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Intertwined reproductive endocrinology: Puberty and polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is a heterogeneous familial disorder often emerging during the peri-pubertal years concomitantly with the onset of gonadarche and adrenarche. Both gonadarche and PCOS reflect functional changes in the hypothalamic-pituitary-ovarian axis. During this transition, normal girls manifest features consistent with PCOS such as irregular menses, mild hyperandrogenism, and multi-follicular ovary morphology. Themes common to puberty and PCOS, neuroendocrine features, androgen exposure, and insulin sensitivity, will be considered to address the possibility that PCOS interferes with the normal pubertal transition.

Keywords

Puberty; Polycystic Ovary Syndrome; Hyperandrogenism; Testosterone; Gonadotropins

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous familial disorder often emerging during the peri-pubertal years. In humans, pubertal transition involves two distinct components, gonadarche and adrenarche. Gonadarche reflects the initiation of hypothalamic-pituitary-ovarian (HPO) axis activity triggered by a reactivation of robust pulsatile GnRH release evidenced by increased gonadotropin secretion. Adrenarche, the pubertal maturation of the adrenal cortex, is accompanied by increased adrenal zona reticularis C19 steroid secretion and precedes gonadarche.

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Both gonadarche and PCOS reflect functional changes in the neuroendocrine axis regulating the ovary (HPO axis). Increased LH secretion is commonly found in women with PCOS, and some data suggest that premature onset of adrenarche precedes development of PCOS. Hence, both components of puberty are intertwined with PCOS. Indeed, confirming a diagnosis of PCOS during the peri-pubertal period is challenging in that normal girls manifest features consistent with PCOS such as irregular menses, mild hyperandrogenism, and multi-follicular ovary morphology [1].

This begs the question as to whether PCOS interferes with normal pubertal transition? Does puberty activate an imprinted organizational susceptibility to develop PCOS? Does excessive persistent ovarian or adrenal C19 androgen secretion influence GnRH and LH secretion? Or perhaps, excessive anti-Mullerian hormone (AMH) secretion from the PCOS ovary disrupts the pubertal transition? Brief reviews of PCOS, gonadarche, and adrenarche to ascertain potential points of intersection are discussed.

PCOS

PCOS is a heterogeneous multifactorial familial disorder affecting 6–15% of reproductive aged women depending on the diagnostic criteria [2,3]. PCOS is characterized by irregular menses, anovulation, hyperandrogenism, polycystic ovary morphology, infertility, and insulin resistance/hyperinsulinemia. Women with PCOS have increased risks for type 2 diabetes, obesity, dyslipidemia, and depression [4,5]. From an evolutionary perspective, PCOS appears to be an ancient disorder [6,7]. Most clinical studies tend to recruit patients with greater symptom severity confounding investigation of the pathophysiology [8].

The HPO axis dysfunction typical of PCOS often begins during the peripubertal years. Increased LH pulse frequency occurs in adolescent girls with hyperandrogenemia [9]. Daughters of women with PCOS manifest features associated with PCOS such as higher LH, androgen, and AMH concentrations as well as pancreatic β-cell dysfunction [10,11,12]. Two biomarkers, longer anogenital distance and increased sebum production, associated with increased *in utero* androgen exposure have been described among daughters of women with PCOS suggesting excessive prenatal androgen exposure [13,14]. In the Swedish nationwide register-based longitudinal cohort, daughters of women with PCOS had a fivefold increased risk to develop PCOS [15].

Twin studies reported high hereditability for PCOS consistent with a role for genetic factors [16,17]. Genome-wide association studies (GWAS) have identified at least 26 replicated loci associated with PCOS. The underlying genetic architecture for PCOS is similar irrespective of diagnostic criteria, NIH or Rotterdam [18]. Identified loci are associated with neuroendocrine, metabolic, and reproductive pathways [18,19].

Gonadarche

Gonadarche represents the culmination of development of the hypothalamic-pituitary-gonadal (HPG) axis, which begins in utero when sex differences are first noticed. In man and other higher primates, male fetuses demonstrate robust GnRH pulsatility as reflected by LH secretion, testicular testosterone secretion, and negative feedback control of

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gonadotropin release by the fetal testis. This *in utero* testicular testosterone secretion programs or imprints the GnRH pulse generator in male fetuses. The fetal testis also secretes AMH which promotes degeneration of the Mullerian ducts. Towards the end of pregnancy, GnRH and gonadotropin secretion are suppressed by the elevation of estradiol and other feto-placental hormones.

Following parturition this hormonal inhibition of GnRH secretion is removed resulting in transient increased gonadotropin secretion labeled as the “mini-puberty” of infancy. Fundamental sex differences in hypothalamic GnRH pulse generator activity are likely operational during this period. [20]. Despite gonadotropin stimulation, gametogenesis does not occur during this time. Subsequently, during the childhood years, the ovary acquires the ability to respond to gonadotropin stimulation. However, the neurobiological “brake” imposed on the GnRH pulse generator maintains low circulating LH and FSH concentrations that guarantee the relative quiescence of the prepubertal ovary until the GnRH pulse generator is reactivated at the time of gonadarche [21,22].

While compelling evidence indicates that kisspeptin expressed by neurons in the infundibular nucleus relays the output of the GnRH pulse generator to the GnRH neuronal network, the molecular mechanisms underlying the onset, duration and inter-pulse interval of intermittent kisspeptin discharges are less well established [23]. At least one stimulatory peptide, neurokinin B, and one inhibitory peptide, dynorphin, appear to be involved. Available data indicate that kisspeptin is not the trigger for puberty onset. Rather, upstream regulatory mechanisms integrate a variety of signals communicating nutritional, metabolic, genetic, and environmental status [22,24]. Kisspeptin neurons in the infundibular nucleus transduce these signals from higher centers and relay them to the GnRH neurons. Kisspeptin neurons also express progesterone receptors (PR), estrogen receptor-α (ERα), and androgen receptors (AR); these neurons may be involved in steroid hormone feedback. GnRH neurons express ERβ receptors and GABA receptors, but do not express AR or ERα receptors [25].

During normal pubertal development, insulin sensitivity temporarily declines with a nadir in mid-puberty [26]. This is accompanied by increased glucose-stimulated insulin secretion [27]. The growth hormone (GH)/IGF-1 axis likely contributes to the insulin resistance of puberty [28].

Genetic and epigenetic influences appear to affect the timing of gonadarche [29,30]. Studies of inherited GnRH-dependent precocious puberty have found that the *MKRN3* gene suppresses GnRH pulse generator activity [31]. A loss of function mutation in another gene associated with central precocious puberty, delta-like homolog 1 (*DLK1*), was identified in two sisters who had early menarche and PCOS [32].

With onset of gonadarche, LH stimulates theca cell androgen synthesis while FSH stimulates aromatase expression and estrogen synthesis by granulosa cells. A normal menstrual cycle is characterized by rising estradiol sufficient to provoke the LH surge and ovulation followed by progesterone secretion by the corpus luteum which slows GnRH frequency and therefore that of LH. The gonadal hormones, estrogen and progesterone, feedback to the hypothalamic-pituitary components of the HPG axis [33]. During the first

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two gynecologic years, most menstrual cycles are anovulatory. Subsequently, coordinated maturation of HPO axis occurs culminating in monthly ovulatory cycles [34]. Despite this transient period of oligomenorrhea, most girls subsequently develop normal HPG axis function.

AMH, a glycoprotein secreted by granulosa cells, modulates ovarian function. AMH slows the transition from primordial to primary follicles to avoid over-recruitment of growing follicles [35,36,37]. In the normal ovary, the delicate balance between AMH, theca cell derived androgens, and estradiol governs follicular growth and dominant follicle selection [38,39]. Circulating AMH concentrations are higher in women with PCOS compared to women without PCOS [40]. The increased serum AMH concentrations are attributed to both an increased number of ovarian secondary preantral follicles and increased AMH secretion per follicle in women with PCOS [41,42]. Higher AMH concentrations persist during pregnancy especially among lean hyperandrogenic women with PCOS [43,44]. It has been suggested that elevated maternal AMH concentrations during pregnancy facilitate placental transfer of maternal androgens contributing to a hyperandrogenic environment for the female fetus [45]. Preclinical data have demonstrated that AMH increases GnRH and LH secretion suggesting that AMH can influence GnRH neuronal migration and GnRH secretion [46, 47, 48].

Adrenarche

Adrenarche is characterized by the development of pubic hair, apocrine body odor, axillary hair, and acne. Adrenarche begins between ages 6–8 years when DHEAS concentrations rise. The proximate signals responsible for the onset of adrenarche remain unknown and appear to be distinct from the signals regulating gonadarche [49]. The physiologic mechanisms governing adrenal zona reticularis C19 steroid secretion also remain unknown; no initiating factors, feedback loops, or regulatory mechanisms have been validated. Available data regarding the relationships between early/premature adrenarche and PCOS are inconsistent [1].

Several common themes emerge when considering features of puberty in girls and PCOS. These themes, neuroendocrine features, androgen exposure, and insulin sensitivity will be discussed below.

Neuroendocrine features

Despite the ongoing mystery regarding the proximate stimulus for puberty, the onset of this developmental period reflects the dynamic integration of stimulatory and inhibitory factors incorporating a variety of inputs to modulate GnRH secretion via the GnRH pulse generator. Sophisticated neuroendocrine networks integrate hormonal, metabolic, nutritional, and environmental signals.

Whereas LH and FSH are synthesized in the same cell, GnRH pulse frequency modulates LH and FSH secretion. Increased GnRH pulse frequency is associated with increased LH secretion relative to FSH secretion [50]. Most women with PCOS have persistent rapid LH pulse frequency, increased LH pulse amplitude, and increased GnRH-stimulated LH

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response. These increased GnRH and LH pulse frequencies drive the theca cells to produce androgens. The increased GnRH pulse frequency decreases FSH concentrations leading to diminished granulosa cell aromatase expression, insufficient conversion of androgens to estradiol and failure to select a dominant follicle.

Women with PCOS required higher concentrations of estradiol and progesterone to suppress LH secretion [51]. Flutamide treatment restored the ability of estradiol and progesterone to suppress LH secretion suggesting that androgens interfere with estrogen and progesterone negative feedback inhibition [52]. However, progesterone insensitivity was inconsistent among obese hyperandrogenic mid-late pubertal girls (Tanner 3–5) [53].

Androgens may influence feedback regulatory loops during different developmental windows and may affect neuronal sites likely upstream of the GnRH neurons. The importance of AR-mediated action in development of PCOS is evident because prenatally androgenized AR knockout mice did not develop PCOS like symptoms [54]. Curiously, neuron-specific AR knockout mice failed to develop PCOS-like symptoms emphasizing the likely importance of neuroendocrine interactions in the development of PCOS [55].

In nonhuman primates, administration of a GABA receptor blocker, bicuculline, led to increased kisspeptin production and earlier onset of gonadarche suggesting that GABA may be a component of the neurobiological brake that delays the onset of gonadarche [56]. Using GnRH-GFP prenatally androgenized mice, increased GABAergic post-synaptic currents in GnRH neurons, elevated dendritic spine density, increased GABAergic contact to GnRH neurons were found in prepubertal female mice indicating that prenatal androgen exposure was able to direct physical changes in the female GnRH neuronal network [57,58]. Anti-androgen treatment reversed these changes suggesting system plasticity; partial restoration of reproductive cycles also occurred [57].

The specific neurobiologic mechanisms and neuronal populations responsible for increased GnRH and LH pulse frequencies in women with PCOS are poorly defined. Consistent with the hypothesis that NKB plays a role in GnRH pulse generation, short term treatment of women with PCOS with an NK3 receptor antagonist, AZD4901, decreased LH pulsatility and testosterone concentrations [59].

Available clinical data also suggest that GABA influences GnRH neuron activity either directly or indirectly. Women with PCOS have higher CSF concentrations of GABA [60]. Medications such as valproate are associated with increased CNS GABAergic tone and risk to develop PCOS-like clinical features. These findings suggest that increased NKB and/or GABA signaling could modulate hypothalamic neurobiology to promote increased GnRH and LH secretion. This finding introduces a potential conundrum in that GABA appears to interfere with LH secretion as a component of the neurobiologic brake to delay gonadarche while later promoting GnRH and LH secretion in women with PCOS.

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Androgen Exposure

Ovarian androgen

During puberty, circulating androgen concentrations increase due to increasing ovarian (and adrenal) androgen secretion. Clinical manifestations include acne, apocrine body odor, and sexual hair growth. The function and the molecular signature of PCOS theca cells differ from normal theca cells [61]. Specific primary differences include increased expression of CYP17A1, CYP11A1, and vascular cell adhesion molecule 1 (VCAM1) and increased androgen biosynthesis [62].

GWAS have identified several loci near genes that could modulate theca cell androgen production including *DENND1A*, *LHCGR* and *RAB5B*. Expression of the alternatively spliced variant, DENND1A.V2, is higher in theca cells obtained from women with PCOS compared to theca cells from normal women. Forced over-expression of this splice variant, DENND1A.V2, in normal theca cells recapitulated a PCOS phenotype with increased androgen production and increased *CYP17A1* expression. Conversely, knockdown of this variant in PCOS theca cells decreased androgen production and *CYP17A1* expression [63].

Available data suggest that LHCGR, RAB5B, and DENND1A.V2 interact to promote ovarian theca cell androgen synthesis [64]. Comparison of miRNA expression profiles from women with and without PCOS showed decreased miR-130b-3p expression in PCOS theca cells; decreased miR-130b-3p was correlated with increased DENND1A.V2 and CYP17A1 expression and DHEA accumulation [65]. The molecular basis for the increased DENNDA1.V2 expression, decreased miR-130b-3p expression, and the dissimilar transcriptome signatures in PCOS theca cells are poorly defined. These findings are consistent with the ovary being a primary source of androgen excess in PCOS [66]. However, the possibility that excessive ovarian androgen production is secondary to neuroendocrine influences cannot be excluded.

Congenital Adrenal Hyperplasia (CAH)

The virilizing CAHs are autosomal recessive disorders characterized by decreased glucocorticoid synthesis, increased ACTH secretion, and increased C19 adrenal steroid secretion [67]. The most common form is 21-hydroxylase deficiency due to mutations in the 21-hydroxylase (*CYP21A2*) gene. Women on adequate hormone replacement therapies generally have monthly menses and normal gonadotropin concentrations. Daughters of women with CAH are not virilized at birth due to the efficiency of placental aromatase to prevent placental transfer of maternal androgens.

However, some women with CAH develop secondary ovarian hyperandrogenism associated with elevated adrenal C19 steroid and progesterone concentrations [68]. In this situation, the finding of elevated progesterone concentrations in CAH raise questions regarding the mechanisms responsible for the proposed progesterone insensitivity in hyperandrogenic women [69]. Women with CAH may be predisposed to secondary ovarian hyperandrogenism as a consequence of prenatal androgen programming [70]. Another possibility is that persistently increased post-natal C19 adrenal steroid secretion disrupts neuroendocrine feedback leading to increased GnRH and LH pulse frequency [71].

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Developmental origins of disease are well established [72,73]. For female fetuses, maternal and fetal exposures to excessive androgen concentrations, nutritional excess, hyperglycemia, and other factors during critical prenatal developmental windows could program neurobiological circuitry [74]. In other words, hormones and other factors organize an enduring property (organizational effects) that may be induced by specific subsequent exposures (activational effects) [75,76]. For example, maternal metabolic dysfunction could compromise placental function resulting in fetal hyperandrogenism and hyperinsulinemia for the female fetus [77]. Another example involves the small for gestational age (SGA) infants who manifest increased DHEAS concentrations, functional ovarian hyperandrogenism, hyperinsulinemia, and rapid post-natal weight gain [78]. The Northern Finland Birth Cohort Study reported with women with PCOS had lower birth weights, earlier adiposity rebound, and greater BMI values [79].

Transgender

Female to male transgender patients are treated with testosterone to induce masculinization and suppression of menses. Most transmales aim to maintain testosterone concentrations in the normal male range. Testosterone, in this scenario, decreases LH concentrations leading to amenorrhea. Uncertainties and inconsistencies exist regarding how testosterone treatment affects ovarian morphology and ovarian function. Data are accumulating to resolve questions about the effects of testosterone treatment on HPO axis function. Successful oocyte retrieval was reported for 16 transmales on testosterone treatment who desired fertility and stopped testosterone 4–6 months prior to undergoing oocyte retrieval. In this small cohort, several years of gender-affirming testosterone treatment did not prevent successful oocyte retrieval [80]. Planned pregnancies, successful oocyte retrieval and live births have been reported in transmen following female-to-male gender transition [81,82]. Thus, in the natal female lacking *in utero* testosterone exposure/imprinting, the HPO axis readily resumes normal function when testosterone therapy is discontinued. These data suggest that testosterone treatment in adult post-pubertal females does not permanently program or activate the neuroendocrine mechanisms controlling GnRH and gonadotropin secretion. Thus, resumption of ovulatory cycles in transgender males emphasizes the importance of ongoing androgen exposure to induce and maintain a PCOS phenotype.

Preclinical Models

Numerous animal models involving prenatal, neonatal, juvenile, and peri-pubertal androgen excess have been studied.[83] Early-to mid-gestation prenatal androgen exposure in nonhuman primates led to reproductive and metabolic PCOS-like features including irregular menses, adipogenic restraint, and pancreatic dysfunction [84,85,86]. Additional studies have expanded and developed the hypothesis that *in utero* androgen exposure plays a substantial role in the molecular pathogenesis of PCOS [87]. Recently, a naturally occurring hyperandrogenic nonhuman primate population has been reported and detailed investigation of this interesting cohort in the future offers the potential to clarify the hormonal, genetic, epigenetic, and environmental factors associated with PCOS-like traits [88,89].

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Hyperinsulinemia, Insulin Resistance, and Obesity

Women with PCOS experience insulin resistance, hyperinsulinemia, and obesity. The extent of the insulin resistance is independent of obesity or changes in body composition [90,91]. Lean women with PCOS have insulin resistance and hyperinsulinemia. The insulin resistance and hyperinsulinemia have been attributed to impaired insulin signal transduction with compensatory increased pancreatic beta cell insulin secretion. Alternatively, however, primary hyperinsulinemia can precede development of peripheral tissue insulin resistance. In addition, androgens may impair insulin clearance contributing to hyperinsulinemia [92]. It is beyond the scope of this article to contrast these perspectives [93].

Insulin resistance is characterized by impaired insulin actions affecting glucose and lipid metabolism whereas its mitogenic actions are generally unimpaired contributing to the paradox of insulin signaling in PCOS. Despite impaired insulin action affecting liver, skeletal muscle, and adipose tissue, the pituitary and steroid secreting tissues remain insulin sensitive [94,95]. Elevated insulin concentrations act as a co-tropic hormone at the ovary and the adrenal to promote C19 steroid secretion. Weight gain appears to be one exacerbating factor in the pathogenesis of PCOS; in one series of 15 year old girls, higher BMI values were associated with persistent oligomenorrhea at age 18 years [96]. The important roles of insulin resistance and hyperinsulinemia in the pathophysiology of PCOS are evident when insulin sensitivity is improved by weight loss or pharmacologic agents, decreased insulin and androgens concentrations and improved ovarian function ensue [97].

Studies suggest that beta cell function and insulin sensitivity may differ beginning in childhood and early adolescence for girls likely to develop PCOS [98,99]. First degree 8–12 year old relatives of women with PCOS have insulin resistance and beta cell dysfunction when compared to age- and BMI-matched girls unrelated to women with PCOS [10,100]. One preclinical study found that adult female rats exposed to androgen excess developed hyperinsulinemia due to increased insulin gene transcription in pancreatic β cells [101].

Adipose tissue secretes hormones influencing the liver, skeletal muscle, pancreas, and brain [102]. Per the adipose tissue expandability hypothesis, nutrient excess and insufficient adipose tissue fat storage lead to hypoxia, lipotoxity, inflammatory changes, insulin resistance, ectopic fat storage, *de novo* hepatic lipogenesis, and hepatic steatosis [103,104]. Importantly, a bidirectional mendelian randomization study showed that increasing BMI leads to PCOS whereas, conversely, PCOS does not intrinsically increase BMI [105,106].

Adipocytes express enzymes that activate and inactivate androgen precursors such as aldo-ketoreductase type 1C (AKR1C3) which converts androstenedione to testosterone. Insulin increased AKR1C3 expression and androgens increased lipid accumulation in adipocytes [107]. Androgens inhibit early-stage human subcutaneous abdominal adipogenesis *in vitro*; if this occurs *in vivo*, the stage is set for ectopic fat distribution and lipotoxicity [108]. Hence, increasing BMI leading to systemic hyperinsulinemia could initiate a persistent cycle of adipocyte androgen production, lipotoxicity, and metabolic dysfunction ultimately affecting neuroendocrine function [109].

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Conclusions

Beginning during early post-menarcheal years, some girls enter a trajectory towards persistent hyperandrogenism, irregular menses, anovulation, and polycystic ovary morphology [110,111]. This PCOS trajectory seems to be activated concurrently with the onset of gonadarche and adrenarche associated with increasing circulating LH, FSH, and C19 steroid concentrations. Eventually, girls maturing along the PCOS trajectory may evolve to fulfill diagnostic criteria for the definitive syndrome [1].

The full biology underlying development of PCOS is remains unclear. Genetic and epigenetic factors, prenatal programming particularly by androgen exposure, hypothalamic mechanisms governing GnRH pulsatility, chronic exposure to mildly elevated postnatal androgen concentrations, hyperinsulinemia, and nutritional excess have been implicated in the pathophysiology of PCOS [112]. Persistent hyperandrogenism, hyperinsulinemia, insulin resistance, elevated AMH concentrations, nutrient excess, and other factors likely maintain this self-perpetuating cycle. At the current time, prevention of this vicious cycle of HPO axis dysfunction through healthy lifestyle interventions is essential [113].

Resumption of HPO axis function in transgender males treated with gender affirming testosterone treatment following withdrawal of androgen replacement has been reported. Hence, post-pubertal androgen excess alone does not appear to imprint the neuroendocrine axis governing gonadarche and HPO axis function. Returning to the question, does PCOS interfere with normal pubertal transition? Based on available data, especially regarding resumption of HPO axis function in transmen, pubertal HPO axis function appears to activate the transition to PCOS in those with underlying and ongoing susceptibility factors. Further investigation will be helpful to delineate the specific mechanisms and interactions between gonadarche, adrenarche, and PCOS.

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non-NIH Rotterdam criteria. The variants identified were associated with hyperandrogenism, gonadotropin regulation, and testosterone levels in affected women.

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Areas for investigation:

1. What is the underlying neurobiology driving the increased GnRH and LH secretion associated with PCOS? Specifically, are the kisspeptin neurons in the infundibular nucleus programmed by *in utero* androgen exposure? If so, what causes the prenatal androgen exposure?
2. Are androgens downstream mediators of primary neuroendocrine dysregulation?
3. What, if anything, is the role of progesterone insensitivity? What is the mechanism of progesterone insensitivity? Does GABA signaling affect progesterone sensitivity? Does GABA signaling differ before and after gonadarche?
4. What is the molecular basis for insulin resistance in PCOS and what is its relationship to the transient insulin resistance during puberty ?
5. What factors influence outcomes: normal reproductive function vs PCOS?
6. How can high risk adolescent girls be identified, and when can preventative measures be instituted to safeguard reproductive and metabolic health in adulthood?