Development of Obesity and Polycystic Ovary Syndrome in Adolescents

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Abstract
Obesity in adolescents is prevalent worldwide. Polycystic ovary syndrome (PCOS) is often associated with obesity in women, and it has serious metabolic and reproductive health implications. Although PCOS does not become clinically visible until early adolescence, its origins are likely much earlier. Therefore, we reviewed the recent literature regarding the mechanisms linking the development of PCOS and obesity in adolescent girls. We found that excess abdominal adipose tissue (AT) initiates metabolic and endocrine aberrations that are central in the progression of PCOS. As an example, abdominal AT impairs insulin action, which interacts with the progression of hyperandrogenism. In addition, excessive androgen levels lead to impaired glucose uptake, which also contributes to insulin resistance, which again increases the deposition of visceral fat. The body composition is influenced by testosterone, which decreases subcutaneous fat lipolysis and influences adipocyte distribution. These mechanisms may explain why PCOS girls have an increased visceral adipose mass independent of body mass index. Therefore, first-line treatment in adolescent PCOS is often lifestyle intervention to prevent the damaging effects of obesity. Pharmacological treatment of adolescent PCOS is not standardized because the long-term effects in adolescents have not yet been evaluated; therefore, drugs should be prescribed cautiously. Although the complex metabolic interrelationships between obesity and PCOS have yet to be fully understood, the co-occurrence of these conditions in adolescent girls tends to increase the severity of the negative health consequences of each condition.

Introduction
Obesity is a worldwide problem that threatens the lives of adults, adolescents and children. Obesity has many associated comorbidities, such as the well-known components of the metabolic syndrome (MetS), which harm health and functioning in men and women. Worryingly, these health risks appear in overweight and obese childhood, which raises the question of how it challenges their future health and especially whether it impairs physiological growth as well as development during the pubertal transition.

Polycystic ovary syndrome (PCOS) is a disorder of ovarian dysfunction often characterized by relatively high androgen concentrations, metabolic abnormalities and many conditions of the MetS. PCOS is one of the...
most common endocrine disorders in females, and affects ~15% [1] of women of reproductive age. In addition to its effect on increasing cardiovascular disease (CVD) risk, PCOS impairs women’s fertility and, due to the distress of its many side effects, it also harms their mental health. The disorder typically emerges during adolescence. Despite this, the prevalence and incidence of the disorder are not extensively evaluated in the adolescent population. It has recently been estimated in two populations that 18.5–26% of adolescent girls have PCOS [2, 3], thus making it a relatively common syndrome. In women, the risk of PCOS is increased among those who are obese, and similarly it is elevated among obese adolescents. Although a tendency towards polycystic ovarian morphology (PCOM) and enlarged paratubal cysts is found in obese pubertal adolescents, the condition varies with ethnicity and has low predictive value of hyperandrogenism (HA) in adolescents [3]. Furthermore, there is evidence that features of PCOS even emerge among obese preadolescent girls.

Given that nearly one third of the European pediatric population are overweight and obese [4], it is likely that the incidence of PCOS will increase in the coming years. Therefore, we reviewed the most recent literature regarding PCOS and obesity in adolescents to investigate how the codevelopment of these conditions is currently interpreted.

**Polycystic Ovary Syndrome**

**Clinical Manifestation of PCOS**

The clinical symptoms of PCOS in women are heterogeneous and include oligoanovulation (OAV), hirsutism, acne, alopecia, acanthosis nigricans and increased body fat mass with increased abdominal fat deposition [5]. Additionally, many women have a history of premature adrenarche/pubarche. Atypical forms of PCOS also occur, such as HA without anovulatory symptoms. The comorbidities of importance include infertility, MetS, and type 2 diabetes mellitus (T2DM) [6–8]. Many, but not all, women with PCOS are also classified as overweight with a body mass index (BMI; kg/m²) >25 or obese (BMI >30). Depending on the study, and hence the source of the population, the estimates of obesity among adult PCOS patients range from 42 to 58% [9, 10].

**Biochemical Characteristics of PCOS**

In general, women with PCOS exhibit lowered levels of sex hormone-binding globulin (SHBG) and elevated levels of circulating free testosterone (cFT), luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio, postprandial glucose, fasting insulin, triglycerides, total cholesterol and a homeostatic model assessment index above 3.8, which indicates insulin resistance (IR) [11]. Several of these conditions are known to be CVD risk factors [8]. Since anti-Müllerian hormone (AMH) reflects some aspects of ovarian function, and PCOS is often characterized by increased antral follicles in ovaries, it may be useful in the diagnosis of PCOS [12]. In women, increased serum concentrations of AMH seem to correlate well with three parameters of PCOS, namely HA, OAV, and PCOM, but it is not yet generally included in the biochemical panel [12].

**Clinical Diagnostic Criteria in Women**

The diagnostic criteria for PCOS come from the 2003 Rotterdam consensus workshop [13]. It defined PCOS as a syndrome of ovarian dysfunction, diagnosed when fulfilling two out of the three following criteria: (1) menstrual dysfunction/OAV; (2) enlarged polycystic ovaries (on ultrasonography); (3) clinical and/or biochemical HA. Additionally, however, other sets of criteria have been proposed [14]. These criteria, listed in table 1 differ in terms of which and how many conditions are necessary for a diagnosis. Nonetheless, these three sets of criteria are in agreement that to establish a diagnosis of PCOS in adult women, conditions with similar phenotypes should be excluded [13]. Because of the broad spectrum of clinical symptoms, these criteria are recommendations rather than standardized for diagnosis.

**PCOS in Adolescents**

**A Diagnostic Challenge**

There is debate about the appropriateness of using the Rotterdam criteria for a diagnosis of PCOS in adolescents since they were developed for use in women. Other criteria for diagnosing PCOS come from the NIH and AES. Just like the Rotterdam criteria, they also include HA as a diagnostic parameter, and these criteria have been proposed for use in adolescents. In adolescence, the normal changes during puberty can bias the interpretation of the biochemical measures typically used in the diagnosis of PCOS. For example, during normal pubertal development in girls, hypothalamic pulsatile secretions of gonadotropin-releasing hormone (GNRH) are established, and these become dynamic and cyclic. During puberty, the
growth hormone (GH)-mediated release of insulin-like growth factor-1 increases, which in turn decreases insulin sensitivity and increases insulin secretion [15]. The resulting hyperinsulinemia (HI) decreases liver production of SHBG, which increases the bioavailability of steroids, resulting in raised cFT. Thus, in adolescent girls elevated levels of circulating androgens are not necessarily a sign of HA per se. Additionally, the reproductive capacity of adolescents also undergoes non-pathological changes during pubertal development that are influenced by the secretion of gonadotropins. These changes are expressed by irregular menstrual patterns and PCOM on ultrasonography, and may even persist for 2 years after menarche [2, 15–17]. Because all three sets of criteria include abnormal ovulatory patterns and PCOM, the diagnosis in adolescence remains challenging. Taken together, these biochemical and physiological aspects of pubertal development suggest that the diagnosis of PCOS in adolescents should be assigned using different criteria from those in women.

**Diagnostic Criteria in Adolescents**

Given these unique aspects of pubertal development, diagnosing PCOS in adolescent girls is a challenge. In a sample of 250 adolescent girls, PCOS was best characterized by clinical HA (hirsutism) and/or biochemical HA and oligomenorrhea [18]. Other groups have suggested that menstrual patterns are classified as pathological in adolescents when menstruation is absent for ≥90 days, or if cycles persist for ≥45 days [19]. Biochemically, HA can be determined by levels of cFT, and dehydroepiandrosterone in adolescent girls [19]. Physiologically, ovarian volume and antral follicle count can be assessed by transabdominal ultrasonography, although these measures may be operator dependent and also of limited use in adolescents [2]. Transvaginal or transrectal ultrasonography in adolescents is questionable or even unethical in young girls prior to sexual debut. Much like in adult women, the diagnostic reliability of AMH in adolescents has yet to be determined [20].

**Biological Origin**

The etiology of PCOS remains largely unknown, but it is thought to be multifactorial, i.e. influenced by epigenetic, genetic and environmental contributions [17, 21].

Prenatal developmental circumstances have been observed to influence the development of PCOS in adult monkeys by in utero exposure to supraphysiological levels of androgens [22]. Interestingly, this discovery in non-human primates has recently been explained by epigenetic alterations which predispose to PCOS [23].

The FTO gene on chromosome 16q12.2 is an obesity-related gene that is of particular interest because single nucleotide polymorphisms (SNPs) at this site are found to have a strong association with increased BMI, greater weight and T2DM. In particular, the A allele is associated with greater BMI. A meta-analysis compared FTO SNPs, rs9939609 in particular, between women with PCOS and the general population. This analysis was in accordance with previous studies and showed that each added copy of the allele (A/C) was associated with an increase in BMI. Further, it showed that there was a greater effect of the

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**Table 1. Different sets of diagnostic criteria for PCOS in adult women [14]**

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Polycystic ovarian morphology is defined as >12 follicles with a 2- to 9-mm diameter or an ovarian volume <10 ml. The three sets of criteria are illustrated in the table.

The presence of a ‘+’ indicates what symptom is accepted in the criteria regime. A ‘+’ or symptom in bold indicates that this specific symptom is a requirement in the diagnosis.
PCOS are thought to be reinforced by obesity more, the clinical phenotype and the development of adiposity has generated a great deal of attention. Further, others do why not all obese girls develop androgen excess whereas different in each individual. These differences might explain the amount of subcutaneous adipocytes is different in each individual. These differences might explain why not all obese girls develop androgen excess whereas others do [27]. Intriguingly, low-birth weight girls who experience spontaneous catch-up growth develop higher dehydroepiandrosterone and lower SHBG together with increased visceral adiposity between 6 and 8 years of age, even though they are not overweight. This may represent a metabolic adaptation that persists into adolescence and adulthood, and therefore exposes them to a higher risk of developing PCOS [26].

**PCOS and Obesity**

Until recently, PCOS has been recognized as a hyperandrogenic disorder originating from hypothalamic-pituitary gonadotropin secretion or ovarian dysfunction [28]. Lately, however, at least some cases of PCOS have been regarded as a disorder of metabolic origin that impairs reproductive function [5]. Since obesity, particularly in the abdominal region, is found in ~50% [9, 29] of women with PCOS, and because obesity appears in mid-childhood and increases during puberty [6, 16, 27], excess adiposity has generated a great deal of attention. Furthermore, the clinical phenotype and the development of PCOS are thought to be reinforced by obesity [2, 7, 27, 30], especially among those who are genetically prone to the disorder [7]. These observed associations highlight the importance of disentangling the relationship between obesity and PCOS, and in particular their common metabolic disorders.
Among obese adolescents, IR is commonly detected and appears similarly in relation to adolescent PCOS [3, 17]. Likewise, insulin-lowering treatment in PCOS with metformin has a positive effect on peripheral insulin sensitivity, PCOM, androgen levels, and obesity [35]. This raises the possibility that IR and HI form a critical link between adolescent obesity and the development of PCOS. Therefore, the endocrinological and metabolic aberrations caused by androgen excess in PCOS might be the explanation for IR and increased adipose tissue (AT). Further studies are warranted as it still remains unclear which comes first: IR, obesity or PCOS.

**Hyperandrogenemia Enhances Fat Storage**

A key characteristic of PCOS is excessive levels of androgens. Aside from their effects on ovarian function and phenotypical features, like alopecia, they also influence where fat is stored in the body. This is partly explained by impaired glucose metabolism and IR [36]. In women with PCOS, there is a different distribution of AT than in women without PCOS. The AT tends to be distributed viscerally, and these women have greater upper body fat accumulation in a pattern that is similar to that of men [37]. The different AT distribution is attributed to the influence of steroids, their metabolism, and the expression of tissue-specific steroid receptors [38]. As this visceral fat is biologically active [39, 40], it likely further contributes to the metabolic and endocrine disturbances in PCOS.

**Androgens Decrease Lipolysis in Subcutaneous AT**

There is great individual variability in the effect of androgens on the accumulation of visceral fat in men and women [41]. Most consistently [37, 38], it is observed that androgens influence adipocyte function and distribution by the inhibition of adipocyte differentiation, which modulates lipolysis and lipogenesis [37, 42]. Also different compartments of fat tissue exhibit phenotypic heterogeneous dysfunction in PCOS [42, 43]. As an example, catecholamine-induced lipolysis is higher in visceral fat than subcutaneous fat [42], which is a possible link to the increased accumulation of fat in this specific depot in women with PCOS. Depressed expression of β2-adrenoceptors and hormone-sensitive lipase in subcutaneous fat might explain why the lipolysis is lower [42].

The mechanisms causing IR in PCOS have many similarities with those seen in relation to visceral adiposity [44]. Accumulation of fat in the visceral compartments is contradictory with the fact that lipolysis in this depot is higher than in subcutaneous fat depots, unless these high rates of fat mobilization are matched by high rates of fat deposition. Dicker et al. [42] proposed that increased lipolysis is important in the development of IR in PCOS. Excess free fatty acids derived from lipolysis/hydrolysis of acylglycerol in adipocytes accumulate in the hepatic portal veins, and this induces hepatic dysfunction [45]. This contributes to elevated glucose secretion, provokes pancreatic insulin secretion and glucose uptake in AT [38, 45]. Androgens are generally thought to have a direct influence on the metabolic aberrations in PCOS, though some studies indicate differently [46].

**Hyperandrogenemia and IR**

As women with PCOS have both HA and IR, it is important to understand how these conditions are associated (fig. 1). To understand how HA influences IR, researchers examined the effects of supraphysiological concentrations of testosterone on subcutaneous adipocytes from women [36]. It was found that testosterone induced IR in subcutaneous adipocytes through the activation of androgen receptors. The effect of insulin on glucose metabolism was impaired due to defects in phosphorylation of a downstream protein, protein kinase-Cζ, which normally mediates the effect of insulin on glucose transport.

Similarly, subcutaneous adipocytes from women with PCOS were studied to see what might cause IR in relation to PCOS [47]. Interestingly, the adipocytes from women with PCOS displayed enhanced glycogen synthase kinase-3β (GSK3β) action. As a consequence, insulin-stimulated glucose transport was impaired and IR developed. Furthermore, overexpression of GSK3β promoted androgen biosynthesis through direct stimulation of P450c17 enzyme activity [47]. Results from these two studies illustrate that continuous exposure to androgens impairs insulin action and contributes to the development of IR [36].

**Excess Insulin Has Multiple Effects**

In PCOS, HI may have unique effects (see fig. 2). Studies in mice have revealed that liver and muscle cells exhibit IR during continuous HI, whereas insulin receptors in pituitary and ovarian cells stay sensitive, an adaptation that increases pituitary hormone secretion and ovarian androgen production [48]. This observation has been used as a model to explain the insulinemic contribution to advanced androgen production and progress to PCOS in women. Accordingly, HI contributes to HA by the direct stimulation of steroidealogenesis in ovarian

**IR, Obesity and PCOS**

Thicker than in subcutaneous fat depots, unless these high
Fig. 1. Interacting mechanisms in obesity and HA. HA and obesity have many similar molecular mechanisms that influence and exacerbate the path of each condition. The origin is individual and therefore varies. Obesity: In presence of excess AT, lipolysis increases, which causes pancreatic secretion of insulin and might eventually cause IR. AT also causes low-grade inflammation through the release of a wide range of mediators that influence body distribution (through activation of androgen synthesis) and increase release of proinflammatory mediators (TNF-α and IL-6). Obesity is often related to ovarian dysfunction due to these aforementioned mechanisms especially through its effects on insulin secretion. Low-grade inflammation is associated with decreased release of HMW adiponectin and causes increased release of proinflammatory mediators; both conditions are associated with IR. Increased secretion of leptin causes gonadotropin secretion, and together with proinflammatory cytokines this causes increased androgen synthesis. HI: Continuous HI causes development of IR, increases fat deposition and influences ovarian function through its direct stimulation of hormonal biosynthesis. HI also influences HA, as described in figure 2. HA is associated with HI, but this relation is not clearly elaborated, but might be related to increased deposition of AT and increased lipolysis during HA. HA decreases adipocyte differentiation and increases lipolysis and lipogenesis in subcutaneous fat, and causes deposition of visceral fat. HA is associated with increased activity in GSK3β, defects in protein kinase-Cζ and stimulation of androgen receptors (ARs). Increased production of androgens affects the hypothalamic-pituitary-ovarian axis and causes ovarian dysfunction, and might induce secretion of adipocytokines. Ovarian dysfunction: Dysfunctional ovaries might directly cause increased androgen biosynthesis, and therefore contribute to the pathogenesis and severity of HA and deposition of AT.

Fig. 2. Influence of excess insulin on HA. Insulin stimulates pancreatic secretion of SHBG which increases the concentration of free circulating testosterone. During HI, the hypothalamus and pituitary remain sensitive to insulin and increase pulse frequency of GNRH secretion, which causes elevation of the LH/FSH ratio, and this induces ovarian androgen production. Also, insulin directly stimulates ovarian hormone production. These mechanisms all contribute to the development of HA.
theca and granulosa cells [49]. Up to a certain level, excess insulin stimulates hypothalamic GnRH secretion, and therefore induces gonadotropin secretion (particularly LH) from pituitary cells, which in turn stimulates androgen production in the ovaries [50]. When HI is established, the pituitary is prompted to secrete large changes in body composition that is possibly mediated by androgens through changes in body composition [54]. Therefore, the combination of abdominal adiposity and androgens (in PCOS) might be additive because both conditions lower HMW adiponectin.

**Obesity-Related Low-Grade Chronic Inflammation May Affect the Pathophysiology of PCOS**

**Leptin/Adiponectin**

In adolescents and women with PCOS, the adipocyte-produced and -released adipocytokines including leptin, adiponectin, visfatin, monocyte chemotactant protein-1, and retinol-binding protein 4 are altered [29, 52, 53]. As an example, a case-control study [29] (31 women with PCOS and 57 controls) showed that levels of leptin in PCOS patients were elevated, whereas adiponectin levels were unchanged or even lowered. This observation is interesting since leptin is able to stimulate gonadotropin secretion, a mechanism that relates to early puberty and is often seen in PCOS and obese girls [15]. Adiponectin is closely related to insulin sensitivity, and IR is connected with lowered adiponectin concentrations [29]. Total adiponectin is not predictive of PCOS, but high-molecular-weight (HMW) adiponectin, which is part of plasma adiponectin that forms multimers, has an inverse association with IR and the inflammatory state from abdominal obesity. Interestingly, HMW adiponectin is lowered in PCOS women independently of BMI and IR, an indirect effect that is possibly mediated by androgens through changes in body composition [54]. Therefore, the combination of abdominal adiposity and androgens (in PCOS) might be additive because both conditions lower HMW adiponectin.

**Proinflammatory Cytokines**

In both adolescent and adult women, several proinflammatory mediators, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), are elevated in obesity and PCOS [55–57]. Whether these cytokines are elevated because of excess AT or because of mechanisms induced by HA in PCOS is of interest.

HA is thought to induce low-grade inflammation by intensifying the sensitivity to glucose-induced oxidative stress, which is caused by the activation of reactive oxygen species that promote the initiation of TNF-α and IL-6 gene transcription. This response is seen in PCOS patients but not in lean reproductive-age women [55, 58]. TNF-α induces IR through decreased expression of glucose transporter type 4 [59] which reduces the transport of glucose and contributes to the development of HI. Liver production of the acute phase reactant C-reactive protein is induced by IL-6, and it has been associated with cardiovascular events including IR, T2DM and MetS [60]. Besides their potential influence on CVD, proinflammatory mediators stimulate steroidogenic enzymes in the ovaries which accelerate androgen production and induce central obesity through the activation of the hypothalamic-pituitary-adrenal axis which again leads to IR that again might, in turn, initiate HA [56, 57]. Therefore, the degree of both obesity and PCOS influences the inflammatory state which exacerbates the severity of PCOS. Despite this, adipocytokines are not believed to be the primary instrumental factor in the development of androgen excess but rather reflect the development of abdominal adiposity observed in PCOS [26].

**Treatment**

Lifestyle interventions are the first-line treatment for PCOS, especially when it is accompanied by obesity. This suggested priority is based on the fact that reduction of central fat ameliorates the PCOS phenotypes, inter alia improved cyclicity and resumption of ovulation [40]. Also weight loss improves the status of cardiovascular risk factors accompanied by a decreased intima media thickness [61]. The effects of lifestyle intervention on normal-weight PCOS patients, however, could not be identified in the literature. Nonetheless, it is plausible that these women could also benefit from these types of interventions. In addition, it is of great importance to address and improve the psychological aspects of the condition (i.e. self-image, depression). Further, given the negative effects of PCOS on reproductive function [13], these issues...
Pharmacological Treatment

Pharmacological treatment may be added to further ameliorate PCOS symptoms, regarding cosmetic issues, metabolic disturbances (glucose and lipid status) and menstrual irregularities (to restore fertility). Oral contraceptives (estrogen-progestin combination pill) and insulin sensitizers (metformin) are currently accepted as effective in adolescents [14, 28] either in combination with lifestyle intervention or when intervention fails. Recently, a study revealed a positive regulatory effect on endocrine biochemical markers and visceral adiposity in non-obese PCOS women after polytherapy consisting of pioglitazone (a PPARγ agonist), flutamide (androgen receptor blocker), and metformin in combination with estrogen-progestagen [64]. However, a further examination of pharmacological treatment modalities is beyond the scope of this review. Although promising, polytherapies such as these have not been evaluated in adolescents. Also, as the long-term metabolic effects of estrogen-progestin pills are not well studied, this should be kept in mind when treating adolescents. Therefore, pharmacological treatment for young girls should be undertaken with great consideration, and should be decided on a case to case basis balancing the indication and potential complications from the disease against drug-induced side effects.

Conclusion

As greater numbers of adolescent girls are becoming overweight and obese, they are potentially facing a greater risk of developing PCOS. The origins of PCOS are multifactorial, and likely there is a genetic component. Obesity and PCOS share many common features in their pathogenesis, with IR and HI playing key roles. Nonetheless, it remains unknown which condition comes first, and research is needed to disentangle the causal pathways among these factors. Although the complex metabolic interrelationships between obesity and PCOS have yet to be fully understood, the co-occurrence of these conditions in adolescent girls tends to increase the severity of the negative health consequences of each condition. Given the serious consequences of PCOS on women’s cardiovascular, reproductive and mental health, it is of great importance to detect girls who are obese in adolescence (and even younger), because counseling and treatment in an early stage of the metabolic disturbances may prevent the future deleterious effects on their health.

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