Adolescence: A High-Risk Period for PCOS Development?

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Polycystic ovary syndrome (PCOS) has long been considered "a riddle wrapped in a mystery inside an enigma" [1], and the relationships among genetic, endocrine, metabolic, environmental, and lifestyle factors in its development are indeed quite complex. Moreover, the underlying causes [2], diagnostic criteria, and recommendations for managing adolescent PCOS [3] remain controversial. The diagnostic features in adult women, such as hyperandrogenemia, obesity, and menstrual disorders, may be part of the normal pubertal process [4]. We thus propose the following three criteria (Fig. 2.1) to make a definitive diagnosis [5].

The prevalence of PCOS has been estimated to range between 0.6 and 12%. In a group of post-menarcheal obese adolescents, Ybarra et al. identified 18.4% cases [6]. Christiansen, in a cross-sectional study including a high number of adolescents between 15 and 19 years, reported a PCOS diagnosis in 3.8%, 10.2%, and 23.10% of the overweight, moderately obese, and extremely obese adolescents, respectively [7].

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1. Hirsutism (progressive)

2. Irregular menses / oligomenorrhea (2 years after menarche)

3. Testosterone concentration > 45-55 mg/dl (follicular phase)

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4. PCO morphology (US)

- **Enlarged ovaries (> 10mL)**
  - **+/- increased stroma**
  - **+ multiple small peripheral cysts**

*** optional :**

- **abdominal obesity**
- **insulin-resistance**
- **AMH concentration > 6.26 ng/mL**
- **risk factors (genetics, SGA, early puberty, EDCs, …)**

Fig. 2.1 Criteria for the diagnosis of PCOS in adolescence

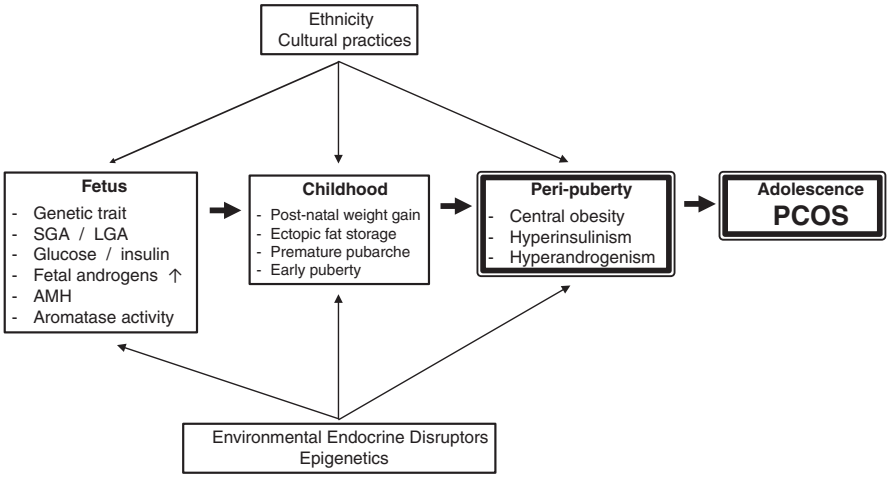

Fig. 2.2 Natural history of adolescent PCOS according to Louwers et al. [57]

Adolescent PCOS may have its origins in fetal life [8] (intrauterine growth retardation, hyperandrogenism) or before puberty (through premature pubarche, obesity, early puberty). In the last few years, evidence has clearly emerged showing that peri-puberty is a high-risk period for PCOS development (Fig. 2.2), through obesity, insulin resistance, metabolic syndrome, and hyperandrogenism (HA). In addition, androgens stimulate appetite, food craving, and recurrent binge eating (Fig. 2.3).

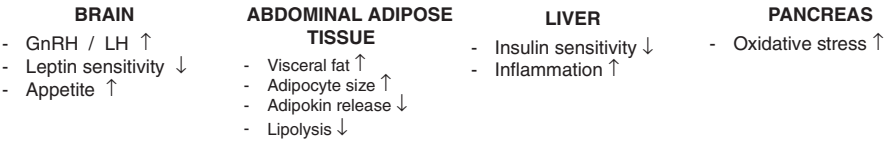

Fig. 2.3 Consequences of HA in women according to Rodriguez et al. [58]

PCOS is an obesity-related condition, with weight gain and obesity in adolescence contributing to its development [9]. In addition, the link between early adiposity rebound in childhood and obesity in adolescence has been established [10, 11].

Moreover, it is well known that the risk of developing a binge eating disorder increases around pubertal onset and continue to rise through adolescence, leading to overweight and obesity.

2.1 The Role of Peri-Pubertal Obesity

According to the ACOG, the prevalence of adolescent overweight and obesity is about 30% and 20%, respectively. The rising prevalence over the last few decades underscores the importance of recognizing its implication at different levels. Adolescent obesity merits special attention as its ramifications persist into adulthood by modulating endocrine, metabolic, and reproductive performances [12].

As obesity during pubertal development is a risk factor for endocrine and metabolic diseases, it has become critical to understand how this occurs [13]. Obesity is, for example, known to modulate pubertal development, as both cross-sectional and longitudinal studies have shown it is associated with earlier puberty [14].

How obesity impacts the relationship between sex steroids and glucose metabolism in early puberty is a matter of active research [13].

Besides, it is well known that girls show a "physiological" decrease in insulin sensitivity during puberty that begins in Tanner stage 2, reaches a nadir in mid to late puberty, and returns to pre-pubertal levels after puberty is completed. This "physiological" insulin resistance is thought to play a role in hyperinsulinemia. The association between childhood obesity and both insulin resistance and hyperinsulinemia has been well documented, especially in Tanner 1–3 girls. The concomitant elevation of insulin and testosterone suggests an interrelationship between these two hormones [15].

It was recently hypothesized that PCOS might be induced by eating disorders occurring at the onset of puberty and associated with stress, mood problems, and low self-esteem [16]. In addition, excessive nutrient intake and the subsequent peripubertal obesity can lead to abnormal endocrine and neuroendocrine activity during puberty, which may predispose to PCOS. High dietary intake of energy, proteins, and polyunsaturated fatty acids are risk factors for overweight and obesity and may exacerbate the hyperandrogenism (HA) occurring in most adolescents.

Even if obesity is evident in pubertal PCOS and increases with age, we still do not know if adolescents with PCOS have a predisposition to gain weight or whether PCOS and obesity are causally related [17].

A key question at this point is the following: Which factors mediate the effects of obesity on the development of PCOS?

In addition to genetic factors, insulin resistance and hyperinsulinemia are involved in androgen [18] biosynthesis by the ovary (in conjunction with LH), the development of metabolic syndrome, and the release of adipokines: adiponectin is lower in PCOS, contributing to insulin resistance [19]. Vistatin is increased and reinforces insulin resistance and metabolic dysfunction.

There is evidence that hyperinsulinemia can induce HA either by directly stimulating ovarian/adrenal production or by indirectly enhancing LH secretion, intensifying LH action on the ovary, or increasing bioavailability of testosterone through the reduction of liver SHBG production [20]. Insulin resistance is commonly associated with a higher prevalence of a chronic low-grade inflammatory state and hypoadiponectinemia, both of which negatively affect ovarian function. Lewi et al. reported profound metabolic derangements detected early in the course of PCOS, including a 50% reduction in peripheral tissue insulin sensitivity, hepatic insulin resistance, and compensatory HA in premenarcheal girls with PCOS [21].

Although the ovary is the major contributor to the hyperandrogenic state, increased circulating levels of DHEAS, an adrenal androgen, is present in 15–45% of PCOS girls. The cause of this increase may be adrenal hyperresponsiveness to ACTH, increased ACTH drive to androgens, or hyperinsulinemia, which is known to stimulate adrenal production of DHEAS.

In addition, it is generally accepted that obesity is a risk factor for the development of PCOS during the adolescence in girls who are genetically predisposed [22].

The amount of abdominal fat is recognized as a major contributor to the significant variation in the severity of PCOS phenotypes, with increased abdominal adiposity exacerbating the endocrine, metabolic, and psychological features of PCOS [23].

Abdominal obesity worsens HA, menstrual disorders, insulin-resistance, dyslipidemia, and metabolic syndrome. Notably, a large proportion of adolescents with PCOS are centrally obese [24].

In these adolescents, insulin resistance and its compensatory hyperinsulinism [25] are intrinsic factors that play a key role in producing hyperandrogenia in PCOS:

- Insulin excess can trigger insulin receptors in the pituitary gland to increase LH release and promote androgen secretion by both the ovary and adrenal gland.
- Increased insulin can inhibit the synthesis of hepatic SHBG and increase the level of free T.
- Enhanced activity of the IGF1 receptor in the ovary promotes androgen production by the thecal cells.

Insulin resistance/dyslipidemia, due to high level of free fatty acid and the inhibition of lipolysis, is the most common metabolic disorder [26].

Metabolic syndrome usually encompasses central obesity, insulin resistance, high fasting glucose, high fasting triglycerides, and low HDL cholesterol [27]. According to the Clinical Practice Guidelines from the American Academy of Pediatrics [28], metabolic syndrome is present when an adolescent meets three or more of the following criteria:

- Waist circumference in at least the 90th percentile for age.
- Systolic or diastolic blood pressure in at least the 90th percentile for age and height.
- HDL-C ≤ 40 mg/dl.
- Fasting triglycerides >110 mg/dl.
- Glucose sensitivity is usually increased on the OGTT, which is performed by measuring glucose before the administration of 75 g of oral dextrose and 30–60–90-120-180 minutes after.
  - Homeostatic model for insulin resistance (HOMA-IR).
  - Tissue sensitivity to insulin (HOMA-S).
  - β-cell function.

which are calculated using an online program [29].

2.2 Hyperandrogenism

Androgen excess is the cardinal feature of PCOS.

HA causes a series of endocrine changes, including insulin resistance, hyperinsulinemia, metabolic syndrome, dyslipidemia, and increased LH secretion.

The free androgen index (FAI) is approximately three times higher in pubertal girls with obesity compared with normal-weigh pubertal girls, reflecting early evidence of obesity-associated HA in early pubertal development.

Previous reports have actually documented an association between obesity and HA in pre- and early pubertal girls (Tanner B1-B3). McCartney et al. first emphasized that obesity was associated with HA in 66–94% of obese girls [30]. Knudsen et al. reported that morning LH and fasting insulin were significant predictors of free T in obese peri-pubertal girls, suggesting that abnormal LH secretion and hyperinsulinemia can promote HA in peri-pubertal girls with obesity [31].

Abdominal obesity has been positively correlated with androgen levels, suggesting that obesity plays an important role in PCOS. Androgens have actually been shown to induce abdominal adipocyte accumulation and may cause abdominal tissue dysfunction, including lipid accumulation, oxidative stress, and inflammation [32]. HA is also associated with the development of white adipose tissue dysfunction, which includes increased visceral adiposity and visceral and subcutaneous adipocyte hypertrophy.

What do we know about the genetic background of HA and PCOS? Approximately 40% of sisters of affected girls have elevated total and bioavailable T level, suggesting a genetic susceptibility to this phenomenon [33].

Pre-menarcheal first-degree relatives have HA, further pointing to a genetic susceptibility to PCOS, which has been confirmed by the evidence of elevated T levels, early metabolic syndrome, and β-cell dysfunction in daughters of women affected with PCOS [34]. Polymorphisms and splice variants in genes such as follistatin, fibrillin-3, CYP11A, insulin receptor, 17βHSDB6, androgen receptor, and 5αreductase have been linked to PCOS [35].

It is likely that gene variations resulting in HA during a key developmental window program the phenotypic feature of PCOS.

Recent studies in young female macaques have suggested that DNA methylation and RNA levels of the genes associated with pathways involved in inflammation, metabolic syndrome, and adipogenesis were involved in the regulation of the white adipose tissue (WAT) transcriptional profile [36]. This contributes to body fat distribution and the modulation of the pathophysiological response to obesity. In addition, these studies reported the synergistic effects of HA and the obesogenic Western-style diet on this process.

Lastly, animal studies currently reinforce the hypothesis that androgen excess plays a key role in the origin of PCOS.

In female monkeys, DHT exposure induces PCOS reproductive traits of cycle irregularity, ovulation dysfunction, and reduced follicular maturations. Simultaneously, a PCOS metabolic characteristic of increased adiposity, adipocyte hypertrophy, and hepatic steatosis was observed.

2.3 GnRH Dysregulation

PCOS is associated with a neuroendocrine abnormality characterized by increased GnRH and LH secretions. It has been reported that HA enhances the GnRH pulse frequency and the subsequently elevated LH secretion. Insulin may increase the frequency and amplitude of GnRH and LH pulse secretion. Insulin has also been reported to stimulate GnRH-mediated LH release from the pituitary.

A reduced dopaminergic tone along with low plasma norepinephrine and serum serotonin has been associated in PCOS women [37]. In a rat model of PCOS, Chaudhari et al. recently demonstrated that GnRH inhibitor neurotransmitter, serotonin, dopamine, GABA, and acetylcholine were reduced, whereas glutamate, an active stimulator of GnRH activity, was increased (Fig. 2.4) [38]. The kisspeptin/GPR54 system is also involved in this stimulation [39]. The dysregulated neurotransmission profile could explain the frequency of low self-esteem anxiety, depression, and mood disorders associated with PCOS adolescents. This neurotransmission dysregulation may be a key feature in PCOS development [40].

2.4 Brain Disorders

PCOS is associated with by psychological distress and episodes of overeating and/or dieting during puberty and adolescence, when body dissatisfaction and emotional problems are present [16].

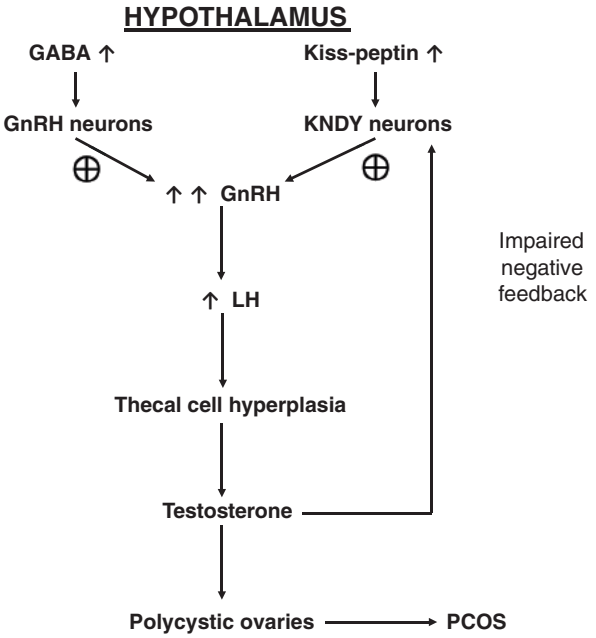

Fig. 2.4 Hypothalamic-pituitary-ovarian axis in adolescent PCOS girls

It is well known that eating disorders disturb endocrine pathways: bulimia can increase insulin level as well as stress. Binge-foods are usually high in fat or sugar and increase the insulin level. Binge-eating and stress induce hypercortisolism. Obesity is also associated with leptin resistance, leading to leptin overproduction. Ghrelin increases food intake and adiposity.

Even if PCOS is associated with psychological issues usually observed in obese girls, some investigators consider that pre-existent mental health problems may contribute to weight gain and the development of PCOS at the vulnerable age of puberty [41]. Screening for anxiety and repression is thus required, and the assessment of eating disorders should be considered in the peri-pubertal period of high-risk adolescents.

Moreover, activation of the hypothalamic-pituitary-ovarian axis during puberty can be epigenetically altered by psychological stressors, which are common during adolescence, and can thus lead to the development of PCOS [40].

Recent studies have revealed that the pathophysiology of PCOS also involves the gut-brain axis (GBA), which plays a critical role in the regulation of appetite, food intake, glucose metabolism, energy maintenance, and body weight.

Gastrointestinal hormones, including ghrelin, glucagon-like peptide, and cholecystokinin, are actually involved in insulin resistance and inflammation disorders.

2.5 Endocrine-Disrupting Chemicals

Within the past few decades, more than 1000 of the 100,000 environmental chemicals in the world have been documented as endocrine-disrupting chemicals (EDCs) [42]. These include diethylstilbestrol (DES), dioxin (herbicide), PCBs (electrical

coolant), PBDEs (flame retardants), DTT (pesticide), atrazine (herbicide), alkylphenols (detergents), parabens and triclosan (cosmetics), phthalates (plastics, cosmetics), and BPA (plastics) [43]. Most of them can mimic estrogen action and interfere with nuclear receptors (and other receptors, such as the aryl-hydrocarbon receptor: AhR), transcriptional factors, growth factors, or enzymatic activity (aromatase).

In several animal studies, EDC exposure was shown to induce endocrine and metabolic expressions that fit the PCOS phenotype [44], including ovarian polycystic morphology on ultrasound [45].

There are some data on the association of PCOS and EDCs in women [46, 47]. According to the investigators, EDCs can modify neuroendocrine modulation [46], adipose tissue development [47], insulin secretion, and metabolic disorders, favoring PCOS development [48].

Very recently, Luo et al. reported novel associations between the UDP-glucuronosyltransferase polymorphisms and EDC concentrations in patients with PCOS, supporting the relevance of genetic differences in EDC metabolism, which might be considered a modulating factor of PCOS development [49].

2.6 Gut Microbiota

It is known that intestinal flora can regulate the synthesis and secretion of insulin, and a variety of endocrine and metabolic diseases are affected by the dynamics and structure of the gut microbiota. Tremelen et al. suggested that the high-sugar, high-fat, and low-fiber diet usually observed in adolescent girls may cause an imbalance in the intestinal flora, which then increases the permeability of the liposaccharides known to activate the immunological system, causing inflammation [50]. Recently, a potential two-way interaction between androgens and the intestinal flora was proposed [51, 52].

We should also consider the role of gut microbiota in addition to the epigenetic regulation of neurotransmitters. Recent studies have shown that dysbiosis of the gut microbiota may be associated with the PCOS phenotype [53]. Some groups have proposed that it may be a potential player in the development of PCOS (Fig. 2.5).

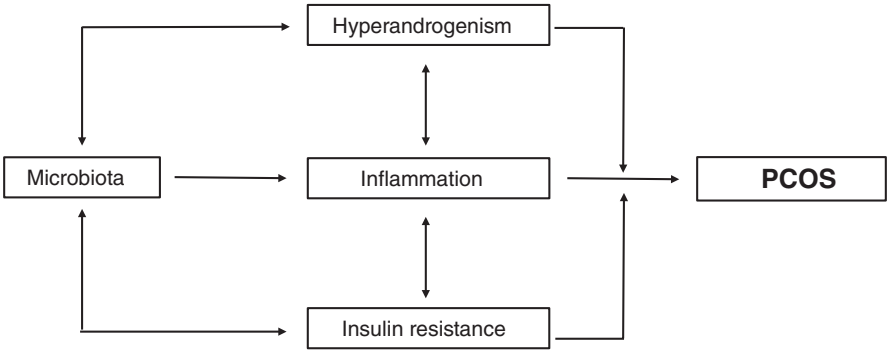

Fig. 2.5 The microbiota as a key factor in the development of PCOS

2.7 AMH

AMH is a new factor involved in the development of PCOS in obese girls. AMH is known to be secreted by the granulosa cells of the ovarian follicles.

Since polycystic ovaries have a larger number of follicles, they produce more AMH. High AMH concentration is considered a marker of adolescent PCOS, but it also contributes to the pathophysiology of PCOS [54]. Recent studies have suggested that AMH may play a role in the development of PCOS by increasing GnRH-dependent LH secretion and inhibiting aromatase activity within the ovary [22].

Previous studies found increased AMH levels in PCOS girls during early puberty, suggesting that an alteration in ovarian follicular genesis may begin early in development [55].

An AMH value of 6.26 ng/mL seems to be an optimal cut-off value in obese girls for predicting PCOS [56].

2.8 Conclusions

Several studies have outlined the multifactorial origin of PCOS, which includes genetic factors, obesity, neuroendocrine dysregulation and HA, metabolic dysfunctions, immune disorders, lifestyle, and psychological disorders. Insulin resistance is one of the main pathological changes (Fig. 2.6).

Although PCOS can manifest at any age in reproductive life, it often develops during adolescence, coincident with pubertal activation of the hypothalamic-pituitary-ovarian axis, eating disorders, and obesity. Identifying peri-pubertal girls at risk of PCOS may prevent that adulthood PCOS. One of the main future

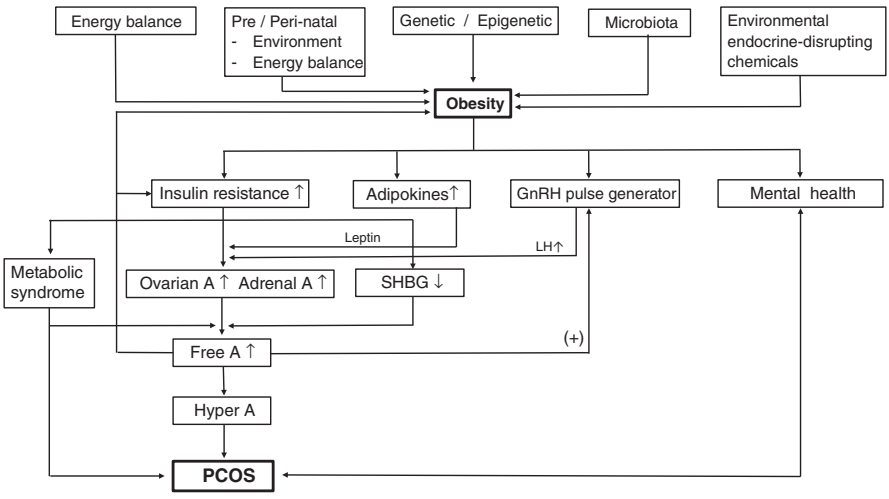

Fig. 2.6 Endocrine and metabolic disorders associated with peri-pubertal abdominal obesity

challenges will be to identify the environmental triggers of PCOS development during adolescence and manage them accordingly.

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