

Adolescent polycystic ovary syndrome: pathophysiology and implications of the disease

Sajal Gupta, Dinah Chen, Katherine O'Flynn O'Brien, Anjali Chandra, Lauren Metterle, Shubhangi Kesavan, Ashok Agarwal

Center for Reproductive Medicine, OB-GYN and Women's Health Institute and Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio, USA

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Corresponding author:

Sajal Gupta, MD
Center for Reproductive Medicine
Cleveland Clinic
9500 Euclid Avenue, Desk A19.1
Cleveland, OH 44195, USA
Phone: 216-444-9485
Fax: 216-445-6049
E-mail: guptas2@ccf.org

Abstract

Polycystic ovary syndrome (PCOS) is one of the most prevalent female reproductive endocrinopathies, affecting many of women worldwide. We have reviewed the literature regarding the linkage between obesity, insulin resistance, and hyperinsulinemia in women with PCOS. Obesity has been reported as an epidemic in developed countries, in adults as well as adolescents. We have discussed the attempts to standardize the definition and diagnostic criteria for PCOS, most notably at the National Institutes of Health (NIH) conference of 1990, the Rotterdam conference of 2003, and the Androgen Excess Society (AES) conference held in 2006. The lack of defined criteria for adolescent PCOS is reviewed in this article. Additionally, the fascinating endocrine and metabolic disorders associated with the syndrome are discussed. Various models that have been proposed to explain the genetic nature of the disease: the "single-gene mendelian" model, the "multifactorial" model, and the "variable expression-single gene" model have also been enumerated. It is critical that the diagnosis of PCOS be made early and periodic screening is essential for the detection of the metabolic consequences of PCOS.

Key words: metabolic syndrome, hyperandrogenism, hyperinsulinemia, obesity, genetics.

Introduction

Polycystic Ovary Syndrome (PCOS) is one of the most prevalent female reproductive endocrinopathies, affecting 5 to 10% of women worldwide [1]. A relatively widespread disorder, PCOS has remained an important topic of research. Along with endocrine and genetic factors, obesity is a key complication related to PCOS. Of the women clinically diagnosed with this syndrome, 50% are overweight or obese and between 50 and 60% reportedly exhibit insulin resistance [2, 3]. Many studies have reported a link between obesity, insulin resistance, and hyperinsulinemia in women with PCOS. Obesity has become an epidemic in developed countries, not only in adults but adolescents as well. In fact, one study estimates that 15% of adolescents are overweight, a percentage that has tripled over the past two decades [4]. Therefore, concern is increasing over the possible effect on obesity related syndromes, such as PCOS, especially in adolescents. Consequently, adolescent obesity and PCOS is currently a topic of intense concern.

Polycystic ovary syndrome is the most common cause of menstrual dysfunction in teenage girls. Although only a few studies focusing on the prevalence of PCOS among adolescents have been conducted, one reported the adolescent incidence to be 3% [5, 6]. More than 50% of adolescents exhibiting the features of this disorder (hirsutism, acne, hyperandrogenemia, etc.) are obese and at high risk for developing type II diabetes [7, 8].

Attempts at standardization

The diagnosis of PCOS remains a subject of contention. Several attempts have been made to standardize its definition and diagnostic criteria, most notably at the National Institutes of Health (NIH) conference of 1990, the Rotterdam conference of 2003, and the Androgen Excess Society (AES) conference held in 2006. The AES requires the specific presence of clinical and/or biochemical hyperandrogenism in combination with either polycystic ovary morphology and/or oligo-anovulation [9]. The NIH consensus of 1990 defined PCOS as the presence of both hyperandrogenism and ovarian dysfunction, with no mention of ovarian morphology. However, the Rotterdam consensus included the presence of polycystic ovary morphology along with hyperandrogenism and oligo/anovulation [10]. Both the NIH and AES criteria also stipulate that other causes of hyperandrogenism, such as Cushing's syndrome or hyperprolactinemia, be excluded [11]. There are three sets of criteria that have been proposed to establish the diagnosis in adult women: the NIH criteria, the Rotterdam criteria, and the Androgen Excess Society guideline.

All three criteria agree that the exclusion of other disorders is necessary. The 2003 Rotterdam criteria require the presence two of three conditions: (1) oligo- or anovulation, (2) clinical and/or biochemical signs of hyperandrogenism, and/or (3) polycystic ovaries on transvaginal ultrasound (12 or more follicles in each ovary measuring 2-9 mm or increased ovarian volume 10 ml of one ovary). This definition would result in four subsets of PCOS: (1) irregular menstrual pattern plus polycystic ovary morphology plus (clinical or laboratory) hyperandrogenism, (2) irregular menses plus hyperandrogenism, (3) hyperandrogenism plus polycystic ovary morphology, and (4) irregular menses plus polycystic ovary morphology. The last category remains in dispute in regards to whether these patients should be diagnosed under the broad rubric of PCOS, because of some similar metabolic findings, or whether such labeling is premature. The Androgen Excess Society, published 2006, underscored the need to define PCOS.

Currently, there is no defined standard to judge and diagnose PCOS in adolescents for a variety

of reasons. First, ovulation is often irregular in early menarche and thus, anovulation cannot be considered a definite indication of the existence of the syndrome [12]. Second, multifollicular ovaries, which normally may be present in adolescent girls, are difficult to differentiate from polycystic ones [12]. Third, transvaginal ultrasounds are not routinely performed in adolescents, which inhibits the visualization of the ovaries and therefore precludes any invasive diagnosis of polycystic morphology [12]. Finally, there is little information regarding normal levels of androgens in adolescents and a lack of consensus on the chemical levels of hyperandrogenemia. Therefore, determining whether levels of androgens are abnormally high is a complex task [12]. It appears that a diagnosis of PCOS in this age group is mainly based upon the criteria of clinical hyperandrogenism and menstrual dysfunction [6].

Associated complications of polycystic ovary syndrome

Because irregular ovulation or anovulation is typical in adolescents, the current basis of diagnosis of PCOS in adolescents relies heavily upon clinical signs of hyperandrogenism. In a recent study, 42% of adolescent girls with oligomenorrhea – 22% of whom also had polycystic ovaries – were found to be positive for PCOS [13, 14]. This finding suggests menstrual dysfunction in addition to polycystic morphology is strong indicators of PCOS in adolescents.

Women and adolescents with PCOS present with certain common physical characteristics. Many experience excess male-pattern hair growth. This symptom, termed hirsutism, is a marker of hyperandrogenism and usually becomes apparent at menarche. The patient may have acne as well as dark pigmentation of the skin, usually around the neck, which is known as acanthosis nigricans. Polycystic ovary morphology is present in some, but not all, women with PCOS. These ovaries are enlarged and contain an increased number of developmentally arrested, small antral follicles [15].

Obesity, and in particular, central adiposity, is another characteristic commonly associated with the syndrome. Obesity increases the severity of insulin resistance and propels hyperandrogenism through various mechanisms [4]. All of these traits are implicated in the internal conditions of the PCOS woman.

Insulin resistance

The effect of insulin resistance on PCOS is complicated. Women with PCOS tend to have more severe insulin resistance than their normal

counterparts. Insulin resistance is found in 50 to 60% [3] of PCOS women, and 31% [16] present with glucose intolerance. Insulin resistance is often accompanied by hyperinsulinemia and hyperandrogenemia. Consequently, both hyperinsulinemia and hyperandrogenism are often present in women with PCOS. As documented, there is a cyclic relationship between hyperinsulinemia and hyperandrogenism in PCOS women; insulin induces the production of androgen, which in turn propels visceral fat accumulation and eventually exacerbates insulin resistance, leading to severe hyperinsulinemia [14].

Hyperandrogenism is compelled by the actions of insulin through various mechanisms. One such mechanism is the dysregulation of sex hormone binding globulin (SHBG). Hyperinsulinemia is known to suppress the function of SHBG [16]. Once concentrations of this globulin fall, it can no longer bind to testosterone. Subsequently, levels of free circulating testosterone rise and androgen production increases. Studies support a negative correlation between the concentration of SHBG and insulin [2].

A second mechanism by which insulin resistance affects the production of androgens is through the activation of gonadotrophin releasing hormone (GnRH). Activation of GnRH leads to elevated levels of luteinizing hormone (LH) [12], which eventually causes the production of androgens at the theca cell level. Conversely, the presence of hyperandrogenemia has been indicated as a possible cause of increased secretion of LH [16]. Once again, the vicious cycle linking insulin resistance to hyperandrogenism manifests itself in this positive feedback system.

Androgen synthesis is further increased through the actions of insulin on the ovary and pituitary gland. The insulin dysfunction characteristic of women with PCOS may occur due to dysfunction of the insulin receptor or defects in the signaling pathways involving insulin [15]. High concentrations of insulin increase androgen secretion by overpowering insulin receptors, which subsequently reduces SHBG levels [15]. Additional androgen production is propelled by the effects of excess insulin, which serves to inhibit the synthesis of insulin growth factor (IGF) binding proteins. This allows IGF-1 to bind on the ovaries and increase androgen production [17].

A study by Sawathiparnich indicates that the level of insulin resistance is elevated in girls with PCOS and is independent of obesity [18]. Glucose intolerance, which has been found to increase the severity of insulin resistance and hyperinsulinemia [19], is also a key component of PCOS. In a study conducted by Palmert et al., 33% of adolescent girls with PCOS exhibited impaired glucose tolerance [18, 20]. Furthermore, another

study demonstrated that glucose intolerance was present at higher percentages among *obese* PCOS adolescents than in PCOS patients with normal body weights [14]. Thus, not only are PCOS adolescents already predisposed to severe insulin resistance, but obese PCOS adolescents suffer the effects of an exacerbated level of glucose intolerance compounded with all other associated symptoms.

Visceral fat/adiposity

Another common phenotypic trait of PCOS women is visceral fat. Women with PCOS demonstrate a comparatively high level of central adiposity, even amongst those who do not present with obesity [21]. The accumulation of fat in the abdominal area has been correlated with an increased presence of menstrual dysfunction, acanthosis nigricans, and severe hirsutism [22]. Studies have further correlated the level of androgens and the amount of visceral fat present [14].

In adult patients and adolescents alike, 50 to 70% have increased central adiposity accompanying PCOS [23, 25]. The consequences of adiposity may be at hand even in adolescence [24], especially in a society in which obesity is rapidly becoming the norm [11, 25]. Increased central adiposity has been shown to be directly proportional to the level of insulin in the body and also to the severity of insulin resistance [14, 26]. Visceral adiposity can incite insulin resistance and metabolic syndrome [11, 25].

Central adiposity causes both androgen production and is stimulated by it, feeding a vicious cycle [27, 28]. Like their adult counterparts, PCOS adolescents are believed to be at an elevated risk level for developing diabetes mellitus or metabolic dysregularities [29] due to androgen excess [11]. Currently, the diagnosis of PCOS does not consider adiposity as an identifier of the syndrome. However, the pathogenic effect of adiposity on hormonal activity cannot be denied [11, 30].

Relationship of obesity and polycystic ovary syndrome

It is generally acknowledged that the existence and proliferation of PCOS is closely tied to obesity. Not only does obesity itself pose a risk in obvious ways, but it also complicates and compels the development of hyperinsulinemia and hyperandrogenism. Women who are obese or overweight naturally exhibit higher levels of endocrine dysfunction. The presence of obesity exacerbates these endocrinal disturbances. Thus, it appears that being overweight both induces and sustains PCOS.

There is an initiatory relationship between obesity and the production of androgens [10]. In a study by McCartney et al., it was determined that obese girls exhibited higher levels of hyperandrogenemia. Furthermore, the production of androgens in itself could be a cause of PCOS [11, 31]. This finding highlights obesity's dynamic role in PCOS: it is apparent that obesity, which is caused by elevated levels of androgens, also increases the production of androgens that lead to the development of PCOS.

Obesity also exacerbates the abnormalities concerning gonadotropin and sex steroid secretion in women with PCOS. Further SHBG down-regulation, a globulin already present in lower levels in women with PCOS, is propelled by obesity [32].

Additionally, obesity negatively affects the ovary by further disrupting the ratio of LH to follicle stimulating hormone (FSH). One study determined that LH levels were increased in obese women with PCOS [4, 33]. This increased LH secretion will also affect the production of androstenedione in theca cells, leading to an increase in androgen levels.

Similarly to adult PCOS patients, obese adolescent girls with PCOS appear to have a higher rate of menstrual disturbance as well as elevated levels of testosterone and free androgens [4]. Levels of SHBG were lower in overweight adolescent females than in PCOS adolescents who were not overweight [24]. Moreover, as a function of overweight and obesity, adolescent PCOS females also exhibit higher levels of insulin which promotes the production of androgen by the ovaries [34]. Ultimately, obesity serves to both exacerbate and instigate the problems of the syndrome. Consequently, it is suggested that the earlier the onset of obesity, the greater the consequences for the young patient [11].

Ovarian dysfunction

Polycystic ovary syndrome impairs the theca and granulosa cells of the developing follicle. Each cell operates under the direction of LH or FSH to produce steroids. The theca cell contains receptors for LH, which stimulates the production of androstenedione from cholesterol when bound. Androstenedione then interacts within the granulosa cell. The periphery of the granulosa cells contains receptors for FSH, which bind and stimulate the aromatase enzyme to convert androgens to estrogens. In the PCOS woman, the roles of each cell are impaired, and the result of this malfunction is hyperandrogenism.

Theca cells

Patients with PCOS exhibit signs of increased steroidogenesis and enhanced androgen activity

due to a greater number of theca cells. It has been suggested that overproduction of androgens is facilitated by the action of insulin on theca cells. Insulin functions to upregulate the expression of the *P450c17* gene in theca cells, in addition to enhancing the LH receptor activity of the cell [35, 36]. The *P450c17* gene encodes the enzyme 17-hydroxylase; this enzyme is responsible for androstenedione production, which eventually is converted to testosterone. Therefore, insulin ultimately leads to the presence of excess testosterone. Additionally, it is thought that insulin may stimulate ovarian steroidogenesis by mimicking LH activity [37]. Thus, hyperinsulinemia plays a key role at the level of the ovaries in PCOS.

Granulosa cells

Aromatase inhibition within granulosa cells plays a critical role in the development of hyperandrogenemia. In women with PCOS, an imbalance in the ratio of LH to FSH persists due to elevated concentration of LH. Follicle stimulating hormone is essential in stimulating the aromatase enzyme for the conversion of androgen to estrogen. However, the increased production of androgens within the theca cells overpowers the capacity of the granulosa cells. Thus, the concentration of androgen remains elevated.

Moreover, Mullerian inhibiting substances (MIS) contribute to the accumulation of androgens and the eventual arrest of follicular development. Mullerian inhibiting substances are thought to inhibit aromatase function [38]. Grossman et al. [39] concluded that the presence of MIS in the granulosa cells leads to a notable decrease in estradiol production [39]. According to a study conducted by Wachs, women with PCOS have 3.4 times the typical amount of MIS [40]. The results of these studies coincide with the belief that MIS promotes androgen excess.

Fetal disposition

Polycystic ovary syndrome manifests during adolescence, suggesting a pre-pubertal or pre-natal predisposition [1, 6, 31, 41]. According to one hypothesis, PCOS occurs when a fetus is overexposed to androgens during its development. Many studies on female animal models support this concept. An analysis of sheep that were exposed to excess androgens in-utero ascertained that the GnRH pulse generator had been reprogrammed, resulting in a decrease in sensitivity to estradiol negative feedback [42, 43]. This alteration of hormone levels leads to elevated LH levels, causing issues in follicular development. Additionally, the exposure seemed to be linked to an increase in follistatin and a decrease in activin, which suppress FSH and obstruct follicular growth [42]. Another

study subjected female rhesus monkeys to high levels of testosterone during in-utero development. Later in life, these monkeys displayed hyperandrogenism, ovulatory dysfunction, and defective insulin secretion, all features associated with PCOS. Increased levels of LH appeared only in monkeys exposed to testosterone during early gestation, which suggests that there is a critical time period during which exposure leads to PCOS [44, 45].

Evidence for pre-natal and pre-pubertal predisposition has also been supported by clinical studies in humans. Both Hague et al. and Barnes et al. conducted a study of women who were prenatally exposed to high androgen levels as evidenced either by congenital adrenal hyperplasia or congenital adrenal virilizing tumors. After birth, androgen levels normalized; however, many women exhibited PCOS later in life [46, 47]. Another study demonstrated an association amongst prenatal androgen exposure, loss of P450 aromatase or SHBG gene function, and PCOS [48, 49]. Unfortunately, the precise mechanism of excessive androgens during fetal development still remains unclear.

Polycystic ovary syndrome in pregnant mothers is a potential cause of PCOS in offspring [50]. Various studies have demonstrated that pre-existing elevated androgen levels in combination with the hyperinsulinemia in pregnant women with PCOS overexposes a fetus to high androgens levels. Under normal conditions, placental aromatase converts excess androgens to estrogens. In the presence of hyperinsulinemia, aromatase activity is inhibited. Consequently, pregnant women with PCOS create a fetal environment with increased exposure to androgens [50-53]. Additionally, exposure to high levels of insulin has been implicated as a cause of low birth weight, and birth weight is a potential marker of PCOS [1].

Extreme birth weight, either low or high birth weight, can result from altered developmental pathways, leading to severe adiposity in conjunction with unhealthy diet patterns. This, in turn, predisposes to hyperinsulinemia, hyperandrogenism, and, after puberty, ovulatory dysfunction due to issues with follicle growth and development. Poor in-utero nutrition results in low birth weight and subsequent fetal growth restriction. As a means of survival, the fetus undergoes permanent physiological and structural changes [54-57]. However, in the post-natal period, with subsequent exposure to adequate nutrition and excessive adiposity, PCOS features can develop [23, 31].

Conversely, women with elevated birth weights maintain high levels of adiposity throughout early childhood due to poor dietary patterns thereby increasing their risk for PCOS [58-60]. Interestingly, women with high birth weights more often exhibit all three major criteria for PCOS diagnosis:

hyperandrogenism, anovulation, and polycystic ovaries; whereas women with low birth weight typically do not present with polycystic ovaries [58].

Childhood obesity, independent of fetal nutrition, represents another potential factor in PCOS development. It is associated with decreased SHBG levels resulting in increased free testosterone and insulin resistance with compensatory hyperinsulinemia. Studies demonstrate obese adolescents exhibit insulin resistance more often than their normal weight counterparts. Increased insulin levels promote ovarian androgen production, leading to hyperandrogenism. Hyperandrogenism subsequently distorts the hypothalamic pituitary ovarian axis, resulting in a persistently rapid pulse from the GnRH pulse generator, making the body resistant to estrogenic negative feedback. Consequently, adolescent women with PCOS have higher LH levels and lower levels of FSH. Altered hormone levels inhibit proper follicular development and lead to the expression of PCOS during adulthood [23, 31, 61, 62].

The role of obesity in the pathogenesis of PCOS has been demonstrated in many studies. The McCartney et al. study of 76 peripubertal girls found that those who were overweight girls showed greater rates of hyperandrogenemia when compared to normal weight girls [31]. Another study reported that total testosterone in obese pre-pubertal girls was 40 to 50% higher than that in age-matched equivalents, although the difference was not statistically significant because of the small sample size [63]. This was also demonstrated in a study of pre-pubertal German girls, which found that obese girls had lower SHBG levels and a median testosterone concentration that was four times greater than that of the normal weight girls [61]. There is currently no definite causal relationship between androgens and adiposity. However, pre-pubertal obesity consistently seems promote hyperandrogenism. Various studies have demonstrated correlations between adiposity and higher levels of testosterone, however some studies conclude the two are independently related and the correlation is attributed to an inverse relationship between SHBG and adiposity [31].

In a recent study, Leibel et al. concluded that the presence of metabolic syndrome in the father of a woman with PCOS seemed to be more related to the maternal PCOS. The prevalence of metabolic syndrome was 1.5 to 2 fold greater in the fathers of daughters with PCOS than in the average population [64]. However, this association needs further investigation.

GnRH pulse generator

The GnRH pulse generator is a group of hypothalamic neurons that release GnRH in

a pulsatile manner. GnRH stimulates the secretion of LH and FSH. Varying levels of LH and FSH control follicular growth and development, effectively regulating the menstrual cycle [65]. The frequency of the GnRH pulse generator modulates the differential production of LH and FSH [65, 66]. Rapid pulses favor the production of LH while slower pulses favor the production of FSH [67-69]. Kirk et al. concluded this occurs as a result of rapid GnRH pulses increasing the expression of follistatin. Follistatin acts to inhibit the effects of FSH by binding to intragonadotrope activin, therefore favoring the production of LH [70]. In women with normal ovulatory function, the GnRH pulses gradually increase during the follicular phase and peak in the later half, increasing LH production and decreasing FSH production. Simultaneously, estradiol production reaches a threshold due to positive feedback, permitting the release of the LH, known as the mid-cycle LH surge; this induces ovulation. Ovulation is followed by the development of the corpus luteum, which manufactures progesterone. The progesterone subsequently slows the GnRH pulse generator, emitting pulses that favor FSH, and creating what is known as an FSH window. This is responsible for initiating the next wave of follicular growth and development [71-75].

Women with PCOS, however, have invariably rapid GnRH pulse frequencies in favor of LH [76]. Thus, these women typically present with persistently elevated LH levels and LH:FSH ratios [77]. LH acts as a stimulant for ovarian androgen production. Women with PCOS, therefore, present with hyperandrogenemia. Blank et al. postulated that the systemic issues in women with PCOS may be the result of failure to suppress GnRH pulsatility [66].

Long-term consequences of polycystic ovary syndrome

Over time, PCOS can cause serious health conditions. It is critical for physicians treating PCOS patients to understand how the varying pathophysiologies of the disease can combine to cause additional health issues. Women with PCOS often develop hyperandrogenism, hirsutism, and insulin resistance and experience excessive weight gain. The synergy of these symptoms can result in health issues such as metabolic syndrome, cardiovascular disease, type II diabetes mellitus, cancer, sub-fertility, and psychological distress [2, 9, 19, 29, 78-93].

Metabolic syndrome

Metabolic syndrome is characterized by several risk factors that can lead to cardiovascular disease, which is a major long-term consequence associated with PCOS. Characteristics of metabolic syndrome

are abdominal obesity, increased levels of triglycerides, hypertension, increased plasma levels of fasting glucose, hyperinsulinemia, and decreased levels of high density lipoprotein cholesterol (HDL-c) [17, 94]. The condition is particularly related to PCOS because of the prevalence of insulin resistance [17]. Furthermore, adolescent girls with PCOS are at higher risk for developing metabolic syndrome because they already exhibit these risk factors at a young age [88]. Coviello et al. reported that the prevalence of metabolic syndrome in young girls with PCOS was 37 vs. 5% in a control group of normal girls. The study also found that obesity and insulin resistance were risk factors for metabolic syndrome but that hyperandrogenemia was the only constant predictor of the syndrome. After adjusting for body mass index (BMI) and insulin resistance, adolescent girls with PCOS had almost four times the risk of metabolic syndrome for every 25% increase in free testosterone in comparison with the control group [95]. Body mass index and waist circumference, a measure of abdominal fat, were found to be predictors of cardiovascular disease [96]. In the Coviello study, the prevalence of metabolic syndrome was 62% in obese women with PCOS and 63% in extremely obese women with PCOS [95].

Adolescence is a critical time to recognize the risks associated with metabolic syndrome because its onset during adolescence is correlated with the development of cardiovascular disease in adulthood [97]. The syndrome also contributes to hyperandrogenemia, further exacerbating the cycle of accumulating risk factors for the disease [95]. The combination of metabolic syndrome and PCOS promotes higher levels of androgens in the body [98], which can act on androgen receptors located on adipocytes, causing further accumulation of intra-abdominal fat [99]. Central adiposity is a factor in both PCOS and MS, which contributes to the vicious cycle of hyperinsulinemia and hyperandrogenemia. Patients with PCOS who suffer from metabolic syndrome also have lower high density lipoprotein cholesterol (HDL-c) levels, higher low density lipoprotein cholesterol (LDL-c) levels, and higher levels of triglycerides than girls who only have PCOS [95]. These factors present an added cardiovascular risk in young PCOS patients [97].

Young PCOS patients should be counseled about ways to prevent metabolic syndrome in order to avoid cardiovascular disease and type II diabetes mellitus in adulthood [17]. Data collected about abdominal fat and triglyceride levels in girls aged 9 through 11 was found to be predictive of whether a patient would develop the syndrome before entering their twenties, demonstrating the necessity to emphasize the importance

of a healthy lifestyle early in life [100]. Furthermore, rates of metabolic syndrome in adolescence increase concurrently with body weight, reaching a prevalence of 50% in excessively obese children [20, 25, 101, 102]. Consequently, it is critical to recognize that the symptoms of PCOS can exacerbate the development of metabolic syndrome and that it is essential for patients with PCOS to initiate proper diet and exercise at an early age to reduce the likelihood of developing the syndrome [95].

Another complication associated with PCOS is nonalcoholic fatty liver disease (NAFLD), which is usually considered the hepatic component of MS [103]. One of the most common causes of liver disease in western countries [104, 105], NAFLD is characterized by steatosis or fibrosis of the liver [105]. A more aggressive form of the disease is nonalcoholic steatohepatitis (NASH), which is characterized by “necroinflammatory changes” and pericellular fibrous degeneration [106]. Patients with NASH are at a greater risk of developing serious conditions such as “advanced fibrosis, cirrhosis, and hepatocellular carcinoma” [107]. NAFLD and NASH share the risk factor of insulin resistance, a common problem associated with PCOS [108-110]. Approximately 50% of PCOS patients exhibit insulin resistance and also have metabolic syndrome.

A study conducted by Cerda et al. determined that the prevalence of NAFLD in PCOS patients was 41%, which was significantly higher than the prevalence of the disease in the control group (19%) [106]. Additionally, the PCOS patients in the study had a much higher frequency of insulin resistance; 63 vs. 31% in the control group. The relationship between insulin resistance and NAFLD in PCOS patients was also related to their BMI: a higher BMI promoted increased levels of insulin resistance, which acted to increase the prevalence of NAFLD [111]. Another serious finding of the study by Cerda et al. is that PCOS women have high levels of aminotransferase, which is an indicator for the development of NASH [106]. Overall, this study demonstrated the importance of early detection and treatment of liver disease in PCOS patients to avoid serious complications like NASH, which is more amenable to treatment during adolescence [104, 112].

Cardiovascular disease

The development of cardiovascular disease and other vascular conditions is a serious consequence associated with PCOS. Similarly, as in the development of metabolic syndrome, the pathophysiology of PCOS is also related to cardiovascular diseases. Obesity, high blood pressure, type II diabetes, insulin resistance, dyslipidemia, abdominal fat, and decreased ability to break down blood clots – all factors that relate to PCOS – also put PCOS women

at a greater risk for heart disease. High androgen levels in the body also play a critical role in the development of heart disease as calcification of the aorta is related to hyperandrogenemia independent of BMI, age, and incidence of PCOS, highlighting their significant role in the development of the disease [113]. All of these are risk factors for heart disease. Obesity during adolescence was also correlated with carotid intimal medial thickening, which may partly explain how PCOS predisposes women with a high BMI and hypertension to vascular diseases [114, 115]. Additionally, another study found that women with PCOS who have a combination of insulin resistance, high blood pressure, and dyslipidemia also have a greater chance for developing cardiovascular disease and cerebral vascular issues [116].

In a recent study by Battaglia et al., PCOS women had higher white blood cell counts than healthy women ($7,273 \pm 789$ vs. $6,182 \pm 1,004$, respectively). Studies have discovered that increased inflammation can lead to the onset and progression of atherosclerosis. Consequently, this finding further emphasizes that women with PCOS are prone to heart disease [117]. The study by Battaglia et al. also found that in PCOS women, the mean (SD) level of homocysteine was 11.5 ± 0.5 vs. 9.8 ± 1.5 $\mu\text{mol/l}$ in the control population. Homocysteine levels have long been recognized as a risk factor for heart disease [118]. The elevation of homocysteine levels combined with advancing age [117] puts PCOS women at risk for heart disease [119].

Furthermore, lipid and androgen levels were linked with cardiovascular disease in patients with PCOS. Previous studies have connected insulin resistance to dyslipidemia, a condition found in PCOS women, because insulin plays a role in the up-regulation of lipoprotein-lipase. However, the Battaglia study found that lipid levels were also correlated with androgen levels, triglyceride levels, and cholesterol, independent of the insulin levels in the body. This finding was confirmed by the fact that the atherogenic index, a marker that is used to determine one’s risk for heart disease [120], is correlated with higher levels of androgens, triglycerides, and cholesterol levels in PCOS women [117]. The atherogenic index is defined as the log (triglycerides/HDL-c) and has been found to be related with one’s risk for heart disease [120]. This relationship highlights the fact that high androgen levels and dyslipidemia may be related to the development of heart disease [117].

The pathophysiology of PCOS also puts women at risk for other vascular problems. Low levels of $\text{NO}_2^-/\text{NO}_3^-$ combined with lipid dysregulation and high levels of androgens impede vasodilation in the endothelium of PCOS women, a condition

which can precede other vascular diseases [117]. Measurements of ophthalmic nerve pressure were obtained from PCOS women and used to estimate cerebral pressure. Polycystic ovary syndrome women had increased pressure in their ophthalmic nerves, which may be due to increased arterial stiffness caused by calcification, lower amounts of $\text{NO}_2^-/\text{NO}_3^-$, and more deposits of triglycerides in the arteries [117]. In obese individuals with PCOS, this effect could be magnified because obesity can put pressure on the right side of the heart and reduce the reuptake of cerebrospinal fluid, which causes increased pressure on the brain [121, 122]. Increased cerebral pressure is also related to another disease called idiopathic intracranial hypertension or IIH [123]. Symptoms include papilledema, impaired vision, increased cerebrospinal fluid pressure, and headache [124-128].

Type II diabetes mellitus

The combination of abdominal fat, obesity, insulin resistance, and β -cell dysfunction in women with PCOS creates an environment in the body that makes them more susceptible to type II diabetes mellitus [83, 85, 88, 100, 129-131]. Type II diabetes mellitus can exacerbate the already fragile vascular state of PCOS patients and can decrease the amount of blood flow to the brain [132]. Women with PCOS are at a greater risk for developing diabetes than healthy women. Long-term studies of women with PCOS have observed that 13 to 16% developed diabetes over a three- to eight-year period [133, 134]. The prevalence of the disease in women without PCOS is only 2% [135]. Additionally, the combination of obesity and PCOS is particularly harmful [136]. Obese women with PCOS have ten times the risk of developing the disease than non-obese PCOS patients [135] and five times the risk of developing type II diabetes mellitus than non-PCOS women when obesity and age were controlled [133].

Gestational diabetes mellitus (GDM), an intolerance to carbohydrates that begins during the early stages of pregnancy, is another problem afflicting PCOS patients, especially those who are already suffering from type II diabetes mellitus [137-142]. Risk factors for GDM non-Caucasian ethnic backgrounds, advanced age, obesity, intolerance to glucose, and a previous experience with GDM during pregnancy [139-143]. The pathophysiological factors of PCOS that predispose women to GDM are obesity, glucose intolerance, and type II diabetes [20, 144-146]. In a study examining the prevalence of GDM in women with PCOS, the authors determined that women with PCOS have twice the risk of developing GDM in comparison to women without PCOS after controlling for age, race, and the number of previous pregnancies [147]. This

finding highlights the necessity for clinicians to counsel their PCOS patients about the development of the disease during their pregnancies and to provide screening.

Cancer

Although no definite correlation between cancer and PCOS has yet been established, women with PCOS are predisposed to cancers, in particular endometrial carcinoma (EC). It is considered conscientious practice to be aware of the relationship between PCOS and EC [148], especially since EC is the most common form of gynecological cancer in the United States [149]. High levels of unopposed estrogen, infertility, and symptoms of metabolic syndrome like obesity, glucose intolerance, and high blood pressure are all risk factors for EC [17, 150]. Persistent estrogen stimulation of the endometrial tissue combined with a lack of negative feedback or opposition by progesterone due to dysregulation of the menstrual cycle has been found to be a risk factor for EC as well [151]. Furthermore, oligomenorrheic women were found to have cancer genes that were activated in their endometrium earlier in life than in normally cycling women [152]. Other studies reported altered expression of genes that are related to EC in women with PCOS [153]. The elevated levels of androgens in women with PCOS have also been correlated with EC; women with EC had three times the levels of androgens than controls [154]. Additionally, women with EC had higher levels of testosterone and androstenedione in their ovarian veins than with women without the disease [155]. Furthermore, androgens were discovered to have stimulatory effects on EC cells [156, 157]. Because of their reduced fertility, women with PCOS are more likely to be nulliparous than the normal women, which is another factor relating to the development of EC [158]. Another hormone that is dysregulated in both PCOS and EC is LH. LH levels are elevated in 65% of women with PCOS and women with EC have an over proliferation of LH receptors, which suggests a possible correlation between the two diseases [159].

Impact of polycystic ovary syndrome on psychological state

Studies have also been conducted to assess the psychological state of women who are suffering from PCOS. The objective in these studies was to determine the effect PCOS has on quality of life or psychological morbidity [160]. Some studies have indicated that women with PCOS have a lower health-related quality of life (HRQoL), especially in regards to sex, self, and health [161]. Women with PCOS also have been determined to have higher

levels of psychological distress than healthy controls [162] and a physiological morbidity of 62.4 vs. 26.4% in the control population [160]. The common symptoms of obesity and hirsutism seen in PCOS contributed largely to the decreased self confidence and body image demonstrated in these women [160]. Women with a higher BMI were found to have a lower quality of life [160] and similarly, women with hirsutism indicated higher levels of social anxiety [163]. These findings are particularly noteworthy for clinicians working with young women with PCOS because adolescence is a sensitive developmental period [164]. Adolescent patients possibly experience negative effects later in life associated with the stress of living with the physical manifestations of the disease at such an early age. However, one study discovered that adolescent patients who received detailed information about the disease had a greater psychological quality of life than other, less informed patients [160]. Therefore, it is critical that clinicians serve as a reassuring and supportive source of information for their adolescent patients.

Lifestyle changes

Although the long-term consequences of PCOS are varied, many stem from the same underlying pathophysiological factors. Lifestyle changes can be utilized to prevent many of the diseases associated with PCOS. Therefore, it is critical to identify PCOS in adolescent girls to initiate these changes immediately and to prevent the onset and progression of other diseases such as type II diabetes, cardiovascular disease, and cancer. These diseases can be avoided by making healthy lifestyle choices such as exercising regularly and maintaining a nutritious, low-fat diet. In addition, it is recommended that women with PCOS be screened for the most common long-term consequences in order to determine their risk for developing these complications and/or detect them early. For example, adolescents with PCOS or high levels of androgens should be screened regularly with oral glucose tolerance test [136].

Genetics of polycystic ovary syndrome

Polycystic ovary syndrome is believed to have a complex genetic trait [165] in which a variety of genes interact with the environment to produce the disease [166]. Because of its varied pathophysiology and the fact that it shares many of its symptoms with other syndromes, it is necessary to rule out other genetic disorders such as 21-hydroxylase-deficient non-classic adrenal hyperplasia (NCAH) when diagnosing PCOS [167]. There are several models that have been proposed to explain the genetic nature of the disease:

the “single-gene mendelian” model, the “multifactorial” model, and the “variable expression-single gene” model [9]. The “single-gene mendelian” model is based on the assumption that the mutation that causes PCOS is unique to the disease and is the result of a single-gene mutation. This would cause the disease to be inherited in a recessive or dominant manner [9]. The “multifactorial model” assumes that the changes that take place in PCOS are not specific to the disease; they may be implicated in other syndromes and already exist in the population, but in combination, they act to cause PCOS [9]. The “variable expression-single gene” model is a combination of the other two models. It proposes that PCOS is caused by a single-gene defect but the severity of the disease is modulated by other genetic or environmental factors [9].

Most studies of the genetic factors underlying PCOS have followed the candidate gene approach, which utilizes genetic markers such as single nucleotide polymorphisms (SNPs) [167]. Geneticists have examined pathways that are related to the pathophysiology of PCOS in order to identify candidate genes for further examination. These pathways include steroid production, folliculogenesis, weight gain, hormone function, and insulin function [9, 167].

Familial studies have also provided evidence to the genetic basis underlying PCOS. Some evidence suggests that the disease is more common in families than in the general population [86]. In a study examining the prevalence of PCOS in female relatives, 35% of premenopausal mothers and 40% of sisters had the disease [168]. These statistics provide a stark contrast with the prevalence of the disease in the general population, which is only 6 to 8% [2, 16]. A study of brothers of mothers with PCOS also revealed that they have elevated androgen levels [86]. Familial studies have also distinguished a genetic basis for insulin resistance and secretion dysfunction [167]. A study performed in the Australian population discovered that in families with a member with PCOS, almost 70% of the other members were resistant to insulin [169]. It was also found that β -cell dysfunction in PCOS may in part be determined by genetic inheritance [170].

The genetic basis of insulin dysregulation was also suggested by examination of cell function. The abnormal uptake and signaling responses of the cells of PCOS women may be due to dysregulation or mutations in the insulin-signaling pathway [171-173]. The regulation of androgens in women with PCOS appears to be unaffected by other hormones and feedback systems. This observation was demonstrated by an experiment in which theca cells removed from women with

PCOS continued to secrete testosterone independently in culture [174].

Recent studies of candidate genes

Recent studies have identified new candidate genes for PCOS in the areas of androgen production and regulation and insulin regulation. Goodarzi et al. studied *SRD5A1* and *SRD5A2*, which code for the isoforms of 5 α -reductase, the enzyme which converts testosterone to dihydrotestosterone (DHT). Levels of this enzyme are frequently elevated in women with PCOS [175-179]. Transcripts of both of the genes were discovered in the ovary, and these may play a role in the arrest of follicle development. The study discovered that the genes had haplotypes related to an increased susceptibility to PCOS. Specifically, for the *SRD5A1* gene, the TA haplotype was found in almost 15% of the PCOS population while only in 10% of controls. The *SRD5A1* gene was also found to have a variant that was related to the severity of hirsutism. In addition to a haplotype, which increased the risk of developing PCOS, gene *SRD5A2* also had a haplotype that decreased the risk of PCOS [167].

Another study of androgen function in PCOS examined the action of the aromatase gene. It has been documented that decreased action of the aromatase enzyme, which converts androgens to estrogens, can lead to PCOS [180]. Furthermore, loss of function mutations in the aromatase gene (*CYP19*) have been observed in PCOS patients [181-183]. Excess levels of androgens in the ovaries were also linked to the stimulation of precocious pubarche [184, 185], a risk factor for PCOS [186]. A recent study by Petry et al. determined that the distal promoter region of the gene that codes for aromatase has genetic variations that are related to androgen levels and hyperandrogenism in young girls. Regulation of androgens was examined in a study of the variations in genes related to the control of dehydroepiandrosterone sulfate (DHEAS) – a marker for the production of adrenal androgen – in women with PCOS. Approximately 25% of women with PCOS have extremely high levels of DHEAS and the majority of PCOS patients have levels that are moderately elevated [187]. DHEA sulfotransferase is coded for by the gene *SULT2A1* and it acts to add a sulfonate group to dehydroepiandrosterone (DHEA), a metabolite of adrenal androgen. Conversely, the sulfonate group of DHEAS is removed by steroid sulfatase (STS). Therefore, these genes are useful markers for examining dysregulation of androgen levels in patients with PCOS. Additionally, DHEAS levels in the body do not seem to be regulated by insulin or hormones suggesting that PCOS is under genetic control [188-192]. One study discovered that

a haplotype and an SNP within the *SULT2A1* gene were both related to lower levels of DHEAS in women with PCOS [193]. However, no association was found between variation in the STS gene and androgen levels in women with PCOS [193]. Furthermore, it seems that DHEAS levels are more influenced by genetic factors in women than in men [194]. The results from this study indicate that the variation in the gene *SULT2A1* may not be a risk factor for the disease but could modulate the amount of excess adrenal androgens in PCOS [193].

A recently proposed mechanism for insulin resistance in PCOS has also been proposed involves abnormal phosphorylation after the binding of insulin to its receptor which causes changes in the signal transduction pathway. It appears that in insulin resistant women with PCOS, serine (Ser) residues were phosphorylated, impeding the activity of the tyrosine kinase activity, which is critical in the normal insulin receptor pathway [17]. Dysregulation of the insulin pathways contributes to the hyperandrogenemia in women with PCOS. Excess levels of insulin can bind to type 1 IGF-1 (insulin growth factor-1) receptors, which increases the response of the thecal cells to LH and produces higher levels of androgens. Additionally, excess levels of insulin decrease the binding ability of SHBG, which also contributes to increased androgen levels in PCOS. High levels of insulin in the body can also prevent the synthesis of the protein that binds with IGF-1, which leads to elevated levels of IGF-1 and hyperandrogenemia [17].

Genetic approaches have also been employed to study ovarian function. A study comparing the pattern of gene expression in the ovary in normal women and those with PCOS found that there were 119 differentially expressed genes. Many of the identified genes were involved in cellular metabolism and control of gene expression, indicating that PCOS is a complex, multifactorial syndrome [195]. One gene that was found to be downregulated in PCOS women is *NR4A1*, which plays an integral role in the induction of apoptosis. It is believed that dysregulation of apoptosis factors in the ovary can lead to an imbalance in the cycles of germ cell death and follicular atresia. This dysregulation could lead to the accumulation of arrested follicles in the ovary. *NR4A1* is mainly expressed by the thecal cells, which suggests that its downregulation in PCOS could be associated with the excess of the theca cells in PCOS women [196]. Another interesting gene identified in this study was the SET (SET translocation) gene, which is involved in the regulation and production of androgens controlled by P450c17. Abnormal expression of this gene may contribute to the high levels of androgens present in PCOS patients [195]. A comparison of the mRNA of oocytes between

women with PCOS and healthy women found that PCOS oocytes have abnormalities in gene expression that could lead to reduced fertility. The 374 genes identified were involved in several areas essential to reproductive function such as chromosome alignment, the regulation of the cell cycle, and the function of the spindle [197]. Additionally, several genes that were categorized as “maternal-effect” genes, which help regulate zygote development [198], were expressed in elevated levels in the oocytes of women with PCOS. These abnormalities in the oocyte could lead to later complications in the development of the embryo [197].

Another mechanism proposed to explain the genetic background of PCOS is the follicle stimulating hormone-granulosa cell (FSH-GC) theory. This theory states that decreased levels of FSH diminish the action of cytochrome P450 aromatase in granulosa cells, causing the accumulation of androgens in the body. This could occur due to various impediments that cause abnormal expression of P450 aromatase such as problems in signaling and insufficient levels of FSH to stimulate the gene expression of P450 aromatase [199].

Limitations

It is important to note that many of the studies discussed in this paper were limited by small control populations and an insufficient number of genetic variants. In addition, the phenotype of PCOS is difficult to determine in all the groups that it affects: young girls, women, and men. Diagnosis is challenging because the phenotypes of the disease are compounded by other syndromes that have similar phenotypes and ethnic factors and the criteria for PCOS has not yet been standardized [167].

Conclusions

Polycystic ovarian syndrome is the most common endocrine disorder in women. Potential complications such as metabolic syndrome (MBS) manifest due to the hyperandrogenemia and insulin resistance associated with the syndrome. Adolescent PCOS may be characterized by earlier onset of hyperinsulinemia and insulin resistance. In adolescents, PCOS classically manifests post menarche, but it is not uncommon for patients to exhibit symptoms of the disease premenarche or in addition to precocious puberty. Review of the existing literature indicates that MS or, alternatively, individual metabolic risk factors may be present in PCOS patients and most importantly that MS may arise at a significantly younger age among PCOS women. The fact that a reproductive disorder like PCOS could have a significant metabolic impact on affected adolescents has

generated medical interest on the mechanisms underlying the multiplicative sequelae of PCOS. Although obesity indisputably compounds the clinical course of women with PCOS, this appears to be just the tip of the iceberg. Insulin resistance and hyperinsulinemia have also been implicated as critical components due to their contribution to the pathophysiology and clinical presentation of both PCOS and MS. Hyperandrogenemia, the predominant endocrine hallmark of PCOS, has also been implicated as a contributing factor to the suggested interrelationship. Polycystic ovary syndrome is believed to have a complex genetic trait in which a variety of genes interact with the environment to produce the disease.

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Polycystic ovary syndrome (PCOS) is a heterogeneous disorder characterized by hyperandrogenism, oligoovulation/anovulation, and/or the presence of polycystic ovaries. The exact pathophysiology is unknown. Reduced insulin sensitivity (peripheral insulin resistance) is present in PCOS, as in metabolic syndrome and hyperinsulinemia. Hyperinsulinemia results in increased androgen production by the ovaries. Metformin for treatment of the polycystic ovary syndrome. In: Post TW, ed. UpToDate. Waltham, MA: UpToDate. <http://www.uptodate.com/contents/metformin-for-treatment-of-the-polycystic-ovary-syndrome>. Last updated September 6, 2016. Accessed February 17, 2017. 18. Legro RS, Arslanian SA, Ehrmann DA, et al. Polycystic ovary syndrome (PCOS) is a highly prevalent endocrine-metabolic disorder that implies various severe consequences to female health, including alarming rates of infertility. Although its exact etiology remains elusive, it is known to feature several hormonal disturbances, including hyperandrogenemia, insulin resistance (IR), and hyperinsulinemia. Insulin appears to disrupt all components of the hypothalamus-hypophysis-ovary axis, and ovarian tissue insulin resistance results in impaired metabolic signaling but intact mitogenic and steroidogenic activity, favoring hyperandrogenemia, w