secretion and action in PCOS, including *FSHB* (FSH subunit beta), *FSHR* (FSH receptor), and *LHCGR* (LH/choriogonadotropin receptor) [9]. Abnormal gonadotropin secretion in part relates to persistently high GnRH pulse frequency due to relative GnRH pulse generator resistance to negative feedback [11]. Although such negative feedback defects can be programmed by prenatal exposure to androgen excess, they appear to require ongoing androgen action in adulthood [11]. Recent studies also imply the potential role of AMH in the GnRH neuron dysfunction of PCOS [12, 13].

Insight from Animal Models with PCOS-Like Features

Investigators have developed a number of animal models with PCOS-like features [6], which permit invasive assessments and experimental manipulation that would be impractical, ethically unacceptable, or both, in girls and women. Although no animal model perfectly replicates PCOS, such animal models have substantially informed our understanding of PCOS pathophysiology.

Prenatally-androgenized (PNA) female rhesus macaques, sheep, and rodents demonstrate many PCOS-like features as adults [6]. For example, adult PNA female monkeys exhibit endogenous hyperandrogenemia, ovulatory dysfunction, polyfollicular ovaries, rapid GnRH pulsatility resistant to sex steroid negative feedback, abnormal gonadotropin secretion, increased adiposity, insulin resistance, impaired β-cell function, and dyslipidemia [6]. Yet complete or partial androgen receptor knockout prevents PCOS-like manifestations in PNA mice [14], suggesting the primacy of androgens in this regard. Recent findings in mice also suggest that the effects of prenatal androgenization can be transmitted through the germline in a transgenerational manner [15]. Although it remains unclear whether prenatal androgenization plays a role in PCOS, some human studies have supported this notion [6, 11].

Other animal models have been instructive as well. For example, peripubertal dihydrotestosterone treatment in female rodents produces many PCOS-like features such as ovulatory dysfunction, polyfollicular ovaries, increased adiposity, and insulin resistance [6]. Of interest, neuron-specific androgen receptor knockout prevented many of the untoward effects of postnatal dihydrotestosterone [16], suggesting the importance of central nervous system involvement in the pathophysiology of PCOS.

Studies in Girls at Risk for Developing PCOS

Within the ethical and practical limitations accompanying pediatric research, investigators have assessed the pubertal ontogeny of PCOS by characterizing the development of abnormalities in girls at high risk for adolescent PCOS: daughters of women with PCOS, girls with a history of premature pubarche, and girls with obesity.

Daughters of women with PCOS

Daughters of women with PCOS (PCOS-d) are expected to share PCOS susceptibility gene variants with their mothers; may be exposed to an intrauterine environment that enhances PCOS risk; and are likely to share postnatal environmental exposures with their mothers. A large Swedish registry study suggested that PCOS-d are approximately 5 times more likely to be diagnosed with PCOS as adults compared to control daughters; and a longitudinal cohort study suggested that Chilean PCOS-d are 10-fold more likely than control daughters to develop PCOS according to Rotterdam criteria [15].

Chilean daughters born to women with PCOS phenotype A (i.e., with hyperandrogenism, oligo-/amenorrhea, and PCOM) have been characterized in a number of studies (Table 1) [17–25]. As infants, these PCOS-d exhibited high serum AMH concentrations and exaggerated LH and estradiol responses to acute GnRH agonist stimulation [17, 22]. During childhood, Chilean PCOS-d exhibited elevated serum AMH, ovarian enlargement, and lower serum FSH concentrations [17, 19–21]. Although Chilean PCOS-d had no demonstrable hyperandrogenemia during childhood, a study of 1–3-year-old U.S. PCOS-d suggested increased 5α-reductase activity [26]. Moreover, Chilean PCOS-d exhibited exaggerated 17-hydroxyprogesterone and dehydroepiandrosterone (DHEA) responsiveness to exogenous ACTH during childhood (ages 4–8 years) and the peripubertal years (9–13 years), and approximately a third had exaggerated adrenarche [21]. Both AMH and ovarian volume appeared to be elevated throughout puberty in Chilean PCOS-d [20, 24]. However, many of the classic reproductive abnormalities of PCOS—elevated testosterone, free androgen index, basal LH, LH/FSH ratio; lower SHBG; and exaggerated 17-hydroxyprogesterone and testosterone responses to acute GnRH agonist challenge—manifested only toward the end of puberty (e.g., Tanner stage 4) [20, 24, 25].

Studies in peripubertal PCOS-d from the U.S. have supported some, but not all of the above findings (Table 2) [26–30]. In two U.S. studies of pre- and early pubertal PCOS-d, AMH levels were not significantly elevated compared to controls, while estimates of free testosterone were increased [28, 30]. Another study suggested no differences in urinary steroids, urinary gonadotropins, or ovarian volume in peripubertal PCOS-d [29].

PCOS-d also exhibit early metabolic abnormalities (Tables 1 and 2). For example, Chilean PCOS-d exhibit exaggerated serum insulin responses to an oral glucose challenge during childhood and puberty, despite no clear anthropometric abnormalities (e.g., body mass index [BMI] z-score, waist-to-hip ratio) [17–21, 23–25]. Similarly, female 8–14-year-old peripubertal first degree relatives of U.S. women with PCOS (PCOS-fdr) exhibited insulin resistance, exaggerated insulin responses to an oral glucose load, and impaired β-cell function—differences that remained after adjusting for differences in BMI z-score [27].

Girls with premature and/or exaggerated adrenarche

Adrenarche represents the developmental rise in adrenal androgen production, heralded clinically by the development of pubic hair (pubarche), axillary hair, and apocrine odor [31]. Premature pubarche—occurring earlier than age 8 years in girls—is typically related to

premature/exaggerated adrenarche and is a common cause of androgen excess in prepubertal children [31, 32].

Premature and/or exaggerated adrenarche may also represent a harbinger of PCOS. Ibanez and colleagues initially observed that approximately half of Catalan (northeastern Spanish) girls with premature pubarche developed post-pubertal oligomenorrhea, hirsutism, hyperandrogenemia, and functional ovarian hyperandrogenism in response to acute GnRH agonist testing [33]. The emergence of PCOS-like abnormalities across puberty was assessed in a number of subsequent studies (Table 3) [34–39]. Prepubertal Catalan girls with a history of premature pubarche exhibited elevated free androgen index, DHEA sulfate (DHEAS), and insulin-like growth factor-1 (IGF-1); hyperinsulinemia after an oral glucose load; and increased total and central adiposity despite normal BMI. These latter two abnormalities were observed throughout puberty. While elevations in total testosterone, free androgen index, and androstenedione were not observed in early puberty, hyperandrogenemia was demonstrable in later puberty. Similarly, while such girls demonstrated variably elevated 17-hydroxypregnenolone and DHEA responses to acute GnRH agonist stimulation throughout puberty, the more typical findings of functional ovarian hyperandrogenism (e.g., exaggerated 17-hydroxyprogesterone and androstenedione responses to acute GnRH agonism) were not apparent until late puberty [34]. Abnormal ovulatory dysfunction became evident after 3-years postmenarche [40].

A quarter to a third of women with PCOS have evidence for adrenal hyperandrogenemia [41], and the potent androgen 11-ketotestosterone predominates among circulating androgens in both girls with premature adrenarche and in women with PCOS [42, 43]. Accordingly, the link between premature/exaggerated adrenarche and PCOS may partly reflect general abnormalities of androgen steroidogenesis, manifesting as adrenal hyperandrogenemia at adrenarche and ovarian hyperandrogenemia at puberty. Premature/exaggerated adrenarche and adolescent PCOS are also linked to increased visceral fat, hyperinsulinemia, and increased free IGF-1 concentrations, with the latter two augmenting adrenal and ovarian theca cell androgen production [3, 39, 44–48]. In Catalan girls with premature pubarche, a history of small for gestational age (SGA) was associated with a more severe phenotype in late puberty [37]. In these girls, peripubertal treatment with metformin reduced total and visceral adiposity, IGF-1 levels, and reduced the risk of hyperandrogenism, oligomenorrhea, and PCOS [49–51].

Peripubertal girls with obesity

Obesity is associated with menstrual dysfunction and higher free testosterone concentrations in women with and without PCOS, and weight loss can ameliorate the manifestations of PCOS in adolescents and adults with obesity [52]. Additionally, PCOS has been associated with a high prevalence of obesity [53], although referral bias partly accounts for this finding [54]. In a large population-based study of 15–19-year-old adolescent girls in the U.S., the prevalence of PCOS was estimated to be 3.0-, 6.7-, and 14.7-fold elevated in girls with overweight, moderate obesity, and more extreme obesity, respectively [55]. Furthermore, in a large meta-analysis of PCOS cases and controls of European descent, linkage disequilibrium-score regression suggested that both childhood obesity and BMI are

genetically correlated with an increased risk of PCOS [10]. Mendelian randomization analyses also suggest that genetic risk scores for BMI are associated with PCOS [10, 56, 57].

Free testosterone levels are approximately 2- to 4-fold higher in peripubertal girls with obesity compared to non-obese controls [30, 58–62]. One study suggested that total testosterone was 4-fold elevated in prepubertal girls with obesity [58], while another suggested that free testosterone was over 8-fold elevated in prepubertal girls with obesity, with absolute levels similar to those in Tanner 5 girls without obesity [59]. Although some studies imply that higher free testosterone is largely attributable to reduced SHBG in these girls [30, 62], others demonstrated elevated total testosterone as well [58, 59, 61], suggesting increased production. Some [58, 61, 63] but not all [30, 62] studies suggest that peripubertal obesity is also associated with adrenal hyperandrogenemia.

Obesity presumably contributes to the pubertal ontogeny of PCOS partly via insulin resistance and compensatory hyperinsulinemia [62]. Some investigators have hypothesized that SGA (intrauterine growth retardation) with postnatal catch-up growth and/or excessive postnatal weight gain in non-SGA children contributes to hepatovisceral fat excess, which increases risk for both premature pubarche and PCOS via insulin resistance, hyperinsulinemia, IGF-1 excess, and hypoadiponectinemia [64, 65]. Moreover, excess adiposity may be associated with altered peripheral steroid metabolism that can enhance hyperandrogenemia (e.g., increased 17β-hydroxysteroid dehydrogenase type 5 activity, increased 5α-reductase activity, altered cortisol metabolism) [52].

Interestingly, available data suggest that early pubertal girls with obesity exhibit reduced LH release without the expected overnight changes in LH pulse frequency and amplitude [66–69], while late pubertal girls with obesity exhibit elevated day and night LH pulse frequency without the expected overnight decrease [66]. The latter finding appears to be related to hyperandrogenemia specifically [69]. Also of interest, LH concentration appeared to be a better predictor of free testosterone than insulin concentration in peripubertal girls with obesity [60, 70].

Recent studies indicate that serum AMH concentration, as a correlate of ovarian antral follicle number, is an important marker of PCOS risk in adolescent girls with obesity. In one study, AMH was 1.9-fold higher in adolescent girls with obesity and PCOS compared to adolescent girls with obesity alone [71]. In another study, girls with obesity born to non-PCOS mothers had similar free testosterone, androstenedione, and DHEAS levels compared to PCOS-d, but PCOS-d—presumed to be at higher risk for PCOS—had 2.7-fold higher AMH [30].

Hypothetical Model for the Pubertal Ontogeny of PCOS

A hypothetical model for the pubertal ontogeny of PCOS is represented in Figure 1. The model involves a genetic predisposition and possible intrauterine programming that promotes childhood hyperinsulinism, exaggerated ovarian and adrenal androgen steroidogenesis in response to stimulation, and post-pubertal neuroendocrine dysfunction. At

adrenarche, ACTH stimulates adrenals primed to secrete excess androgen; at neuroendocrine puberty, gonadotropins stimulate ovaries primed to secrete excess androgens; and both of these phenomena are enhanced by hyperinsulinemia and elevated IGF-1 levels. Moreover, entry into neuroendocrine puberty in a hyperandrogenemic milieu impairs negative feedback at the GnRH pulse generator. This, along with elevated AMH, promotes rapid GnRH pulse frequency, increasing LH and limiting FSH release. These neuroendocrine defects further enhance hyperandrogenemia and impair ovulatory function, supporting a progression to full-blown PCOS. Although not represented in the necessarily-simplistic illustration (Figure 1), numerous other factors contribute to various nodes and circuits underlying PCOS pathophysiology.

Concluding Remarks

It is not currently possible to diagnose pre-symptomatic, or even early symptomatic, PCOS in peripubertal girls. However, the study of peripubertal girls at high risk for PCOS has provided important insights into the developmental pathophysiology of PCOS. In addition to enhancing our fundamental understanding of PCOS, such research may suggest novel preventive strategies. These considerations underscore the importance of continued research into the pubertal ontogeny of PCOS.

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Key Points:

- The initial manifestations of PCOS often arise during or shortly after puberty, presumably related to the pubertal increase in gonadotropins and, in turn, ovarian androgen production.
- The pubertal ontogeny of PCOS is difficult to study in humans because the pathophysiology is typically well entrenched before the diagnosis can be substantiated.
- Several groups appear to be at higher risk for developing adolescent PCOS—daughters of women with PCOS, girls with premature pubarche, and girls with obesity—and the study of these groups can offer insight into the pubertal ontogeny of PCOS.
- Available data supports the hypothesis that the pubertal etiology of PCOS involves various combinations of genetic predisposition, intrauterine programming, hyperinsulinism, and other abnormalities, that provoke reproductive symptoms (e.g., hyperandrogenism, ovulatory dysfunction) in response to the pubertal increase in gonadotropin secretion.

Synopsis:

The pathophysiology of symptomatic PCOS often unfolds across puberty, but the ontogeny of PCOS is difficult to study because, in general, its pathophysiology is well entrenched before the diagnosis can be confirmed. However, the study of high-risk groups—daughters of women with PCOS, girls with premature pubarche, and girls with obesity—can offer insight in this regard. Available data supports the hypothesis that the pubertal etiology of PCOS involves various combinations of genetic predisposition, intrauterine programming, hyperinsulinism, and numerous other abnormalities, that provoke reproductive symptoms (e.g., hyperandrogenism, ovulatory dysfunction) in response to the pubertal increase in gonadotropin secretion.

Clinics Care Points

- Symptoms and signs of PCOS may initially manifest during puberty, but it is not currently possible to diagnose pre-symptomatic, or even early symptomatic, PCOS in peripubertal girls.
- Certain populations of girls are at higher risk for adolescent PCOS and should be monitored by symptoms: daughters of women with PCOS, girls with premature adrenarche, and girls with obesity.
- Definitive recommendations for prevention or early treatment in young girls at risk for PCOS are not available due to poorly understood early etiologies.
- Given that insulin resistance has been associated with the development of PCOS, healthy lifestyle (e.g., diet, exercise) and maintenance of healthy weight are presumably important goals for adolescents at higher risk for PCOS; however, such approaches would not address all possible etiological mechanisms.
- For peripubertal adolescents with potential symptoms or signs of nascent PCOS, but who do not clearly meet diagnostic criteria, continued follow-up is prudent so that the diagnosis is not unnecessarily delayed.

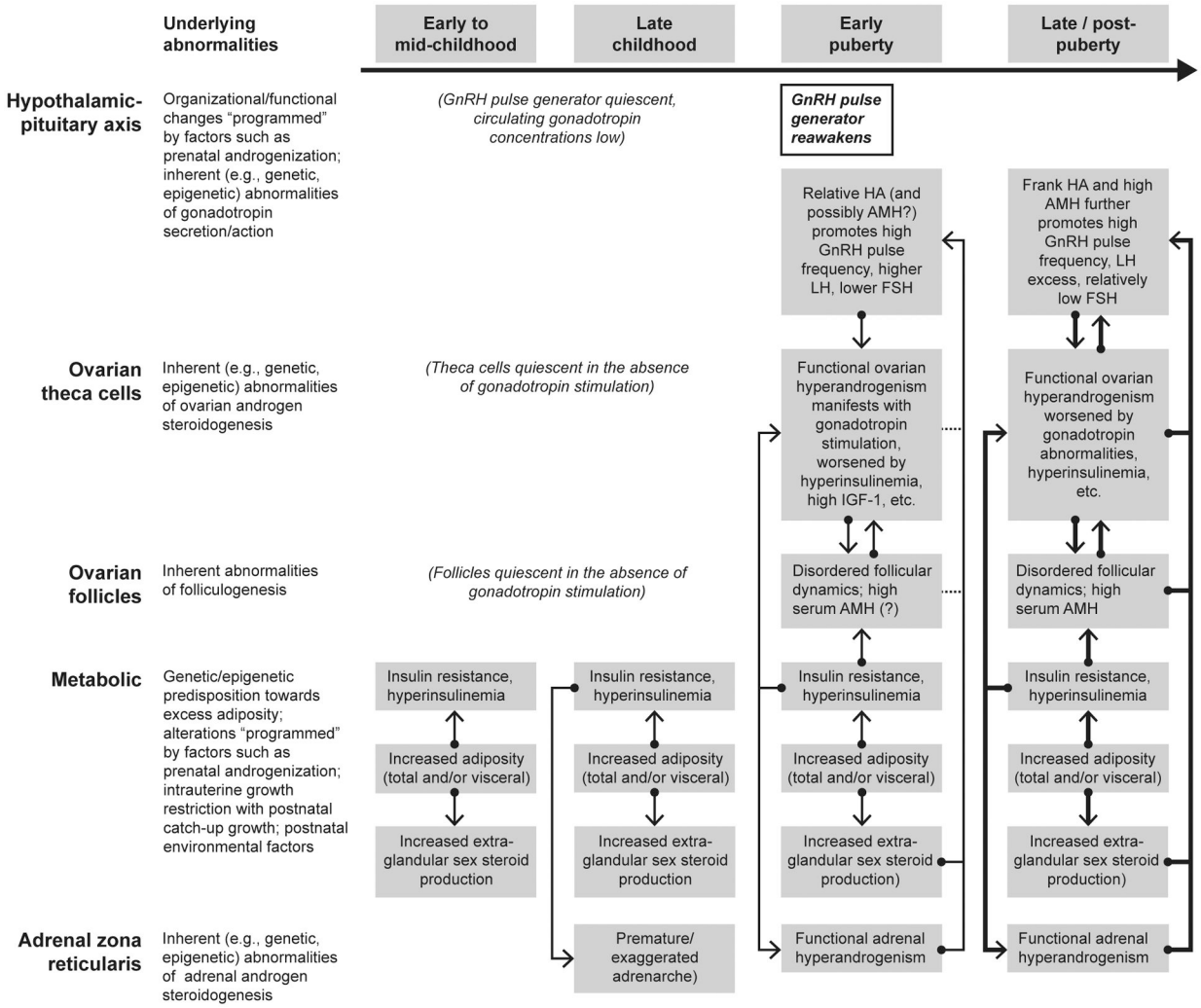

Figure 1.
Hypothetical model for the pubertal ontogeny of PCOS. HA = hyperandrogenemia.

Table 1.

Selected findings in Chilean daughters of women with PCOS

Putative feature of PCOS	Infancy (age 2–3 months) References 17, 22	Mid- to late childhood; prepubertal References 17, 18, 20, 21, 23, 24	Early puberty (Tanner 2–3) References 20, 23, 24	Late puberty (Tanner 4–5 and/or postmen archeal) References 20, 23–25	Peripubertal (age 8–16 years, Tanner 1–5) References 18, 19, 21
Higher total testosterone	−	−	−	+	+
Lower sex hormone-binding globulin	−	−	−	+	+/−
Higher free testosterone estimate		−	−	+	+
Higher androstenedione	−	−	−	−	−
Higher 17-hydroxyprogesterone	−	−	−	(−)	−
Higher dehydroepiandrosterone sulfate		−			+
More hirsutism		−	−	+	
Exaggerated 17-hydroxyprogesterone responsiveness (GnRH agonist)	−	−	−	+/−	
Exaggerated androstenedione responsiveness (GnRH agonist)	−			+	
Exaggerated testosterone responsiveness (GnRH agonist)	−	−	−	+/−	
Exaggerated estradiol responsiveness (GnRH agonist)	+				
Exaggerated 17-hydroxyprogesterone responsiveness (exogenous ACTH)		+			+
Exaggerated dehydroepiandrosterone responsiveness (exogenous ACTH)		+			+
Higher LH	−	−	−	(−)	−
Lower FSH	−	(−)	−	−	−
Higher LH-to-FSH ratio		−	−	(−)	
Higher GnRH agonist-stimulated LH	+	−	−	+	
Higher anti-Müllerian hormone	+	+	+	+	+
Greater ovarian volume		+	+	+	+
Greater global adiposity (e.g., BMI z-score)	−	−	−	−	−
Higher waist circumference	−	−	−	−	−
Higher waist-to-hip ratio	−	−	−	−	−
Higher fasting insulin		−	−	(−)	−
Higher fasting glucose		−	−	−	−
Higher insulin after oral glucose load		+	+	+	+
Insulin resistance by oral glucose tolerance test		−	−	+/−	
Higher triglycerides		−	−	+/−	+
Lower adiponectin		+	−	−	−
Higher leptin		−	−	−	−

Key: “+” = available data suggests presence; “+/−” = data mixed; “(−)” = most but not all data suggests against presence; “−” = available data suggests against presence; blank = data not reported in these studies.

Table 2.

Selected findings in North American daughters (PCOS-d) or first-degree relatives (PCOS-fdr) of women with PCOS

	Young childhood (age 1–3 years)	Pre- and early pubertal (age 8–12 years; Tanner 1–3; premenarcheal)	Mid-childhood (prepubertal)	Early pubertal (Tanner 2–3)	Late pubertal (Tanner 4–5)	Peripubertal (age 8–14 years)
	PCOS-d from Illinois, U.S.	PCOS-d and PCOS-fdr from Illinois and Pennsylvania, U.S.	PCOS-d from Pennsylvania, U.S.			PCOS-fdr from Quebec, Canada
Putative feature of PCOS	**Reference 26**	**References 28 and 30**	**Reference 29**			**Reference 27**
Higher total testosterone (serum or urine)		+/−	−	−	−	−
Lower sex hormone-binding globulin		+/−				+
Higher free testosterone estimate		+				−
Higher androstenedione (serum or urine)		−	−	−	−	−
Higher 17-hydroxyprogesterone (serum or urine)			−	−	−	−
Higher dehydroepiandrosterone sulfate (serum or urine)		−	−	−	−	
Increased apparent 5α-reductase activity	+					
Increased apparent 11β-hydroxysteroid dehydrogenase activity	−					
Hirsutism			−	−	+	
Higher LH (serum or urine)		−	−	−	−	
Lower FSH (serum or urine)		−	−	−	−	
Higher LH-to-FSH ratio (urine)			−	−	−	
Higher anti-Müllerian hormone		−				
Greater ovarian volume			−	−	−	
Greater global adiposity (e.g., BMI z-score)	+	+/−	−	−	−	+
Increased central adiposity		−	−	+/−	−	−
Higher fasting insulin		−				+
Higher fasting glucose		−				−
Higher insulin after oral glucose load (serum or saliva)		−	−	−	−	+
Insulin resistance by oral glucose tolerance test						+
Abnormal β-cell function by oral glucose tolerance test						+
Insulin resistance by frequently sampled intravenous glucose tolerance test		−				+

Endocrinol Metab Clin North Am. Author manuscript; available in PMC 2022 March 01.

Putative feature of PCOS	Young childhood (age 1–3 years)	Pre- and early pubertal (age 8–12 years; Tanner 1–3; premenarcheal)	Mid-childhood (prepubertal)	Early pubertal (Tanner 2–3)	Late pubertal (Tanner 4–5)	Peripubertal (age 8–14 years)
	PCOS-d from Illinois, U.S.	PCOS-d and PCOS-fdr from Illinois and Pennsylvania, U.S.	PCOS-d from Pennsylvania, U.S.			PCOS-fdr from Quebec, Canada
	Reference 26	References 28 and 30	Reference 29			Reference 27
Abnormal β-cell function by frequently sampled intravenous glucose tolerance test		+				+
High triglycerides		–				–
Low adiponectin						–
High leptin						+

Key: “+” = available data suggests presence; “+/−” = data mixed; “−” = available data suggests against presence; blank = data not reported in these studies.

Table 3.

Selected findings in Catalan girls with a history of premature pubarche

Putative feature of PCOS	Mid- to late childhood; prepubertal References 35–37, 39	Early puberty (Tanner 2; premenarcheal) References 34–37, 39	Early/mid-puberty (Tanner 3; premenarcheal) References 34–37, 39	Late puberty (Tanner 4–5 and postmenarcheal) References 34–39
Higher total testosterone	+	−	+/−	+
Lower sex hormone-binding globulin	+/−	+/−	+/−	+
Higher free testosterone estimate	+	−	+	+
Higher androstenedione		−	−	+
Higher 17-hydroxyprogesterone		−	−	+/−
Higher dehydroepiandrosterone sulfate	+	+	−	(+)
Higher peak 17-hydroxypregnenolone (GnRH agonist)		+	−	+
Exaggerated 17-hydroxypregnenolone responsiveness (GnRH agonist)		−	+	+
Higher peak dehydroepiandrosterone (GnRH agonist)		+	+	+/−
Exaggerated dehydroepiandrosterone responsiveness (GnRH agonist)		+	−	+/−
Higher peak 17-hydroxyprogesterone (GnRH agonist)		−	−	+/−
Exaggerated 17-hydroxyprogesterone responsiveness (GnRH agonist)		−	−	+/−
Higher peak androstenedione (GnRH agonist)		−	−	+
Exaggerated androstenedione responsiveness (GnRH agonist)		−	−	+/−
Higher peak testosterone (GnRH agonist)		−	−	+
Higher peak estradiol (GnRH agonist)		−	−	+
Exaggerated 17-hydroxyprogesterone responsiveness (exogenous ACTH)				−
Exaggerated androstenedione responsiveness (exogenous ACTH)				+
Exaggerated dehydroepiandrosterone responsiveness (exogenous ACTH)				+
Higher LH		−	−	+/−
Lower FSH		−	−	−
Higher GnRH agonist-stimulated LH		−	−	−
Greater global adiposity (e.g., BMI)	−	(−)	(−)	−
Higher waist-to-hip ratio	+	+	+	+
Total body fat mass (dual-energy X-ray absorptiometry)	+	+	+	+
Precentage fat mass (dual-energy X-ray absorptiometry)	+	+	+	+
Truncal fat mass (dual-energy X-ray absorptiometry)	+	+	−	+
Abdominal fat mass (dual-energy X-ray absorptiometry)	+	+	+	+

Putative feature of PCOS	Mid- to late childhood; prepubertal References 35–37, 39	Early puberty (Tanner 2; premenarcheal) References 34–37, 39	Early/mid-puberty (Tanner 3; premenarcheal) References 34–37, 39	Late puberty (Tanner 4–5 and postmenarcheal) References 34–39
Higher fasting insulin	+	−	−	+
Higher insulin after oral glucose load	+	+	+	+
Insulin resistance by oral glucose tolerance test	–	−	+/−	+/−
Higher IGF-1	+	−	−	−
Lower IGFBP-1	+	−	−	+
Higher triglycerides	+/−	+/−	+/−	+

Key: “+” = available data suggests presence; “(+)” = most but not all data suggests presence; “+/−” = data mixed; “(−)” = most but not all data suggests against presence; “−” = available data suggests against presence; blank = data not reported in these studies.