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History of Polycystic Ovary Syndrome, Premature Adrenarche, and Hyperandrogenism in Pediatric Endocrinology

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Abstract
Descriptions of probable PCOS can be found in ancient Roman writings and in Renaissance art. Attention to domesticated animal reproduction led ancient observers to understand the role of the testes in male phenotypes, proven experimentally by testicular transplantation (in chickens) in 1849. Testosterone was isolated and its structure determined in the 1930s, but the multiple pathways of androgen synthesis have only been delineated recently. Adrenarche as an event separate from puberty was described in 1937, but the mechanism(s) triggering its onset remains unclear, although most work points to intraadrenal events. The identification of 11-ketotestosterone as the principal adrenal androgen is very recent (2018). Definitions of PCOS have evolved with the elucidation of its complex biology. PCOS is now recognized as a complex disorder characterized by irregular menses and hyperandrogenism often associated with infertility; its prevalence may be as high as 20% of reproductive age women. Work in the 1980s associated premature exaggerated adrenarche with PCOS, linking the adrenal to an "ovarian" syndrome. Obesity has long been noted in many patients with PCOS, and associated insulin resistance was noted in the 1980s, possibly associated with fetal developmental events such as low birth weight, but the mechanistic link between carbohydrate metabolism and hyperandrogenism remains unclear, despite intensive investigation. Genome-wide association studies have identified apparently associated genes, but mechanistic links are apparent for only some of these. Adrenarche, PCOS, and adrenal and ovarian hyperandrogenism remain very active areas of clinical and basic research.

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous familial disorder characterized by irregular menses, clinical and/or biochemical hyperandrogenism (HA), and infertility. Depending on diagnostic criteria, the prevalence is 6–20% of reproductive-aged women. Associated comorbidities include metabolic, reproductive, and psychological conditions. Using the lens of evolutionary medi-

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cine, the overlap of PCOS risk alleles in women from both European and Chinese populations suggests that PCOS is an ancient disorder [1]. Details regarding the pathophysiology of PCOS are reviewed elsewhere [2–4]. Herein, we recount selected aspects shaping our current understanding of PCOS; the contributions of pediatric endocrinologists are highlighted in boldface type.

Initial Accounts of PCOS

Hirsutism, often yet inconsistently associated with menstrual disturbances and sterility[1], has been recorded throughout history[2]. Around 400 B.C., Hippocrates described two women on the island of Kos notable for their beards; one woman had developed sudden cessation of menses and died shortly thereafter [5]. The other was Phaethusa, the wife of Pytheus, who had borne a child. Following her husband's banishment, she missed her menses and developed generalized hirsutism [6].

The Greek physician and gynecologist, Soranus of Ephesus (c. 98–138 AD), who practiced in Alexandria and Rome, noted that *"[s]ometimes it is also natural not to menstruate at all… It is natural too in persons whose bodies are of a masculine type… we observe that the majority of those not menstruating are rather robust, like mannish and sterile women*" [7]. This description suggests that the existence of androgenized and oligo-amenorrheic women was known in Ancient Greece. According to Hippocratic and Galenic beliefs, cessation of menses (when not pregnant or lactating) was troubling because it indicated dysfunction of a woman's purgative systems [8].

One thousand years later, the medieval Sephardic Jewish philosopher, astronomer, and physician, Maimonides (1135–1204 AD) recorded that "*…there are women whose skin is dry and hard, and whose nature resembles the nature of a man. However, if any woman's nature tends to be transformed to the nature of a man, this does not arise from medications, but is causes by heavy menstrual activity*" [9]. Again, the impression given is that menstrual dysfunction and hirsutism were deemed unremarkable in the Middle Ages. Some 300 years later, the French surgeon and obstetrician Amboise Paré (1510–1590 AD), in his *Concerning the Generation of Man*, underscored that androgenized oligo-amenorrheic women were not rare [10].

Lamentably, throughout the history, hirsute women were often viewed as oddities and "displayed" at carnivals. In Macbeth, Shakespeare portrays the three witches as bearded women [11]. Earnest inquiry regarding the causes of hirsutism began in the late 13th or early 14th century when the ban on human anatomical dissections was lifted [12]. In 1697, Henry Sampson (1629? –1700), an English nonconformist minister and physician, described a girl who grew axillary, pubic, and beard hair at the age of 6 years and suddenly died [13, 14]. Whereas this case likely depicts the features of an androgen-secreting adrenocortical carcinoma, the concept that the adrenal was the principal seat of the "male essence" and androgenization in women remained firmly in place until the early 20th century [15]. In 1912, Glynn summarized and reported a large series of patients with adrenal tumors; he indicated that only a few had features of androgen excess and ovarian tumors [16].

In the 18th century, Antonio Vallisneris (1661–1730) described, in 1721, large ovaries in a young married moderately obese infertile woman who had died after falling from a tree [17]. Subsequently, the pathologist Carl von Rokitansky (1804–1878) reported sclerocystic multicystic ovaries in many women [18].

Discovery of Hormones

Beginning in the mid-19th century, a convergence of medical observations laid the foundation for what we now know to be PCOS. Arnold Adolph Berthold (1803–1861) transplanted testes from roosters to capons. Upon finding increased "androgenic" behavior, Berthold concluded that a testicular substance traveling through the bloodstream was responsible for these changes [19]. Subsequently, Charles-Édouard Brown-Séquard (1817–1894) dramatically (and subjectively) observed the effects of a "male essence" in self-experiments. He claimed that self-injection of a slurry of guinea pig and dog testicle secretions boosted his libido, improved his bowel function, and increased his strength [20, 21][3]. In 1855, Claude Bernard (1813–1878) proposed the existence of internal secretions and put forth the concept of homeostasis [22].

[1] Celebrated "La Barbuda", a 52-year-old bearded woman is shown nursing her child in José (Jusepe) de Ribera's oil on canvas (now El Prado Museum, Madrid, Spain). The picture notes (in an annotated tablet in the picture itself) that she became markedly hirsute at the age of 37 after having had three spontaneous abortions. The picture created in 1631 and commissioned by the Duke of Alcala serves to place on record that hirsute women do and have become mothers.

[2] Remembering that human records are less than 5000 years old, with the oldest coherent texts from about 2600 BC in Sumerian cuneiform script.

[3] Effects that Brown-Séquard described likely represented a placebo response for at least two reasons. First, insignificant quantities of testosterone are stored in testes. Second, the injections contained an aqueous mixture of testicular vein blood, semen, and animal testis extract unlikely to solubilize steroids. Nevertheless, his report stimulated future endocrine discovery.

Following his discovery of secretin, Ernest Starling (1866–1927) coined the term "hormone," derived from the Greek verb, hormaein, meaning "to rush" or "to set in motion" [23]. Subsequent observations relating hirsutism to metabolic and/or adrenal dysfunction consolidated the concept of the internal milieu [24–28].

Starting in the 1930s, several scientific reports influenced our understanding of PCOS. Robert Towner Hill (1905–1986) made the seminal observation that the ovaries (at least of mice) produced male-like hormones [29, 30]. Adolf Butenandt isolated androsterone from 15,000 L of male urine (from policemen); he then went on to isolate DHEA and determine its chemical structure [31]. Ernst Laqueur et al. isolated 15 mg of crystalline testosterone from several tons of steer testes [32], a finding critical to identifying the androgenizing substance in men and women. In 1935, Irving Freiler Stein (1887–1976) and Michael Leo Leventhal (1901–1971) described seven women in whom "amenorrhea was associated with the presence of bilateral polycystic ovaries" [33]. Of these women, three were obese, five were hirsute (one obese), and one was thin and acneic. Wedge resection of the ovary resulted in two pregnancies and regular cycles in the remaining subjects.

Stein and Leventhal were the first to recognize the clustering of amenorrhea, hirsutism, and polycystic/sclerocystic ovaries. Curiously, they paid limited attention to the androgenization of their patients and instead suggested that the bilateral cystic ovaries were most probably the result of some hormonal stimulation, most likely the result of "anterior pituitary secretions" [34]. Further, it seems Stein never fully grasped the magnitude of their discovery, instead creating a series of conditions that led to a very narrow definition of the so-called Stein-Leventhal syndrome. Toward the end of his life, he noted that *"It is a fact rarely disputed that the Stein-Leventhal syndrome plays but a small part in the overall picture of female sterility"* [35], suggesting that Stein considered this syndrome to be rare. Indeed, only within the past 2 decades has the medical community appreciated that PCOS affects approximately 6-20% of women depending on the diagnostic criteria [3, 36, 37].

Advances in Methodology

Beginning in the 1950s, endocrinologists were engrossed in ascertaining the hormonal correlates for puberty and the menstrual cycle [38–41]. Implementation of the radioimmunoassay technology developed by Yalow and Berson [42] revolutionized science and medicine. This technology enabled hormone determinations which led to investigation of the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal axes. Upon ascertaining that cyclic gonadotropin secretion governed sex steroid secretion with different patterns for females and males [43], Midgely and Jaffe [44] expanded their studies to investigate gonadotropin secretion in humans during puberty and at different timepoints of the menstrual cycle [45]. Urinary gonadotropin assays demonstrated that increased LH and FSH excretion were associated with the onset of gonadarche consistent with the prevailing hypothesis that the development of secondary sex characteristics was dependent on pituitary gonadotropin secretion [46, 47].

Gonadotropins, Puberty, and the Menstrual Cycle

Robert Penny et al. [48] found that gonadotropin concentrations correlated with pubertal stages were normal in patients with premature adrenarche and premature thelarche and were elevated in girls with premature ovarian insufficiency due to Turner syndrome. By 1975, the development of pubic and axillary hair growth was noted to be associated with rising adrenal DHEA secretion. Available data indicated that DHEA/DHEAS concentrations rose prior to the onset of pubertal gonadal steroid secretion [49–51].

Concurrently, Ernst Knobil et al. [52, 53] observed that LH secretion was pulsatile in ovariectomized nonhuman primates and, using pulsatile GnRH infusions, were able to recapitulate the gonadotropin pattern typical of a menstrual cycle. Using this model, changes in pulse frequency rather than pulse amplitude were noted to lead to profound alterations in gonadotropin concentrations; doubling GnRH pulse frequency increased LH concentration, and decreased FSH concentrations [54]. Ensuing studies using a variety of animal models illuminated our current understanding of the hypothalamic-pituitary-gonadal axis and the role of a neural pulse generator extrinsic to GnRH neurons to drive GnRH and gonadotropin secretion [55–57].

Gonadotropins and PCOS

Detailed characterization of women with PCOS began in the late 1950s and early 1960s when Janet MacArthur, Joseph W. Goldzieher, and others considered this condition. In 1958, McArthur et al. [58] collected 24-hour urine samples and measured serial daily urinary interstitial-

cell-stimulating hormone (ICSH/LH) excretion with a functional bioassay using immature rat testis and prostate weights. They reported higher ICSH urinary excretion among patients diagnosed to have Stein-Leventhal syndrome [58]. Based on their findings related to gonadotropin secretion, Yen et al [59] hypothesized that aberrant hypothalamic regulation of gonadotropins might be causally related to the PCOS phenotype.

With the confirmation of aberrant gonadotropin secretion in PCOS, clinical investigators began to explore various aspects of the pathophysiology. Rebar et al. [60] in 1976 described heightened pituitary sensitivity to GnRH and suggested that "the abnormal gonadotropin secretion seen in these patients is not due to an inherent defect of the hypothalamic-pituitary system but is the result of a functional derangement consequent to chronic inappropriate estrogen feedback. Based on these observations, it would appear that a vicious cycle is present which perpetuates chronic anovulation; high levels of LH stimulate the ovary to secrete increasing amounts of androgens. These androgens, particularly androstenedione, are converted to estrogens, which in turn, augment the pituitary sensitivity to endogenous LRF, and this results in an exaggerated pulsatile LH secretion and in the maintenance of an inappropriately elevated circulating LH" [60]. Thus, Rebar et al. [60] were prescient about the repetitive cycle of neuroendocrine and ovarian dysfunction in PCOS.

Using every 10-minute gonadotropin determinations, Crowley et al. [61] reported increased LH pulse amplitude and frequency in women with PCOS, whereas FSH secretion was lower. Based on these data, the authors suggested that increased GnRH pulse frequency contributed to partial pituitary desensitization [61]. To investigate the hypothesis that neuroendocrine features of PCOS led to reduced sensitivity of the GnRH pulse generator to the inhibitory effect of estradiol and progesterone, Marshall et al. [62, 63] showed that androgen blockade with flutamide improved the sensitivity of the GnRH pulse generator to estradiol and progesterone. Marshall et al. [64] attributed the greater variability observed in adolescents to the immaturity of the neuroendocrine axis. These findings emphasized a neuroendocrine component to the pathophysiology of PCOS.

Puberty and Premature Adrenarche

Earlier clinical and nonhuman primate studies had cataloged human puberty into two distinct events: gonadarche and adrenarche. Gonadarche signifies reactivation of the GnRH pulse generator, which ultimately culminates in menarche and fertility [57]. Adrenarche describes adrenal pubertal maturation characterized by enzyme activity changes in the zona reticularis [65, 66]. Specifically, increased 17,20-lyase, increased DHEAS sulfotransferase, increased P450 oxidoreductase, and decreased 3β-hydroxysteroid dehydrogenase activities accompanied by increased cytochrome b_5 expression result in increased adrenal C19 steroid secretion by the zona reticularis [67].

By convention, premature pubarche in girls is defined as pubic hair development prior to 8 years of age. One common cause of premature pubarche is premature adrenarche, which reflects a premature increase in zona reticularis C19 steroid/DHEAS secretion [68]. Androgen concentrations among girls with premature adrenarche are typically comparable to normal Tanner II girls with minimal progression until an appropriate age for puberty is attained [69, 70]. ACTH stimulation and dexamethasone suppression tests confirmed the adrenal origin of the C19 steroids [71].

In 1993, a small retrospective study reported that approximately 50% of adolescent girls with history of premature pubarche had later developed oligo/amenorrhea, hirsutism, and elevated androgen concentrations [72]. Many of these girls appeared to have predominantly ovarian HA, while a few also had an adrenal component [73]. Hyperinsulinemia occurred in this population [74]. These initial findings inspired several decades of inquiry exploring possible associations between adrenarche, hyperinsulinemia, and PCOS.

Onset of PCOS

Yen et al. [75] described hyperinsulinemia with normal glucose tolerance, elevated LH concentrations, low IGFBP1 concentrations, and enlarged ovaries in thirteen hyperandrogenic girls ranging in age from 11 to 18 years. These studies emphasized a few features associated with PCOS such as HA, insulin resistance, and enlarged ovaries. Thus, for some girls, ovarian HA during puberty appeared to precede PCOS [76]. **Allen Root** and **Thomas Moshang** [77] recognized HA-PCOS in three girls with history of central precocious puberty who evolved to a HA-PCOS state. They suggested potential mechanisms such as excessive adrenal androgen secretion at adrenarche, abnormal regulation of LH secretion, and enzymatic abnormalities in ovarian/adrenal steroidogenesis [77].

Insulin Emerges onto the Scene

The intertwined relationship of HA and metabolic dysfunction was recognized as far back as 1914 [25]. In 1976, Kahn et al. [78] described women with acanthosis nigricans, glucose intolerance, hyperinsulinemia, and insulin resistance; ensuing evaluation distinguished 2 patient categories – those with insulin receptor gene mutations and those with the HAIR-AN syndrome [78]. HAIR-AN syndrome refers to a multisystem disorder characterized by HA, insulin resistance (IR), and acanthosis nigricans [79]. First, Burghen et al. [80] and subsequently Chang et al. [81] identified IR in women with PCOS, reinforcing the importance of IR and hyperinsulinemia in the PCOS phenotype. Based on the accumulating data, Robert Barbieri and Kenneth Ryan proposed that a positive feedback loop between IR and HA initiated and sustained PCOS [79].

In the search for the physiologic basis for the IR and hyperinsulinemia associated with PCOS, Barbieri et al. demonstrated that insulin-stimulated androgen biosynthesis occurred in cultured theca cells derived from both normally cycling women and from women with the HAIR-AN syndrome [82, 83]. In 1989, euglycemic-hyperinsulinemic clamp techniques revealed IR and hyperinsulinemia independent of body composition, glucose tolerance, and insulin clearance in adult women with PCOS [84]. Successive studies continued to validate the relevance of IR and hyperinsulinemia in the pathophysiology of PCOS. However, insulin receptor gene mutations were found to be rare causes of ovarian HA [85, 86].

In 1995, Apter et al. [75] reported IR and hyperinsulinemia independent of BMI among hyperandrogenic adolescent girls, again highlighting the importance of IR in the pathophysiology of PCOS. Using hyperinsulinemic clamp studies, **Silva Arslanian** et al. [87] demonstrated decreased peripheral insulin sensitivity, increased hepatic IR, and compensatory hyperinsulinemia in adolescent girls with PCOS. With the elucidation of insulin signal transduction pathways, it became apparent that insulin has both metabolic and mitogenic actions. Regarding PCOS, IR impacted carbohydrate metabolism, whereas the mitogenic response remained intact. This mitogenic response promoted ovarian and adrenal steroidogenesis where insulin acted as a costimulator with the endogenous hormones, LH and ACTH, respectively [88, 89].

Adrenal, Ovary, and Steroidogenesis

Hyperandrogenism is a fundamental characteristic of PCOS. As mentioned above, the adrenal zona reticularis increases secretion of C19 steroids at adrenarche, which is semi-arbitrarily defined as a DHEAS concentration exceeding 40–50 μg/dL. These adrenal-derived C19 steroids, DHEA, DHEAS, and androstenedione, are preferably termed as "pre-androgens" because they do not appreciably bind to the androgen receptor. More recently, liquid chromatography/tandem mass spectrometry has underscored the importance of the 11-oxygenated metabolites of androstenedione and testosterone in adrenarche. Indeed, available data indicate that 11-ketotestosterone is the predominant circulating bioactive C19 androgen during normal and premature adrenarche [90].

Following mini-puberty in infancy, the ovary remains quiescent until the hypothalamic GnRH pulse generator is reactivated at the time of gonadarche. Unlike the adrenal cortex, the ovary consists of two distinct compartments – theca and granulosa. More detailed information regarding ovarian function is available elsewhere, simplistically; LH promotes ovarian C19 steroid production, predominantly androstenedione, which diffuses to the granulosa cell where FSH-stimulated aromatase activity converts the C19 steroid to a C18 steroid such as estradiol [91, 92].

To clarify whether the androgens were secreted by the ovary or adrenal, a variety of stimulation and suppression studies were performed. **Robert Rosenfield** et al. [93, 94] identified excessive GnRH agonist stimulated 17-hydroxyprogesterone responses as indicative of functional ovarian HA. These studies emphasized the key role of excessive ovarian androgen secretion in these patients [95]. For some women, adrenal HA also contributed to the HA [96, 97].

With the advent of sonography, Adams et al. [98] detected polycystic ovary morphology (PCOM) in women presenting to a gynecologic clinic with oligo-amenorrhea or hirsutism. Additional studies indicated that although PCOM was initially identified in women with PCOS, this ovarian morphology was also present in normal women [99]. Longitudinal evaluation of a cohort of normal adolescent girls demonstrated that ovarian morphology varied and was not associated with the development of persistent HA or metabolic abnormalities [100]. Rather, ovarian morphology among adolescent girls is typically multifollicular, reflecting the increased activity of the hypothalamic-pituitary-ovarian axis.

Premature Adrenarche and the Developmental Origins of Health and Disease Hypothesis

As noted above, a variety of tests such as GnRH agonist (leuprolide acetate) stimulation, ACTH stimulation, dexamethasone suppression, and ovarian suppression were used to distinguish ovarian and adrenal HA. In 1986, **Rosenfield** et al. [101] described exaggerated adrenarche suggesting adrenal HA contributed to the androgen excess in some women. A few years later, **Lourdes Ibàñez** et al. [102] reported that postpubertal girls previously diagnosed with premature pubarche showed an increased GnRH-stimulated 17-hydroxyprogesterone response, interpreted as indicating functional ovarian HA. These data supported the concept that functional ovarian HA began during puberty [103].

Following the report by Barker et al. [104] proposing that the fetal environment as reflected by low birth weight was associated with an increased risk for ischemic heart disease in adulthood, **Ibàñez** et al. [105] proposed a sequence with low prenatal birth weight, premature pubarche, hyperinsulinism, and ovarian HA [104, 105]. This concept was later modified to include a mismatch between low prenatal weight and greater postnatal weight gain, leading to hepatovisceral fat excess, culminating in progression to PCOS [106]. More recent studies connecting low birth-weight have been inconsistent regarding an association between low birth weight and development of PCOS [107–109].

Definition of PCOS

To provide clarity, the proceedings of an NIH conference held in April 1990 on the topic, leveraging a survey carried out among participants at the meeting, suggested that the diagnostic criteria for PCOS included HA and/or hyperandrogenemia, oligo-anovulation, and exclusion of other disorders [110]. In 2003, an expert conference was held in Rotterdam, and the proceedings added PCOM to the list of potential diagnostic criteria; PCOS could be diagnosed when two of the following three criteria were identified: oligo-anovulation, clinical and/or biochemical HA, and PCOM after exclusion of other disorders [111]. The Androgen Excess Society (now Androgen Excess & PCOS Society) published an expert assessment in 2006, noting that PCOS diagnostic criteria included clinical and/or biochemical HA, ovarian dysfunction including oligo-anovulation and/or polycystic ovaries, and exclusion of other disorders [112, 113]. In 2012, the NIH held a consensus conference and made a number of recommendations, including that, to the extent possible, clinicians and investigators should use the broader Rotterdam criteria, and that the specific PCOS phenotype be stated when doing so [114]. The 2013 Endocrine Society Practice Guideline recommended using HA and persistent irregular anovulatory menstrual cycles adult criteria to diagnose PCOS in adolescent girls [115]. The Evidence-Based International Guidelines, which endorsed the Rotterdam criteria, brought together professionals and consumers to review diagnostic criteria and offer constructive therapeutic options [3].

Notwithstanding efforts to distinguish PCOS among adult women, application of the adult PCOS diagnostic criteria to adolescent girls has been particularly challenging because irregular menses, acne, and multifollicular ovaries occur as part of the normal pubertal sequence. To address this diagnostic conundrum, international pediatric endocrine societies along with adolescent medicine and reproductive endocrinology specialists reviewed available data to delineate PCOS in the adolescent girl [116–118]. Use of these revised adolescent criteria in the longitudinal Australian Raine cohort study reduced over-diagnosis of PCOS and emphasized the importance of early healthy lifestyle interventions to hinder transition to PCOS [119].

Genetics of PCOS

Daughters of women with PCOS have a fivefold increased risk of being diagnosed with PCOS [120]. Yet, known PCOS loci account for approximately 10% of the estimated 70% hereditability [121, 122]. Genome-wide association studies performed in Chinese and European cohorts identified >20 loci associated with PCOS [123–125]. These loci include genes readily recognized as candidate genes such as *LHCGR*, *FSHR*, and *FSHB*. Other loci provide novel targets for discovery such as *DENND1A*, *ZNF217*, and *RAB5* [126, 127]. Additional investigations may describe the potential consequences and mechanisms of intrauterine androgen exposure, elucidate anti-Mullerian hormone actions, and clarify possible associations with the gut microbiome [128–134]. Current efforts include ongoing interrogation of candidate loci [135].

Opportunities

Many questions regarding PCOS remain to be answered. One addresses the relationship, if any, between premature adrenarche and PCOS. A longitudinal study involving a cohort of Finnish girls showed that premature adrenarche was associated with lower SHBG concentrations, but not ovarian dysfunction [136]. In an ongoing Chilean study, girls with elevated DHEAS concentrations at 7 years showed earlier thelarche, pubarche, and menarche without significant differences in ovarian morphology 1-year post-menarche [137]. A second question explores the long term outcome for girls designated "at risk for PCOS". Also, a third question considers the role of prenatal androgen and/or AMH exposure on the developing fetus [138, 139]. A fourth question relates to the usefulness of AMH measurements to identify PCOM and applicability to adolescent and emerging adult girls [140]. Additional longitudinal prospective studies are needed to answer these important questions.

Disorders of androgen excess in women have long fascinated humanity as illustrated by portrayals of bearded women as oddities [141]. Over the past century, the diagnosis of PCOS has been honed as a complex, multi-faceted, heterogeneous familial phenotype characterized by androgen excess, IR, hyperinsulinemia, and ovarian dysfunction. Evolutionary medicine proposes that PCOS represents a mismatch between our ancient biology and our modern lifestyle, an environment typified by nutrient excess and decreased physical activity [142]. From a pediatric/adolescent point of view, the ability to identify girls "at risk" for PCOS and those with PCOS is critical to facilitate targeting of resources to promote healthy lifestyle interventions for these girls and their families [143, 144].

Statement of Ethics

Not applicable.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Selma F. Witchel, Ricardo Azziz, and Sharon E. Oberfield contributed to the conception and writing and reviewing of the report. All reviewed multiple versions and approved the final one.

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