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Pcos in Adolescent Girls: Pathophysiology and Clinical Features

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Abstract

The Polycystic Ovarian Syndrome is a complex condition in women associated with psychological, reproductive & metabolic features.

The syndrome is diagnosed when following three criteria are present:

1. Anovulation/ Oligo ovulation. 2. Biochemical hyperandrogenism. 3. Polycystic ovaries observed ultrasonographycally.

Clinical and biochemical features of PCOS can arise due to excess androgen secretion by ovary due to LH secretion from genetically programmed HP unit long before puberty likely during intrauterine life. Puberty triggers PCOS in predisposed girls. Syndrome is result of interaction of genetic and environmental factors. Diagnosis of PCOS in adolescent girls is based on abnormal uterine bleeding pattern and evidence of hyperandrogenism. PCOS is known to be associated with reproductive morbidity and increased risk of endometrial cancer. Diagnosis is important because of increased metabolic and and cardiovascular risk.

Keywords: Polycystic Ovarian Syndrome; Adolescence; Hyperandrogenism; Insulin Resistance Anovulation.

Introduction

The Polycystic Ovarian Syndrome is a complex condition in women associated with psychological, reproductive & metabolic features. It is a chronic disease with omnifarious manifestations spreading across the lifespan & represents a major health & economic burden.

Polycystic ovary syndrome (PCOS) is a heterogeneous condition often associated with oligo-ovulation, clinical or biochemical hyperandrogenism due to ovarian dysfunction. Ovarian dysfunction continues to be the pivotal feature that makes this syndrome the major cause of anovulatory associated infertility in developed countries [1,2].

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Diagnostic Criteria

According to the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) consensus on the diagnostic criteria of PCOS (2003), the syndrome is diagnosed when two of the following three criteria are present:

1. Anovulation or oligoovulation.
2. Biochemical hyperandrogenemia or hyperandrogenism.
3. Polycystic ovaries observed ultrasonographically [3].

PCOS is also accompanied by a number of metabolic disorders, such as insulin resistance and hyperinsulinemia, dyslipidemia and obesity. However, the metabolic manifestations of the syndrome are not included in its criteria.

Three percent to 35% of mothers have PCOS [9,10] and metabolic syndrome prevalence is high in parents and siblings [4–8].

PCOS – Programming During Intrauterine Life

Prepubartal puberty before the age of 8 years maybe a clinical Marker for PCOS in adolescence and adult life [9] Clinical and biochemical features of PCOS can arise due to Excess androgen secretion by ovary due to LH secretion from genetically programmed hypothalamic pituitary unit long before puberty likely during intrauterine life [10] Programming HP unit causes LH secretion. This programming may have genetic background, encourages abdominal adiposity, encourages insulin resistance that has profound influence of phenotype PCOD.

While the first signs of PCOS can be perceptible even during childhood, the unique features of the syndrome in puberty are not yet clear . Despite these difficulties, an early diagnosis of PCOS is of great importance, since its presence is related to a greater risk of future infertility, type II diabetes mellitus, metabolic syndrome and cardiovascular disease. The diagnosis of PCOS in puberty can be difficult, as anovulation is very common in young girls (1/2 menstrual cycles are anovulatory in the first two years after menarche), while ultrasound display of multiple follicles is also a fairly common finding during puberty.

In 1935, Stein and Leventhal published a case series of seven women with amenorrhea, hirsutism, and bilateral polycystic ovaries; a condition that later came to be known as polycystic ovary syndrome (PCOS) [11].

Puberty triggers PCOS in predisposed girls

Metabolic and endocrinological changes common in normal puberty and in PCOS are

- Hyper pulsatile gonadotropin.
- Excess ovarian and adrenal androgen production.
- Insulin resistance or hyperinsulinemia.
- As consequences of hyperinsulinemia, hyperandrogenicity.

Because of this shared feature, it has been speculated that puberty triggers PCOS in predisposed girls [12].

Like the central features of PCOS, certain metabolic changes that are associated with PCOS, are also physiologic during puberty. Hyperinsulinemia is common in healthy adolescents; insulin sensitivity decreases by about 50% and there is a compensatory rise in insulin secretion, which later returns to prepubertal levels in adulthood [13,14]. However, both insulin resistance and hyperinsulinemia are more severe in adolescents with PCOS compared with the general adolescent population [15].

Pathohysiology

PCOS is defined by specific clinical, biochemical and ultrasonographic criteria [16]. Clinical manifestations include menstrual irregularities, signs of androgen excess and obesity [17]. It is characterized by endocrine and metabolic disorders. Although the clinical manifestations of the syndrome depend on the age of the woman, ovarian malfunction and hyperandrogenism are common features at any age.

The pathogenesis of PCOS is unknown; however, it is believed that the syndrome is the result of interactions between genetic and one or more environmental factors. Although the precise role of certain genes was not yet elucidated, a number of study findings are indicative of a genetic predisposition among family members [18,19]. Considerable evidence suggests that PCOS has diverse causes, arising as a complex trait with contributions from both heritable and environmental factors that affect ovarian steroidogenesis [20, 21]. Recently, the promoter -1031(T/C) polymorphism in tumour necrosis factor-alpha was linked to PCOS [22,23].

Anovulation is indicated by abnormal uterine bleeding, which exists when menstrual cycle length is outside the normal range or bleeding is excessive: cycles outside 19 to 90 days are always abnormal, and most are 21 to 45 days even during the first postmenarcheal year. Continued menstrual abnormality in a hyperandrogenic adolescent for 1 year prognosticates at least 50% risk of persistence. Hyperandrogenism is best indicated by persistent elevation of serum testosterone above adult norms as determined in a reliable reference laboratory [24].

Biochemical hyperandrogenemia or hyperandrogenism with hair excess are at present the main findings indicating diagnosis of the syndrome at this age. Besides that, there are some studies that claimed that there is a strong association between PCOS and certain types of congenital uterine anomalies suggesting that there is a developmental defect that could be found in early ages even before adolescence [25,26]. Moreover, other studies claimed that there are some inflammatory markers closely related to the PCOS syndrome that could explain the pathogenesis of the syndrome in short time [27]. Although the exact etiology of PCOS is unclear, androgen excess is proposed to be a core defect. Increased androgen levels, primarily produced by the ovaries (with a smaller contribution from the adrenals and peripheral

adipose tissue) interfere with hypothalamic sensitivity to negative feedback from the ovary, thereby increasing GnRH pulse frequency [28].

This persistently rapid pulse frequency favors increased LH secretion- which in turn stimulates the ovarian theca cells to produce more androgens. The relative decrease in FSH secretion leads to less aromatization of androgens to estradiol and impaired follicular development, resulting in the prolonged periods of oligomenorrhea that are characteristic of PCOS [29].

Insulin stimulates ovarian theca cell synthesis of androgens [30] and inhibits hepatic production of sex hormone-binding globulin [31]. Together, these effects result in increased circulating free androgen levels, thus perpetuating the underlying pathophysiology of PCOS. In addition, insulin resistance promotes release of nonesterified fatty acids from the liver and adipose tissue due to decreased lipoprotein lipase activity, which contributes to the dyslipidemia that is associated with PCOS.

Differential Diagnosis of PCOD

Although the differential diagnosis of PCOS is fairly long , most disorders other than physiologic adolescent anovulation are uncommon to rare. All guidelines recommend screening for nonclassic congenital adrenal hyperplasia (NCCAH), which is the most likely disorder to mimic PCOS although it accounts for only 5% of hyperandrogenic anovulation.

Most recommend screening for hypothyroidism because it causes menstrual irregularity and coarsening of hair (rather than true hirsutism). Some recommend screening all hyperandrogenic women for hyperprolactinemia; most endocrinologists find it to be rare, but it has been reported in as many as 16% of young women presenting with PCOS symptoms [32]. Other disorders are undeniably rare, including the only life-threatening disorder in the differential diagnosis, androgen-secreting tumor, the prevalence of which is 0.2%. The central adiposity and hirsutism of PCOS often raise concern for Cushing's syndrome, which rarely presents as PCOS. Some rare disorders are clinically subtle early on but easy to screen for (eg, insulin-like growth factor-I for acromegaly).

The approach to the differential diagnosis begins with a thorough medical history and physical examination. Because PCOS is but one of many causes of anovulation and only approximately half of hyperandrogenic patients have cutaneous signs of hyperandrogenism, the initial evaluation often includes determination of the serum gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Low LH suggests a hypogonadotropic disorder of neuroendocrine origin, whereas high FSH suggests primary ovarian failure. A pregnancy test is indicated in any sexually mature teenager with amenorrhea.

Clinical Features

Evidence of an Abnormal Degree of Anovulation in Adolescents: Physiologic adolescent anovulation is a well-known phenomenon: the greater length of menstrual cycles and greater degree of menstrual irregularity in adolescents than adults is due to their higher frequency of anovulatory cycles. Cycles shorter than 19 days or longer than 90 days are abnormal at any stage, 75% of menstrual cycles range from 21 to 45 days during the first postmenarcheal (gynecologic) year, and 95% of girls achieve 21– to 40–day adult menstrual cyclicity by their fifth gynecologic year. Thus, most adolescent anovulation is asymptomatic, with cyclic menstrual bleeding usually occurring at 21- to 45-day intervals even in the first postmenarcheal year. Serum hormonal changes during normal adolescent menstrual cycles confirm that substantial but immature cyclic follicular development occurs in such girls and some aluteal adolescents [33–35].

However, the risk for ongoing anovulation is greater for hyperandrogenemic anovulatory adolescents than for nonhyperandrogenemic ones. Among girls evaluated for abnormal menstrual bleeding without clinical signs of hyperandrogenism, approximately half have elevated androgen levels [36,37]. Reevaluation of such patients has shown that hyperandrogenemia resolves in approximately half and that PCOS is the single most common cause of residual ongoing menstrual disorder [38,39]. Robert rosenfield states that in the absence of clinical evidence of an endocrine disorder, persistent abnormal menstrual bleeding for 1 year carries an approximately 50% risk of ongoing menstrual irregularity, and approximately half of the ongoing cases will have PCOS. However, if clinical evidence of PCOS is present, such as hirsutism, the risk of ongoing hyperandrogenic menstrual abnormality is high.

Clinical and Biochemical Evidence of Hyperandrogenism in Adolescents: The development of sexual hair (terminal hair that develops in a male like pattern) and most sebaceous glands is dependent on androgen [40]. Hirsutism is considered clinical evidence of hyperandrogenism and equivalent to

Table 1. Diagnostic Criteria for PCOS in Adolescents:

Otherwise unexplained combination of:	
1. Abnormal uterine bleeding pattern	a. Abnormal for age or gynecologic age
	b. Persistent symptoms for 1–2 yr
2. Evidence of hyperandrogenism	a. Persistent testosterone elevation above adult norms in a reliable reference laboratory is the best evidence
	b. Moderate-severe hirsutism is clinical evidence of hyperandrogenism
	c. Moderate-severe inflammatory acne vulgaris is an indication to test for hyperandrogenemia

Based on Witchel S, Oberfield S, Rosenfield R, Codner E,Bonny A, Ibáñez L, et al. The Diagnosis of Polycystic Ovarian Syndrome during Adolescence Horm Res Pediatr. 2015;83 (6):376–89.

biochemical evidence of hyperandrogenism in all adult criteria for PCOS because documentation of hyperandrogenemia can be problematic [41]. However, this criterion is controversial because mild hirsutism is due to ethnic or familial factors rather than hyperandrogenemia half of the time, in contrast to moderate-severe hirsutism, which is usually due to hyperandro-genemia [42].

Insulin Resistance & Obesity

Obesity prevalence likewise varies widely among populations, averaging approximately 50%. The insulin resistance of PCOS seems to be associated with increased abdominal fat depots independent of BMI [43] and superimposed excess adiposity further increases all fat depots and insulin resistance [44]. Metabolic syndrome, a cluster of glucose abnormalities, central (android) obesity, hypertension, and dyslipidemia, is the variable result of insulin resistance interacting with obesity and age. [45,46]. Its prevalence is highest in obese subjects. It is present in 25% of adolescents with PCOS [45-49]. The comorbidity of metabolic syndrome makes PCOS a risk factor for the early development of type 2 diabetes mellitus, sleep-disordered breathing, and ultimately, the threat of cardiovascular disease. Insulin resistant hyperinsulinism, in part related to coexistent obesity, is the most common nonsteroidogenic factor. The complex interactions generally mimic an autosomal dominant trait with variable penetrance: the disorder is correlated in identical twins [50]; about half of sisters are hyperandrogenic, and half of these also have oligo-amenorrhea and thus PCOS [51,52]; and polycystic ovaries appear to be inherited as an autosomal dominant trait [52,53].

Discussion

Since archaic times, ovary has presented as an inquisitive organ. The earliest reference to ovary is in the writings of Aristotle (384–322 B.C.E.) but still its endocrine functions are meagrely understood & treatment options are undergoing metamorphosis [54]. Polycystic Ovarian Syndrome; a complex condition, still baffles gynaecologists with its heterogeneous signs and symptoms. It is an ovarian dysfunction caused by hyperandrogenism & hyperinsulinemia which inhibits folliculogenesis and leads to polyfollicular morphology ultimately disturbing the menstrual cycle and leading to anovulation. Often called the thief of womanhood where women feel 'abnormal' and not 'proper' women , is a frustrating experience. It has desolating reproductive, metabolic, cardiovascular and psychological impact across lifespan. It is one of the most common hormonal disorders affecting women of reproductive age group. Usually beginning during menarche, it's transitions to include infertility and complications tend to increase with time, which persist even after menopause. This deeply stigmatising condition presents an array of signs and symptoms. The amalgamation of chronic anovulation manifesting as oligomenorrhea or amenorrhea, anovulatory cycles leading to DUB and decreased fertility, hirsutism, acne, androgenic alopecia, acanthosis nigricans, premature pubarche, obesity, Type 2 diabetes, psychological features like anxiety, depression, progression causing endometrial , breast & ovarian cancer make PCOS a complex & multifarious disease & is befittingly called as a syndrome [55,56].

Although PCOS is known to be associated with reproductive morbidity and increased risk for endometrial cancer, diagnosis is especially important

because PCOS is now thought to increase metabolic and cardiovascular risks. Adolescent girls with PCOS are at increased risk for:

- Impaired glucose tolerance,
- Type 2 diabetes mellitus,
- Hypertension.

Cardiovascular disease is believed to be more prevalent in women with PCOS, and it has been estimated that such women also have a significantly increased risk for myocardial infarction. Many lipid abnormalities (most notably low high-density lipoprotein cholesterol levels and elevated triglyceride levels) and impaired fibrinolysis are seen in women with PCOS [57].

Further research is necessary to elucidate the mechanisms by which PCOS disrupts the endocrine harmony of the young female body in that crucial, transitional period of a woman's life.

Conclusions

PCOS is a syndrome and not a disease. It reflects multiple etiologies and various clinical presentations. It is commonest endocrine disorder in women of reproductive age. It is diagnosed in 5–10% of women between adolescence and menopause.This condition frequently has its origin in adolescence, it has an impact on physical and mental health of the young girl. The biochemical features form the basis of clinical consequences at adulthood. These biochemical features are more easily treatable and reversible if identified at young adolescent age. Menstrual irregularities is the earliest clinical manifestation of PCOS in adolescent. In view of genetic origin and family history, it is essential to evaluate family history for both PCOS and metabolic diseases.

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