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Polycystic ovary syndrome in adolescent girls

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Polycystic ovary syndrome (PCOS) has traditionally been thought of as a triad of oligomenorrhea, hirsutism, and obesity. PCOS is now recognized as a heterogeneous disorder that results in overproduction of androgens primarily from the ovary leading to anovulation and hirsutism and is associated with insulin resistance. Symptoms in the adolescent include oligomenorrhea, hirsutism, acne, and weight gain. These symptoms are often attributed to normal pubertal events, which can lead to a delay in diagnosis. Insulin resistance, impaired glucose tolerance and diabetes have been shown to occur in adolescents with PCOS. Treatment should be instituted early to decrease symptoms and long-term sequellae of PCOS. Weight loss, oral contraceptives and antiandrogens are very effective in treating the symptoms of this disorder. Insulin-sensitizing medications show promise, but should be used with caution until larger randomized trials have shown short- and long-term benefit and efficacy over traditional therapies in the adolescent population.

Polycystic ovary syndrome (PCOS) has traditionally been thought of as a triad of oligomenorrhea, hirsutism, and obesity and synonymous with the Stein–Leventhal syndrome first described in 1935. PCOS is now recognized as a heterogeneous disorder that results in overproduction of androgens primarily from the ovary and is associated with insulin resistance. The disorder is characterized by oligo- or amenorrhea and signs of hyperandrogenism, but not necessarily obesity. The "cysts" referred to on the ovary are misleading: they are not the cause of the disorder, but rather reflect the altered hormonal milieu within the ovary that leads to anovulation. PCOS affects 5% to 10% of reproductive age women,[1,2] making it one of the most common endocrinopathies in this population. Since many women with PCOS have the onset of symptoms during adolescence it is important to be able to recognize and understand this disorder.

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Pathophysiology

The cause of PCOS remains unknown and is an area of active investigation. Theories focus on neuroendocrine abnormalities, such as the impact of leuteinizing hormone (LH) stimulation of the ovary, and the role of insulin in causing ovarian hyperandrogenism.

Neuroendocrine abnormalities

Ovarian function is dependent on the interaction between the hypothalamus, anterior pituitary and the ovaries. Gonadotropin releasing hormone (GnRH) is secreted in a pulsatile pattern in the hypothalamus leading to secretion of follicle stimulating hormone (FSH) and LH from the anterior pituitary, which in turn stimulates production of androgens and estrogen from the ovary and ovulation. In women and young

girls with PCOS, there is an aberrant pattern of GnRH secretion demonstrated, specifically an increase in the frequency and amplitude of GnRH secretion.[3-5] As a result, androgen production is preferentially stimulated from the ovary and the normal process of follicular development and ovulation is disrupted leading to irregular or absent menses.

Insulin resistance

Insulin resistance is defined as the decreased ability of insulin to act on peripheral tissues to stimulate glucose metabolism or inhibit hepatic glucose output. A consequence of insulin resistance is hyperinsulinemia. Insulin resistance has been demonstrated in up to 60% of women with PCOS,[6] although it has been postulated that all women with PCOS may have insulin resistance.[7] Insulin resistance has been demonstrated to be greater in both lean and obese women with PCOS compared with non-PCOS women of comparable weight, suggesting that the defect is intrinsic to this disorder.[8]

While women with PCOS demonstrate peripheral insulin resistance, the action of insulin in the ovary, promoting production of androgens, appears not to be affected. There are several theories to explain this apparent paradox. The most widely accepted theory proposes that serine phosphorylation of the receptor inhibits its signaling.[1] This defect has been demonstrated in approximately 50% of women with PCOS.[9] In addition, serine phosphorylation of cytochrome P450c17α stimulates production of androgens from the ovary, thus providing a possible explanation for abnormal peripheral insulin action and preservation of insulin's action in the ovary.[10]

Insulin has also been shown to stimulate ovarian androgen production directly via its own receptor and through the IGF receptor by a number of mechanisms.[1]

Clinical presentation

PCOS is a heterogeneous endocrinologic disorder and patients can present with a wide range of symptoms and laboratory abnormalities. Typical clinical findings are those associated with hyperandrogenism, such as hirsutism and acne, and anovulation. In the adolescent these signs and symptoms are often associated with, or attributed to, "normal" adolescence, which can lead to a delay in diagnosis. Since the symptoms of PCOS can be devastating to a young girl, prompt diagnosis and early intervention is important. The recent PCOS consensus meeting held in Rotterdam determined the diagnostic criteria for PCOS as follows: (1) oligo- or anovulation, (2) clinical and/or biochemical signs of hyperandrogenism, and (3) polycystic ovaries on ultrasound, with exclusion of other etiologies. Two out of the three are required for the diagnosis of PCOS.[11]

Menstrual irregularity is a significant component of PCOS. Oligomenorrhea, defined as menstrual bleeding at intervals of $>$40 days, and amenorrhea are most commonly seen. However, irregular frequent bleeding can also be seen with anovulation. Since menstrual irregularities are commonly seen in adolescents, it may be difficult to make the diagnosis of PCOS. However, oligomenorrhea, as opposed to irregular menstruation, which persists from the time of menarche well into adolescence, is consistent with PCOS.[12] In addition, oligomenorrhea has been associated with hyperandrogenic symptoms in adolescent girls, supporting the association between oligomenorrhea and PCOS.[4]

Hirsutism and acne are the most common manifestations of hyperandrogenism in PCOS and can be a cause of embarrassment among female adolescents. Hirsutism is defined as the growth of pigmented, coarse hair in androgen-dependent areas such as the face, chest, back, and lower abdomen. The distribution and severity of the hirsutism can be quantified using the Ferriman and Gallway score, with a score of $\geq$8 signifying significant hair growth. Ethnic and racial differences exist in body hair type and distribution and should be taken into consideration when assessing hirsutism. The leading cause of hirsutism in adolescence is PCOS. Premature adrenarche and hirsutism that occurs before puberty have also been associated with PCOS in adolescents.[13]

Acne is also a sign of hyperandrogenemia and may occur in the absence of hirsutism. Over one-third of women presenting to a dermatology clinic with acne are diagnosed with PCOS.[14] It may be a more sensitive sign of androgen excess than hirsutism in adolescents because of the length of time it takes hair to grow. In adolescents age 12 to 18 years of age with acne and no hirsutism, 88% had at least one elevated androgen level.[15]

The ovarian cysts referred to as part of PCOS are actually follicles containing oocytes that are arrested in development due to the abnormal hormonal environment within the ovary. These "cysts" typically do not become large or cause pain nor do they need to be surgically removed. However, an individual with PCOS may develop an ovarian cyst that does become symptomatic from an unrelated cause. Polycystic-appearing ovaries on ultrasound are now considered part of the diagnostic criteria for PCOS. Ultrasound criteria for PCOS includes the presence of $\geq$12 follicles, 2 to 9 mm in diameter and located peripherally on the ovary, and increased ovarian volume $>$10 mL.[11] One ovary with ultrasound criteria for PCOS is sufficient for diagnosis. In oligomenorrheic adolescents the incidence of polycystic appearing ovaries was found to be 45% compared with 9% in normally menstruating girls.[16] Polycystic ovaries, however, can also be seen in normally menstruating individuals, congenital adrenal hyperplasia, hypothalamic amenorrhea, and hyperprolactinemia.[17] Since polycystic ovarian morphology can be seen in a variety of pathologic conditions as well as in normal individuals, ultrasound alone is not considered sufficient to make the diagnosis of PCOS.

Acanthosis nigricans is a raised, velvety, hyperpigmentation of the skin seen in the axilla, neck, and intertrigenous