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REVIEW

Polycystic Ovary Syndrome in the Pediatric Population

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Abstract

Polycystic ovary syndrome (PCOS) is a common disorder characterized by hyperandrogenism and disordered gonadotropin secretion, often associated with insulin resistance. The syndrome, which modulates both hormonal and metabolic processes, is the most common endocrinopathy in reproductive-age women and increases a woman's risk of infertility, endometrial pathology, and cardiometabolic disease. As it is currently defined, PCOS most likely encompasses several distinct diseases with similar clinical phenotypes but different underlying pathophysiological processes. However, hyperandrogenism remains the syndrome's clinical hallmark. The clinical manifestations of PCOS often emerge during childhood or in the peripubertal years, suggesting that the syndrome is influenced by fetal programming and/or early postnatal events. However, given that the full clinical spectrum of PCOS does not typically appear until puberty, a "two-hit" hypothesis has been proposed: (1) a girl develops hyperandrogenism via one or more of many different potential mechanisms; (2) the preexisting hyperandrogenism subsequently disturbs the hypothalamic–pituitary–ovarian axis, resulting in ovulatory dysfunction and sustained hyperandrogenism. No consensus guidelines exist regarding the diagnosis and management of PCOS in the pediatric population; however, because the syndrome is a diagnosis of exclusion, the clinical evaluation of girls suspected of having PCOS is aimed at excluding other causes of androgen excess and menstrual dysfunction. For the syndrome's management, emphasis is placed on lifestyle and symptom-directed treatment.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinopathy affecting an estimated 5–10% of reproductive-age women in the Unites States.[1–4] Furthermore, the syndrome increases a woman's risk of infertility, dysfunctional uterine bleeding, endometrial carcinoma, depression, type 2 diabetes, hypertension, dyslipidemia, and metabolic syndrome, independent of obesity or insulin resistance.[1–8] In the United States alone, it is also associated with an economic burden exceeding four billion dollars.[9]

PCOS is primarily characterized by: (1) Menstrual dysfunction (oligo- or amenorrhea), (2) cutaneous signs of hyperandrogenism (acne, hirsutism, or alopecia), (3) obesity, (4) disordered gonadotropin [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)] secretion, and (5) polycystic ovaries by ultrasonography.[10–14] However, the syndrome is also associated with defects in insulin action (insulin resistance) and/or insulin secretion (pancreatic β-cell dysfunction). Although the clinical and biochemical presentation of PCOS is heterogeneous, hyperandrogenemia is the most consistent biochemical abnormality, and thus is considered the hallmark of the syndrome.[15] Furthermore, although various signs and symptoms of hyperandrogenism can manifest prepubertally, the onset of menstrual dysfunction in PCOS typically occurs peripubertally. The syndrome has also been associated with the childhood antecedents of reduced fetal growth, followed by excessive postnatal catch up and premature adrenarche/pubarche,[16,17] suggesting a developmental aspect to its etiology. Moreover, being overweight or obese, a common problem in the pediatric and adult populations, amplifies the clinical severity of the syndrome and increases the risk of metabolic dysfunction.[4]

Definitions

The diagnosis of PCOS remains controversial and is based on various signs, symptoms, and/or laboratory findings that are not universally accepted. The four most common definitions of the syndrome are presented in Table 1. The 1990 National Institutes of Health (NIH) definition requires the simultaneous presence of hyperandrogenism (clinical and/or biochemical) and menstrual dysfunction in the absence of other causes,[18] highlighting the importance of hyperandrogenism in the syndrome's etiology. In contrast, the 2003

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Table 1. Commonly Used Definitions of Polycystic Ovary Disease

Definition/year	*Diagnostic criteria*[a]
NIH/1990	Requires the simultaneous presence of: 1. Hyperandrogenism (clinical and/or biochemical) 2. Ovarian dysfunction
Rotterdam (ESHRE/ASRM)/2003	Requires the presence of at least two criteria: 1. Hyperandrogenism (clinical and/or biochemical) 2. Ovulatory dysfunction 3. Polycystic ovarian morphology[b]
AES/2006	Requires the presence of hyperandrogenism (clinical and/or biochemical) and either: 1. Ovulatory dysfunction 2. Polycystic ovarian morphology[b]
Androgen Excess and PCOS Society/2009	Requires the simultaneous presence of: 1. Hyperandrogenism (clinical and/or biochemical) 2. Ovarian dysfunction (ovulatory dysfunction and/or polycystic ovarian morphology[b])

[a]All of the diagnostic criteria for PCOS require the exclusion of other disorders such as nonclassical congenital adrenal hyperplasia, Cushing syndrome, hyperprolactinemia, hypothyroidism, acromegaly, premature ovarian failure, a virilizing adrenal or ovarian neoplasm, or a drug-related condition.

[b]The ultrasound definition of polycystic ovarian morphology is the presence of $\geq$12 follciles with a 2- to 9-mm diameter on the ovary. An ovarian volume $>$10 mL is also suggestive. Only one ovary consistent with polycystic ovarian morphology is sufficient for the diagnosis.

Abbreviations: NIH, National Institutes of Health; ESHRE, European Society for Human Reproduction and Embryology; ASRM, American Society for Reproductive Medicine; AES, Androgen Excess Society.

Rotterdam [European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine (ESHRE/ASRM)] definition requires only two of the following three criteria: (1) Hyperandrogenism (clinical and/or biochemical), (2) ovulatory dysfunction (oligo- or anovulation), and (3) ultrasonographic evidence of polycystic ovaries in the absence of other causes.[19] Importantly, the Rotterdam criteria broadened the PCOS phenotype to include women with ovulatory dysfunction and polycystic ovaries but without hyperandrogenism, and eumenorrheic women with hyperandrogenism and polycystic ovaries (often called "ovulatory" PCOS).[20] However, the 2006 Androgen Excess Society (AES) definition reemphasized the importance of hyperandrogenism in the etiology of PCOS, requiring: (1) The absence of other hyperandrogen-causing disorders, syndromes of severe insulin resistance, thyroid dysfunction, and hyperprolactinemia, (2) hyperandrogenism (clinical and/or biochemical), and (3) ovulatory dysfunction (oligo- or anovulation) or polycystic ovarian morphology.[15] The 2009 Androgen Excess and Polycystic Ovary Syndrome Society's definition also emphasized the importance of hyperandrogenism in the syndrome's etiology, requiring: (1) Hyperandrogenism (clinical and/or biochemical), (2) ovarian dysfunction (oligo- or anovulation and/or polycystic ovaries), and (3) the exclusion of other androgen excess or related disorders.[21]

However, diagnosing PCOS in adolescents using the above criteria poses several challenges. First, using menstrual irregularity to diagnose PCOS is difficult in adolescents, given that greater than 50% of menstrual cycles are anovulatory in the first 2 years after menarche.[22,23] However, menstrual irregularity for more than 2 years after menarche is not considered physiological and is predictive of continued irregularity.[24] Second, nonpathologic acne and mild hirsutism are common in the peripubertal years.[25,26] Third, children develop physiologic insulin resistance during puberty.[27–29] Fourth, limited normative data of androgen levels by body mass index (BMI) and pubertal stage exist.[19] Fifth, ovarian size appears to be maximal in the perimenarchal period; $\approx$25% of adolescent girls have multifollicular ovaries, and polycystic-type ovaries can occur in up to 20–30% of reproductive-age women and 10% of healthy, regularly menstruating girls,[30–32] making the differentiation of "normal" versus "abnormal" ovaries difficult for even experienced specialists.[33] Moreover, a transvaginal ultrasound is often inappropriate for pediatric patients, particularly virginal girls, and the use of a transabdominal ultrasound yields limited resolution of ovarian morphology and has been shown to underestimate the presence of the syndrome.[34]

Thus, in an attempt to overcome these limitations, an alternative method for diagnosing the syndrome in adolescents has been advocated to avoid mislabeling an adolescent girl with transitional functional hyperandrogenism and menstrual irregularity as having PCOS.[35] According to this proposal, four out of the following five criteria would be required for a PCOS diagnosis in adolescents: (1) Oligo- or amenorrhea 2 years after menarche, (2) clinical hyperandrogenism (hirsutism, acne, and/or alopecia), (3) biologic hyperandrogenism (an elevated testosterone concentration), (4) insulin resistance or hyperinsulinemia (acanthosis nigricans, abdominal obesity, and/or glucose intolerance), and (5) polycystic ovaries. However, the criteria used to diagnose PCOS in clinical studies are currently the same for all females, limiting the ability to study the syndrome's incidence and prevalence in the pediatric population.

Pathogenesis

PCOS is a complex multifactorial disorder influenced by the synergistic impact of environmental factors on a predisposed genetic background, which modulates both hormonal and metabolic processes.[3,36–38] Moreover, several lines of evidence suggest a developmental origin of the syndrome.[39,40] In particular, studies from nonhuman primates have shown that prenatal exposure to androgen excess *in utero* leads to the

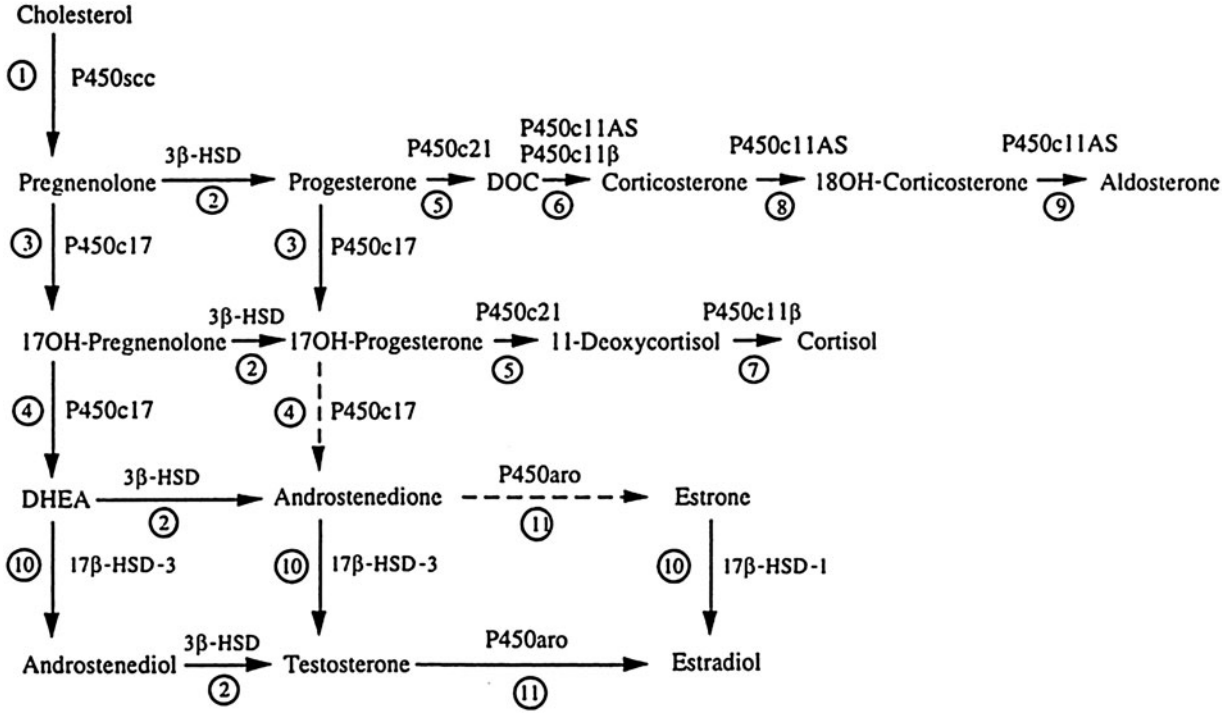

FIG. 1. Integrated view of human steroidogenesis, showing adrenal and gonadal pathways. Reaction 1: P450scc converts cholesterol to pregnenolone. Reaction 2: 3β-hydroxysteroid dehydrogenase (3β-HSD) converts Δ^5 steroids [pregnenolone, 17OH-pregnenolone, dehydroepiandrosterone (DHEA), androstenediol] to the corresponding Δ^4 steroids (progesterone, androstenedione, testosterone). Reaction 3: P450c17 catalyzes the 17α-hydroxylation of pregnenolone and progesterone. Reaction 4: The 17,20-lyase activity of P450c17 converts 17OH-pregnenolone to DHEA; the conversion of 17OH-progesterone to androstenedione occurs in cattle and rodents, but human P450c17 cannot catalyze this reaction efficiently. Reaction 5: P450c21 catalyzes the 21-hydroxylation of progesterone and 17OH-progesterone. Reaction 6: Deoxycorticosterone (DOC) can be converted to corticosterone by either P450c11AS (in the adrenal zona glomerulosa) or P450c11β (in the adrenal zona fasciculata). Reaction 7: P450c11β converts 11-deoxycortisol to cortisol. Reactions 8 and 9: P450c11AS catalyzes 18 hydroxylase (reaction 8) and 18 methyl oxidase activities (reaction 9) to produce aldosterone in the adrenal zona glomerulosa. Reaction 10: Two isozymes of 17βHSD activate sex steroids: 17β-HSD1 produces estradiol and 17β-HSD3 produces androgens. In peripheral tissues 17β-HSD5 has similar activity to 17β-HSD3, and 17β-HSD2 and 4 catalyze the "reverse" reactions to inactivate sex steroids. Reaction 11: P450aro aromatizes C19 androgenic steroids to C18 estrogens.

development of the human PCOS phenotype in adult monkeys,[41–45] reinforcing the fetal origins of adult disease hypothesis (i.e., the Barker hypothesis).[46,47]

Androgen sources

The production of all steroid hormones, including androgens, begins with cholesterol. It is then the tissue specificity of the various steroidogenic enzymes and the availability of their substrates/cofactors that determine the type of steroid produced by a particular gland.[48] Although no gland expresses every steroidogenic enzyme, their interrelationships are demonstrated in the integrated pathway shown in Fig. 1. The major enzymes involved in adrenal and ovarian androgen production are shown in Figs. 2 and 3, respectively. In the past, the source of hyperandrogenemia in women with PCOS had been a topic of debate. However, the observation that hyperandrogenemia persists when ovarian steroidogenesis is suppressed with a long-acting gonadotropin-releasing hormone (GnRH) agonist[49,50] and when adrenal steroidogenesis is suppressed with dexamethasone[51,52] suggests that both glands play a role.

In ovarian tissue from women with PCOS, *in vitro* studies have demonstrated overexpression of steroidogenic enzymes (in particular, P450c17 and 3β-hydroxysteroid dehydrogenase) in theca cells.[53] The majority of hyperandrogenic women with PCOS also have abnormal responses to GnRH agonists.[50,54] In addition, adrenal hyperresponsiveness to adrenocorticotropic hormone (ACTH) occurs in ≈25% of women with PCOS, resulting in excess dehydroepiandrosterone

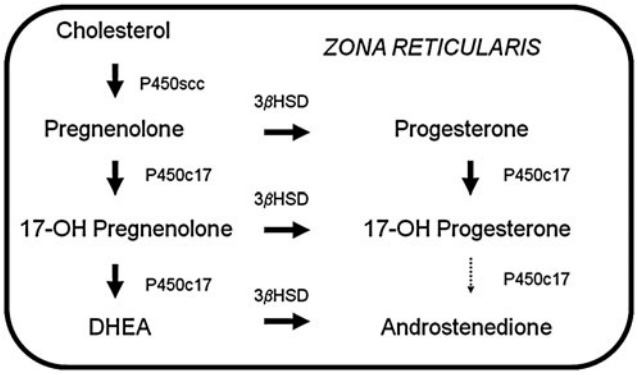

FIG. 2. Adrenal sex steroid synthesis. Sex steroid synthesis in the adrenal gland occurs in the zona reticularis in the cortex of the adrenal gland. Dehydroepiandrosterone (DHEA) and androstenedione are the principal androgen precursors produced in the adrenal gland. 3βHSD, 3β-hydroxysteroid dehydrogenase.

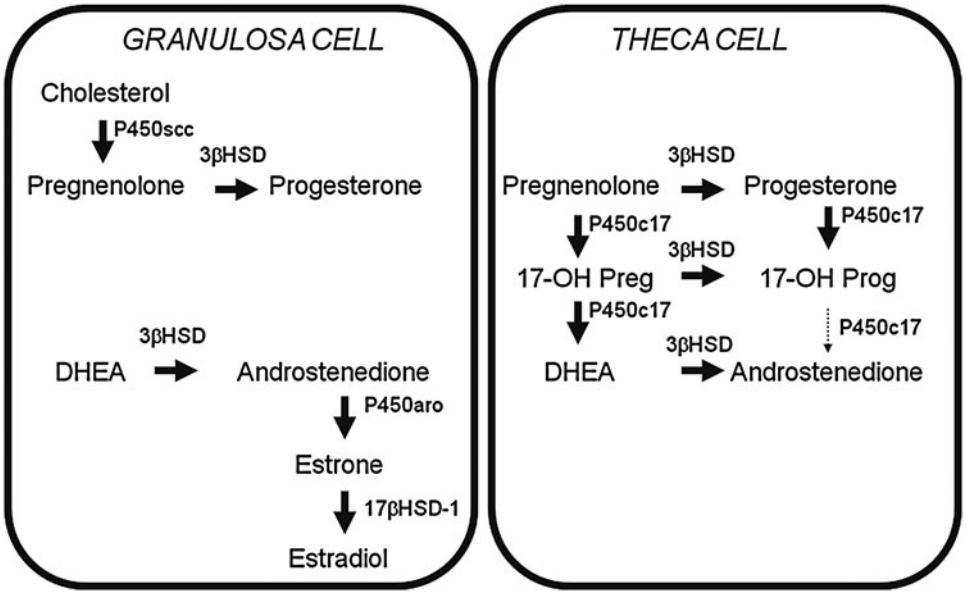

FIG. 3. Ovarian sex steroid synthesis. Sex steroid synthesis in the ovary occurs in both the granulosa and theca cells. However, P450c17, the "qualitative" regulator of steroidogenesis, is only expressed in the theca cell. Androstenedione is the principal androgen precursor produced in the ovary. Isozymes of 17β-hydroxsteroid dehyrogenase (17βHSD) can convert androstenedione to testosterone; alternatively, aromatase (P450aro) can convert androstenedione to estrogens. 17-OH Preg, 17-OH pregnenolone; 17-OH Prog, 17-OH progesterone.

(DHEA), DHEA-sulfate (DHEA-S), and androstenedione.[55,56] Interestingly, the adrenal glands may be an even more important source of hyperandrogenism in nonobese subjects.[57] Furthermore, although the ovaries and adrenal glands are the principal sources of excess androgen production in women with PCOS, enhanced 5α-reductase activity in the liver and peripheral tissues (e.g., adipose tissue) may also increase conversion of testosterone to the biologically more potent androgen, dihydrotestosterone (DHT).[58]

Androgen production

Whereas the steroidogenic enzyme P450scc is the "quantitative regulator" of steroidogenesis, determining the net "capacity" of a steroidogenic cell, the "qualitative regulator" of steroidogeneisis, the factor that determines whether a steroid precursor will become a mineralocorticoid, a glucocorticoid, or a sex steroid, is the microsomal enzyme P450c17. P450c17 is expressed in both the adrenal glands and gonads[59] and sequentially catalyzes both 17α-hydroxylase activity and 17,20-lyase activity on sex steroid hormone precursors (see Fig. 1).[60–62] In the absence of P450c17, a steroidogenic cell produces C_{21} 17-deoxysteroids (e.g., progesterone in the ovarian granulosa cell or aldosterone in the adrenal glomerulosa cell). If only the 17α-hydroxylase activity of P450c17 is present (e.g., in the adrenal zona fasiculata), C_{21} 17-hydroxysteroids (e.g., cortisol) are produced. If both the 17α-hydroxylase and 17,20-lyase activities of P450c17 are present (e.g., in ovarian theca cells, testicular Leydig cells, or adrenal zona reticularis), C_{19} precursors of sex steroids (e.g., DHEA) are produced. A detailed discussion of sex steroid production is beyond the scope of this article, but has recently been reviewed elsewhere.[63,64]

The ratio of P450c17's 17α-hydroxylase to 17,20-lyase activity determines the ratio of C_{21} to C_{19} steroids generated, varies in different cell types, and can be developmentally regulated (e.g., during human adrenarche). Specifically, regulation of P450c17's enzymatic activity is mediated posttranslationally by at least three factors: (1) The electron-donating protein P450 oxidoreductase (POR), (2) cytochrome b_5, and (3) serine phosphorylation.[65] Importantly, increased activity of P450c17 has been specifically implicated in the etiology of PCOS,[66,67] and identifying the molecular factors regulating this enzyme is an area of active investigation.

Neuroendocrine abnormalities

The most common neuroendocrine aberration observed in women with PCOS is an alteration in their GnRH pulse frequency.[68,69] As opposed to the cyclic variation seen with regular, ovulatory menstrual cycles, the GnRH pulse frequency in women with PCOS is ≈1 pulse/h.[70] This rapid GnRH pulse frequency favors pituitary LH secretion over FSH secretion,[71–73] resulting in elevated LH levels and LH:FSH ratios.[74] The high LH concentrations then stimulate ovarian theca cells to produce androgens, whereas the "relative" FSH deficiency impairs aromatization of the androgens to estrogens in the granulosa cells, follicular development/maturation, and luteal progesterone release, leading to both sustained hyperandrogenism and ovulatory dysfunction.

Given that the observed GnRH pulse frequency of ≈1 pulse/h in women with PCOS is both comparable to the maximal GnRH pulse frequency that occurs during a normal, ovulatory menstrual cycle in the late follicular phase[75] and similar to the GnRH pulse frequency that occurs in isolated hypothalamic GnRH neurons[76] and hypogonadal women,[77,78] the persistently rapid GnRH pulse frequency in PCOS is considered the result of impaired ovarian hormone feedback as opposed to an inherent acceleration of the GnRH pulse generator. Of the ovarian sex steroids, progesterone appears to be the primary modulator of GnRH pulse frequency,[79] although estradiol also probably plays a permissive role by inducing the expression of progesterone receptors in the hypothalamus.[80] Evidence to support the importance of progesterone in the regulation of the GnRH pulse generator stems from the observations that GnRH pulse frequency decreases during the endogenous luteal phase rise in progesterone during normal, ovulatory cycles,[75] and exogenous progesterone slows GnRH pulse frequency in both ovulatory and postmenopausal women.[78,81]

However, in women with PCOS, the importance of progesterone in the regulation of the GnRH pulse generator poses

two potential issues. First, endogenous progesterone secretion is limited due to frequent anovulatory cycles. Second, the sensitivity of the hypothalamus to progesterone is impaired by androgens.[82] This then creates a cycle whereby preexisting hyperandrogenism leads to further hyperandrogenism by impairing the sensitivity of the GnRH pulse generator to progesterone, leading to increased LH secretion from the pituitary, stimulating further ovarian androgen production (see Fig. 4).

Genetics

A genetic predisposition for PCOS certainly exists,[36] and the syndrome has been found to aggregate in families.[83–87] However, despite a large number of genetic studies, no one single gene has been associated with the development of all the syndrome's phenotypes.[88–90] Although a comprehensive review of the genetics of PCOS is beyond the scope of this review, to date, the most promising candidate gene associated with PCOS maps to a locus on chromosome 19p13.2 within an intron of the fibrillin-3 gene, which interestingly is located near the insulin receptor gene.[91–94] Although the biological function of fibrillin-3 is unknown, fibrillins can bind transforming growth factor-β (TGF-β) and have been implicated in early follicle development and theca cell formation,[95] presenting a potential link to the inherent ovarian dysfunction associated with the syndrome. Other potential genes associated with PCOS include those encoding 17β-hydroxsteroid dehydrogenase type 6, sex hormone-binding globulin (SHBG), the androgen receptor (AR), and aromatase.[96–98] More comprehensive genome-wide association studies (GWAS) evaluating the genetic variation of women with a PCOS-like phenotype are currently ongoing; however, given its clinical and phenotypic diversity, the syndrome is most likely polygenic in nature.

Fetal programming

Interestingly, females exposed to high levels of androgens in the intrauterine environment, including women with virilizing congenital adrenal hyperplasia (CAH) due to

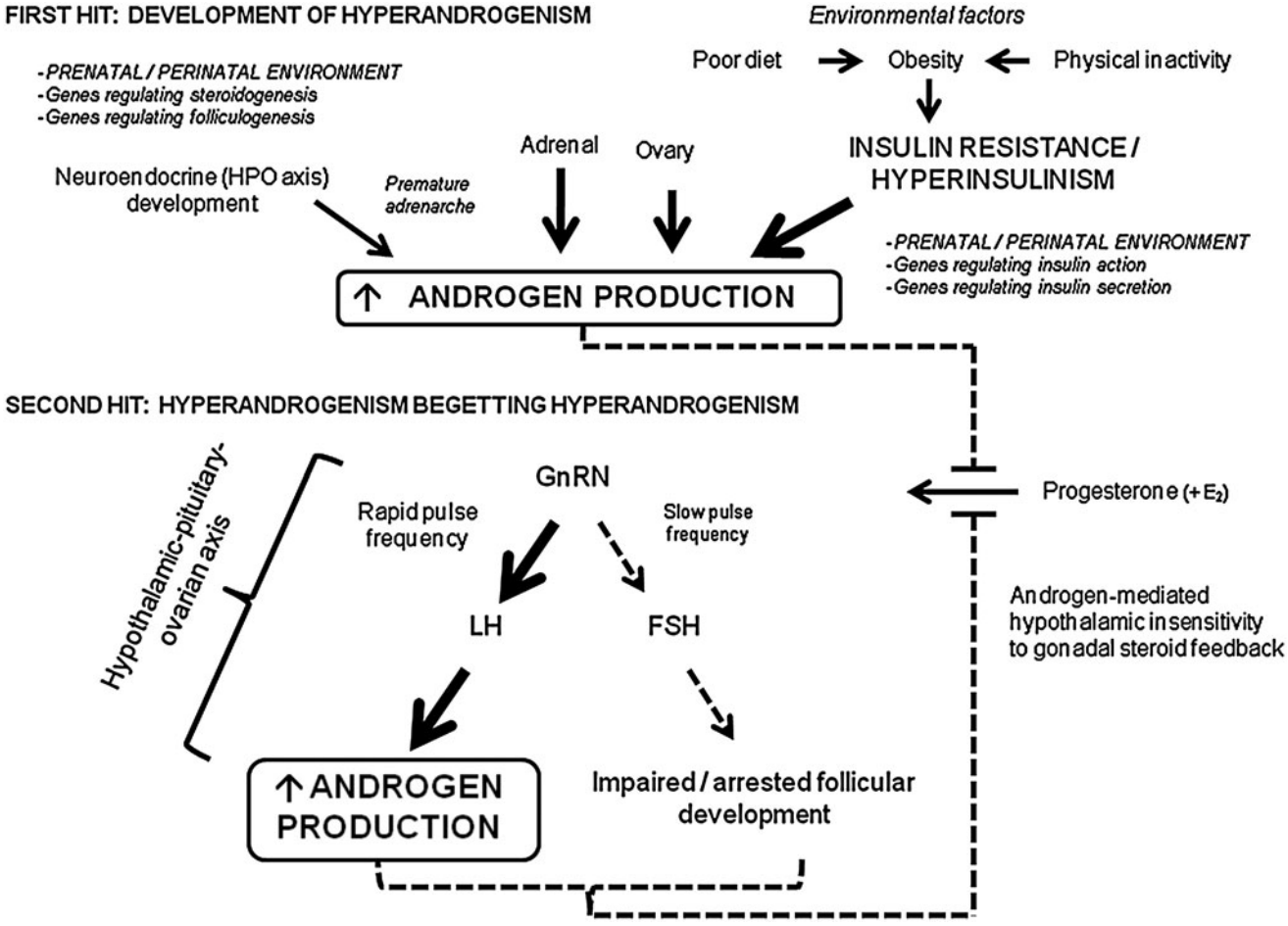

FIG. 4. The "two-hit" hypothesis of PCOS. The "two-hit" hypothesis of polycystic ovary syndrome (PCOS) suggests that two insults are required for the syndrome's full phenotypic expression. For the first "hit," one or more of a number of different mechanisms, including: (1) Primary adrenal, ovarian, and/or neuroendocrine abnormalities; (2) insulin resistance and hyperinsulinemia; and/or (3) prenatal, immediate postnatal, and/or peripubertal androgen exposure, lead to increased androgen production. For the second "hit," the preexisting hyperandrogenism reduces the sensitivity of the gonadotropin-releasing hormone (GnRH) pulse generator to progesterone-mediated slowing during pubertal maturation, thereby initiating a series of changes in the hypothalamic–pituitary–ovarian (HPO) axis that result in ovulatory dysfunction and sustained hyperandrogenism. Thus, a cycle is established whereby the presence of hyperandrogenism, the final common pathway for the development of PCOS, begets more hyperandrogenism. E_2, Estradiol; LH, luteinizing hormone; FSH, follicle stimulating hormone; E_2, estradiol. (Figure based on ref. 32.)

21-hydroxylase deficiency and congenital adrenal virilizing tumors, have an increased risk of PCOS in adolescence, despite the normalization of androgen levels after birth.[99] Furthermore, prenatal exposure of female nonhuman primate fetuses to excess androgens *in utero* has been shown to disturb both the hypothalamic–pituitary–ovarian (HPO) and hypothalamic–pituitary–adrenal (HPA) endocrine axes and recapitulate the development of the human PCOS phenotype (hyperandrogenism, LH hypersecretion, oligo- or anovulation, and insulin resistance) as the monkeys age.[41–45,100,101] The hyperandrogenic fetal environment in these monkeys specifically appears to upregulate P450c17's 17,20-lyase activity, leading to increased androgen production.[44,102] In addition, intrauterine androgen exposure in these monkeys leads to the development of insulin resistance associated with visceral adiposity, impaired glucose metabolism, and dyslipidemia.[101] The above observations in both humans and monkeys thus support a potential role of epigenetics and fetal programming in the syndrome's pathogenesis.

However, in the nonhuman primate studies in particular, pregnant dams were given very large doses of androgens and had androgen concentrations much higher than those typically observed in pregnant women with PCOS.[103] Nevertheless, studies in hyperandrogenic pregnant women suggest that increased maternal androgens may be a source of *in utero* androgenicity[103] and can adversely affect the intrauterine environment and retard fetal development.[104,105] However, it is unlikely that maternal androgens in most pregnancies exceed the normal safeguards of high maternal circulating concentrations of SHBG and placental aromatase (which converts maternal androgens to estrogens), and cross the fetoplacental barrier in quantities sufficient to "androgenize" the fetus.[106] Thus, the potential contribution of the fetal adrenal glands and ovaries to intrauterine "androgenization" must be considered. In fact, studies suggest that the fetal ovary is indeed capable of synthesizing androgens *in utero*,[107] and clinical and biochemical manifestations of PCOS have been noted in young adults with nonclassic CAH.[108] Furthermore, even if the fetal ovary does not produce enough androgen to cause prenatal virilization, it may nonetheless contribute to the "programming" of the HPO axis and may be genetically predisposed to hypersecrete androgen when the HPO axis is stimulated.[4]

Moreover, in other animal studies, exposure of fetuses to high levels of androgens *in utero* appear to mediate the postnatal development of obesity through increased food intake and decreased energy expenditure, and produce features of the metabolic syndrome.[109] Interestingly, the dyslipidemia and hepatic steatosis found in the prenatally androgenized offspring appear to be regulated by prenatal androgenization-induced adiposity; in contrast, the hyperinsulinemia in the offspring appear to be regulated by prenatal androgenization directly.

Postnatal events

Despite the syndrome's genetic predisposition, the severity of PCOS and its phenotypic expression result from the

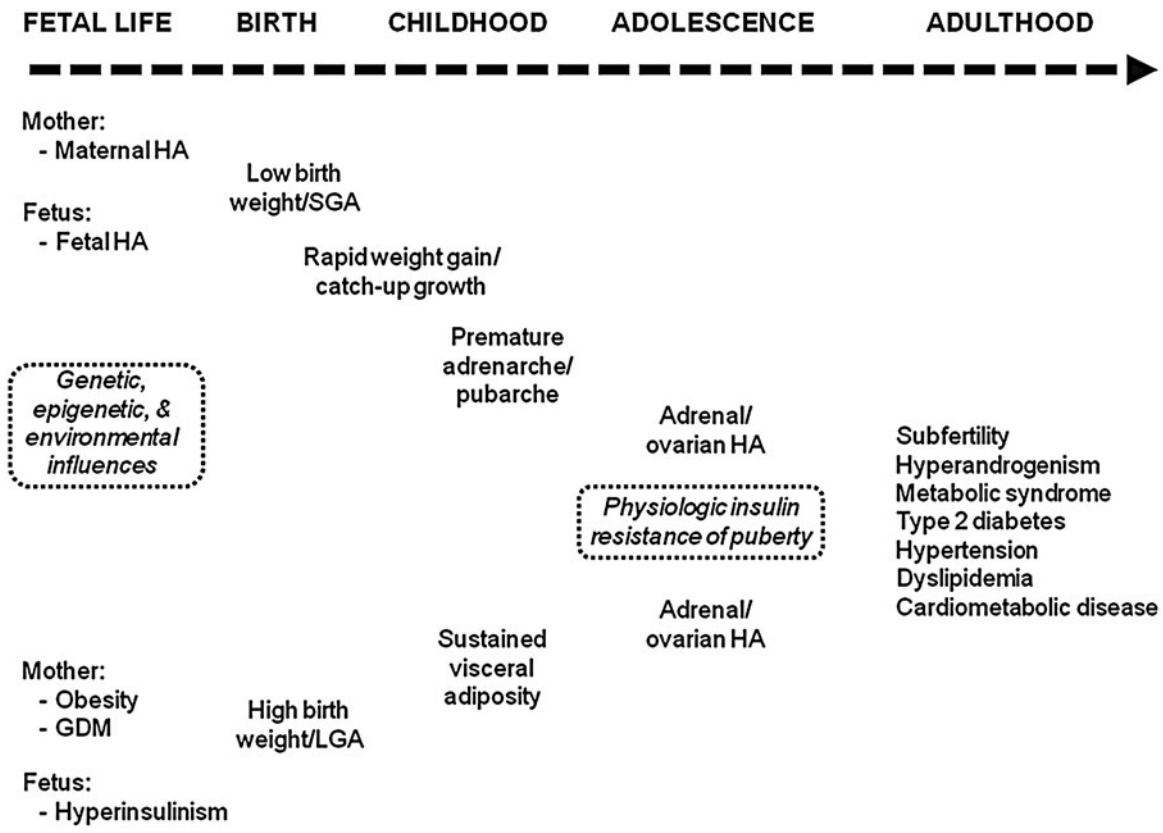

FIG. 5. Proposed natural history of PCOS from fetal life to adulthood. The severity of polycystic ovary syndrome (PCOS) and the evolution of its phenotypic expression result from the impact of environmental influences (both pre- and postnatal) on genetic and epigenetic factors *in utero*. HA, Hyperandrogenism; GDM, gestational diabetes mellitus; SGA, small for gestational age; LGA, large for gestational age. (Figure based on ref. 204.)

impact of environmental influences on genetic and epigenetic factors (see Fig. 5).[110]

First, premature adrenarche, a term used to describe an early increase in adrenal androgen production before 8 years in girls (and 9 years in boys), has been linked to the development of PCOS and metabolic syndrome during adolescence.[17,33,111] The increased androgen production associated with adrenarche, which has been recently reviewed,[112] typically leads to the development of pubic hair, or pubarche. Girls with premature adrenarche/pubarche also appear to have: (1) Adrenal hyperresponsiveness to ACTH, (2) elevated levels of insulin and insulin-like growth factor 1 (IGF-1), and (3) decreased levels of the binding proteins SHBP, thereby increasing free testosterone concentrations, and insulin-like growth factor binding protein 1 (IGFBP-1), thereby increasing free insulin and IGF-1 concentrations.[113,114] Despite extensive evaluation, the cause of premature adrenarche currently remains unknown. One postulated reason for the condition is hypersecretion of a cortical adrenal stimulating hormone from the pituitary gland sharing amino acids 79–96 of proopiomelanocortin (POMC)[115]; however, *in vitro* studies have failed to confirm this hypothesis.[116] Another theory is that the zona reticularis, the site of adrenal androgen production, develops prematurely.[117] Early activation of P450c17's 17,20-lyase activity could also account for premature adrenal androgen secretion.[118] Furthermore, corticotropin-releasing hormone (CRH) has been found to potentially affect adrenal androgen section, suggesting a role for this hormone in premature adrenarche as well.[119,120]

Second, rapid weight gain in small for gestational age (SGA) girls in the first few years of life and sustained adiposity in large for gestational age (LGA) girls during childhood accelerate the prepubertal appearance of PCOS, characterized by visceral obesity, insulin resistance, and premature adrenarche/pubarche.[17,111,121,122] The final PCOS phenotype is then expressed during puberty following activation of the HPO axis. Interestingly, although a definitive biological mechanism has not been identified, women with a history of high birth weight are also more likely to have a polycystic ovarian morphology on ultrasound evaluation than women with low birth weight.[121] Furthermore, hyperandrogenemia during childhood appears to alter normal pubertal development,[123] increase the risk of postpubertal ovarian hyperandrogenism,[123] and is a risk factor for metabolic syndrome independent of obesity.[7] Hyperandrogenemia may also be involved with the development of central obesity and affect insulin, androgen, and glucocorticoid metabolism.[124]

Third, the normal physiologic insulin resistance that develops during puberty[27–29] may aggravate the syndrome's symptoms and phenotypic expression. Specifically, a physiologic increase in insulin resistance and androgen levels occurs in response to growth hormone (GH) secretion, which peaks during adolescence[125]; this then leads to an increase in insulin and a decrease in SHBG concentrations, both of which may exacerbate the clinical manifestations of hyperandrogenism.[27,126]

Fourth, the "adipose tissue expandability hypothesis" may also account for the early origins of PCOS in some individuals.[127] By suggesting that subcutaneous adipose tissue has a limited capacity to increase its mass safely, influenced by both environmental and genetic factors, this hypothesis accounts for the development of insulin resistance in states of obesity as well as the apparent paradox of insulin resistance in states of adipose tissue deficiency.[128–131] According to this theory, an individual's "metabolic set-point" determines the caloric load that can be safely stored in their adipose tissues. Caloric loads exceeding this "set point" results in lipotoxicity, a condition associated with elevated free fatty acids (FFAs), hypertriglyceridemia, and an unfavorable adipocytokine profile, including low levels of adiponectin and high levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), and the potential for ectopic fat deposition (i.e., the deposition of fat in nonadipose tissues such as the liver, skeletal muscle, and pancreas), both of which could adversely affect insulin action. Thus, this theory suggests the concept of an "adiposity threshold" at which insulin resistance and other markers of lipotoxicity emerge. A caloric load in excess of a girl's ability to expand her subcutaneous adipose tissue in a metabolically safe manner (whether she be obese or of normal weight) could then potentially contribute to insulin resistance and hyperinsulinemic androgen excess.[127]

Effects of androgens

In addition to affecting insulin sensitivity, androgens can also influence adipocyte function.[132] The AR is located in both the subcutaneous and visceral components of fat; however, its expression is higher in visceral preadipocytes than subcutaneous preadipocytes.[133] Moreover, the observation that androgens can act in a sex-dimorphic manner in many tissues[133] may account for the beneficial effects in fat mass distribution seen in testosterone-treated hypogonadal men but the visceral fat accumulation seen in hyperandrogenic PCOS women.[124] Androgens also appear to regulate lipolysis in adipose tissue depots. Specifically, testosterone causes a dose-dependent AR-mediated decrease of catecholamine (β-adrenergic)-stimulated lipolysis in differentiated preadipocytes from abdominal subcutaneous fat depots but not from omental fat depots.[134] This phenomenon has been observed in women with PCOS[135] and may thus contribute to the development of upper-body obesity, an established risk factor for insulin resistance. However, the differential regulation of lipolysis between subcutaneous and omental fat does not explain the high prevalence of visceral adiposity in women with PCOS. Rather, androgen-mediated lipogenesis and lipid deposition may be the major factors involved. Specifically, androgens mediate lipoprotein lipase (LPL), the key enzyme for the hydrolysis of triglycerides into FFAs and glycerol and subsequent lipid storage in adipose tissue. In addition, androgens appear to stimulate lipogenesis in visceral adipose tissue by increasing the expression of several key lipogenic genes.[136]

Androgen excess is also associated with an atherogenic lipid profile in women.[137,138] Specifically, testosterone lowers high-density lipoprotein cholesterol (HDL-C)[139] and may contribute to increased circulating low-density lipoprotein cholesterol (LDL-C) concentrations.[138] Beyond its metabolic effects, androgens may also act directly on the vasculature to promote endothelial dysfunction[140,141] and accelerate atherosclerotic changes.[142] Furthermore, although testosterone levels have been reported to be directly associated with the risk for hypertension in PCOS,[143] the frequent prevalence of obesity in these women confounds this association.[144] However, given that androgens stimulate the intrarenal

renin–angiotensin–aldosterone system and modulate renal sodium homeostasis by increasing angiotensinogen and renin gene expression,[145] augmenting proximal tubular transport,[146] and upregulating expression of the α-subunit of the epithelial sodium channel (ENaC),[147] they do have prohypertensive properties. Androgen excess may also play a role in the low-grade, chronic inflammation and oxidative stress associated with PCOS.[148–150]

The role of insulin

Hyperinsulinemia secondary to insulin resistance is common in PCOS and occurs independent of obesity or BMI.[57,151,152] The degree of hyperinsulinemia also correlates with the syndrome's severity.[153] Although it has been debated whether hyperandrogenism results from hyperinsulinemia, hyperinsulinemia results from hyperandrogenism, or they are each independent variables linked in a noncausal relationship, data showing that bilateral oophorectomy,[154] or the administration of a long-acting GnRH agonist[155,156] or an antiandrogenic compound,[157] do not affect the hyperinsulinemia in women with PCOS suggest that hyperinsulinemia is the primary factor driving increased androgen production. If elevated levels of androgens were causing insulin resistance and hyperinsulinemia, the opposite effect would be expected. Conversely, androgen excess can cause insulin resistance. For example, women receiving testosterone[158] and women with CAH[159] have decreased insulin sensitivity. However, high levels of endogenous androgens do not cause insulin resistance in normal men; thus, the causal relationship between hyperandrogenemia and insulin resistance in women remains unclear.

Importantly, insulin has several direct and indirect effects in women with PCOS that potentiate the hyperandrogenic state. First, insulin may act alone to stimulate ovarian androgen secretion directly, and/or augment LH-stimulated androgen secretion.[160–162] Second, insulin may act indirectly to: (1) Potentiate ACTH-mediated adrenal androgen production,[163] (2) enhance the amplitude of GnRH-stimulated LH pulses,[164,165] (3) decrease hepatic production of SHBG (thereby increasing free testosterone levels),[166,167] and/or (4) decrease production of IGFBP-1.[168,169] This latter effect would not only increase the availability of free insulin, but also the availability of free IGF-1, which can also stimulate androgen production.[113,170] Furthermore, insulin may contribute to mid-antral follicular arrest,[171] a characteristic feature of the polycystic ovary.

Mechanisms of insulin resistance

Most women with PCOS have decreased insulin sensitivity, independent of their degree of adiposity, body fat topography, and androgen levels.[172] However, PCOS patients do not typically have structural abnormalities of their insulin receptors (IRs),[173,174] decreased IR number,[175,176] or altered insulin binding affinity.[175,176] Therefore, a postreceptor mechanism causing insulin resistance is most likely responsible.

In particular, the potential role of serine phosphorylation of the IR as a cause of insulin resistance in women with PCOS has been widely studied. Mechanistically, serine phosphorylation of the IR's β-subunit (IRβ) inhibits IR tyrosine autophosphorylation without affecting insulin binding.[177–180] Furthermore, serine phosphorylation of IRβ has been found to occur in many women with PCOS.[176] Although the mechanism causing IRβ serine phosphorylation remains undefined, it appears to involve a serine/threonine kinase extrinsic to the receptor[181]; alternatively, it may involve an inhibitor of a serine/threonine phosphatase.[176,182]

Insulin resistance in PCOS patients without IRβ serine phosphorylation may be due to other postreceptor defects. For example, serine phosphorylation of insulin receptor substrate-1 (IRS-1) inhibits IRS-1-dependent signaling pathways[183–185] and may contribute to the insulin resistance induced by FFAs[186] and TNF-α,[187] both of which can be elevated in PCOS.[188–190] Furthermore, factors such as inflammatory cytokines (e.g., IL-1 and IL-6),[191] glucosamine,[192] and other proteins involved in the insulin signaling pathways, such as IRS-2[193] and the β isoform of Akt (Akt2),[194] may also play a role.

Tissue-selective insulin resistance

Importantly, not all tissues in women with PCOS are insulin resistant. Rather, the insulin resistance appears to be tissue selective. Specifically, resistance to the metabolic actions of insulin has been reported in the skeletal muscle, adipose tissue, and the liver[172,195]; however, sensitivity to the steroidogenic actions of insulin persists in the adrenal gland and ovary. In fact, insulin potentiates adrenal and ovarian androgen production *in vitro*.[160–162] Hence the paradox: Whereas some tissues (muscle, fat, and liver) are insulin resistant in women with PCOS, others (the adrenal gland and ovary) are insulin sensitive.[10,11,196]

To explain this paradox, it has been suggested that insulin could act on the ovaries through either homodimeric IGF-1 receptors (IGF-1Rs) or heterodimeric receptors having one IR subunit and one IGF-1R subunit.[196] Although the clinical observation that female patients with profound insulin resistance due to mutations in both IR alleles (i.e., female patients with leprechaunism) have severe hirsutism and elevated androgen levels[197] suggests that the dominant action of insulin on the ovary in these individuals is mediated through a non-IR-specific mechanism, the finding that antibodies against IGF-1R do not inhibit insulin-stimulated sex steroid production in ovarian tissue from PCOS women suggest that other factors must be involved.[171,198] Furthermore, data suggest that only insulin's action on glucose transport and metabolic pathways are affected in PCOS[12,119]; in fact, even in the ovary itself, the metabolic effects of insulin seem to be impaired whereas its ability to potentiate steroidogenesis is preserved.[200–202]

Thus, to date, the "paradox" remains unexplained, and the biological mechanisms underlying the apparent tissue-selective insulin resistance in PCOS remain unclear.

Hyperandrogenemia and insulin resistance: the serine phosphorylation hypothesis

Although P450c17's 17α-hydroxylase and 17,20-lyase activities are catalyzed on a single active site,[60–62] they are differentially regulated. Specifically, serine phosphorylation of P450c17 dramatically increases the enzyme's latter (17,20-lyase) but not former (17α-hydroxylase) activity.[118] Because serine phosphorylation of IRβ impairs insulin signaling[179,180] and many women with PCOS have excess serine phosphorylation of IRβ,[176] it has been postulated that a gain-of-function mutation in a hypothetical kinase (or in a regulator of a hypothetical kinase) might potentially serine phosphorylate both IRβ, causing insulin resistance, and P450c17, causing hyperandrogenemia.[118,203] However, while the

serine phosphorylation hypothesis provides a common biological mechanism for hyperandrogenemia and insulin resistance (two cardinal features of PCOS), it remains an unproven hypothesis until such time as the hypothetical kinase or its regulatory factors are identified and activating mutations are found.[203]

The "Two-Hit" Hypothesis of PCOS

Given that the full clinical spectrum of PCOS does not typically appear until pubertal maturation, a "two-hit" hypothesis has been proposed.[4,32,204,205] For the first "hit," one or more of a number of different mechanisms, including primary adrenal, ovarian, and/or neuroendocrine abnormalities, insulin resistance and hyperinsulinemia, and/or prenatal, immediate postnatal, and/or peripubertal androgen exposure, lead to increased androgen production. For the second "hit," the preexisting hyperandrogenism reduces the sensitivity of the GnRH pulse generator to progesterone-mediated slowing during pubertal maturation, thereby initiating a series of changes in the HPO axis that result in ovulatory dysfunction and sustained hyperandrogenism (see Fig. 4). Thus, a cycle is established whereby the presence of hyperandrogenism, the final common pathway for the development of PCOS, begets more hyperandrogenism.

This "two-hit" hypothesis further reinforces the importance of diet and physical activity, and their effects on maintaining insulin sensitivity and appropriate body weight, on a woman's health. Although insulin resistance is common in PCOS, its presence is not invariable. But, as described above, insulin resistance and its resulting hyperinsulinemia can certainly promote androgen synthesis. Therefore, even in a genetically susceptible girl, the maintenance of insulin sensitivity may limit the syndrome's phenotypic expression. Alternatively, the presence of overweight/obesity can have additive adverse effects in PCOS[206,207] and promote hyperandrogenism by diminishing insulin sensitivity (i.e., increasing insulin resistance) and/or upregulating peripheral 17β-hydroxysteroid dehydrogenase action.[208] Furthermore, although neither necessary nor sufficient for the development of the syndrome, overweight/obesity amplifies the clinical severity of PCOS and increases the risk of metabolic dysfunction.[4] This is particularly alarming given that an evaluation of the National Health and Nutrition Examination Survey (NHANES) data estimates that ≈30% of girls ages 6–19 in the United States are either overweight or at risk for becoming overweight.[209] Thus, in approximately one third of U.S. adolescent girls, the presence of extra body fat may lead to PCOS-type symptoms in an otherwise asymptomatic girl, accelerate the syndrome's clinical manifestations, and/or aggravate the syndrome's clinical course. Furthermore, overweight and obese girls with PCOS are at increased risk for impaired glucose metabolism and have a greater than threefold increased risk of developing type 2 diabetes later in life.[210]

Thus, in the natural history of PCOS, environmental influences (mainly diet and physical inactivity leading to obesity) may perpetuate not only the metabolic, but also the endocrine aberrations of the syndrome.

Clinical Evaluation

Given that PCOS is a diagnosis of exclusion, the clinical evaluation of the syndrome is aimed at excluding other causes of androgen excess and menstrual dysfunction, such as late-onset CAH, hyperprolactinemia, thyroid dysfunction, and premature ovarian failure. Furthermore, although only androgen levels (testosterone, free testosterone, and DHEA-S) are included in the diagnostic criteria for PCOS, reliable specialized assays, particularly for the measurement of sex steroid hormones in children, are inconsistently available.[211] Moreover, the interpretation of the results must be made in the context of age-appropriate reference ranges. It is also important to remember that existing laboratory measurements do not permit the evaluation of hormonal bioactivity, explaining the poor correlation between circulating androgen levels and clinical symptoms.[212] In addition, the importance of a complete medical history, including a detailed family history, information on menarche and the nature of a woman's menstrual cycles, and a history of any predisposing factors to PCOS (low birth weight with excessive catch-up growth or premature adrenarche/pubarche), and a thorough physical examination, specifically documenting any clinical signs of hyperandrogenism (hirsutism, acne, and/or alopecia) or insulin resistance (acanthosis nigricans), and an assessment of regional adiposity, cannot be overemphasized. The importance of the family history is exemplified by the observation that pubertal girls born to women with PCOS tend to have higher serum testosterone and lower SHBG concentrations compared to age- and BMI-matched controls.[213] Moreover, determination of the waist-to-hip ratio (WHR), which is noninvasive and can easily be measured at each clinic visit, can be used as a surrogate marker for central fat accumulation, with a value greater than 0.8 suggestive of visceral adiposity.[26]

Although no consensus guidelines exist regarding the evaluation of suspected PCOS in the pediatric population, many practitioners measure the following analytes during the diagnostic evaluation: FSH, LH, prolactin, thyroid stimulating hormone (TSH), 17-hydroxyprogesterone (17-OHP), total and free testosterone, SHBG, a lipid panel, and a random blood glucose level. If the girl is overweight or has cutaneous signs of insulin resistance (acanthosis nigricans), fasting glucose and insulin levels are frequently obtained and a 2-h oral glucose tolerance test (OGTT) is performed.[25,32,205] Although a pelvic ultrasound (transabdominal if the girl is virginal) may be performed in a girl with high testosterone levels or rapidly progressive hirsutism or virilization to evaluate for malignancy, routine ovarian imaging is not indicated for the diagnosis of PCOS in adolescents.[214] If the evaluation suggests a potential adrenal tumor, a computed tomography (CT) scan or a magnetic resonance imaging (MRI) study should be performed.

Girls diagnosed with hyperandrogenism should then also be screened for other metabolic abnormalities (such as hypertension [using the appropriate age- and height-percentile reference values], dyslipidemia, and impaired glucose metabolism) given the approximately four-fold increased risk of metabolic syndrome in adolescents with PCOS independent of body weight.[7,8]

Treatment

The treatment of PCOS in adolescents is primarily focused on the symptomatic management of the reproductive, metabolic, and cosmetic manifestations of the syndrome. Given that most adolescent girls are not trying to conceive and

unaware of the metabolic aberrations that can occur in PCOS, the dermatological manifestations and menstrual dysfunction (i.e., abnormal bleeding) associated with the syndrome are typically the most common concerns.

Lifestyle modifications

Certainly for overweight or obese girls with PCOS, a serious attempt at weight loss and increased physical activity should be first-line therapy.[215] In nonobese girls with PCOS, weight management should be the goal. A weight loss of 5–10% has been shown to decrease testosterone concentrations, increase SHBG, normalize menses, and improve fertility in women with PCOS[216–222]; it can also attenuate insulin resistance and other metabolic aberrations.[223] A low-calorie diet of ≈1,000–1,200 kcal/day typically reduces total body weight by ≈10% over 6 months.[224] Moreover, a modest 500–1,000 kcal/day reduction in caloric intake typically results in 1–2 pounds of weight loss per week. The intake of sugar-sweetened beverages in particular is associated with weight gain[225–228] and indices of insulin resistance in the adolescent population[229] and thus should also be avoided. In addition to dietary modifications, regular physical activity is essential for weight loss and long-term weight management, and a minimum of 30 min of moderately intense exercise at least 3 days per week is recommended.[230] Increased physical activity also decreases insulin resistance[231–233] and has been associated with improved indices of insulin sensitivity in the pediatric population.[229]

Dermatological interventions

Hirsutism, the most common cutaneous sign of hyperandrogenism, appears to be progressive in women with PCOS. Therefore, the sooner it is treated, the better the outcome. Waxing, plucking, shaving, depilation, electrolysis, and laser hair removal techniques can all be used to remove current hair; however, pharmacological interventions are often needed to prevent new hair growth. Unfortunately for the affected adolescent, it may take up to 12 months to reverse the androgen-induced transformation of vellus to terminal hairs and see clinical improvement in hirsutism due to the prolonged growth cycle of hair.[25] Eflornithine cream (Vaniqa®), an inhibitor of ornithine decarboxylase, is another option for the treatment of hirsutism, but it is expensive, not often covered by insurance carriers, and needs to be used continuously to yield its desired effect.[234] For acne, topical treatment with salicylic acid, benzoyl peroxide, clindamycin/benzoyl peroxide preparations, tretinoin, and clindamycin/tretinoin combinations can be used. If topical therapies for acne are ineffective, oral isotretinoin can be used. However, given its teratogenicity, isotretinoin is typically only used in severe cases of acne and in combination with effective forms of contraception.

Combined hormonal agents

Combined hormonal oral contraceptive pills (OCPs) containing both estrogen and progestin are the most common form of therapy in adolescents with PCOS,[235] improving hirsutism, acne, and menstrual irregularity. The estrogen component both suppresses LH secretion (and thus ovarian androgen production) and increases hepatic SHBG production (decreasing the amount of free testosterone); the progestin component protects the endometrium from unopposed estrogen.[236] Combined OCPs also inhibit 5α-reductase in the skin, decreasing its exposure to DHT.[237] Although no significant clinical differences with respect to androgenicity appear to exist among the progestins in currently available OCPs, the fourth-generation progestin drospirenone (Yasmin® [30 μg of ethinyl estradiol + 3 mg drospirenone] and Yaz® [20 μg of ethinyl estradiol + 3 mg drospirenone]) has been suggested as the ideal choice given that it is a derivative of spironolactone (equivalent to ≈25 mg of spironolactone) and thus has direct antiandrogenic activity. Both high-dose (30–35 μg of ethinyl estradiol) and low-dose (20 μg of ethinyl estradiol) OCPs appear comparable[238]; the preparation with the fewest side effects is preferable. OrthoEvra®, a transdermal contraceptive patch, is also a treatment option for girls with PCOS; however, it may be associated with an increased risk for venous thromboembolic events compared to OCPs.[234] The NuvaRing®, a transvaginal contraceptive ring, is another option.[234] Although combined hormonal agents have been shown to increase insulin resistance,[239] this effect is not thought to outweigh their therapeutic benefits in PCOS. Furthermore, given that an imbalanced LH-to-FSH ratio is often the driving force for hyperandrogenism in lean girls with the syndrome, combined hormonal agents may be especially useful in this population.[32]

Antiandrogens

Antiandrogen medications either block androgen binding to the AR or inhibit 5α-reductase, limiting the conversion of testosterone to the more biologically potent androgen DHT. The most commonly used antiandrogen in the United States is spironolactone, which functions mainly as a competitive AR antagonist; however, it also inhibits 5α-reductase and decreases testosterone production.[205,240] The recommended dosage is typically 100–200 mg/day in divided doses. The AR inhibitor flutamide is another antiandrogen that is commonly used in Europe.[241] Although it appears to be well tolerated at the recommended dosage of 250–500 mg/day, the risks of hepatotoxicity and fetal abnormalities limit its use outside of clinical studies. Finasteride, a 5α-reductase inhibitor, is another antiandrogen that has demonstrated comparable efficacy with spironolactone and flutamide for the treatment of hirsutism at its recommended dosage of 5 mg/day[242]; however, it is rarely used clinically.

Insulin-sensitizing agents

Insulin-sensitizing agents are also frequently used in the management of PCOS.[243,244] Of these agents, metformin is the most commonly prescribed, particularly in adolescents with impaired glucose tolerance, insulin resistance, and/or obesity.[245,246] Metformin inhibits hepatic glucose production and increases peripheral tissue insulin sensitivity,[247] and in women with PCOS, appears to improve insulin sensitivity, insulin and androgen levels, lipid parameters, and menstrual cyclicity.[245,246,248] Moreover, it is effective in reducing the incidence of diabetes in those at high risk.[249] Several studies evaluating the use of metformin in both obese and nonobese adolescents with PCOS (at dosages ranging from 750 to 2,250 mg/day) have been performed,[250–257] and in general

they all demonstrate the agent's efficacy. However, there is a lack of large, randomized controlled trials, and there are no prospective studies examining the long-term effects of metformin in the prevention or reduction of PCOS-associated metabolic complications. Although the observation that metformin's normalizing effects are reversed soon after therapy is discontinued[258] is a concern, the favorable safety profile of metformin and its potential to benefit both the cardiometabolic as well as reproductive aspects of PCOS make it an attractive therapeutic agent.[246] The thiazolidinediones (TZDs) (troglitazone, rosiglitazone, and pioglitazone) are another class of insulin-sensitizing agents that act as agonists for the nuclear peroxisome proliferator-activated receptor γ (PPARγ).[259,260] Like metformin, they improve peripheral insulin sensitivity, androgen levels, and ovulatory function in women with PCOS.[261–264] However, they have not been studied widely in the pediatric population. Moreover, given their potential side effects, they are unlikely to replace metformin as the insulin-sensitizing drugs of choice.

Other agents

Octreotide (Sandostatin®), an analog of somatostatin, has also been used in patients with PCOS.[265–267] Mechanistically, somatostatin inhibits pancreatic insulin release[268] in addition to decreasing pituitary GH secretion[269] and blunting the LH response to GnRH.[270] However, due to the parenteral nature by which the drug has to be given and its extensive side-effect profile, octreotide therapy is unlikely to play a major role in PCOS treatment.

Combination therapy

Given that no single pharmacological agent adequately addresses all of the symptoms associated with PCOS and each available agent has different mechanisms of action, combination regimens are common. In the United States, the combination of ethinyl estradiol/drospirenone-containing OCPs (Yasmin® or Yaz®) with metformin is often used, particularly in overweight girls.[271] The combination of ethinyl estradiol/drospirenone, metformin, and flutamide has been studied in Europe and appears to have additive benefits on the syndrome's phenotype.[272–274] However, as described above, flutamide is not widely used outside of clinical studies given its potential toxicities.

Conclusions

PCOS is a common endocrinopathy characterized by hyperandrogenism and disordered gonadotropin secretion, often associated with insulin resistance. The syndrome, which modulates both hormonal and metabolic processes, affects an estimated 5–10% of reproductive-age women in the United States and increases a woman's risk of infertility, endometrial pathology, and cardiometabolic disease. As it is currently defined, PCOS most likely includes a group of distinct diseases with similar clinical phenotypes but different underlying pathophysiological processes. However, hyperandrogenism remains the syndrome's clinical hallmark. The clinical manifestations of PCOS often emerge during childhood or in the peripubertal years, suggesting that the syndrome is influenced by fetal programming and/or early postnatal events. However, given that the full clinical spectrum of PCOS does not typically appear until pubertal maturation, a "two-hit" hypothesis has been proposed: (1) A girl develops hyperandrogenism through one or more of many different potential mechanisms; and (2) the preexisting hyperandrogenism, by whatever source, then disturbs the HPO axis, resulting in ovulatory dysfunction and sustained hyperandrogenism. No consensus guidelines exist regarding the diagnosis and management of PCOS in the pediatric population; however, because the syndrome is a diagnosis of exclusion, the clinical evaluation of suspected PCOS is aimed at excluding other causes of androgen excess and menstrual dysfunction. For the management of PCOS, the importance of lifestyle should not be overlooked, and a symptom-directed treatment strategy should be used.

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