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Neuroendocrine dysfunction in polycystic ovary syndrome

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Abstract

Polycystic ovarian syndrome (PCOS) is a common disorder characterized by ovulatory dysfunction and hyperandrogenemia (HA). Neuroendocrine abnormalities including increased gonadotropin-releasing hormone (GnRH) pulse frequency, increased luteinizing hormone (LH) pulsatility, and relatively decreased follicle stimulating hormone contribute to its pathogenesis. HA reduces inhibition of GnRH pulse frequency by progesterone, causing rapid LH pulse secretion and increasing ovarian androgen production. The origins of persistently rapid GnRH secretion are unknown but appear to evolve during puberty. Obese girls are at risk for HA and develop increased LH pulse frequency with elevated mean LH by late puberty. However, even early pubertal girls with HA have increased LH pulsatility and enhanced daytime LH pulse secretion, indicating the abnormalities may begin early in puberty. Decreasing sensitivity to progesterone may regulate normal maturation of LH secretion, potentially related to normally increasing levels of testosterone during puberty. This change in sensitivity may become exaggerated in girls with HA. Many girls with HA—especially those with hyperinsulinemia—do not exhibit normal LH pulse sensitivity to progesterone inhibition. Thus, HA may adversely affect LH pulse regulation during pubertal maturation leading to persistent HA and the development of PCOS.

Keywords

Polycystic ovarian syndrome; Gonadotropin releasing hormone; Obesity; Puberty; Hyperandrogenemia; Neuroendocrine

1. Introduction

Polycystic ovary syndrome (PCOS) is a common disorder affecting 6–8% of reproductive age women and is characterized by hyperandrogenemia (HA), oligo-anovulation, and polycystic ovarian morphology. This disorder is also associated with infertility, hirsutism,

acne and obesity, in addition to an increased risk of the metabolic syndrome, insulin resistance, and type 2 diabetes mellitus [1–3]. Although PCOS is the leading cause of anovulatory infertility and one of the most prevalent endocrine disorders in women, its etiology remains unclear. The symptoms of PCOS often begin during or shortly after puberty, indicating that the pathophysiology of PCOS likely begins during or before puberty [4–6].

While this condition is well-recognized clinically, there is some controversy surrounding the precise clinical definition of PCOS given its variable clinical presentations. It is clinically defined by ovulatory dysfunction and hyperandrogenism—with or without polycystic ovarian morphology on ultrasound—with the exclusion of other conditions of androgen excess or ovulatory disorders. The National Institutes of Health (NIH), Rotterdam consensus group [7,8], and the Androgen Excess Society have all proposed different criteria for the clinical diagnosis of PCOS. The guidelines of the Androgen Excess Society (AES) affirm the heterogeneity of the disorder but require the presence of HA, recognizing that androgen excess is the hallmark of PCOS. Their criteria for diagnosis include the presence of all three of the following criteria: clinical and/or biochemical hyperandrogenism, ovarian dysfunction (i.e., oligo-anovulation and/or polycystic ovarian morphology) and exclusion of other androgen excess or ovulatory disorders [9]. For the purposes of this review, clinical research subjects who are adolescents with HA form the basis for the theses presented.

The criteria for PCOS in adolescents follow the same clinical guidelines as those for adults. Diagnosis, however, is complicated by the fact that it is often difficult to differentiate physiologic anovulation—common in girls immediately after menarche—from true ovulatory dysfunction. Secondly, ultrasound diagnosis of ovarian morphology is problematic in young girls. Trans-abdominal ovarian ultrasound, especially in obese individuals, is less sensitive for identifying polycystic ovaries compared to trans-vaginal ultrasound, which may be undesirable in virginal girls [10]. Moreover, polycystic ovarian morphology on ultrasound may be found in half of normal adolescent girls, suggesting that it could be a variant of normal or a normal developmental stage during puberty [11]. Despite these problems, early recognition of the condition, particularly HA, in adolescent girls is critically important for understanding the under-pinnings of the disorder. In this review, we present evidence that the neuroendocrine hormonal dysregulation associated with PCOS begins before or during pubertal maturation.

2. Neuroendocrine abnormalities in PCOS

While the etiology of PCOS is uncertain, neuroendocrine abnormalities including increased gonadotropin-releasing hormone [GnRH] pulse frequency and hence luteinizing hormone [LH] pulsatility and relative follicle stimulating hormone [FSH] deficiency are a nearly universal finding in PCOS and contribute to its pathogenesis [12,13]. Women with PCOS demonstrate persistently rapid GnRH pulse frequency, which in contrast to normal ovulatory cycles, has lost its typical pattern of slowing during the luteal phase of their often anovulatory cycles. Normal luteal slowing of GnRH and LH pulse frequency occurs via feedback inhibition by increased progesterone levels (in the presence of estradiol, which induces hypothalamic progesterone receptors [14]) during the luteal phase [15]. Previous studies using combined oral contraceptive pills and/ or progesterone showed that in the setting of HA, the sensitivity of the GnRH pulse generator to suppression by progesterone is impaired [16,17]. Recording directly from rodent-derived fluorescent labeled GnRH neurons in intact hypothalamic slices, progesterone (with estradiol) inhibits the firing of GnRH neurons. In the same model, dihydrotestosterone impairs the ability of progesterone to slow GnRH neuronal firing rates [18]. The persistently rapid GnRH pulse frequency favors LH production over FSH [19]. The increased LH pulse frequency subsequently promotes theca

cell production of androgens, while the relative FSH deficiency interferes with granulosa cell aromatization to estrogens and impairs follicle maturation and ovulation [20,21]. Thus a “vicious cycle” of excess androgen production and impaired GnRH suppression is created. Further evidence for a causal role of HA is seen in human studies using androgen receptor blockade with flutamide. In women with PCOS, GnRH pulse generator sensitivity to progesterone was restored to normal after 4 weeks of anti-androgen therapy [21]. Overall, these *in vitro* and *in vivo* studies support the idea that HA may play a key role in the neuroendocrine abnormalities seen in PCOS.

3. Importance of puberty in pathogenesis of PCOS

The origins of persistently rapid GnRH secretion are unknown but appear to evolve during puberty [22]. Changes in LH pulse patterns, similar to those seen in adult women with PCOS, are also seen in adolescent girls with HA at risk for PCOS. Early pubertal premenarchal girls with HA already demonstrate rapid GnRH pulse secretion [23], similar to adults. Further studies by McCartney et al. demonstrated that early pubertal obese girls with HA had enhanced daytime pulse secretion resulting in a more mature LH pulse pattern than non-HA girls at the same pubertal stage [24] (Fig. 1). Together, these studies suggest that abnormalities of LH secretion develop even before first menses.

4. Role of sex steroid feedback in normal puberty

Decreasing sensitivity to progesterone may play an important role in the regulation of LH secretion during normal puberty and the development of daytime LH pulses. Girls in early puberty have an exquisite sensitivity to progesterone inhibition, demonstrating almost complete extinction of LH pulse frequency after progesterone administration [25] (Fig. 2A). Later in puberty, this sensitivity to progesterone diminishes, as older adolescent girls show reductions in LH pulse frequency similar to normal adult women after exposure to progesterone [25] (Fig. 2B). In pubertal girls, we have observed a two-fold rise in progesterone levels overnight [24]. The timing of this overnight rise in progesterone may contribute to the daytime reduction of GnRH secretion observed in girls during early puberty. GnRH (and hence LH) secretion during daytime hours increases gradually as puberty progresses [23,24]. In normal puberty, decreased hypothalamic sensitivity to progesterone inhibitory feedback may play a role in the development of daytime LH pulses.

5. Role of androgens in sex steroid sensitivity during puberty

Our theories regarding the mechanism of this normal decrease in hypothalamic sensitivity to progesterone during puberty have originated from studies investigating origins of PCOS in HA girls. Half of adolescent girls with HA have impaired GnRH sensitivity to progesterone inhibition [25], again similar to adult women with PCOS [17]. If androgens interfere with progesterone feedback in adolescents as they do in adults, then androgens may contribute to the development of GnRH regulation abnormalities observed during pubertal maturation in HA girls. Although the scenario of HA involves exaggerated androgen levels, smaller increases in androgens during normal pubertal development may contribute to physiologic decreases in progesterone sensitivity seen in normal girls. Testosterone levels gradually increase during the course of puberty in normal girls [22,26]. Mitamura et al. demonstrated that testosterone levels are increased significantly in girls less than 1 year before breast development (thelarche) compared to values more than 1 year before thelarche. By the time of thelarche, morning levels of testosterone in girls reach similar levels as adult women [26]. If androgens during puberty impair progesterone inhibition of GnRH in a similar manner to adult women, then the gradual increase in testosterone levels during pubertal progression may gradually impair progesterone inhibition of daytime GnRH secretion (Fig. 3A). As the overnight rise in progesterone becomes less effective in suppressing GnRH frequency during

the next day, more GnRH/LH pulses might be observed during daytime hours leading to the eventual loss of the diurnal variation of GnRH pulses (Fig. 3B). This would lead to maintained daytime GnRH secretion and a longer duration of GnRH secretion over a 24-h period. Thus, normal early pubertal increases in androgen production may be important to the maturation of daytime GnRH pulses during normal puberty.

6. Source(s) of pre-pubertal androgens

The source of prepubertal androgens during normal maturation has yet to be determined. We propose that the first exposure to androgens normally arises from the adrenal glands and then subsequently from the ovaries. Adrenarche—a developmental stage of increased adrenal androgen production—either precedes or coincides with the onset of normal hypothalamic-driven puberty. Thus, adrenarche may provide the initial androgens required to impair steroid feedback, resulting in the extended daytime GnRH secretion observed during normal pubertal maturation. Normal adrenarche occurs at a time when ovarian sex steroid production is thought to be negligible. Further support for the importance of adrenal androgens is found in data from girls with premature adrenarche, who develop early axillary and pubic hair growth. Studies by Ibanez et al. suggest that they are at increased risk for subsequent ovarian HA and the development of PCOS [27,28]. These data lend support to the concept that girls with early or excess androgen exposure develop accelerated adult GnRH pulse patterns resulting in a premature loss of diurnal variation. Precise information on the amount of ovarian androgen production during early puberty is not available. Given that plasma estradiol levels are quite low before puberty, ovarian sex steroid production in general is probably low during this time. Therefore, the adrenal glands may be the initial source of androgen production in pre/ early pubertal girls.

Excess testosterone exposure before or during puberty may modify the set-point for steroid feedback at the hypothalamic level, predisposing girls to rapid GnRH/LH pulse frequency. The increased LH pulse frequency observed in pre- and post-menarchal girls with HA may be related to decreased sensitivity to progesterone inhibition (Fig. 3A and B). Approximately half of adolescents with HA have reduced LH pulse suppression after administration of progesterone [25] (Fig. 2C). This subset of girls may have a higher risk of progression to PCOS as adults. Thus a significant neuroendocrine abnormality contributing to increased LH pulse frequency in girls with HA is an impaired ability of progesterone to inhibit GnRH pulse secretion. The consequent persistently rapid GnRH pulse secretion favors LH and not FSH synthesis, maintaining androgen production and impairing normal follicular maturation during puberty (Fig. 4). Early exposure to excess testosterone may play a critical role in this reduced sensitivity to progesterone.

7. Role of insulin resistance in androgen excess

Pre- or peripubertal androgen excess—compared to levels during normal puberty—has several potential sources. Obesity and hyperinsulinemia may augment androgen secretion in adolescent girls. Insulin has been shown to act as a co-gonadotropin with LH, to promote ovarian androgen production in adult women with and without PCOS [29,30]. In addition, treatments that reduce hyperinsulinemia have been shown to decrease androgen levels and restore normal ovulation in women and adolescents with PCOS [31,32]. Seventy percent of obese girls (body mass index >95 percentile- for-age) have HA at all pubertal stages [33]. Thus, adolescent obesity with hyperinsulinemia may predispose to excess androgen production and PCOS in susceptible adolescents. Potentially, some girls may have enhanced adrenal or ovarian sensitivity to insulin due to inherited enzymatic differences. The susceptibility to impaired progesterone feedback may also be related to insulin resistance. While free testosterone levels were similar, insulin levels were elevated in girls insensitive

to progesterone compared to girls who remained progesterone sensitive [25,34]. Hyperinsulinemia is also associated with a decrease in SHBG levels leading to increased free testosterone levels [29]. In addition, treatments that reduce hyperinsulinemia have been shown to decrease androgen levels and restore normal ovulation in women and adolescents with PCOS [31,32]. The recent increase in obesity in children—with one in five girls aged 6–18 years meeting the criteria for obesity [35,36]—suggests that many more adolescent girls may have hyperinsulinemia and therefore be at risk for the development of HA and PCOS.

8. Timing of androgen exposure

The stage of maturation which HA affects these systems remains uncertain. Animal studies have shown that exposure to marked elevation of androgens during gestation, results in CNS and ovarian changes during subsequent puberty, which closely resemble those seen in PCOS [37,38]. Female rhesus monkeys, exposed to testosterone excess early in gestation, exhibit subsequent HA, oligomenorrhea, enlarged polyfollicular ovaries, LH hypersecretion, insulin resistance and abdominal obesity [38,39]. Sheep exposed to excess testosterone during gestation have high LH, anovulatory cycles and impaired progesterone inhibition of LH during subsequent maturation [40]. In young rodents, exposure to testosterone blocks estradiol induction of hypothalamic progesterone receptors [41]. Prenatal exposure to androgens in rats predisposes them to rapid GnRH neuron firing in adulthood, which is blocked by metformin [42]. In aggregate, animal studies provide compelling evidence that exposure to high levels of testosterone during gestation result in manifestations similar to those seen in adult women with PCOS.

Data for the relevance of prenatal androgen exposure to the development of LH abnormalities in humans is uncertain. A group of unselected adolescent girls showed no statistically significant relationship between maternal serum androgen levels during gestation and adolescent clinical hyperandrogenism or ovarian morphology [43]. However, elevated testosterone levels may be found in maternal plasma during pregnancies of selected women with PCOS [44]. In another study, umbilical vein testosterone levels were found to be elevated to male levels in female newborns born to women with PCOS [45]. Furthermore, daughters of women with PCOS have a higher prevalence of also developing PCOS in adulthood [46], suggesting that prenatal androgen exposure may predispose girls to PCOS. However, abnormalities in girls born to women with PCOS may begin much earlier, with manifestations as exaggerated adrenarche in childhood/early puberty [47] and elevations in LH and testosterone by late puberty [48]. Similarly, other disorders causing prenatal androgen exposure suggest a role for prenatal androgen exposure in polycystic ovary syndrome. Women with well-treated congenital adrenal hyperplasia, with excess androgen exposure during gestation but limited adrenal androgens postnatally due to glucocorticoid therapy, are at risk for elevations in LH levels [49]. Therefore, while present data are conflicting, it seems that prenatal exposure to HA in humans may have detrimental effects on neuroendocrine function later in life.

9. Conclusions

In summary, recent studies have identified the presence of distinct neuroendocrine abnormalities in women with PCOS. It remains unknown whether these are primary events or secondary to elevated androgen exposure before or during pubertal maturation. Impaired sex steroid feedback appears important in the development of persistently elevated GnRH pulse frequency secretion and hence LH drive to the ovary in older adolescents and adults. The disruption of the normal GnRH pulse pattern favors LH secretion over FSH, further enhances HA, impairs follicular development, and promotes progression to the PCOS

phenotype. Our data suggest that some girls who experience HA in early adolescence, already have impaired progesterone inhibition of GnRH pulse frequency during puberty, predisposing girls to ovarian androgen overproduction [25]. Antiandrogen treatment with flutamide improves the sensitivity to progesterone in adult women with PCOS. It remains unknown if an early intervention aimed at reducing androgen excess in girls during early puberty would maintain appropriate sex steroid-hypothalamic feedback and prevent the subsequent development of PCOS. Further studies are needed to investigate if other factors (such as insulin) enhance adrenal or ovarian androgen production in some girls during puberty. Determining which girls are at highest risk for the development of HA will be key to targeting strategies for the prevention of PCOS.

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Fig. 1.

Late evening [surrogate for daytime] and overnight luteinizing hormone (LH) pulse frequency characteristics in obese [defined as body-mass-index percentile- for-age >95] (solid) and non-obese (open) girls stratified by breast Tanner stage. Overnight LH pulse frequency is similar throughout pubertal maturation in nonobese girls. * $p < 0.05$ compared to baseline sample. ^a $p < 0.05$ compared to non-obese girls. Modified with permission from McCartney CR, Prendergast KA, Blank SK, Helm KD, Chhabra S, Marshall JC. Maturation of luteinizing hormone (gonadotropin-releasing hormone) secretion across puberty: evidence for altered regulation in obese peripubertal girls. *J Clin Endocrinol Metab* 2009;94:56–66 [24]; Copyright 2009, The Endocrine Society.

Fig. 2.

The percent change in luteinizing hormone (LH) pulse frequency per 11 h following 7 days of oral estradiol and progesterone in breast Tanner stage 1–2 normal control (NC) (A), Tanner 3–5 NC (B), and hyperandrogenemic (HA) (C) adolescent girls. The data are plotted as a function of mean plasma progesterone on day 7. The Tanner 1–2 subjects are labeled with the Tanner stages of the individual subjects. The shaded areas represent the ranges of responses to 7 days of oral estradiol and progesterone in NC adult women. T = testosterone. Modified with permission from Blank SK, McCartney CR, Chhabra S, Helm KD, Eagleson CA, Chang RJ, et al. Modulation of gonadotropin-releasing hormone pulse generator sensitivity to progesterone inhibition in hyperandrogenic adolescent girls—implications for regulation of pubertal maturation. *J Clin Endocrinol Metab* 2009;94:2360–6 [25]; Copyright 2009, The Endocrine Society.

Fig. 3.

(A) Schematic representation of testosterone levels and hypothesized changes in hypothalamic sensitivity to feedback inhibition by sex steroids in normal and hyperandrogenemic (HA) adolescent girls during puberty. (B) Schematic representation of the evolution in 24-h patterns of gonadotropin-releasing hormone (GnRH; solid line) and sex steroids (dashed line) during puberty in normal (top) and HA (bottom) girls. Shaded areas represent periods of sleep. Modified from Blank SK, McCartney CR, Marshall JC. The origins and sequelae of abnormal neuroendocrine function in polycystic ovary syndrome. *Hum Reprod Update* 2006;12(4):351–361 by permission of Oxford University Press [50].

Fig. 4.

Schema of proposed effects of hyperandrogenemia (HA) on gonadotropin-releasing hormone (GnRH) secretion and subsequent luteinizing hormone (LH) and follicle-stimulating hormone (FSH) production during puberty in susceptible adolescent girls. E₂, estradiol; P, progesterone. Modified with permission from Blank SK, McCartney CR, Helm KD, Marshall JC. Neuroendocrine effects of androgens in adult polycystic ovary syndrome and female puberty. *Semin Reprod Med* 2007;25:352–359 [51].