Polycystic Ovary Syndrome: Appreciating the Complexities and Implications of Diagnosis for Primary Care

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ABSTRACT

Polycystic Ovarian Syndrome (PCOS) is a common, complex endocrine disorder that has serious implications for women from adolescence to beyond menopause. This paper provides an overview of the diagnostic criteria for PCOS and outlines the goals of care to help physicians and other healthcare providers to move beyond the debates about diagnosis and to embrace an approach to management that is responsive to patients. Women with hyperandrogenism as a presenting feature of PCOS are known to have metabolic and cardiovascular risks, including type 2 diabetes mellitus and dyslipidemia. Despite the serious consequences of PCOS, women are not being identified early in the course of the disease or managed effectively across the lifespan in order to reduce their long-term health risks. Optimizing detection and management of patients with PCOS may reduce the prevalence of type 2 diabetes mellitus and unmanaged dyslipidemia. With effective management, women may be able to conceive earlier and experience fewer adverse obstetrical outcomes. PCOS affects women physically, psychologically, and socially, and challenges their healthcare providers to take a proactive and comprehensive approach to treat symptoms and manage long-term risks.

KEYWORDS: *polycystic ovary syndrome, hyperandrogenism, hirsutism, oligomenorrhea, amenorrhea, anovulation, obesity*

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common, complex endocrinopathy with lifelong implications for patients and their families. The genetic and environmental etiologies of PCOS are not yet fully understood,[1] but one hypothesis is that genetic factors promote fetal androgen secretion and this predisposes certain females to hyperandrogenism, oligo-ovulation or anovulation, with an associated increase in the number of follicles in the ovary.[2] The prevalence of the disease is commonly cited as affecting four to seven percent of women of reproductive age,[3] though estimates based on diagnostic criteria that include ultrasound are as high as 17.8%.[4] It is particularly concerning that 69% of women who met diagnostic criteria for PCOS in this study were undiagnosed.[4] As a consequence of undiagnosed disease, many women are living with unmonitored and unmanaged physical, psychological, and social challenges. Evidence strongly suggests that in addition to their presenting complaints during their reproductive age, women with PCOS have significant health risks including obesity, the metabolic syndrome (METS), type 2 diabetes mellitus (T2DM), and certain cardiovascular risk factors.[5] The high prevalence of the disease means identifying women with PCOS and managing their risks proactively across the lifespan will potentially prevent or mitigate the consequences of this chronic disease.

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THE DIAGNOSTIC CHALLENGE: A SINGLE PROFILE OR MULTIPLE PHENOTYPES?

In the last ten years, two consensus groups have revised diagnostic criteria and highlighted health risks associated with PCOS. Since PCOS is a syndrome with elements common to other disorders (including thyroid dysfunction, hyperprolactinemia, non-classical adrenal hyperplasia, and Cushing's syndrome), it is a diagnosis of exclusion in the presence of two of the following three criteria: oligo– or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasound. According to the Rotterdam Consensus Group, any two of these three criteria are adequate for diagnosis.[6] The inclusion of ultrasound criteria (presence of 12 or more follicles and/or increased ovarian volume) is significant because prior to 2003, the diagnosis was based on the presence of two criteria, to the exclusion of other etiologies: chronic anovulation and hyperandrogenism. As a result of including the ultrasound criteria, there are four possible phenotypes of women who could receive the diagnosis of PCOS: women with all three criteria, women with hyperandrogenism and oligo– or anovulation, women with hyperandrogenism and polycystic ovaries, and women with oligo– or anovulation and polycystic ovaries. In an extensive review of

the Rotterdam criteria, Geisthövel argued that these criteria may prompt over-diagnosis because the criteria are vaguely defined.[7] He proposed using androgenization as the criterion for diagnosing the condition and distinguishing between phenotypes. The phenotypic diversity also presents clinical challenges because women with the same diagnosis may represent different risk profiles.

The most recent consensus group, formed by the Androgen Excess and PCOS Society, concluded that hyperandrogenism is a necessary criterion for diagnosis, in addition to at least one of oligo-anovulation or polycystic ovarian morphology.[8] Under these criteria women with the milder phenotype of polycystic ovaries and oligo– or anovulation are not diagnosed as having PCOS. Significant endocrine abnormalities and increased body mass index and waist circumference are characteristic of women with phenotypes including androgen excess and oligo-anovulation, with only milder abnormalities evident in the phenotypes with only polycystic ovaries and either androgen excess or oligo-anovulation.[9] The risk of cardiovascular disease is increased in the hyperandrogenic phenotypes of PCOS,[5] however, this risk is yet to be confirmed in normoandrogenic phenotypes. PCOS patients lacking androgenic variations are at lower risk for metabolic syndrome and insulin insensitivity.[10] These early insights about the characteristics of the main phenotypes demonstrate that women with PCOS are a complex population who could require different approaches to management.

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Even with consensus guidelines, achieving an accurate diagnosis is challenging for clinicians because of variability in ultrasound evaluation, unreliability of serum androgen levels, subjectivity in measuring hirsutism, and inaccuracy in timing serum progesterone testing.[11] Lujan et al. conclude that a conservative approach to diagnosis (for instance, including androgen excess as an essential criterion) will promote research and intervention to improve care of women with PCOS.[11] Yet, these authors support the Rotterdam criteria because these criteria include the widest phenotypic variation. This tension can be attenuated with a clinical emphasis on identifying women with androgen excess as accurately as possible with current diagnostic capabilities, while researchers explore strategies for improving diagnostic investigations and clarify the variation in health risks among phenotypes. Until diagnostic standards and the related clinical implications are determined, managing lower-risk phenotypes should be a dynamic process of responding to individual needs in light of emerging research.

RECOGNIZING AND APPRECIATING THE IMPACT OF PCOS

As a syndrome, PCOS has multiple characteristics derived from common mechanisms.[12] The following discussion highlights some common clinical manifestations and complications of PCOS. Hyperandrogenism is the most consistently emphasized diagnostic feature of PCOS, and manifests clinically or as elevated serum androgen levels. Hirsutism is the most common clinical manifestation of hyperandrogenism, and can be experienced by adolescent and adult women with PCOS, affecting 50-76% of women with the diagnosis.[13] Adult acne or severe adolescent acne is also evidence of hyperandrogenism and affects 10-34% of PCOS patients.[13] The second diagnostic feature central to PCOS is ovulatory dysfunction, which commonly (though not exclusively) manifests as menstrual irregularity or the absence of menses.

Impact of PCOS on health status

Obesity

Though not all women with PCOS are overweight or obese, the average body mass index (BMI) of women with PCOS is higher than normal, and obesity is common in women with PCOS.[3] There is evidence that PCOS influences women's metabolic activity in cases of normal and high BMI. For instance, women of normal weight with PCOS consume an average of about 400 kilocalories less than women of normal weight without PCOS despite no significant difference in physical activity.[14] Women of normal weight with PCOS also report difficulty maintaining their weight.[15] The relationship between obesity and PCOS is complex in that adipocytes in women with PCOS behave differently than those of women without PCOS with regard to appetite regulation and steroid hormone metabolism. Obesity worsens the PCOS phenotype, and hyperandrogenemia contributes to central (android) obesity, which worsens insulin resistance.[16-19] Strategies for weight management that are broadly applied to people who are overweight or obese may need to be adjusted for women with PCOS as their metabolic environment is influenced by their disease.

Type 2 diabetes mellitus

Insulin resistance and impaired glucose tolerance (IGT) are precursors to T2DM. An estimated 40% to 58% of women with PCOS have insulin resistance,[19] in contrast to 7.2% of lean women without PCOS.[20] IGT and T2DM may be present in 9.4% and 1.6% of women with PCOS respectively.[20] Other researchers found 10% of adolescents and 20% of adult PCOS patients have IGT, irrespective of BMI.[21] Women with PCOS have a high rate of conversion from IGT to T2DM,[22] and have a relative risk of 4.0-6.0 of developing diabetes. PCOS patients contribute 15% to 36% of the overall disease burden of T2DM in white women, which is consistent with the number of women with T2DM with undiagnosed PCOS.[23] Oligomenorrhea presents a 2-2.5 times greater risk of T2DM, regardless of PCOS diagnosis,[24] which points to a relationship between menstrual irregularities and systemic complications.

Metabolic syndrome

Insulin resistance has a number of systemic effects that increase the risk of cardiovascular events and T2DM, and these effects together comprise the metabolic syndrome (METS). In addition to diagnostic criteria for PCOS, the 2003 consensus group defined criteria for METS in women with PCOS to include at least three of the following: waist circumference >88 cm (35 in), triglycerides ≥150 mg/dL, HDL-C <50 mg/dL, systolic blood pressure ≥130 or diastolic blood pressure ≥85, and fasting glucose 100-126 mg/dL or a glucose tolerance test with a 2-h glucose 140-199 mg/dL.[6] Recent analyses suggest that the prevalence of METS is on the rise among women of childbearing age.[25] METS has up to a 46% prevalence rate in adults and adolescents with PCOS and is more common in women under 30 years old.[26,27] Stress is one possible explanation for the correlation between PCOS and METS.[28] Women with a family history of T2DM, obesity, and elevated fasting insulin levels are more likely to manifest more components of METS.[27]

Lipid abnormalities and cardiovascular risk

Elevated triglycerides and reduced high-density lipoprotein levels, which are exacerbated by obesity, are among the components of METS that are cardiovascular risk factors. As part of METS, lipid variances are common to women with PCOS regardless of BMI.[29] In addition, there are well–documented variations in markers of atherosclerosis, such as increased carotid intima-media thickness and coronary artery calcification.[5] Research is wanting in terms of cardiac events, in part because of the lack of clarity around the risks associated with each of the phenotypes of PCOS.[30] One research group calculated that the risk of myocardial infarction increases four– to seven-fold in women with PCOS.[24] Multifactorial risk for cardiovascular disease in women with PCOS warrants careful consideration of screening practices and preventive management.

Gynecologic and obstetric complications

Infertility is a common presenting complaint for women with PCOS. Women who meet the waist circumference criteria for METS (greater than 88 cm) and have a BMI greater than 30 have a 50% reduced likelihood of spontaneous conception,[22] regardless of their PCOS status. When obesity is combined with the irregularly ovulatory or anovulatory states typical of PCOS, the chance of conception is likely lower. Pregnancy is also associated with increased risks for obese women, who are at risk for gestational diabetes and hypertension during pregnancy and their children are at risk for congenital anomalies, including cardiac defects.[22] Recurrent miscarriage is more common in women who are obese, however, there is no conclusive evidence for this association.[31] In one study, 56% of women with recurrent miscarriage also had PCOS, and although this is a higher prevalence than the normal population, the authors concluded that PCOS was not an independent etiological factor for recurrent miscarriage.[32]

Further reproductive health outcomes for women with PCOS include increased rates of hysterectomy (odds ratio of 4:1), usually for benign reasons like fibroids or persistent vaginal bleeding.[33] Given infrequent shedding of the endometrium in oligo– or anovulatory women, the risk of endometrial cancer is increased in women with PCOS, though the precise risk has not been defined.[34] Clinicians should therefore maintain a low threshold for recommending endometrial biopsy in these women because they are at increased risk for hyperplasia and carcinoma.

Mental health issues and quality of life

PCOS frequently manifests itself at puberty or during young adulthood with features like hirsutism and obesity, which affect self-image, self-esteem, and quality of life of young women.[35] Women with PCOS experience psychopathology more often than women without PCOS. More than half of women with PCOS have anxiety on clinical assessment, and this anxiety is often undiagnosed.[36] Over 60% of women with PCOS have depressive disorders, but again, there is insufficient evidence as of yet to determine phenotypic variations.[37] Eating disorders affect 35% of women with hirsutism, many of whom have PCOS.[38] Obesity is closely associated with eating disorders, and eating disorders are ten times more common in hirsute patients than in the general population.[38] One explanation for the 16% of PCOS women with bulimia is that androgens stimulate appetite and decrease impulse control, so the circulating levels of these hormones promote inappropriate eating behaviours.[39]

In addition to being over-represented in populations with psychiatric illness, women with PCOS rate their quality of life lower than not only healthy women, but in the psychological aspect, quality of life scores are 20% lower than people with many other chronic diseases like asthma, epilepsy, diabetes, and coronary heart disease.[15] Among adolescents with PCOS, lower scores on quality of life indicators seem to correlate with increased BMI,[40] but in adult women with PCOS, the reduced quality of life is independent of BMI.[35]

RESPONDING TO WOMEN WITH PCOS

Presenting to a clinician with sub-fertility is the only time in their lives when many women receive care for PCOS. This means women who meet diagnostic criteria for PCOS but delay childbearing, never attempt to conceive, or have no difficulty conceiving are unlikely to receive a diagnosis or management for PCOS. Clinicians should be alert to the variety of issues with which women with PCOS may initially present and maintain a low threshold for performing comprehensive clinical assessment to identify or rule out PCOS.

Goals and challenges of clinical management

The overall goals of care for women with PCOS are to promote regular menses, ovulation, and fertility, while reducing cardiovascular risk, effects of insulin resistance, hirsutism and acne, risk of endometrial carcinoma, and incidence of T2DM.[41,42] Diagnosing PCOS in adolescence and offering early treatment may mitigate the effects of hyperandrogenemia on the hypothalamus and slow the evolution of PCOS,[43] and at the very least delay or prevent serious consequences: psychopathology, T2DM, and cardiovascular risks. Educating women about PCOS and management strategies is in itself an intervention that may improve quality of life.[35]

Lifestyle interventions

Diet and physical activity guidance can dramatically influence the course of PCOS in women and should be implemented in the care of all women with this condition.[6] The goal of diet and physical activity interventions, according to some authors, is weight loss, which can be difficult to achieve in PCOS.[42-44] In addition to reducing metabolic sequelae of PCOS, weight loss will also promote fertility[22] and quality of life.[15] Other authors contend that women with PCOS achieve the benefits of physical activity and healthy eating regardless of BMI and that metabolic risk profiles and quality of life should be the primary goals of lifestyle management.[45,46] Regardless of the goals, the interventions should be medically monitored,[24] and this follow-up seems more important than the composition of the recommended diet.[47]

Pharmacotherapeutics

The use of pharmacotherapeutics in PCOS is largely informed by women's symptomatology and goals of care. The phenotypic diversity of PCOS brings different problems and priorities for individual patients, so there is no single stepwise treatment regimen. As many goals of care can be met with pharmacotherapeutics, Badawy[41] offers a current overview of pharmacological strategies. In what follows, we summarize some general recommendations. All oligomenorrhoeic or amenorrhoeic women should receive some form of treatment to prevent endometrial hyperplasia, which is a consequence of chronic exposure to unopposed estrogen that results from oligo– and anovulation. For women in which lifestyle management or insulin sensitizers do not induce regular cycles, treatment can take the forms of cyclic progesterone to induce regular bleeds, or menstrual suppression with hormonal contraceptives. Women who are not receiving continuous menstrual suppression should have an induced bleed or menses at least every three months. Metformin (Glucophage) and statins can be used in PCOS to address the metabolic problems related to insulin resistance, including hypercholesterolemia. Spironolactone (Aldactone), flutamide (Euflex), and finasteride (Propecia) are various effective antiandrogens. Oral contraceptives are commonly used to induce regular bleeds (thus preventing endometrial hyperplasia and cancer) and to treat hirsutism and acne in women who also seek contraception. Many of these pharmacologic interventions that are useful for women with PCOS can be implemented in primary care, but more specialized treatments are appropriate for consultant practice in dermatology, reproductive endocrinology, or other areas of medicine.

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Monitoring

The first step in meeting some of the goals of care is regular laboratory screening. Though some suggest adhering to T2DM screening guidelines and offering women fasting blood glucose testing,[48] many other authors suggest this test is not sensitive enough in the PCOS population and routine, even annual, screening for IGT and T2DM with oral glucose tolerance testing is warranted in all patients from adolescence through post-menopausal life.[20-22,43,49] However, this is not yet the standard of care for women with PCOS.[22] Regular lipid profiles are recommended for all women with PCOS to assess those components of METS and overall cardiovascular risk.[29]

CONCLUSION

Women with PCOS experience significant health risks and should have access to early diagnosis and management to prevent metabolic and psychosocial sequelae. Healthcare providers should maintain a high index of suspicion for the disease and offer risk-appropriate management to women presenting with signs of PCOS. Care by specialist physicians is often indicated for particular complications, but many important aspects of management are well-suited to a comprehensive approach in primary care.

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How Genomics is Changing Medical Practice

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ABSTRACT

Exponential improvements in genomic technology allows researchers to focus on the information contained in the human genome, in the hope of applying that knowledge clinically. The field of genomics, where all of an individual's genes are considered at once, has already begun to change medical practice. For instance, chromosomal microarrays are already being utilized to diagnose autism spectrum disorder, development delay, intellectual disability, and birth defects. By recognizing duplications and deletions, which are too small to identify with traditional chromosome analysis, we are able to improve diagnostic yield for these disorders. Whole genome sequencing has been used to diagnosis genetic illnesses, even in cases when the clinical picture or diagnosis is unclear. Through pharmacogenomics, which can help explain how genetic variants affect drug metabolism, we will be able to decrease the staggering incidence of adverse drug reactions, and guide physicians in medication choice for individual patients. With a better understanding of the relationship between genomic compositions, susceptibility to illness and treatment options, physicians will be able to practice more personalized medicine, offering more effective and safer treatment. Genomics has already begun to impact medical care and will likely revolutionize how medicine is practiced in the near future.

KEYWORDS: *genomics, personalized medicine, pharmacogenomics, chromosomal microarray, whole genome sequencing*

THE FIELD OF GENOMICS IS BORN

Following the completion of the Human Genome Project (HGP) in 2001, scientists and researchers were able to spell out the sequence, or code, of the human genome.[1] Since the completion of the HGP more than 10 years ago, there have been exponential improvements in the technology.[2] For instance, sequencing is now 100,000 times less expensive, and the newer generation machines are able to read sequences 50,000 times faster. While it took 13 years to complete the human genome project, it is now possible to sequence a human genome in a day.[2] With the technology ever-improving, scientists are able to focus on the information being produced.

THE TREMENDOUS POTENTIAL IN SEQUENCING THE HUMAN GENOME: PERSONALIZED MEDICINE

Advances in genomic research have resulted in an increasing awareness of the tremendous potential in interpreting and understanding the sequence of the human genome. One of the early discoveries was its sheer complexity, as there is incredible variation amongst the genomes of even two healthy individuals.[3] In fact, each individual differs in their sequence by as much as 0.5%. For instance, when compared to the reference human genome, each individual will have between 3 and 3.5 million single nucleotide variants (SNVs), and approximately 1,000 relatively large copy number variants (CNVs).[3] SNVs involve changes to single nucleotides, such as the substitution of one base pair for another (single nucleotide polymorphisms or SNPs), or the deletion or duplication of a single nucleotide. In contrast, CNVs occur when a particular portion of the genome is either duplicated or deleted, and therefore leads to a divergence from each person having two copies of each gene, one from each parent.[3] While seemingly daunting, for scientists, these variations were seen as an opportunity to harness these sequences in order to better understand disease and treatment options.[2,3] Better understanding of the human genome will result in increasingly personalized medicine, "a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease.[4] Genomics has already begun to impact medical

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