Reproductive endocrinology of adolescent polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among reproductive-aged women, and it typically presents during adolescence. The objective of this review is to describe the clinical manifestations of PCOS in adolescent girls and the underlying basis for the altered reproductive physiology. Recognising adolescents at risk for PCOS and taking the appropriate steps to reduce circulating androgen levels is critical in reducing the clinical symptomatology of this disorder, and the development of adulthood infertility, diabetes, and metabolic syndrome in patients with PCOS.

Keywords Adolescents, gonadotrophin secretion, hyperandrogenemia, irregular menses, polycystic ovaries, polycystic ovary syndrome.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy of reproductive-aged women, affecting 6–8% of this population.1 The major clinical features are excessive hair growth (hyperandrogenism), menstrual irregularities (anovulation), and polycystic ovaries. This triad of symptoms is commonly accompanied by obesity, insulin resistance, and infertility. Women with PCOS are also at increased risk for diabetes mellitus, endometrial carcinoma, and cardiovascular disease.2,3 Notable reproductive–metabolic abnormalities include overproduction of ovarian androgens, increased pituitary luteinizing hormone (LH) secretion, incomplete maturation of ovarian follicle development, and insulin resistance with compensatory hyperinsulinemia. The etiology of PCOS remains uncertain, despite recognised abnormalities of hypothalamic–pituitary–gonadal function, and disordered metabolic processes.4–7 The symptoms of PCOS usually emerge at or soon after puberty, which may, in some cases, lead to a failure of diagnosis and potentially to a delay in the initiation of treatment. In this review, we will discuss the underlying basis for the altered reproductive physiology and describe the clinical manifestations of PCOS in adolescent girls.

Inappropriate gonadotrophin secretion

It has been well documented that hyperandrogenemic girls with PCOS exhibit gonadotrophin secretion patterns that are similar to those found in adult women with PCOS.8–11 Increased concentrations of serum LH are accompanied by an increase in pulse frequency and amplitude, which are significantly greater than those of normal controls. Because the onset of PCOS commonly can be traced to the events of puberty, this disorder may involve the alteration of regulatory factors or processes that initiate gonadal function during puberty. In childhood, the activity of hypothalamic gonadotrophin-releasing hormone (GnRH) appears to be suppressed by a central mechanism that has not yet been defined. In Tanner stage-I girls, gonadotrophin secretion is minimal, and occasional LH pulses may be observed during sleep. With the onset of puberty there is an initial rise in serum follicle-stimulating hormone (FSH), followed by increases in LH at midpubertal development. The increments in gonadotrophin release are accompanied by noticeable increases in LH pulse frequency that appears to achieve adult patterns by Tanner stages IV–V.12

The process by which gonadotrophin secretion in PCOS girls diverges from normal release is not readily apparent.
It has been reported that premenarchal hyperandrogenemic (HA) girls demonstrated higher LH levels while awake, and during sleep, compared with those of developmentally matched control subjects without androgen excess. After menarche, HA girls showed greater LH pulse activity during waking hours, with little slowing during sleep. By comparison, in postmenarchal normal girls, LH levels were lower and the pulse frequency was reduced while awake. Similarly, during sleep LH pulse frequency was significantly less in normal girls than that of HA girls. The pattern of gonadotrophin secretion in postmenarchal normal controls resembled that of younger premenarchal HA girls. These findings suggest that the transition through neuroendocrine puberty may be accelerated in HA girls compared with normal puberty. Moreover, the data pose the question as to whether there is a chronological difference in the onset of increased LH levels and pulse frequency between HA and normal pubertal girls.

Recent studies have indicated that excess androgen production may have a profound influence on LH pulse frequency in women with PCOS. Previously, it has been shown that the administration of progesterone, either alone or in combination with estrogen (oral contraceptive), results in a greater suppression of mean LH and LH pulse frequency in normal women compared with that of women with PCOS. In a series of elegant studies, pre-treatment with an androgen-blocking agent prior to the administration of estrogen and progesterone to PCOS women resulted in the restoration of LH pulse frequency to that observed in normal women. These findings suggested that in PCOS LH secretion is relatively insensitive to progesterone inhibition because of high circulating androgen levels.

It is unclear, however, when this insensitivity to progesterone develops. If GnRH responsiveness to steroid inhibition is impaired during pubertal maturation, low levels of progesterone in the perimenarcheal period may not be sufficient to suppress GnRH pulse release. The resultant GnRH pulse frequency will lead to excessive LH secretion, relative FSH deficiency, and elevations in testosterone. Chhabra et al. showed that this abnormality of steroid feedback exists in some HA adolescents who did not demonstrate a decrease in LH pulse frequency after progesterone administration, compared with normal adolescents. However, not all HA adolescents in this study demonstrated impairment of progesterone inhibition of LH pulse frequency. There was a subset of HA adolescents that did show a progesterone-induced slowing of LH pulses similar to that of normal control adolescents. The difference between those two subsets of HA adolescents was that the progesterone-suppressed group was all of Hispanic descent, which would suggest a possible genetic basis to this impairment in progesterone feedback inhibition.

Excessive androgen production

Detection of PCOS in adolescent girls is predicated primarily on hyperandrogenic symptoms such as hirsutism and acne, which arise as a result of increased serum androstenedione and testosterone levels. In addition, the most likely source of these androgens is the ovaries, rather than the adrenal glands. In normal puberty, increased production of adrenal androgens dehydroepiandrosterone (DHEA) and DHEA sulphate (DHEA-S) mark the onset of enhanced steroidogenesis, and stimulates the growth of pubic hair. This is followed by increases in ovarian androgens, which facilitate the development of sexual hair growth. In PCOS girls, it has been suggested that the adrenal contribution to the androgen pool may be greater than that of the ovary. Increased adrenal androgen may be a significant factor in the pathogenesis of PCOS, as accelerated pubic hair growth in girls before the age of 8 years, termed premature pubarche, increases the risk of functional ovarian hyperandrogenism, insulin resistance, and polycystic ovaries following puberty. This is particularly true of premature pubarche girls with oligomenorrhea, compared with those with regular cycles. Moreover, in these girls the acquisition of hyperandrogenism and hyperinsulinemia is correlated with a progressive reduction in recorded birth weight. The link between low birth weight and insulin resistance in children appears to be persistent throughout life, as indicated by studies performed in early and late adulthood. Low birth weight is commonly associated with fetal adrenal hypoplasia, and correspondingly low serum DHEA-S levels. However, adrenarche has been found to be most dramatic in children who were small for gestational age at birth, and, in particular, in those that exhibit postnatal catch-up growth. In this regard, it has been demonstrated in pairs of discordant siblings with similar weights in childhood that DHEA-S levels were higher in those of low birth weight compared with those born with normal weight. Increased DHEA-S secretion in girls serves as an endocrine marker for adrenarche, which is independent of and precedes gonadarche by several years. Thus, if as proposed, fetal growth modulates adrenarche, then increased DHEA-S may have reflected an exaggerated adrenarche in these children. Alternatively, it is unclear whether the relationship of premature pubarche and risk of PCOS is predicated on increased androgen production by the adrenal glands, a collective increase in circulating androgens (adrenal plus ovarian), or greater androgen bioactivity.

The rather broad range of LH secretion in PCOS suggests that other mechanisms may be instrumental in the excessive production of androgens. In particular, the presence of hyperinsulinemia and insulin resistance may enhance androgen production in adolescent girls at risk for PCOS. Previous studies have localised receptors for...
insulin, as well as insulin-like growth factor I (IGF-I) and IGF-II, to the theca compartment of ovaries from both normal adult women and PCOS patients. Accordingly, in vitro studies of normal human theca tissue have demonstrated that these growth factors are capable of enhancing androgen responses to LH, as well as independently stimulating androgen production. These findings are consistent with the observation that a reduction of hyperinsulinemia has been associated with significant decreases of serum androgens, without corresponding changes in LH, in women with PCOS treated with insulin-lowering drugs, and indirectly suggest a role for insulin in LH-stimulated androgen synthesis. Whether the physiological insulin resistance of puberty increases the risk of hyperandrogenemia in girls predisposed to PCOS is unknown.

Another mechanism that may impact hyperandrogenism is increased androgen bioactivity. Specific to girls with premature pubarche and those at risk for adolescent PCOS, hyperinsulinemia and hyperandrogenemia have been correlated to lowered sex-hormone binding globulin (SHBG), which provides an increased availability of free testosterone. In particular, the coexistence of obesity may lead to hyperandrogenism through several pathways. Reduction in SHBG and increased free testosterone levels are directly correlated with obesity. In addition, obese adolescents, particularly those with evidence of acanthosis nigricans, are highly likely to have insulin resistance with compensatory hyperinsulinemia, which may further suppress SHBG, leading to increased bioactive androgens. Finally, hyperandrogenemia, itself, may depress SHBG production.

Menstrual irregularity
In adult PCOS, irregular menstrual bleeding generally denotes anovulation, and is helpful in establishing the diagnosis. In contrast, menstrual abnormalities in the years immediately following menarche are common in normal girls, and, therefore, are considerably less reliable as a feature of PCOS. Little is known about the mechanisms that determine the onset of ovarian activity at puberty, and the duration of time required to achieve regular ovulatory cyclicity. However, this interval of chronic anovulation is associated with prolonged unopposed estrogen secretion, which may lead to excessive endometrial proliferation. When endometrial thickness extends beyond the available blood supply, the superficial layers slough, and breakthrough bleeding occurs. Conversely, a sudden decline in estrogen secretion may result in a loss of endometrial support, and withdrawal bleeding may occur. In adult PCOS, the basis for chronic anovulation has been attributed, at least in part, to a lack of FSH or FSH bioactivity. Whether a similar mechanism underlies postmenarchal anovulation is not known. Nevertheless, the irregular bleeding patterns among adolescent girls with PCOS and postmenarchal girls are indistinguishable.

Because irregular bleeding is a characteristic feature of PCOS, efforts have been made to study young adolescents in the absence of hirsutism. In nonhirsute girls with persistent anovulatory cycles for at least 2 years beyond menarche, 35–63% demonstrated increased levels of serum LH. Within this group of individuals, LH secretion was also characterised by increased pulse frequency and amplitude, as well as by desynchronisation of the circadian profile compared with the pattern found in girls with menstrual irregularities and normal serum LH concentrations.12,26 Despite the lack of hirsutism, in the girls with high LH levels, serum androgen concentrations were significantly increased compared with normal ovulatory girls of similar age. Collectively, these findings would suggest that nonhirsute adolescent girls with irregular menstrual cycles and elevated serum LH might be at an increased risk for PCOS.

The above studies included only non-obese or lean adolescent girls. Similar studies have been conducted in obese girls, as these individuals are at increased risk for irregular menstrual cycles, insulin resistance, and increased androgen production. In postmenarchal obese girls with oligomenorrhea and no clinical or biochemical evidence of hyperandrogenism, Yoo et al.40 showed that gonadotrophin secretion was essentially equivalent to that observed in obese girls with adolescent PCOS. In particular, increased LH pulse frequency and sleep–wake patterns of LH release were nearly identical in these two groups. It should be noted that androgen levels and the free androgen index in the nonhirsute oligomenorheic group were about two-fold lower than those in the PCOS girls, and were somewhat higher compared with the normal non-obese controls. These findings are consistent with studies that have demonstrated increased episodic LH release in non-obese, nonhirsute girls with irregular menses or oligomenorrhoea, although serum androgen levels were significantly increased compared with normal controls.41 Whether in early adolescence the presence of oligomenorrhoea alone without hirsutism is sufficient to denote inappropriate gonadotrophin secretion is unknown. However, compared with normal controls, the raised androgen levels in both obese and non-obese girls suggest a common link related to increased LH secretion.

Ovarian morphology
The classic description of polycystic ovaries included bilateral ovarian enlargement, with numerous peripheral small-antral follicles and increased central stroma. The ultrasound appearance of polycystic ovaries has been recently codified as more than 12 follicles per ovary or an ovarian...
The ovarian follicle population in PCOS is also distinctive in that histomorphometric studies have revealed a two- to three-fold increase in the numbers of primary, secondary and tertiary follicles, compared with those of the normal ovary.44 Whether the ovaries are endowed with a greater number of follicles, whether the rate of entry into the growing pool is increased or whether the rate of programmed cell death is decelerated has not been determined. Recent studies have suggested that anti-Müllerian hormone (AMH) might be, in part, responsible for the increased follicle population in polycystic ovaries. AMH, an exclusive product of the granulosa cells of growing pre-antral and small-antral follicles, appears to negatively regulate the advancement of follicle maturation.45 Its expression in growing pre-antral follicles of polycystic ovaries is decreased compared with that of normal ovaries.46 Interestingly, women with PCOS have circulating AMH levels that are elevated by two- to three-fold compared with those of normal women; however, this might reflect the increased numbers of growing pre-antral and small-antral follicle populations in polycystic ovaries.47

A mechanism for the morphogenesis of the polycystic ovary has not yet been established, although a role for androgen excess on follicle growth and development has been suggested from ovarian morphology in hyperandrogenic women with congenital adrenal hyperplasia and androgen-producing ovarian tumours.48–50 In particular, polycystic ovaries have been demonstrated in female to male transsexuals receiving long-term androgen treatment.51–53 The underlying basis for androgen-induced follicle formation in non-human primates has been explored in studies that demonstrated increased ovarian size and follicle number following subcutaneous placement of silastic capsules containing testosterone.54

Compared with adult women, there are relatively few comprehensive studies of polycystic ovary morphology in adolescent girls. The utility of ultrasonography in young girls is commonly limited by: (1) the necessity of an abdominal versus vaginal approach, and (2) the difficulty of securing adequate imaging in obese girls. In non-obese adolescent girls with hirsutism and oligomenorrhoea, it has been demonstrated that ultrasound imaging may be used for the detection of polycystic ovaries, which are morphologically similar to those described in adult women.10 In contrast, the results of ovarian imaging by ultrasound in obese PCOS girls have been of poor quality, which frequently has precluded accurate interpretation. To overcome these obstacles, assessment of ovarian morphology by magnetic resonance in obese adolescent girls with hirsutism and oligomenorrhoea revealed superb images of follicle structure and classical polycystic ovaries.55

As an alternative to ovarian imaging it has been proposed that AMH may serve as a surrogate for follicle number per ovary based on the strong correlation between serum values and small antral follicle count.56 Relevant to adolescence, preliminary studies have shown that in PCOS girls AMH levels are similar to those reported for adult women with PCOS.57 In addition, it was demonstrated that oligomenorrhoeic girls without hyperandrogenism exhibited AMH levels that were comparable with values observed in PCOS individuals. These findings suggest that the small antral follicle population in nonhirsute adolescent girls with irregular menstrual bleeding may resemble that of the polycystic ovary.

**Conclusions**

The diagnosis of PCOS in adolescents is made difficult by several factors, including similarities in the irregular bleeding patterns among adolescent girls with PCOS and normal postmenarchal girls, the inability to perform transvaginal ultrasounds, and the difficulty in visualising the polycystic ovaries on transabdominal ultrasounds in obese adolescents. With more future studies, ultrasound surrogates such as AMH may become available to assist in the diagnosis of polycystic ovaries in adolescents. Nevertheless, PCOS should be considered in any adolescent with hirsutism in the presence of irregular menses. In non-hirsute adolescents who are at risk for PCOS (obese, insulin resistant, diabetic, or those with strong family history of these risk factors), androgen levels should be measured to detect those with higher levels of circulating androgens. Recognising adolescents at risk for PCOS and taking the appropriate steps to reduce circulating androgen levels by treatment with oral contraceptive pills, progestins, antiandrogens, or insulin-
lowering drugs is critical in reducing the development of adulthood infertility, diabetes, metabolic syndrome, and endometrial carcinoma in patients with PCOS.

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