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Hyperandrogenemia in adolescent girls: origins of abnormal GnRH secretion

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Abstract

Polycystic ovarian syndrome is a common disorder characterized by ovulatory dysfunction and hyperandrogenemia (HA). Its origins begin peripubertally, as adolescent HA commonly leads to adult HA and decreased fertility. HA reduces inhibition of gonadotropin releasing hormone pulse frequency by progesterone, causing rapid LH pulse secretion and further increasing ovarian androgen production. Obese girls are at risk for HA and develop increased LH pulse frequency with elevated mean LH by late puberty. Many girls with HA 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.

Keywords

polycystic ovarian syndrome; gonadotropin releasing hormone; GnRH pulse generator; obesity; puberty; hyperandrogenemia; adolescent

Introduction

Polycystic ovarian syndrome (PCOS) is the leading cause of infertility, affecting approximately six to eight percent of reproductive-age women and is associated with obesity in 60% of affected women in the United States, insulin resistance and hyperinsulinemia in 50–70%, diabetes mellitus in 4–10%, and markers of cardiovascular disease risk in 33%.[1–3]

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Adolescents with PCOS have a 30–60% prevalence of metabolic syndrome, which is four to five times increased compared to age- and body mass index (BMI)-matched girls.[4] Hallmarks of PCOS are clinical and/or biochemical evidence of hyperandrogenemia (HA) (*i.e.* excessive acne, hirsutism, or elevated free testosterone (T) levels) and evidence of anovulatory cycles (*i.e.* oligo/amenorrhea). Different definitions of PCOS currently contribute to heterogeneity of clinical and pathophysiological features within the diagnosis. The National Institutes of Health (NIH) criteria (1990) require hyperandrogenism and ovulatory dysfunction, but not polycystic ovarian morphology. The Rotterdam criteria (2003) identify women having two out of three features: androgen excess, ovulatory dysfunction, and polycystic morphology on ovarian ultrasound. This definition is more inclusive, as HA is not a required feature of PCOS. The inclusion of ovarian morphology in the definition of PCOS has been less validated and may not be useful in adolescent girls. Enlarged ovarian volume occurs in 50% of asymptomatic adolescent post-menarcheal girls, likely a developmental stage of maximal ovarian size and a normal variant in most girls.[5] Therefore, the ability to discern abnormalities of morphological change in pubertal girls via ovarian ultrasound may be limited.

Evolution of PCOS

The origins of PCOS are possibly pre- or peri-pubertal, as clinical manifestations of the disorder frequently develop shortly after menarche. Both adolescents and adult women with PCOS have disruptions in the regulation of the gonadotropin releasing hormone (GnRH) pulse generator, characterized by rapid luteinizing hormone (LH) (and hence GnRH) pulsatility[6, 7] with impaired inhibition by progesterone.[8, 9] LH pulse sensitivity to slowing by progesterone can be restored in women with PCOS by antiandrogen therapy, suggesting that HA is responsible for the impaired feedback.[10] HA during adolescence is recognized as a forerunner to adult PCOS, since it is associated with higher androgen levels in adulthood and lower fertility rates.[11] Obese adolescents are at increased risk of HA[12] and later development of PCOS.[13]

In-utero factors have been suggested by Barker and others to be an important contributor to insulin resistance and HA. Animal models support this idea, as intrauterine androgen exposure in primates[14] and sheep[15, 16] cause changes in LH secretion, LH pulse sensitivity to progesterone feedback, and insulin metabolism, especially when the animals are overfed postnatally.[16] Low birth weight seems to be a factor in the development of PCOS in some girls in Spain and Italy.[17, 18] However, studies in Finland, Amsterdam, and the United Kingdom have not supported this relationship in their populations.[13, 19, 20]

Role of hyperandrogenemia

In premenopausal women, approximately half of circulating T is derived from peripheral conversion of androstenedione, particularly in adipose tissue,[21] with the remaining derived from ovarian and adrenal sources. Obesity alone increases androgen production, since adipose tissue, particularly from the abdominal region, has enzymes of steroidogenesis.[22] LH is a major physiologic stimulus for ovarian androgen production from theca cells. Additionally, hyperinsulinemia related to obesity can contribute to HA through several mechanisms. Insulin can act as a co-gonadotropin with LH on ovarian theca cells to increase androgen production,[23, 24] can increase adrenal responsiveness to ACTH for further androgen production,[25] can potentiate hCG-mediated ovarian follicle arrest,[26] and can cause pituitary hyperresponsiveness to GnRH for increased LH secretion in *in vitro* studies.[27] Women with PCOS often have elevated LH and insulin levels and are obese, leading to compounded mechanisms for increased androgen production.

HA is associated with excess weight during puberty,[12, 28, 29] with a prevalence between 60–94% in our cohort of obese girls (BMI-for-age ≥95%),[12] and can be ameliorated with weight loss.[28, 29] Circulating androgen levels normally rise slightly during puberty, with early morning elevations of serum T seen in prethelarchal girls.[30] In normal weight pubertal girls, levels of total T increase and sex hormone binding globulin (SHBG) decrease, leading to higher circulating free T levels.[12, 28] Obese girls have even higher levels of T, with diminished SHBG throughout all stages of puberty, leading to marked elevations of free T (Fig. 1).[12] Dehydroepiandrosterone sulfate (DHEA-S), an adrenal androgen, is modestly increased in obese compared to normal weight girls in early puberty, but differences disappear by the end of puberty.

Hyperandrogenemia and the GnRH pulse generator

GnRH pulse frequency designates preferential production of LH (via high frequency pulses) versus follicle stimulating hormone (FSH) (via low frequency pulses) in normal adult women.[31] Pulse frequency is regulated by progesterone in the presence of estradiol[8] such that increased progesterone production by the corpus luteum slows LH pulse frequency to favor FSH production, which aids in follicular development for the next menstrual cycle (Fig. 2). Women with PCOS have abnormally rapid LH pulses with reduced response to progesterone feedback,[8] contributing to elevations in serum LH:FSH ratios. Since LH stimulates theca cell steroid production and FSH regulates follicular conversion of androgen to estrogen, this relative increase in LH leads to increased ovarian androgen synthesis with limited aromatization to estradiol. The resultant increase in serum T contributes to maintaining increased LH pulse frequency,[10] creating a vicious loop leading to production of more ovarian androgens.

Clues to the etiological factors related to the instigating events leading to PCOS might be learned from adolescents. In girls, LH is independently and positively correlated with free T when adjusting for age, pubertal stage, BMI, DHEA-S, and insulin.[28] This might suggest that pre-existing neuroendocrine abnormalities affecting LH production during puberty lead to HA. Alternatively, HA might impair inhibition of the GnRH pulse generator, leading to high frequency pulses that favor LH production. Therefore, further study of normal and abnormal development of GnRH pulse generator regulation during puberty may help discern more precise etiological mechanisms for the HA in PCOS.

The maturation of the GnRH pulse generator undergoes a typical developmental progression during childhood. During infancy in girls, the GnRH pulse generator is active, producing FSH to high adult levels by about two months of age and LH to early pubertal levels by about four months of age, which both then decrease slowly over the first year to prepubertal levels finally by four years.[32] As early as age five to six years (prethelarchal), small pulses of LH (and by inference GnRH) can be seen intermittently throughout the day with pulses of increased amplitude entrained to sleep,[30, 33, 34] which are quite sensitive to progesterone inhibition.[9] These augmented nighttime LH pulses are associated with overnight increases in sex steroid production (primarily progesterone and T), which diminish during the following daytime hours.[30, 35] As puberty progresses, LH pulses gain increasing amplitude and frequency initially throughout the nighttime hours and then during the day.[34, 35] By the end of puberty, daytime LH pulses have higher frequency than nighttime pulses with increased amplitude during sleep (Fig. 3).[34, 35]

Girls with obesity, however, have altered maturation of the GnRH pulse generator (Fig. 3). Initially, their LH pulses have lower amplitude and frequency overnight compared to normal weight girls, consistent with lower mean LH concentrations.[35] By mid-puberty, however, they surpass normal weight girls in LH pulse frequency during both day and night, although

their pulse amplitude and mean LH concentrations remain lower. By the end of puberty, obese girls have significantly higher LH pulse frequency which diminishes only slightly with sleep. Although they still have lower LH pulse amplitude, their mean LH concentrations have now become elevated as in adults with PCOS, likely reflecting the increased LH pulse frequency. Obese girls with clinical evidence of PCOS have even less nighttime diminution of LH pulse frequency, greater pulse amplitude, and significantly higher mean LH concentrations compared to obese girls of similar pubertal stage without clinical evidence of PCOS. Perhaps this designates a continuum of developmental LH pulse abnormalities during puberty which leads to adolescent PCOS symptoms in more affected individuals.

Possible mechanisms for abnormal development of GnRH pulse regulation

During early puberty, the GnRH pulse generator is exquisitely sensitive to inhibition by progesterone. LH pulses are essentially abolished by administered progesterone during early pubertal stages.[9] As puberty progresses, normal girls exhibit reduced sensitivity to progesterone inhibition, similar to normal adult women (Fig. 4). In adolescents with HA, however, approximately 60% do not appropriately suppress LH pulsatility after progesterone administration, similar to adult women with PCOS (Fig. 4).[9] Interestingly, in girls with HA, the reduction in LH pulse frequency after progesterone decreases with increasing fasting insulin levels, suggesting that hyperinsulinemia may further contribute to impaired GnRH regulation.[9]

Progressively diminishing sensitivity to inhibition by progesterone may help determine the developmental patterns of the GnRH pulse generator during puberty. Progesterone levels increase overnight during early puberty in normal girls at the same time as the development of detectable sleep-associated LH pulses.[35] The following day progesterone again falls to lower levels. In subsequent stages of puberty, daytime progesterone levels diminish to a lesser degree with a continued slight rise overnight.[35] The overnight rise of progesterone may contribute to the subsequent suppression of daytime LH pulses during early puberty through exquisitely sensitive feedback inhibition. Free T has a similar overnight rise in plasma,[30] whereas estradiol does not; however, levels of both hormones increase during daytime as puberty progresses (Fig. 5).[35]

Given that androgens decrease feedback inhibition of LH pulsatility by progesterone in adult women with PCOS,[10] we hypothesize that increasing androgen levels throughout puberty gradually impair the inhibitory effects of the overnight rise in progesterone. This would result in progressive daytime increases in LH pulsatility, as is seen in normal weight girls as they progress through puberty (Fig. 3). In obese girls with HA, increased androgen levels may further impair the normal patterns of progesterone inhibition during puberty, leading to earlier development of elevated daytime LH pulsatility.[7] Over time, this change in the maturational pattern of LH pulses could enhance ovarian androgen production, especially in later puberty, leading to a symptomatic PCOS phenotype.

Further studies are needed to elucidate the precise mechanisms for the development of abnormal GnRH regulation in obese girls. The source of overnight increases in progesterone is unclear, since ovarian hormone production is thought to be minimal in early puberty. Alternatively, the adrenal gland and not the ovary may be responsible for this diurnal variation in progesterone levels, similar to diurnal cortisol variability. The role of androgens in decreasing progesterone sensitivity during pubertal maturation and the impact of progesterone inhibition also remain to be demonstrated. Studies to determine whether antiandrogen administration to obese girls could restore sensitivity to progesterone and normalize development of LH pulsatility are required to establish this concept.

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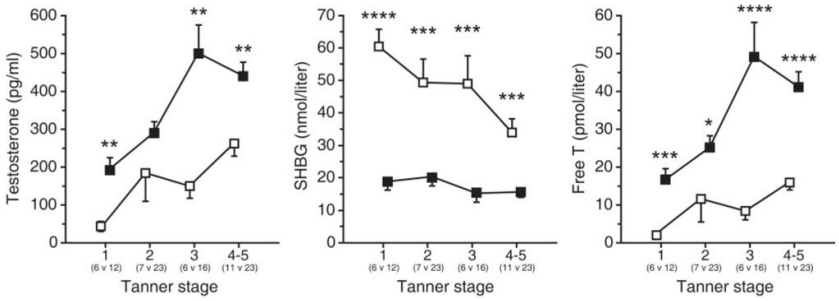

Fig. 1.

Early morning hormone levels in nonobese (*open squares*) and obese (*solid squares)* peripubertal girls by breast Tanner stage. Data are presented as mean ± SEM. Differences were assessed with Wilcoxon rank sum tests before Bonferroni correction: * $p < 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, *** $p \leq 0.0001$. Conversion from conventional to SI units: total T × 3.47 (nmol/L). (McCartney *et al*, 2007,[12] adapted with permission from The Endocrine Society.)

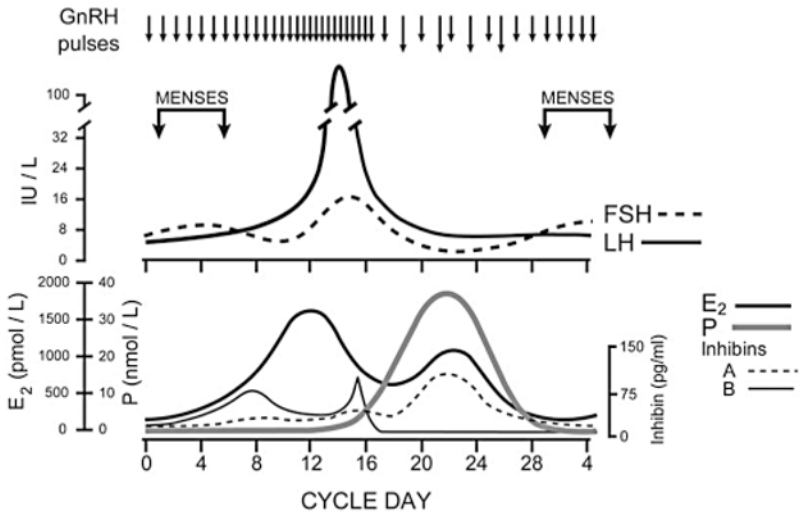

Fig. 2.

Schematic diagram of hormonal patterns during an ovulatory menstrual cycle. (Marshall JC and Eagleson CA, 1999,[36] with permission from Elsevier.)

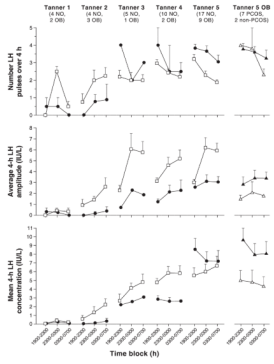

Fig. 3.

Late evening and overnight LH characteristics in nonobese (*open squares*) and obese (*solid circles)* peripubertal girls by breast Tanner stage. Data are presented as mean ± SEM. The numbers of subjects are *below* the Tanner stage labels: NO = nonobese, OB = obese. The last column shows *obese Tanner 5 girls only* with PCOS (*solid triangles)* and without PCOS (*open triangles*). Due to blood volume constraints, time point 1900–2300 (subject awake) is used as a surrogate for daytime hormone levels. (McCartney *et al*, 2009,[35] with permission from The Endocrine Society.)

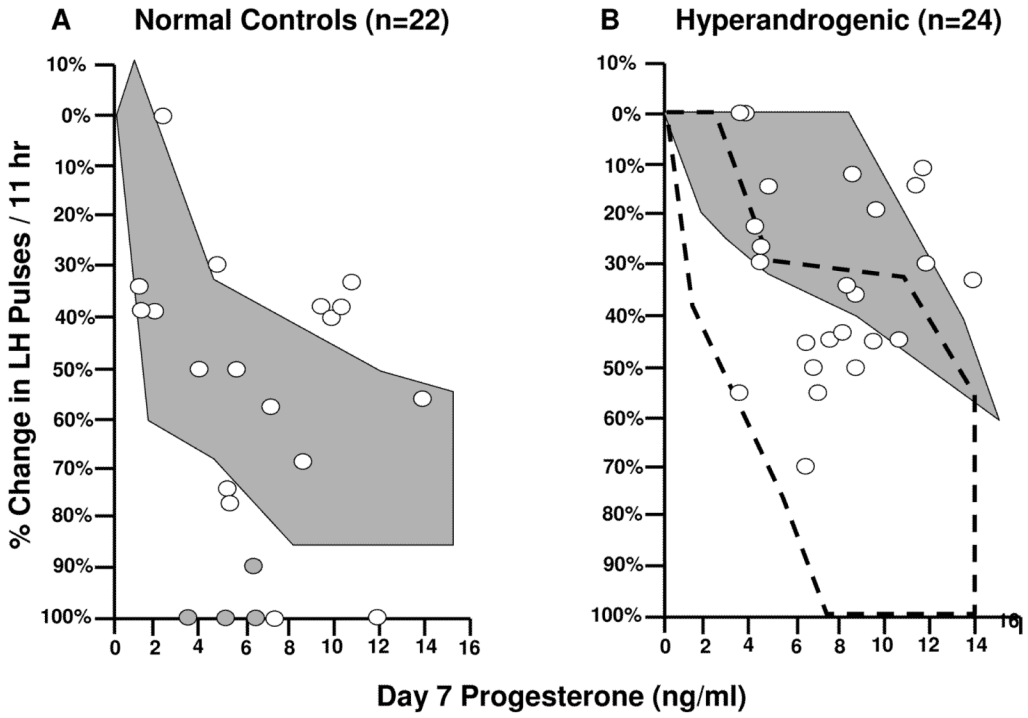

Fig. 4.

Percent change in LH pulse frequency during 11 hr following 7 days of oral E_2 and P plotted as a function of mean plasma P on day 7 in control (A) and HA (B) adolescent girls. Shaded circles represent girls with breast Tanner stage 1–2; open circles represent girls with Tanner stage 3–5. The shaded background areas represent range of response to a similar protocol in adult control women (A) and women with PCOS (B). The outlined area in B represents the range of responses in control adolescent girls. Conversion from conventional to SI units: P × 3.18 (pmol/L). (Blank *et al*,[9] 2009, with permission from The Endocrine Society.)

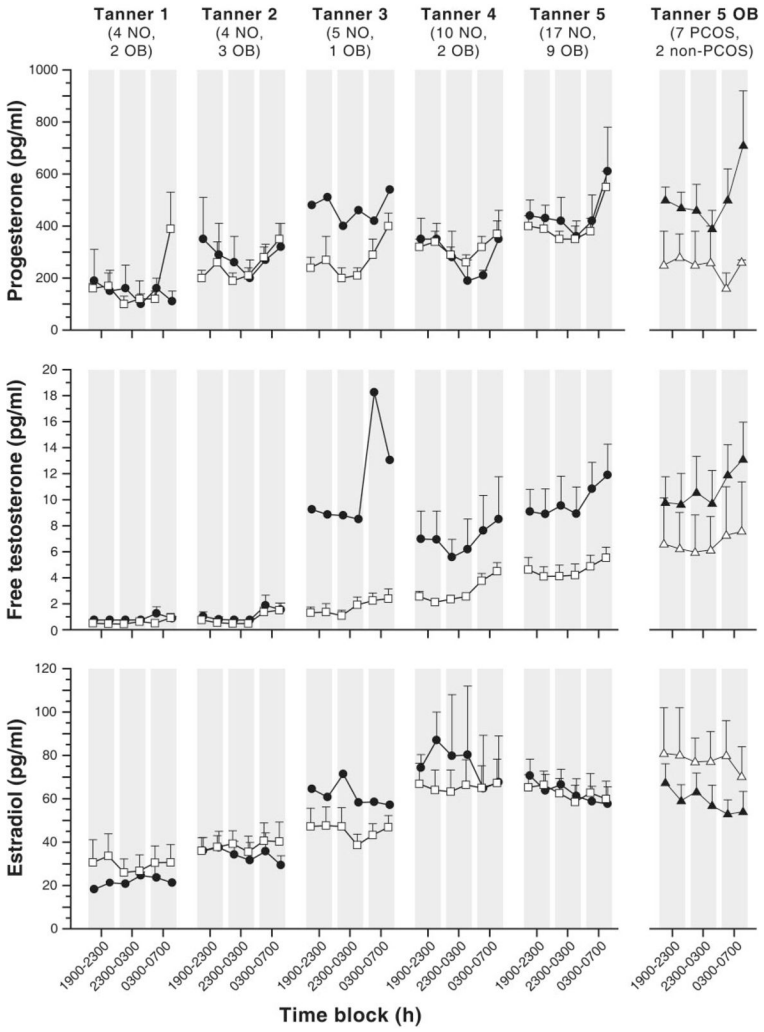

Fig. 5.

Late evening and overnight sex steroid concentrations in nonobese *(open squares)* and obese (*solid circles*) peripubertal girls by breast Tanner stage. Data are presented as mean ± SEM. The numbers of subjects are *below* the Tanner stage labels: NO = nonobese, OB = obese. The last column shows *obese Tanner 5 girls only* with PCOS (*solid triangles)* and without PCOS (*open triangles*). Conversion from conventional to SI units: P × 3.18 (pmol/L); free T (pmol/L); E_2 × 3.671 (pmol/L). (McCartney *et al*, 2009,[35] with permission from The Endocrine Society.)