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REVIEW ARTICLE

Curtailing PCOS

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Polycystic ovary syndrome (PCOS), characterized by hormonal imbalance and ovarian dysfunction, often starts during adolescence. Inconsistent diagnostic criteria, variable provider knowledge, and lack of consensus pose specific challenges for the care of women with PCOS. These factors encourage inaccurate diagnosis with both under and overdiagnosis. This unfavorable diagnostic experience exasperates affected women and limits timely opportunities for intervention to minimize associated comorbidities, especially during the transition from pediatric to adult care. Recognition of these issues in the care of adolescents and women with PCOS inspired the development of the International Evidence-Based PCOS Guidelines, which emphasize the prevention, screening, and treatment of PCOS across the reproductive lifespan. The Guidelines and accompanying meta-analyses focus on three major categories of associated comorbidities: (1) reproductive; (2) metabolic; and (3) psychological. With the exception of infertility, this article considers common manifestations and comorbidities associated with PCOS throughout the lifecycle. Healthy lifestyle interventions with prevention of excess weight gain comprise the primary intervention for all comorbidities. Hence, early identification of girls "at risk" for PCOS and those with PCOS is a priority. Extensive guidelines for provider and patient education aim to decrease the medical, psychosocial, and economic burdens attributable to PCOS and its associated comorbidities.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting reproductive aged women. Depending on the population studied and definitions used, the prevalence of this heterogeneous familial disorder is 8–13% in women and 6% in adolescent girls.[1–3] Signs and symptoms of androgen excess, irregular menses, chronic anovulation, and infertility characterize the clinical phenotype. Women with PCOS have increased risks to develop diabetes mellitus, obesity, dyslipidemia, hypertension, anxiety, and depression.[4] PCOS influences women's health throughout the lifecycle beginning prior to conception and extending through the post-menopausal years (Fig. 1).

HISTORY AND GUIDELINE DEVELOPMENT

In 1935, Drs. Stein and Leventhal reported a series of women with amenorrhea and polycystic ovaries.[5,6] Subsequently, several diagnostic definitions focusing on the clinical symptoms were developed. These definitions included the 1990 NIH Criteria, 2003 Rotterdam Criteria, and 2006 Androgen Excess-PCOS Criteria.[7–9] However, these definitions differed creating inconsistent diagnostic criteria that confound the diagnosis and investigation of women with PCOS. In addition, the predominance of severely affected women in the most available studies likely contributes to an ascertainment bias impeding comprehensive understanding of this disorder.[10]

Variable provider knowledge and lack of consensus has led to inaccurate diagnosis with underdiagnosis, overdiagnosis, or misdiagnosis. Underdiagnosis and delayed diagnosis occur frequently contributing to patient distress and distrust, while simultaneously limiting opportunities for prevention and intervention.[11] Research among those women affected by delayed diagnosis highlights the importance of avoiding such a scenario and of providing women with insights into their symptoms and concerns. Evidence also shows that diagnosis itself does not distress patients, rather the related comorbidities are the main cause of concern. Overdiagnosis or misdiagnosis may generate anxiety regarding potential risks for infertility, diabetes, cardiovascular disease, and obesity.[12] Misdiagnosis may instigate unnecessary exposure to potential side effects of oral contraceptives, spironolactone, or metformin. Another deleterious consequence of misdiagnosis is inaccurate labeling for health insurance that may impede access to future health insurance coverage.

The initial manifestations of PCOS such as irregular menses, acne, and multi-follicular ovary morphology may develop during adolescence. However, these features, characteristic of normal pubertal development, can confound accurate and timely diagnosis of PCOS. Hence, judicious opportunities to prevent and address associated comorbidities, especially during the transition to adult health care providers, may be missed.[13]

Recognition of multiple issues in the diagnosis and care of adolescent and emerging adult women with PCOS inspired a pediatric endocrinology international update to expand PCOS awareness.[14] Subsequently, an international effort involving 38 societies and 71 countries developed the International Evidence-Based Guideline for assessment and management of PCOS across the lifespan. Multi-disciplinary guideline development groups including patients (consumers) were established to systematically review available data and develop practice

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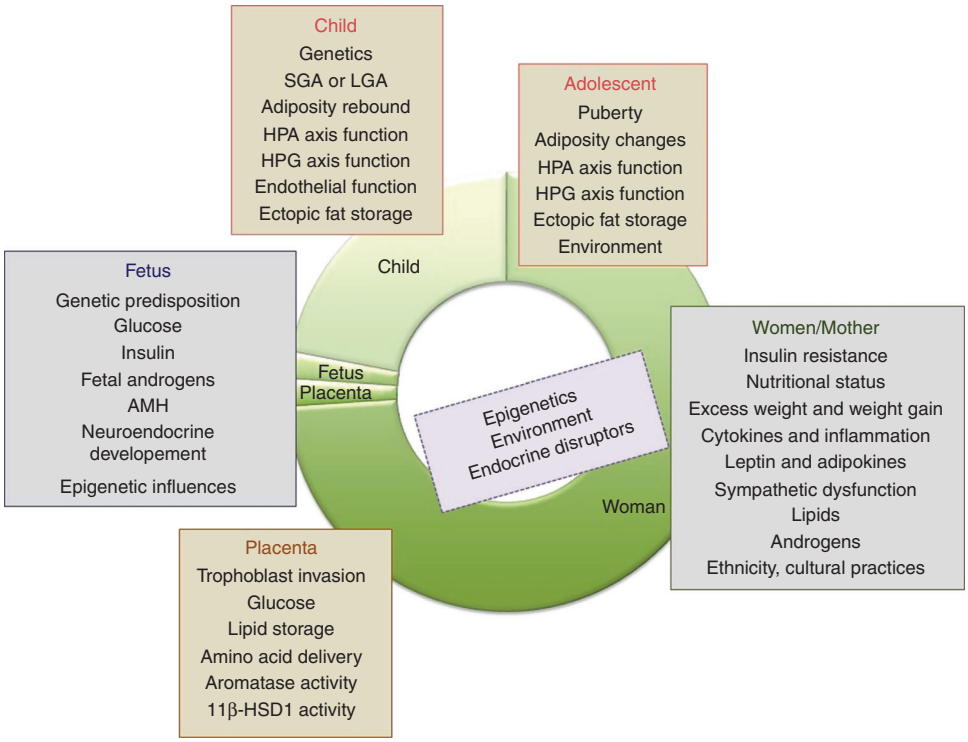

Fig. 1 PCOS through the lifecyle. The circle shows the lifecyle of affected women with PCOS. The complexities and interactions of some of the relevant modulating factors are listed inside the squares from perinatal period to adolescence to adulthood

recommendations using meticulous paradigms. This guideline used the Appraisal of Guidelines for Research and Evaluation-II process. The resulting rigorous scrutiny provides evidence-based consistent guidelines covering five broad topics relevant to PCOS: (1) screening, diagnosis, and risk assessment during life stages; (2) screening, diagnosis, and treatment of emotional well-being; (3) lifestyle interventions; (4) pharmacological treatment for non-fertility indications; and (5) assessment and management of infertility.[15] These guidelines emphasize accurate diagnosis, and the prevention, screening, diagnosis, and treatment of the comorbidities associated with PCOS. Common comorbidities can be organized into three categories: (1) reproductive; (2) metabolic; and (3) psychological. The reproductive comorbidities include hyperandrogenism, irregular menses, subfertility, and pregnancy complications. The metabolic comorbidities include insulin resistance, hyperinsulinemia, obesity, dyslipidemia, impaired glucose tolerance (IGT), type 2 diabetes mellitus (T2DM), hypertension, and cardiovascular disease risk factors. The psychological comorbidities include anxiety, depression, eating disorders, low self-esteem, psychosexual dysfunction, and poor quality of life (QoL).[16] The medical, emotional, and health cost burdens across these comorbidities are substantive.[17] These international recommendations advocate good clinical practice standards and offer extensive e-health information resources for both women and health professionals. (https://www.monash.edu/medicine/sphpm/mchri/pcos). Given the impact of PCOS on women's health, we will focus on diagnosis, clinical manifestations, and prevention of the comorbidities associated with PCOS throughout a woman's lifespan.[18]

PATHOPHYSIOLOGY

The underlying pathophysiology responsible for PCOS is multifactorial and likely heterogeneous among affected individuals. Multiple aspects of the hypothalamic-pituitary-ovarian (HPO) axis are dysfunctional. Intrinsic ovarian differences in steroidogenesis, neuroendocrine dysfunction, insulin resistance/hyperinsulinemia, nutrient excess, ectopic fat storage, inflammatory factors, genetic influences, and epigenetic changes interact with environmental exposure to culminate in PCOS.[19] Despite apparent autosomal dominant family patterns, no single gene defect has been identified. Rather, genome-wide association studies involving women of Han Chinese and European origins have identified 19 susceptibility loci associated with the PCOS phenotype.[20–24] The identified loci are linked to genes plausibly associated with the metabolic and reproductive characteristics of PCOS. These studies suggest that body mass index and insulin resistance contribute to PCOS pathophysiology.[23] In addition to genetic factors, epigenetic modifications may influence development of PCOS. Epigenetic modifications include DNA methylation, post-translational histone modification, non-coding RNA, chromatin remodeling, and possibly mitochondrial DNA changes.

MATERNAL–FETAL DYAD

The prenatal environment, influenced by maternal obesity, diet, stress, and hormones, provides a trajectory predicting long-term health.[25] Osmond and Barker established that lower birth weights were associated with higher risks for coronary heart disease, diabetes, and hypertension among adults.[26] Subsequent studies confirming the association of lower birth weights with higher risks for chronic diseases highlight the importance of the prenatal environment. Compared to women without PCOS, women with PCOS were more likely to have pre-existing medical conditions, utilize ovulation induction and in vitro fertilization, and experience pregnancy complications. Compared to women without PCOS, the infants of women with PCOS had increased risks for preterm birth, occurrence of congenital anomalies, and perinatal mortality.[27,28] Pregnancies of women with PCOS are often complicated by obesity and/or gestational diabetes mellitus (GDM).

To maintain nutrient supply to the fetus, insulin resistance normally increases during pregnancy.[29] Women with PCOS, T2DM,

IGT, or obesity may experience exacerbation of the pre-existing insulin resistance. Maternal hyperglycemia and obesity expose the fetus to nutrient excess, which increases the risks for offspring to develop T2DM, metabolic syndrome, and cardiovascular disease in adulthood.[30,31]

Women with PCOS have higher pre-conception body mass index (BMI) and manifest greater gestational weight gain. These factors increase the risk for GDM, gestational hypertension, pre-eclampsia, fetal loss, and preterm delivery.[32,33] A meta-analysis demonstrated that: (1) women with PCOS have an increased prevalence of IGT and T2DM; (2) that obesity increased the risk for dysglycemia; and (3) that the prevalence varied by ethnicity being highest among Asian women.[34]

Maternal insulin resistance compounded by an overabundance of glucose, amino acid, and fat concentrations influences placental development and function ultimately controlling the fetal environment. In the face of this nutrient excess, the fetal pancreas secretes more insulin, which is a major fetal growth hormone. In addition to increased risk for neonatal hypoglycemia, consequences of fetal hyperinsulinism include organomegaly, cardiac septal hypertrophy, increased inflammatory factors, and increased lipid storage in adipose tissue and liver.[35] Other sequelae of prenatal overnutrition include alterations in mesenchymal stem cell differentiation, mitochondrial function, and appetite regulation in the offspring.[36,37]

Infants of diabetic mothers are often large for gestational age with increased risks for adverse perinatal outcomes and congenital anomalies.[37] Complications in the immediate neonatal period include hypoglycemia, hypocalcemia, neonatal respiratory distress syndrome, polycythemia, and hyperbilirubinemia.[38,39]

Reports emphasizing disparities between prenatal weight and postnatal weight gain strengthen the applicability of the developmental origins of disease hypothesis to PCOS. Following birth in most countries, infants are generally exposed to nutrient excess. One longitudinal prospective population-based study, the Northern Finland Birth Cohort Study, reported that women with PCOS had lower birth weights, experienced adiposity rebounds at younger ages, and had higher adult BMI values.[40] Low birth weight followed by excessive adiposity rebound appears to be associated with increased risks for PCOS, ectopic fat storage, and hepatic steatosis.[41–43]

One conundrum has been to identify the source of prenatal androgen exposure because placental aromatase largely prevents maternal androgens from crossing the placenta. Infant girls born to women with congenital adrenal hyperplasia and androgen-secreting tumors are generally not virilized. Anogenital distance provides information regarding prenatal androgen exposure to female fetuses. Two observational case–control studies reported increased anogenital distances among women with PCOS.[44,45] Anogenital distance was reported to be longer in newborn daughters of women with a PCOS diagnosis compared to those without a PCOS diagnosis.[46] In a pilot study, using sebum production as a surrogate measure of prenatal androgen exposure, sebum production was greater among infants of PCOS mothers.[47]

Potential explanations for in utero hyperandrogenism include fetal ovarian androgen secretion, impaired aromatase activity, genetic programming, and metabolic factors.[48] As evident in female infants with insulin receptor gene mutations, fetal hyperinsulinism can be associated with acanthosis nigricans, clitoromegaly, cystic ovaries, hyperandrogenism, and hyperinsulinemia.[49] Does mild prenatal hyperinsulinemia secondary to maternal nutrient excess provoke ovarian androgen synthesis? Another possible explanation is that similar to girls with classical congenital adrenal hyperplasia, excessive antenatal endogenous androgen exposure may imprint the neuroendocrine mechanisms governing gonadotropin secretion increasing the risk to develop PCOS-like ovarian phenotypes.[50] Another hypothesis largely based on preclinical studies suggests that elevated maternal anti-Müllerian hormone (AMH) concentrations affect placental enzyme expression, resulting in greater fetal androgen exposure; this potential explanation warrants additional examination.[51,52]

DIAGNOSIS OF PCOS

The guidelines endorsed use of the Rotterdam PCOS Diagnostic Criteria in adult women (Table 1). Importantly, PCOS is a diagnosis of exclusion. Other disorders with similar clinical features need to be excluded from diagnostic consideration. For adult women, the Rotterdam criteria required fulfilling two of three findings: (1) oligo-anovulation; (2) clinical and/or biochemical hyperandrogenism; and (3) polycystic ovary morphology on ultrasound. When both ovulatory dysfunction and hyperandrogenism occur in the adult woman, ultrasound is not necessary for diagnosis.

For the adolescent girl, diagnosis of PCOS requires both ovulatory dysfunction now clearly defined according to time post menarche and persistent clinical and/or biochemical hyperandrogenism (Table 1). Importantly, the guidelines advance the field by highlighting that ultrasound studies to assess for polycystic morphology are not needed for this purpose until 8 years post menarche due to a lack of sensitivity and specificity at this life stage.[15] Clinical hyperandrogenism includes hirsutism and severe acne. High-quality testosterone assays are essential to confirm biochemical hyperandrogenism. Calculated free testosterone, free androgen index, or calculated bioavailable testosterone can be used. Direct free testosterone assays should be avoided because these assays show poor sensitivity, reproducibility, and accuracy. Although commonly identified in affected women, obesity and insulin resistance are not diagnostic features.[15]

AMH, a member of the tumor growth factor-β family, is secreted by ovarian granulosa cells. The highest AMH secretion occurs during the antral stage of folliculogenesis. This glycoprotein hormone inhibits the transition of primordial to primary follicle; it also inhibits follicle-stimulating hormone (FSH)-induced aromatase expression impeding selection of a dominant follicle. Since serum AMH concentrations are elevated in women with PCOS, it has been suggested that AMH concentrations could be used in place of ovarian ultrasound studies.[53] However, at the present time, lack of standardized assays and appropriate normative ranges preclude the use of AMH for the diagnosis of PCOS in women or adolescents.[15,54]

PCOS IN THE ADOLESCENT

The initial signs and symptoms of PCOS often emerge during adolescence. However, the diagnosis of PCOS in adolescent girls can be challenging because the major clinical features, menstrual irregularity, mild clinical hyperandrogenism, and polycystic ovary morphology, may be normal findings in adolescent girls during puberty. Pediatric, gynecologic, and adolescent medicine health care providers are thus confronted with the task of distinguishing features associated with normal maturation of the HPO axis from early manifestations of a chronic health disorder.[14,15,55,56] Other disorders associated with irregular menses and/or hyperandrogenism also need to be excluded from diagnostic consideration. Specifically, these disorders include congenital adrenal hyperplasia, androgen-secreting tumors, hyperprolactinemia, thyroid dysfunction, Cushing's syndrome, exogenous exposures, lipodystrophy syndromes, and severe insulin resistance syndromes.[57,58]

WOMEN WITH PCOS

PCOS is a chronic multisystem disorder with both acute and chronic manifestations. As noted above, the initial manifestations of PCOS become apparent in adolescent and young adult women.

Table 1. Diagnostic criteria for polycystic ovary syndrome

Menstrual/ovulatory function
- Primary amenorrhea: No menses by age 15 years or >3 years post thelarche (breast development)
- Irregular menstrual cycles are defined as:
  - Normal in the first year post menarche
  - From 1–3 years post menarche: <21 or >45 days
  - From 3 years post menarche to peri menopause: <21 days or >35 days or <8 cycles per year
  - Any menstrual cycle >90 days for any one cycle >1 year post menarche
- Ovulatory dysfunction can still occur with regular cycles. Anovulation can be confirmed by measuring appropriately timed progesterone concentrations

Hyperandrogenism

Clinical
- Comprehensive history and physical examination to assess for hirsutism and severe acne
- Use of modified Ferriman–Gallwey (mFG) score, >4–6 according ethnicity, as the standardized visual scale to evaluate hirsutism
- No validated visual assessments for scoring acne are available
- Ask about self-treatment for hirsutism because it commonly occurs and can affect clinical assessment. Similar prevalence for hirsutism across ethnicities. The mFG cutpoints diverge due to differences in skin hair density
- Use Ludwig visual score for evaluation of androgenic alopecia

Biochemical
- Use high-quality assays such as liquid chromatography-mass spectroscopy or extraction/chromatography immunoassays for total or free testosterone
- Assess calculated free testosterone, free androgen index, or calculated bioavailable testosterone
- Androstenedione and dehydroepiandrosterone sulfate can be considered if total or free testosterone concentrations are within normal range. However, these hormone values provide limited additional information in the diagnosis of PCOS
- Avoid direct free testosterone assays due to poor sensitivity and reproducibility
- Biochemical hyperandrogenism cannot be accurately assessed when the patient is using hormonal contraceptives
- Laboratory values need to be interpreted based on normal reference ranges of the testing laboratory
- Where androgen levels are markedly above laboratory reference ranges, other causes of biochemical hyperandrogenism need to be considered as informed by clinical history and physical examination

Ovarian morphology
- Ultrasound is not needed for diagnosis and should not be performed *for this purpose* in those with gynecological age <8 years

The following sections will consider specific comorbidities commonly associated with PCOS.

Reproductive

Irregular menses, chronic anovulation, infertility, hyperandrogenism, and complications of pregnancy comprise major reproductive manifestations of PCOS. In the ovary, the dynamic balance between dormant and growing follicles culminating in ovulation is influenced by luteinizing hormone (LH), FSH, AMH, and androgens. The normal dynamic balance becomes dysfunctional in PCOS. Excessive adrenal and/or ovarian androgen production occurs. Ovarian morphology is characterized by an overabundance of small follicles with failure to select a dominant follicle. Changes in kisspeptin, gonadotropin-releasing hormone, LH, and FSH secretion accompany the ovarian dysfunction. The importance of androgen actions in neuroendocrine function has been highlighted.[59] Obesity impairs oocyte quality and is associated with an atypical ovarian microenvironment.[60–62] The International Evidence-Based Guidelines provided extensive recommendations regarding diagnosis and management of the reproductive manifestations and comorbidities associated with PCOS.[15]

Metabolic

Metabolic comorbidities include insulin resistance, IGT, T2DM, GDM, nonalcoholic fatty liver disease (NAFLD), and metabolic syndrome. After adjusting for BMI, education, and family history of T2DM, women with PCOS have an increased risk to develop T2DM at an earlier age; this risk is exacerbated by obesity.[63,64] Hence, glycemic status should be evaluated in all women at the time of PCOS diagnosis and reviewed regularly according to the presence of other risk factors such as BMI (>25 kg/m^2 or >23 kg/m^2 if Asian), history of dysglycemia, family history of T2DM, GDM, hypertension, or high-risk ethnicity.[15]

Even lean women with PCOS have intrinsic insulin resistance independent of obesity and androgen concentrations.[65,66] These metabolic findings are already present in adolescent girls; normal-weight adolescent girls with PCOS have peripheral insulin resistance, increased liver fat, and muscle mitochondrial dysfunction compared to normal-weight control girls.[67] As would be anticipated, increasing BMI exacerbates insulin resistance. The combination of both abdominal obesity and hyperandrogenism promotes dyslipidemia and likely negatively impacts long-term health of women with PCOS.[68]

The molecular mechanism(s) responsible for insulin resistance associated with PCOS remains unclear. Both primary insulin resistance and primary hyperinsulinemia are possible mechanisms. Primary insulin resistance occurs when insulin signal transduction is impaired resulting in compensatory increased β cell insulin secretion and hyperinsulinemia. One potential mechanism for primary hyperinsulinemia involves mild hyperglycemia triggering increased β cell insulin secretion, down-regulating insulin receptors, increasing muscle lactate, activating inflammatory pathways, and inducing insulin resistance. Importantly, these mechanisms are not be mutually exclusive. Genetic factors, epigenetic modifications, prenatal exposures, extra-uterine environmental influences, and inconsistent adaptations to nutrient excess likely contribute to the development of insulin resistance and hyperinsulinemia. Reviewing the details of these opposing

viewpoints, primary insulin resistance vs. primary hyperinsulinemia, is beyond the scope of this review.[69]

Continual cross-talk between adipocytes, pancreas, liver, and muscle orchestrates metabolism. Following observations that generalized lipodystrophies are associated with insulin resistance, the concept of decreased adipocyte storage capacity leading to ectopic fat storage in liver, skeletal muscle, and pancreas was developed.[70] In face of nutrient excess, adipocytes release free fatty acids that promote hepatic gluconeogenesis, de novo hepatic lipogenesis, and hypertriglyceridemia. Fat accumulation in these non-adipocyte tissues causes lipotoxicity characterized by insulin resistance, and inflammation.[71] Ectopic fat deposition in the liver causes hepatic steatosis and NAFLD. Women with PCOS have higher incidence of NAFLD than unaffected women.[72] NAFLD is associated with increased risk for cardiovascular events, T2DM, and hepatocellular carcinoma.[73] Whether hyperandrogenism exacerbates the NAFLD remains to be clarified.[74]

An integrative genomic analysis supports the concept that limited peripheral adipose tissue storage contributes to the development of insulin resistance and suggests that multiple common genetic variants influence this risk.[75] In contrast, healthy adipose tissue expands by recruitment and differentiation of pre-adipocytes, adipocyte hyperplasia, thus avoiding the metabolic complications of obesity.[76] The factors that influence whether adipocytes recruit pre-adipocytes or manifest limited expandability due defective adipose tissue plasticity are unclear.[76]

The term "metabolic syndrome" is used to describe a cluster of features associated with increased risk for cardiovascular disease. These features include hypertension, increased waist circumference, dyslipidemia, and impaired fasting glucose concentrations. Women with PCOS have early onset and higher incidence/risk of many of these features.[77] Hence, women with PCOS have a higher risk for metabolic syndrome.[78] All overweight and obese women with PCOS should be evaluated for cardiovascular risk factors, including weight, waist circumference, activity levels, blood pressure, lipid profile, glucose abnormalities, and smoking. Special consideration may be required in high-risk ethnicities; for example, higher BMI and metabolic features in Africans and increased central adiposity, insulin resistance, diabetes, and metabolic risks in South East Asians and indigenous Australians.[15]

A meta-analysis reported that women with PCOS have higher carotid-intimal media thickness compared to control women.[79] Compared to controls, middle-aged women with PCOS showed an increased prevalence of coronary artery and aortic calcifications, markers for cardiovascular disease risk.[80] Obese adolescent girls with PCOS have increased arterial stiffness, which is another early marker of cardiovascular disease.[81] Despite the increased occurrence of cardiovascular risk markers, whether PCOS is truly associated with an increased number of cardiovascular events remains to be clarified.[82,83] The guidelines recognize that cardiovascular risk factors are increased and identified at younger ages. In addition, T2DM frequently develops. However, the guidelines acknowledge the uncertainty of long-term cardiovascular disease events, recommend risk factor monitoring, and advocate healthy lifestyle interventions.[15]

Psychological

Psychosocial comorbidities include depression, anxiety, eating disorders, reduced QoL, negative body image, and psychosexual dysfunction. Women with PCOS have a higher risk of existing depression as well as higher rates for development of new depressive symptoms.[84,85] The frequency of anxiety disorders is also increased.[16] Moderate to severe anxiety and depression are common among women with PCOS. Eating disorders with bulimia and binge eating are more prevalent among women with PCOS compared to controls in a cross-sectional study.[86] Obesity, hirsutism, menstrual dysfunction, and infertility likely contribute to these psychological comorbidities. One meta-analysis confirmed that the depressive symptoms among women with PCOS are independent of obesity.[16] Health-related QoL reflects patient reported outcomes in chronic diseases and is lower among women with PCOS. A specific measure for QoL in PCOS is available and includes emotions, body image, weight, infertility, and menstrual cyclicity.[87] Factors such as self-esteem, depression, and anxiety likely modulate health-related QoL. Impaired sexual function in women with PCOS hampers sex life and relationships; comparable studies are not available for adolescent.[88] Appropriate screening and prompt management of all psychological comorbidities are essential for holistic care of affected women and will improve well-being and adherence to lifestyle and medical interventions.[15,89]

DERMATOLOGIC, CANCER CONSIDERATIONS, AND OBSTRUCTIVE SLEEP APNEA

Reproductive, metabolic, and psychological comorbidities constitute major comorbidities for women with PCOS. Nevertheless, dermatologic, endometrial cancer, and obstructive sleep apnea (OSA) trouble patients and their physicians. These topics are briefly discussed below.

Dermatologic

Hirsutism, acne, and androgenic alopecia are the most common dermatologic features associated with androgen excess. The modified Ferriman–Gallwey (mFG) scoring system provides a semi-objective measure of the extent of hair growth in androgen-dependent regions. The cutpoints for the mFG vary depending on ethnic background; the guidelines recommends cutpoints of ≥4–6 depending on ethnic background.[15] Self-reported hirsutism should be acknowledged irrespective of the severity due to substantial impact on psychosocial comorbidities. Accurate values for prevalence of acne and androgenic alopecia are lacking.[90] Acanthosis nigricans reflecting insulin resistance is also common. These cutaneous features of PCOS trouble affected women, contribute to poor self-esteem, and should be appropriately managed.

Cancer considerations

Risk factors for cancer such as unopposed estrogen exposure related to chronic hyperandrogenism with aromatization, chronic anovulation, hyperinsulinemia, and obesity occur among women with PCOS. The risk for endometrial cancer is higher among women with PCOS, especially when prolonged amenorrhea and abnormal vaginal bleeding occur.[15,91] Although breast cancer is the most common cancer among women, the incidence of breast cancer is not increased among women with PCOS.[92] However, data may be skewed due to variable diagnostic criteria, associated risk factors, and ascertainment bias.[91] No apparent increased risk for ovarian cancer exists.

Obstructive sleep apnea

OSA is associated with instability in the upper airways during sleep resulting in recurrent upper airway obstructions and snoring. Alterations in heart rate, blood pressure, sympathetic activity, intrathoracic pressure and oxygen saturation occur in OSA. Sleep architecture is disrupted with numerous nocturnal awakenings.[93] OSA is associated with increased risk for cardiovascular disease and hypertension.[94,95]

Systematic reviews and meta-analysis demonstrated higher prevalence of OSA in obese women with PCOS.[96] A small retrospective chart review reported occurrence of OSA and metabolic dysfunction in adolescent girls with PCOS.[97] How OSA impacts the health of women with PCOS remains to be clarified.[98] However, given that treatment for OSA does not improve metabolic outcomes, the focus in PCOS associated with OSA

should be on symptoms.[15] Symptoms such as snoring, daytime sleepiness, and obstructive sleep episodes should prompt further evaluation for OSA.

GENETICS, EPIGENETICS, AND ENVIRONMENT

Consequences of PCOS manifest throughout a woman's lifespan beginning with the consequences for the fetus.[99] Hyperglycemia, IGT, GDM, T2DM, dyslipidemia, inflammation, obesity, and hyperandrogenism complicate pregnancies in women with PCOS.[100] These features affect the pregnant woman, her fetus, and the fetal germ cells. For the fetus, these complications can disrupt the normal developmental program. The placenta and the developing embryo respond to the ambient nutritional, metabolic, and inflammatory indicators within the uterine microenvironment to prepare for the anticipated postnatal environment.[101] Hence, fetal adaptations to the prenatal environment are plastic. These adaptations can lead to adverse long-term health consequences when the prenatal phenotype diverges from the postnatal environment triggering a developmental mismatch.[102] For example, infants exposed to maternal diabetes showed a significantly greater BMI gain between 10 and 13 years of age; such weight gain is associated with an increased risk for continued obesity during adulthood.[103] A meta-analysis involving 14 studies with 132,180 persons showed that both low birth weight (<2500 g) and high birth weight (>4000 g) are associated with increased risks to develop T2DM generating a U-shaped curve. Hence, both arms of this U-shaped curve are associated with increased risk for T2DM.[104]

Epigenetic modifications may contribute to transgenerational inheritance. For example, with obesity and diabetes, three generations may be simultaneously exposed to an unfavorable metabolic environment—the patient, her fetus, and germs cells of the fetus. Rather than being mediated by classical genetic changes, the "messaging" can be mediated by epigenetic modifications.[105] Whereas animal studies support transgenerational inheritance, human data are limited partly due to the challenges inherent in collecting adequate longitudinal data.[106–108] Using a nonhuman primate model, fetuses of mothers fed a western style diet during pregnancy had increased hepatic fat in the early third trimester, increased hepatic inflammation, reduced pancreatic α cell mass, increased body weight, and altered hypothalamic melanocortin signaling.[109–111] Questions regarding the extent of the plasticity and specific mechanisms responsible for these adaptations remain to be answered. Another question is whether critical windows exist for developmental events. The impact of environmental influences such as food availability, activity, shared family lifestyles, and stress cannot be excluded.

CURTAILING PCOS

PCOS affects women throughout the lifespan from pre-conception to post menopause. Diagnosis has been challenging for health professionals and affected women, now clarified in the recent International Evidence-Based PCOS guidelines.[15] Care for women with PCOS has also been fractured compelling better coordination among subspecialists using the recent consistent care guidelines.[15,112] Once the disordered physiologic changes develop in PCOS, a vicious cycle ensues. Primary goals include timely and accurate diagnosis, education of both health care providers and patients, treatment of issues with the greatest impact on quality of life and prevention of comorbidities. Achieving these goals will hopefully reduce the medical, psychosocial, and economic burdens attributable to PCOS and its associated comorbidities. Greater understanding of the genetics, epigenetics, hormonal dysregulations, and environmental factors is essential to inform new therapies and curtail the emotional distress, chronic health issues, and economic burden of this common disorder.[113]

Available data suggest that multicomponent healthy lifestyle interventions comprise the principal therapeutic options to treat PCOS and prevent its comorbidities.[15] With upsurging rates of excessive weight gain in PCOS, lifestyle intervention is still equally effective in women with and without PCOS. However, most available data regarding the efficacy of lifestyle interventions report outcome in obese patients and, here, efficacy of lifestyle alone is somewhat limited, supporting the guideline emphasis on healthy lifestyle for prevention of excess weight gain.[114] For pregnancy in the general population, individual patient data meta-analysis has shown efficacy of lifestyle intervention with reduction in GDM and cesarean sections.[115] Can individualized innovative behavioral strategies focused on prevention and treatment of excess weight improve adherence, optimize specific interventions, improve emotional health, and minimize relapses? Does adherence to healthy lifestyle decrease the comorbidities associated with PCOS? Answers to these and other questions are needed to identify effective interventions that curtail PCOS and its comorbidities.[25,116–118]

Early identification of girls "at risk" for PCOS and those with the condition is a priority.[14,15] Diagnosis of PCOS in a woman should prompt evaluation of other family members due to their increased risks to develop T2DM and metabolic syndrome.[119–121] Women with PCOS serve as probands or "early warning alerts" for their extended family members. The Evidence-Based Guidelines have clarified the diagnostic criteria and refined the diagnosis of PCOS in the adolescent girl.[15] In addition, the guidelines have provided evidence-based data to improve screening, diagnosis, and treatment of the comorbidities associated with PCOS.[15] Importantly, key questions for future research have been identified. The guidelines recommend women with PCOS adopt healthy lifestyles for themselves and promote healthy lifestyles for their extended families to ensure the realization of healthy habits from early childhood for their children.[15]

FUTURE STUDIES

- Longitudinal studies of natural history of PCOS in community-based women from childhood to post menopause.
- Longitudinal studies to assess the actual incidence of cardiovascular disease events in women with PCOS.
- The role of AMH in diagnosis of PCOS.
- Knowledge gaps regarding risk for NAFLD and cancer.
- Identification of timing of critical exposure periods and optimal interventions.
- Improved understanding of adipocyte biology vis-à-vis cell fate decisions and plasticity.

AUTHOR CONTRIBUTIONS

S.F.W., H.J.T., and A.S.P. substantial contribution to conception, design, acquisition of data, and interpretation of data. S.F.W., H.J.T., and A.S.P. drafting the article and revising it critically for important intellectual content. S.F.W., H.J.T., and A.S.P. final approval of version to be published.

ADDITIONAL INFORMATION

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