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Mini-Review

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Update on PCOS: Consequences, Challenges, and Guiding Treatment

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Abbreviations: AMH, anti-Müllerian hormone; COC, combined oral contraceptive; CVD, cardiovascular disease; DM, diabetes mellitus; FNPO, follicle number per ovary; GnRH, gonadotropin-releasing hormone; mFG, modified Ferriman-Gallwey; PCOM, polycystic ovary morphology; PCOS, polycystic ovary syndrome.

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common reproductive endocrine disorders in women and despite this, diagnostic challenges, delayed diagnosis, and less-than-optimal treatment regimens plague the condition. The International PCOS network, consisting of geographically diverse international experts in PCOS as well as consumers, engaged in a multi-year international evidence-based guideline development process that was jointly sponsored by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM). The guideline was published in 2018 and endorsed by more than 40 international societies involved in PCOS. Translation of this evidence-based guideline to medical practice and consumer groups remains a priority. However, there remain many challenges to both understanding the diagnosis and treatment of PCOS. Evidence suggests that both clinicians and consumers are not satisfied with the timeliness of diagnosis and treatment options. This review summarizes the important findings for diagnosis and treatment from the guidelines and expands on recent developments in the literature since its publication. Special attention to diagnosis at the ends of the reproductive spectrum are discussed and remaining areas of controversy are noted. Additionally, the review highlights some of the remaining challenges in the understanding and management of PCOS to help guide clinicians and investigators in this perplexing condition.

Key Words: PCOS, pathophysiology, diagnostic criteria, metabolic disease, lifestyle intervention

Polycystic ovary syndrome (PCOS) is the most common endocrinologic condition in women, affecting from 8% to 13% of reproductive-aged women (1, 2). It is an enigmatic condition that, while extremely common, creates challenges in its diagnosis and management, as leading symptoms may vary with age, and treatment may be tailored

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to specific requirements of individual need. The vast array of possible diagnostic schemes, treatment offerings, and often conflicting recommendations, led to the formation of a large international consortium to examine the evidence in a rigorous way and produce evidence-based guidelines on diagnosis and management published in 2018 (3, 4). What was clear, however, in this published guideline is that there remain many challenges in the diagnosis and treatment of PCOS. Additionally, research has exposed the still-large gap between the available evidence and its translation to improved diagnostic timing and evidence-based treatments (5, 6). There are still knowledge gaps in different disciplines of medicine (e.g., Obstetrics and Gynecology (OBGYN), Medicine, Pediatrics, Dermatology) regarding the diagnosis and treatment of PCOS, and women with PCOS report significant delays in the diagnosis (7), dissatisfaction with the treatment and recommendations they receive (8), and a lack of satisfactory treatment options. This gap is not limited to practicing physicians who completed training before the international guidelines were published, but recent assessment of OBGYN residents in training identified significant deficiencies in the knowledge of the diagnostic criteria for PCOS. In one recent survey of US-based OBGYN residents, 85.4% of 347 trainees completing the survey reported using Rotterdam criteria to diagnose PCOS. However, only 55% correctly identified the 3 main criteria used in the diagnosis (9).

This paper will review the diagnostic criteria and the challenges that continue to present for clear diagnosis. PCOS impacts all aspects of the reproductive hormone physiology; however, the precise pathophysiology remains incompletely elucidated. The current evidence for leading pathophysiologic disturbance in PCOS will be reviewed, as well as the best evidence of reproductive, psychological, and metabolic consequences. Finally, an update on the best evidence-based treatments for PCOS will be reviewed. This review will highlight the challenges that remain in the diagnosis and treatment of PCOS and bring forth the most recent evidence to support the recommendations.

Search Strategies

This mini-review is a limited qualitative narrative review of the literature in PCOS, intended to inform clinical guidance in PCOS and summarizing and building on the International Evidence-Based Guidelines published in 2018 (3). In addition to the literature reviewed by the international guidelines (3), PubMed was searched with the MeSH term of *Polycystic Ovary Syndrome*, combined with the subcategories of *clinical trials*, *meta-analysis*, *systematic reviews* for the period from June 2017 to June 2020. Articles were excluded from the review if they were pilot trials, only included animal data, limited in population scope, or the focus was not on PCOS. Articles from the international guidelines were referenced (15 references from this guideline cited here) if there was specific quality without substantive change or additional guidance in more recent literature.

Pathophysiology

The pathogenesis of PCOS is complex and multifactorial, including genetic, environmental, and transgenerational components. These sources drive the underpinnings of unbalanced hypothalamus-pituitary-ovarian axis signaling, promoting ovarian and adrenal hyperandrogenism. The syndrome is also burdened with insulin resistance that is worsened by hyperandrogenism-related adipose tissue accumulation and dysfunction with lipotoxicity and oxidative stress (10). Thus, the full clinical spectrum of the syndrome involves metabolic, reproductive, and psychological impairments. In addition to genetic factors, environmental factors likely also play a role. The link between obesity and the prevalence of PCOS is highly correlated; among women with body mass index (BMI) <25 kg/m^2, the prevalence is 4.3%, and in women with BMI > 30kg/m^2 it is 14%, although selection bias may play a role in assessment (11).

Neuroendocrine link to PCOS

Women with PCOS present with gonadotropin-releasing hormone (GnRH) neuronal network dysfunction and increased pulse amplitude for pituitary activity, shown as high serum luteinizing hormone levels and high ovarian androgen response, most likely relating to decreased responsiveness to steroid hormone negative feedback (12). Different animal models have successfully been able to recapitulate the hyperandrogenism driven neuroendocrine pathology of PCOS and other central mechanisms involved (13). Recently, aberrant neuroendocrine signaling was linked with adipose tissue dysfunction in a murine model (14), whereas other studies have proposed high anti-Müllerian hormone (AMH) promoting GnRH neuron activation and PCOS onset (15). Given the central role of hyperandrogenism and obesity in the impairments in neuronal circuitry and the high prevalence of psychological distress among women with PCOS, the central dysfunction most likely involves larger and more complex neuronal networks than previously recognized (16, 17)

Genetic factors

The genetic factors and familial clustering are described in the early PCOS literature (18); however, as more genetic data has started to accumulate, it has become obvious that the syndrome harbors multigenetic background. Indeed, the genome-wide association studies have identified a total of 19 risk gene loci for PCOS located in the neuroendocrine, metabolic, and reproductive pathways (19), with the reproductive and metabolic populations segregating in a recent unsupervised clustering analysis (20). In line with this, Mendelian randomization analyses suggest a causal link between PCOS and variants associated with BMI, fasting insulin, menopause timing, depression, and male-pattern balding (21). From all genes of interest, the gene loci with the most potential, namely *THADA, FSHR, INS-VNTR*, and *DENND1A*, would require validation in the future. Interestingly, the clinically validated PCOS cases have similar genetic profile to the self-reported ones, allowing data generation in the future also through less burdensome and more inexpensive means (21). Known genetic risk alleles account for less than 10% of PCOS heritability; therefore, other etiological factors also have to be considered.

Transgenerational transmission of PCOS

Animal studies and human data show the syndrome having transgenerational origins, with a 5-fold higher risk for daughters born to mothers with PCOS for inheriting the syndrome (13, 22). In a murine model, prenatal androgen excess alone can predispose to transgenerational transmission of PCOS. Early androgen exposure may increase susceptibility to the syndrome. Longer anogenital distance (AGD) has been shown in infant girls born to PCOS mothers, and daughters of PCOS mothers have higher metabolic and androgenic risk (22, 23). Maternal testosterone in women with PCOS was found to be a predictor of infant AGD (24). The mechanism through which the daughters are exposed to hyperandrogenism remains elusive, although AMH could be one of the players. Interestingly, a recent study showed that mice subjected to high levels of AMH at late pregnancy produced PCOS offspring with high luteinizing hormone pulsatility and increased androgen levels (25). The mechanism was thought to transit via AMH effect on aromatase activity in the placenta, promoting hyperandrogenism. Even though AMH levels have been reported to be high in the second and third trimesters in women with PCOS (25, 26), the role of AMH on transgenerational transmission in humans warrants further studies.

Diagnosis

Criteria for diagnosis

There is no specific diagnostic test that unequivocally identifies PCOS, but rather the diagnosis is based on the varying presence of 3 specific elements, namely oligo-anovulation, androgen excess, either clinical or biochemical, and the ultrasound assessment of ovarian morphology. The International Evidence-Based Guideline (3) endorsed the use of the Rotterdam criteria (27) that requires 2 of the 3 diagnostic criteria be present for the diagnosis in adult women. Exclusion of thyroid disease (thyroid stimulating hormone, TSH), hyperprolactinemia (prolactin), and nonclassic congenital adrenal hyperplasia (screening with 17-hydroxy progesterone) is recommended. Further evaluation is recommended in those with amenorrhea and more atypical features, with consideration to assess for hypogonadotropic hypogonadism or Cushing disease, and where there is a more severe androgenic picture, consideration for evaluation for androgen-producing tumors. Severe androgenic profiles are present if serum androgen measures are elevated more than 2-fold the upper limits of normal for the local clinical assay standard. The guidelines also endorse the use of phenotype descriptions when diagnosing PCOS and present 4 phenotypes (A-D) based on the presence or absence of the 3 diagnostic criteria (*see* Table 1). The specific clinical implications or natural history of each of the phenotypes remains unclear at this time, although recent study has found, using unsupervised phenotypic clustering analysis, reproductive and metabolic phenotypes segregating by novel genetic findings (20). Moreover, a review of metabolic features and phenotypes noted that while androgenic phenotypes were more often associated with more severe metabolic dysfunction, this was confounded in most studies by the presence of adiposity, with increased adiposity leading to more severe complications and not all studies controlled for BMI (28, 29). Diagnostic features of the condition also vary across the lifespan and by ethnicity, which complicates the categorization and natural history.

Table 1. Phenotypes of PCOS Based on Rotterdam Criteria

Phenotype	Androgen excess	Ovulatory dysfunction	PCOM on ultrasound
A	√	√	√
B	√	√	
C	√		√
D		√	√

Abbreviations: PCOM, polycystic ovary morphology; PCOS, polycystic ovary syndrome.

The recommendations for the diagnostic criteria from the international guidelines are noted in Table 2. Androgenic status can be assessed by either biochemical measures or clinical measures. The presence of androgenic excess is clinically indicated by cutaneous manifestations such as the presence of hirsutism (indicated by modified Ferriman-Gallwey (mFG) score) (30), acne, or alopecia. There is significant ethnic variation in clinical androgenic expression and examination is often limited by self-treatment of hirsutism. There are limited data from diverse populations, making the interpretation of the mFG score challenging. Current recommendations in the guidelines are based on limited controlled data, with an overall reduction in mFG score threshold required to be consistent with hyperandrogenism. Ovulatory dysfunction is signaled by oligo-anovulation, with irregular menses as the marker based on published data as noted in Table 2. If irregular menses is present along with hyperandrogenism, biochemical or clinical, then the use of pelvic ultrasound is not required for diagnosis. Although assignment of the full phenotype is limited without this measure, clinical diagnosis is possible without ultrasound.

Table 2. Definitions of Features of PCOS for Diagnosis

Feature	Definition
Irregular menses	• > 1 year and < 3 years post menarche: < 21 or > 45 days • > 3 years post menarche: < 21 or > 35 days • > 1 year post menarche: any cycle > 90 days • Primary amenorrhea at age 15 or > 3 years post thelarche
Biochemical hyperandrogenism	• Calculated free testosterone or free androgen index • Calculated bioavailable testosterone • Liquid chromatography/mass spectrometer with extraction is the preferred method of assay measure; reference range upper limits of normal free testosterone 1.06 ng/dL, total testosterone 60 ng/dL • Can consider androstenedione or DHEAS if testosterone is normal and high index of suspicion for hyperandrogenism
Clinical hyperandrogenism	• Examination specifically for acne, alopecia, and hirsutism • For adolescents use severe acne and hirsutism • Use standardized visual scale of mFG ≥ 4-6 recognizing there are ethnic variations that are not well defined
Ultrasound criteria	• Ultrasound should be transvaginal and using high resolution • In this setting follicle count per ovary should be ≥ 20 or ovarian volume ≥ 10 mL • Ultrasound should not be used in those < 8 years post menarche

Adapted from the International Evidence-Based Guideline for the diagnosis and management of Polycystic Ovary Syndrome 2018 https://www.monash.edu/__data/assets/pdf_file/0004/1412644/PCOS_Evidence-Based-Guidelines_20181009.pdf

Abbreviations: DHEAS, dehydroepiandrosterone sulfate; mFG, modified Ferriman-Gallwey.

Challenges for the ultrasound diagnostic criteria and role of AMH

Ultrasound morphology is the most challenging of the criteria, as there has been variation in the standards in the reporting of the follicle count cutoffs. As technology has improved, the ability to see more follicles increases, so the cutoffs previously published were not based on current technology (31) and are no longer valid to distinguish populations. The Androgen Excess and Polycystic Ovary Syndrome Society published guidelines in 2014 (32). Reviewing the available literature, the guideline recommended using follicle number per ovary (FNPO) for the definition of polycystic ovary morphology (PCOM) and recommended the threshold be set at ≥25, but only when using newer technology that affords maximal resolution of ovarian follicles (ie, transducer frequency ≥8 MHz). The guidelines recommend the use of ovarian volume for diagnosis of PCOM if such technology was not available for routine daily practice. When using ultrasound in PCOS research, use of newer technology to adequately characterize follicle count is suggested. The International Evidence-Based Guideline (3) included a systematic review (11 studies with 2961 adult participants) of ultrasound for FNPO criteria in the diagnosis of PCOM and concluded that the optimal sensitivity and specificity for FNPO was ≥20 follicles per ovary in at least one ovary. The available ovarian volume data did not indicate a recommended change in the ovarian volume criteria for PCOM at ≥10 mL.

AMH levels have been considered as a surrogate marker or as an alternative to ultrasound FNPO count for the diagnosis of PCOM or as an independent marker of PCOS. Overall serum AMH levels are 2- to 3-fold higher in women with a diagnosis of PCOS than in women with normal reproductive function and the levels correlate with FNPO ultrasound measures. The assays utilized vary significantly between reports, with PCOS median AMH levels ranging from 20 to 81.6 pmol/L and normal control medians from 16.7 to 33.5 pmol/L (33-36). There are recognized challenges in the AMH measurement (37), such as proteolysis,

changes in the AMH dimer, or interfering substances that lead to poor performance of the assay in predictive models. Additionally, there are variations across the reproductive lifespan in AMH ranges, making it difficult to distinguish cases from controls on this criterion (38). Recent study also showed overlap between PCOS and hypogonadotropic hypogonadism as for AMH measure, warranting awareness and in some cases also further serum assessments to discriminate between these 2 phenotypes (39). Given all this and the limitations of AMH measurement, AMH alone is not sufficient to establish the diagnosis. A recent systematic review of the use of AMH in replacing ultrasound in PCOS diagnosis identified the research gaps that remain before AMH can be considered in the diagnostic algorithm (40).

Special age-group considerations

Adolescence, the period of time between 10 and 19 years of age and the time of pubertal maturation, represents a distinct dilemma in the diagnosis of PCOS. The diagnosis in adolescence is challenged by the overlap of normal pubertal physiology changes and those that mimic adult diagnostic criteria for PCOS, namely irregular menstrual cycles and multifollicular ovaries. Additionally, the time from menarche to full maturation of the reproductive axis (41-43) can be variable post menarche, which may bridge young adulthood (44). Since there is evidence for the underpinnings of PCOS presenting in adolescence and the normal pubertal overlap, there is the risk of both underdiagnosis (7) and that of overdiagnosis, without adequate support for disease. As such, it is recommended that the diagnosis of PCOS not be made early in the post menarchal timeframe. The recommendation for diagnosis in adolescence cannot depend on pelvic ultrasound findings given the increased overlap with normal ovarian findings in this age group and instead is based on irregular menses and hyperandrogenism. Care should be taken when using biochemical evidence of hyperandrogenism to establish a normative range for the assay used in this population. AMH is also unhelpful in distinguishing PCOS in this age group. In adolescents, levels are high and overlap considerably between adolescents with and without diagnostic features of PCOS (38). Menstrual cycles may not establish a regular pattern until >2 years post menarche (45). In a recent study of 317 Danish 16-year old adolescents, the majority had regular cycles within 3 years post menarche (46). Therefore, the diagnosis should not be made within 2 years of menarche to allow for this maturation. There is a recommendation regarding adolescents who are not yet at the developmental stage for full endorsement of a PCOS diagnosis, but who demonstrate concerning features like persistent irregular menses or clinical androgen concerns requiring clinical intervention, that they be considered "at risk for PCOS." There may therefore be utility in reinvestigating the possibility of PCOS in the future. It is then recommended that further evaluation of androgens and consideration for ultrasound at the appropriate gynecologic age be completed to fully assess the diagnosis (47). On the other end of the reproductive spectrum, there are challenges to diagnosis in women in the peri- and postmenopausal reproductive spectrum. The average age of menopause is 51 years, but menstrual changes occur much earlier than this in normal aging (48), so ovulatory dysfunction is unreliable as a diagnostic criterion. In fact, there is evidence of increase in regular menstruation in women diagnosed with PCOS as they approach perimenopause (49-51). Also, ovarian volumes and follicle counts decline with age. Ovarian androgen production may decline in both groups, but clinical hyperandrogenism may be more prevalent due to decline in estrogen levels in menopause (52). At this point, there is insufficient evidence about natural history to specifically distinguish the phenotype in menopausal women. The Guidelines suggest that a diagnosis of PCOS could be considered if there is a past diagnosis of PCOS, a long-term history of irregular menstrual cycles, and hyperandrogenism, and/or PCOM, during the reproductive years, but they do not endorse specific diagnostic criteria separately (53).

Consequences

What is known

Metabolic/obesity

PCOS is associated with an increased risk of metabolic complications starting from a young age. These comorbidities include traditional cardiovascular disease (CVD) risk factors such as obesity, impaired glucose tolerance, type 2 diabetes (DM), dyslipidemia, and hypertension. Obesity is one of the most common concerns expressed in surveys of patients with PCOS (7). Depending on the ethnicity and study population assessed, the obesity rate varies from 50% to 80%. According to an examination of high-quality studies in a large meta-analysis, the risk of obesity in women with PCOS was reported to be 4-fold higher compared with controls and also higher in white women compared with Asian women (54). Importantly, women with PCOS have been shown to present with long-term overweight or obesity, with the onset of BMI trajectory deviation occurring as early as age 5 (55). Evidence from cross-sectional studies suggests that the risk of overweight/obesity persists beyond the fourth decade of life (56) and a few longitudinal studies also suggest an increase in weight with age (57). The increased preference for abdominal fat deposition, seen primarily in

the hyperandrogenic phenotype, further predisposes this population to other cardiometabolic complications (58). The risk of impaired glucose tolerance is 3-fold higher with PCOS, independent of BMI, and highest in women living in Asia and in North and South America (59). Although the risk of DM is also increased in this reproductive-age population, there are mixed data regarding these findings independent of weight. In women over age 40, a few longitudinal studies and other cross-sectional studies indicate an increased risk of type 2 DM independent of BMI (56). In adolescents with PCOS, there are only a few small studies examining the risk of DM, and these show an overall low prevalence. When examining the differences based on PCOS phenotype, a large cross-sectional study showed a similar risk of DM in all 4 phenotypes (60). Dyslipidemia, reflected by high triglycerides and low high-density lipoprotein cholesterol, is the commonest metabolic abnormality detected in PCOS (61). Some studies have performed deep lipid phenotyping and demonstrate high low-density lipoprotein cholesterol levels, an increase in atherogenic lipoproteins and a decrease in high-density lipoprotein cholesterol efflux capacity, indicating increased CVD risk (62). When examining the risk in different age groups, there are few studies in adolescents and those in older women show a higher prevalence of dyslipidemia in the hyperandrogenic phenotype (63). The association between hypertension and PCOS is mixed. Most studies do not demonstrate a higher risk of hypertension independent of BMI, although longitudinal data demonstrate elevated blood pressure even in lean women with PCOS (64). The few studies in adolescents and older women do not show significant differences compared with control groups (65). Given that most of the data on metabolic risk is derived from cross-sectional studies, the long-term significance of mild to moderately abnormal values for blood pressure measurements and serum lipids is not clear. Another approach is to evaluate the prevalence of metabolic syndrome as it assesses early evidence of dyslipidemia, hypertension, glucose intolerance, and obesity as a composite score and may predict long-term risk of DM and CVD. Reproductive-age women with PCOS have a 2-fold increased risk of metabolic syndrome (66), with a higher risk in the hyperandrogenic phenotype (29). More importantly, in adolescents with PCOS, the risk of metabolic syndrome is at least 2-fold higher than in girls without PCOS (67).

Reproductive/obstetric

Women with PCOS are at an increased risk of endometrial hyperplasia and infertility related to anovulation. Premenopausal women with PCOS may have a 4-fold increased risk of endometrial cancer (68). For women with PCOS who are seeking pregnancy, the ovulation induction agent letrozole is associated with higher live birth rates compared with clomiphene citrate (69). Use of metformin in conjunction with these medications may improve the ovulation rate in a subpopulation of obese women. Depending on the ethnicity and study population assessed (eg, clinical cohorts vs population-based studies) the obesity rate varies from 50% to 80% (70). Metformin, on the other hand, has not been shown to reduce the risk of gestational diabetes (GDM); thus, its use should be limited to prior to pregnancy for metabolic management and to facilitate weight loss. Once pregnant, women with PCOS are at an increased risk of miscarriage, GDM, pregnancy-induced hypertension, and preeclampsia (71). These complications are increased in the hyperandrogenic phenotypes.

Behavioral/emotional

PCOS is associated with a higher prevalence of psychiatric disorders. Both moderate-to-severe depressive and anxiety symptoms are increased in cross-sectional studies (72), while a few longitudinal studies support an increased risk of incident depression and anxiety (73). However, there is limited data on the persistence of depressive and anxiety symptoms in adolescents and beyond the fourth decade, although recent data implies psychological distress prevailing long-term (74, 75). In addition, women with PCOS have a higher prevalence of disordered eating (76) and body image distress (77). Interestingly, in the latter study various aspects of body image distress predicted anxiety and depressive scores, indicating that improvement in body image could potentially decrease anxiety and depressive symptoms. Both eating disorders and body image distress add to difficulty in losing weight, highlighting the importance of routine screening for these disorders and use of interventions such as cognitive behavioral therapy (72, 78).

Quality of life

PCOS symptoms and comorbidities burden women with PCOS. Women with PCOS report poorer health status than non-PCOS counterparts (79) and indeed, health professionals and women should be aware of the adverse impact of PCOS on health-related quality of life (80, 81), which seems to prevail at least until the late reproductive years (79).

What remains to be clarified

Cardiovascular disease

The risk of dyslipidemia, DM, and metabolic syndrome in older women with PCOS have been compared in fewer studies relative to the outcomes of obesity and impaired glucose tolerance. Most of the available data in perimenopause and beyond is obtained from small cross-sectional

studies that included women with a presumed diagnosis of PCOS, limiting the validity of the findings. In order to adequately counsel patients, the prevalence of traditional CVD biomarkers needs to be assessed in different phenotypes of PCOS. There is some evidence for increased subclinical atherosclerosis in young women with PCOS. Increase in carotid intima media thickness measurements have been described (82), with data suggesting an increased risk for stroke and myocardial infarction (64). Ultimately, we need more longitudinal studies examining the incidence of cardiovascular events in this populations. Although there is some evidence from population-based studies for increased cardiovascular events in late reproductive-age women with PCOS, most studies lack adequate power to evaluate these outcomes and do not include menopausal women with well-defined PCOS. (83)

Perimenopausal disease course

In a large proportion of women, the clinical features of PCOS improve with age, such that by the fourth decade the menstrual cycles become more regular and serum androgen levels normalize (51). High serum levels of AMH and high antral follicle counts suggest increased ovarian reserve in early reproductive years. These biomarkers also decrease with age, and their trajectory suggests that women with PCOS may go through menopause later than controls (84).

Management

The management of comorbidities related to PCOS such as obesity, type 2 DM, and all health impairments related to metabolic syndrome and psychological distress should be treated following the current common guidelines regardless of PCOS diagnosis. What should be noted is that PCOS increases the risk for all these comorbidities at least 2- to 3-fold (mental distress even up to 5-fold), with the onset occurring several years earlier than in other women. This should be considered when screening and testing for these comorbidities.

The new international PCOS guideline recommends assessing weight and measuring waist circumference during every visit and otherwise every 6 to 12 months also giving high importance for weight gain prevention and pre-pregnancy weight management (3). Given that even lean women with PCOS are insulin resistant, all women should be tested for glycated hemoglobin A1c (HbA1c) levels every 3 years and administered an oral glucose tolerance test every 1 to 3 years if any known risk factors for type 2 DM. During pregnancy, an oral glucose tolerance test should initially be performed in the first trimester and repeated in the second, in gestational weeks 24 to 28, if normal in the first trimester. Obesity has been shown to be a high-risk factor for GDM also in PCOS, although PCOS also presents as an independent risk factor (85).

Hypertension should be screened annually, whereas dyslipidemia should be considered and tested for in overweight and obese women at diagnosis, although according to a recent Nordic study among women <35 years, only a minority have values warranting statin medication (86). Considering the different PCOS phenotypes and risk profiles for different comorbidities, future studies should target building algorithms or tools facilitating targeted screening for women with PCOS with high metabolic risk.

Mental disorders should be tested and treated similarly to common guidelines for the general population. However, psychological distress should be systematically screened in all women with PCOS by using the common tools and short questionnaires and further assessed and/or referred for assessment if needed. Regarding adolescents, similar increases in emotional disturbance are noted; thus, there is a need to address the management of mental distress in this population, as well.

Lifestyle interventions

Obesity worsens the presentation of the symptoms of PCOS and weight management has been proposed as an initial treatment strategy (3). Lifestyle intervention consists of changes in diet, exercise, and behavioral interventions designed to improve weight. Women with and without PCOS have similar diet and physical activity levels (87), suggesting that interventions can focus on general healthy principles. However, interventions have been studied in only small populations in PCOS and the evidence is of low quality. Meta-analysis of lifestyle interventions (88) demonstrated improvement in weight, free androgen index, and BMI with weight reduction from lifestyle interventions (low-quality evidence). However, there was no specific impact on livebirth or menstrual regularity. An additional randomized trial of behavioral modification in PCOS with a primary outcome of menstrual regularity was reported in 2019 (89). A 4-month intervention resulted in significant weight reduction (–2.1%) and improved menstrual irregularity but did not show improvements in ovulation (89). The majority of women in the trial had moderate-to-severe distress in a global index of psychological wellbeing. There was evidence of improved anxiety, reduced depressed mood, and overall higher general health in the intervention group with no change in the minimal intervention group (90). Exercise alone as intervention in PCOS has been studied (91). Most studies of exercise intervention are small and involved varying exercise interventions—aerobic, resistance,

and combined exercise. There was little evidence of impact on exercise alone on reproductive or hormonal outcomes but evidence for reduction in BMI was moderate.

Adherence to diet and physical activity recommendations for lifestyle intervention is challenging. Critically, such adherence is important to achieve goals, and therefore real-world outcomes of lifestyle interventions may be significantly less over time (92). A review of studies in PCOS involving lifestyle intervention did not provide significant data on adherence to the programs in the majority of trials (93). A detailed look at 4 randomized trials of lifestyle intervention in PCOS involving a total of 221 women showed that attrition from the programs was 47.1%. However, weight loss of ≥5% occurred in 63% of the women. Women who were more likely to experience attrition had higher depressive indices at baseline and those who had better appointment attendance had lower attrition and greater weight reduction (94). It is likely that many genetic, psychosocial, sociodemographic, and physiological factors impact the success of a lifestyle/weight loss intervention. The inclusion of behavioral support in these interventions is suggested based on psychological factors that are present with higher attrition from these programs. Overall available evidence suggests that lifestyle intervention involving weight reduction has a positive effect on hyperandrogenism and metabolic features of PCOS as well as on quality of life, however there is less support for improvements in reproductive and fertility outcomes.

Medical interventions

PCOS symptoms

The International PCOS guideline set recommendations for treating PCOS-related symptoms that are core to diagnosis, namely, irregular cycles, hirsutism, and anovulation. As hyperinsulinemia promotes hyperandrogenism, medical treatment is recommended only as second-line therapy after lifestyle modification. For medical interventions, combined contraceptives (COCs) are effective in treating irregular cycles and they are also superior for the treatment of hirsutism and acne compared with progestin-only preparations. Given that there are no data showing superiority for any particular estrogen-progestin combination, the choice for COC can be done according to administration preference and minimizing the side effect profile to ensure compliance (3). Of note, as recommended by the World Health Organization, 35 μg estrogen in combination with cyproterone acetate should only be used as a second-line choice for persistent acne or hirsutism, given the increased risk for vascular thromboembolism related to these preparations.

Metformin-only therapy exerts only mild-to-moderate changes on cycle regularity and hyperandrogenism and has been reported to be inferior to COC treatment. However, as a novel approach, the new guideline encourages combining metformin with COCs, especially in overweight or obese women with PCOS. This recommendation also applies to adolescents. The data regarding antiandrogen medication were limited due to a lack of high-quality studies, and the already existing data did not show antiandrogens having major advantages when combined with COCs. A recent placebo-controlled randomized controlled trial also confirmed this, as only minimal additional benefit was shown when combining bicalutamide, an androgen receptor antagonist, with COC treatment for 12 months (95). In clinical practice, when treating reproductive-aged women, the risk of virilization of the male offspring in case of pregnancy should be noted, warranting effective contraception when prescribing antiandrogens.

Metabolic outcomes

Metformin, especially in combination with lifestyle modifications, has the most data on improving menstrual cycles, glucose levels, and adiposity in PCOS; mild-to-moderate alleviation of insulin resistance and minimal-to-moderate effect on improving lipid profile (96). Low cost, availability, and the low adverse event profile of metformin supports its use. The most common side effects related to metformin are gastrointestinal symptoms, which are important to emphasize in patient consultation to ensure adherence to the treatment. The use of obesity drugs is limited by their high price and availability, but emerging evidence suggests their efficacy, especially glucagon-like peptide-1 (GLP-1) receptor agonists, in treating obesity in women with PCOS, compared with metformin (97). Future efforts should aim to assess the efficacy of combination therapies, for example metformin and GLP-1 receptor agonist agents, and to anticipate when these obesity drugs will become available in low-income countries and communities.

Reproductive outcomes

A recent meta-analysis concluded that letrozole improves live birth and clinical pregnancy rates and reduces time-to-pregnancy compared to clomiphene citrate and was it recommended as the first-line treatment for women with PCOS and infertility (70). As for metformin, a recent review suggests very modest improvement of ovulation and live birth with metformin over placebo. However, the benefit of combining metformin with clomiphene citrate was inconclusive (98). The data on the benefit of myoinositol for improving live birth rate or clinical pregnancy rate in subfertile women with PCOS undergoing in vitro fertilization are poor and therefore inadequate to form a recommendation. A recent Cochrane analysis was not able to draw a conclusion on inositol benefit due to insufficient data

(99). Future studies should focus on assessment of whether priming with metformin before ovulation induction with letrozole would have beneficial effects on live birth rates in PCOS. In cases where in vitro fertilization is needed, an antagonist protocol with GnRH trigger is preferred to reduce the risk for ovarian hyperstimulation syndrome.

Surgical interventions

Surgical interventions can sometimes relieve PCOS-related symptoms. Bariatric surgery is an effective treatment for obesity and PCOS symptoms after all other treatment options have failed and it should be offered to severely obese patients (100). The risks, however, include surgical and dietary complications and pregnancy should not be pursued during the 12 months following the surgery.

Laparoscopic ovarian drilling is a procedure in which ovarian tissue is destroyed with a laser beam or with a surgical needle using minimally invasive laparoscopic techniques, aiming to rebalance and improve ovarian function in PCOS. The procedure is not commonly used, but it has remained as an option in cases of clomiphene citrate–resistant ovaries and when letrozole is not an option due to off-label use. However, the recent Cochrane Review summarized that although reducing the number of multiple pregnancies and the risk for ovarian hyperstimulation syndrome, laparoscopic ovarian drilling may actually decrease the live birth rate in women with anovulatory PCOS and clomiphene citrate resistance compared with medical ovulation induction alone (101). One should also bear in mind that laparoscopic ovarian drilling also subjects women to the risks associated with surgery, such as complications from anesthesia, infection, and adhesions.

Cognitive behavioral therapy

Recent studies have also suggested that cognitive behavioral therapy (CBT) may be effective in treating women with PCOS (78). A recent randomized controlled trial reported 3-component treatment, including diet, exercise, and CBT, improved depression and self-esteem in obese women with PCOS (102).

Conclusions

Despite its prevalence in reproductive-aged women, the diagnosis and management of PCOS remains challenging. Some of these challenges are highlighted in Table 3. Clear diagnostic protocols should allow for more timely and accurate diagnosis, which will address the concerns of both clinicians and consumers resulting from diagnostic delay. The pathogenesis of PCOS is complex and multifactorial. New insights into the pathophysiology of PCOS suggest that there may be antenatal drivers for development of PCOS, specifically, evidence of hyperandrogenism in mothers appears to influence development of PCOS features in offspring. Insulin resistance is a near-uniform finding in PCOS and is worsened by hyperandrogenism-related adiposity. The role for abnormal AMH in the pathophysiology is also emerging, but AMH is not yet a diagnostic tool for PCOS. Comorbidities in PCOS are well-described and it is important to evaluate and address these comorbidities early in the treatment course, including attention to mental health and quality-of-life measures. While metabolic abnormalities are well described, the role of PCOS in cardiovascular disease remains uncertain. Evidence-based treatment guidelines include recommendations for lifestyle intervention as primary management for metabolic disease, although

Table 3. Highlights of Controversial Areas in the Diagnosis and Treatment of PCOS

Controversy	Current recommendation
Use of AMH in diagnosis	While AMH is typically elevated in women with PCOS and reflects the increase in follicle pool, AMH is not currently recommended as a diagnostic criteria as there is overlap with normal reproductive measures and it does not sufficiently distinguish PCOS.
Diagnosis in adolescence	Adolescents must be at least 2 years post menarche to consider the diagnosis. Ultrasound is not recommended in this age group before 8 years post menarche due to overlap with normal physiologic findings. Consideration may be given to the label "at risk for PCOS" for those in transition where the diagnostic criteria are uncertain.
Diagnosis in perimenopause	Menstrual regularity improves with aging in PCOS; therefore, a retrospective diagnosis is necessary in this age group.
Use of metformin without evidence of diabetes	While there is little support as a single agent for use in ovulation induction, there is evidence of improved metabolic parameters with the use of metformin. There is modest impact to reduce weight and prevention of diabetes development noted in other populations and can be considered for these indications in PCOS.
Type of oral contraceptive	There is no evidence that one type of combined oral contraceptive is better than another for either improvement in menstrual cycles or for suppression of hyperandrogenism.
Use of combination therapy with metformin	There is evidence that adding metformin to combination oral contraceptives may improve response particularly in obese women with PCOS.

Abbreviations: AMH, anti-Müllerian hormone; PCOS, polycystic ovary syndrome.

specific benefit in reproduction is not yet defined in weight loss trials. Oral contraceptives remain a first-line therapy for management of hyperandrogenism and irregular cycles and the role for metformin, while limited, may still add benefit for metabolic dysfunction and weight management, including in adolescents. There remain a number of challenges in the management of PCOS. A high prevalence of obesity is a significant contributor to morbidity. Early attention to weight gain in childhood and adolescence in those at risk for PCOS may be an important measure of prevention, since early markers of PCOS are better defined.

Additional Information

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