Racial and Ethnic Differences in Physiology and Clinical Symptoms of Polycystic Ovary Syndrome

Shunping Wang, PhD[1] Ruben Alvero, MD[1]

[1] Department of Obstetrics and Gynecology, University of Colorado Denver, Aurora, Colorado

Address for correspondence Ruben Alvero, MD, 12631 East 17th Avenue, Suite 4517, Aurora, CO 80045 (e-mail: ruben.alvero@ucdenver.edu).

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders and affects approximately 5 to 10% of women of reproductive age. There exists substantial variation of physical stigmata and clinical symptoms among women, but PCOS has been known to be associated with irregular periods, infertility, increased pregnancy complications, as well as nonreproductive health problems arising from its association with the metabolic syndrome. Over the years, there have been various consensus statements regarding the diagnostic criteria, but the varying pronouncements suggest that the underlying cause is still not well understood and may be multifaceted. Importantly, the interaction of genetic predisposition and local environment is possibly responsible for the heterogeneity of phenotypes seen; it has been demonstrated that there is substantial ethnic and racial variation in the clinical presentations among PCOS patients and related individuals may vary in appearance based on nutritional and other aspects of locale. The differences in phenotype and clinical symptoms of PCOS related to the clinical, hormonal, and metabolic characteristics among various ethnic backgrounds, including Hispanics, African Americans, Asians, and Indians, need to be considered when assessing and treating these individuals. Future research must address the importance of interactions between genotype and the environment.

Keywords

- polycystic ovary syndrome
- ethnic/racial difference
- prevalence

Background—Pathophysiology of Polycystic Ovary Syndrome

A commonly cited phrase in medicine is that *genotype plus environment equals phenotype*. This truism can reasonably be applied to the polycystic ovary syndrome (PCOS) and its varying manifestations among women from different backgrounds and from different regions. The theory of the *thrifty gene*, which supposedly provides a survival advantage in times of food scarcity but is responsible for diabetes and possibly overweight in times of nutritional plenty, may also be invoked in PCOS.[1] Unfortunately, there is an appalling lack of data to accurately determine whether genetic background, environment, or both are responsible for the clinical manifestations as well as success of interventions in women with PCOS. To properly conduct studies, better definitions of the condition need to be established. Multiple conferences and workshops have been organized, but their frequency and variability in consensus statements suggest that much work still needs to be done.

The National Institutes of Health (NIH) Evidence-based Methodology Workshop on Polycystic Ovarian Syndrome was held in December 2012.[2] The workshop attempted to integrate the research and knowledge that had accumulated over the decades since Stein and Leventhal initially described what later would become the PCOS.[3] Panel members considered the various consensus statements that had been issued by several studies over time, from the NIH 1990 consensus conference, the Rotterdam 2003 conference, and the Androgen Excess Society statement from 2006.[4–6] They also agreed that because the underlying cause of PCOS is still not determined and maybe multifaceted, much work needed to be done to further delineate the specific causes of PCOS. Implicit in the report was the fact that treatments may vary based on

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the underlying cause of the disorder. Panel members additionally felt that specific phenotypes should be reported explicitly in all research studies to better develop methods to assess androgen excess, to improve the methods and criteria used to assess ovulatory dysfunction, and to more precisely identify the criteria by which PCOS could be determined. It is clear that PCOS has been associated with irregular periods, acne, obesity, hirsutism, alopecia, and ovarian polycystic appearance. The biological effects of high insulin levels are important in many, if not most, women with PCOS and obesity appears to worsen the condition, with the degree of obesity and vulnerability to insulin resistance potentially varying by ethnic background. Panel members also noted that genetic predisposition to PCOS is significantly influenced by the environment. Therefore, specifically addressing the genetic predisposition based on ethnicity also must be tempered by the environment that the patient is in. The workshop also addressed the psychosocial aspects of PCOS, with mental health also highlighted as a critical aspect of the care of these patients.

Insulin resistance is an important aspect in many, if not most, women with PCOS. In general, the heavier or more obese the patient is, the more severe the PCOS phenotype with resulting excess of androgen and associated anovulation. Women who meet the diagnostic criteria for the diagnosis of PCOS but who still have moderately normal cycles are probably metabolically less abnormal. It is also quite evident that there can be differences in body mass index (BMI) among the women from different ethnic background, especially based on where they live.[7,8] The key to understanding the processing of sugar among PCOS women is the distribution of body fat when compared with weight-matched controls. In general, women with worse metabolic syndrome have greater abdominal visceral fat and adiposity and have a greater insulin resistance as a result.[9] In addition to the genetic predisposition for obesity among some populations, there is also an aberration in the postreceptor modulation of the insulin receptor. Women with PCOS appear to have excessive serine phosphorylation at the level of the insulin receptor. The abnormal insulin metabolism has downstream effects on the level of the ovary and adrenals where the key androgen regulatory enzyme, P450c17, is also apparently affected, and serine phosphorylation at this receptor also increases the amount of androgen excess. An area of future possible evaluation and research could be identification of variation in the genetic defects among PCOS women at the level of the ovarian and adrenal insulin receptor. It is thought that insulin acts through its own receptor at these organs rather through the insulin-like growth factor 1 receptor. Obesity itself appears to be an independent factor in addition to the PCOS phenotype with underlying predisposition to insulin resistance. Patients who are not obese but have PCOS may have insulin resistance or diabetes mellitus, but the presence of obesity superimposed on the genetic predisposition appears to worsen the disorder.[7]

Reproductively, PCOS patients may have irregular menstrual cycles; indeed, this is one of the three Rotterdam criteria. Irregular menstrual cyclicity may serve as a marker for type II diabetes.[10] The risk for developing type II diabetes in women with highly irregular menstrual cycles may not be completely explained by their BMI. This again suggests a significant overlap of phenotypic predisposition for insulin resistance and diabetes in women who also have an associated irregular menstrual cycle. Overall, PCOS patients, whatever their menstrual, BMI, and glucose processing manifestations, have adverse reproductive outcome when they are successful in becoming pregnant. Women with PCOS have a significantly higher risk of developing gestational diabetes, preeclampsia, or other manifestations of pregnancy-induced hypertension and early delivery. Their infants also have a significantly higher risk of admission to a neonatal intensive care unit and other postpartum morbidities.[11] In evaluating patients with polycystic-appearing ovaries by Rotterdam criteria, the association of this polycystic ovary morphology did not, however, associate itself with underlying metabolic or reproductive outcome.[12] It remains to be seen whether this polycystic ovarian morphology also varies by ethnicity.

Polycystic Ovary Syndrome and Ethnicity

While there are no population-wide studies examining prevalence of PCOS among various populations, either in the United States or from other nations or regions, some inferences can be made from available data.

The metabolic syndrome is present in a significant percentage of men and women in the United States. The prevalence among Latin American and specifically Mexican American patients is significantly higher than in the black and to some extent the white population.[9] Age-specific prevalence appears to be highest in Mexican American women. Because of the significant overlap between the metabolic syndrome and PCOS, it stands to reason that the prevalence of the disorder is going to be higher in this population as well. One study performed in Los Angeles evaluated 156 unselected consecutive women of reproductive age from their population in the Mexican American coronary artery disease project, which sought to study Mexican American families with a parent with coronary artery disease.[13] Patients were given a questionnaire and self-reported their symptoms and menstrual irregularities as well as clinical signs of hyperandrogenism. Patients in the study were evaluated using the homeostasis model assessment index of insulin resistance and also the hyperinsulinemic–euglycemic clamp test. On the basis of the study, approximately 13% of Mexican American women were assessed as having the PCOS. This prevalence is significantly higher than the 5 to 8% that is conventionally used in the population at large. However, a cross-sectional study of 150 female Mexican volunteers aged 20 to 45 performed in Mexico City cast some doubt on whether the prevalence is indeed that high among Mexican women. The participants recorded their menstrual cycles and hirsutism was graded. Pelvic ultrasound was performed to assess for the presence of PCOS-appearing ovaries as per Rotterdam, and androgen levels, including total testosterone and dehydroepiandrosterone, were also recorded. PCOS was diagnosed by a combination of the NIH 1990 criteria as well as the

Rotterdam 2003 criteria. In this study, approximately 6% of women were diagnosed with PCOS.[14] This is comparable with other ethnic groups, but significantly lower than expected based on other studies.[13] As has been suggested previously, there is the possibility that location and environmental factors, which were not assessed in these studies, may play a role in the subjects' phenotype.

In a very large Kaiser study of more than 11,000 women diagnosed with PCOS during 2002 to 2004, the prevalence among women aged 25 to 34 was around 2.6%.[15] Unfortunately, the manuscript did not break out the prevalence of PCOS among the various ethnic backgrounds. It is noteworthy that among the subgroup of these women, Asian women have the lowest prevalence of obesity (BMI $\geq$30 kg/m^2), while African Americans and Hispanics have the highest. Asian and Hispanic women had a 12% rate of type II diabetes, highest among the groups. The prevalence of hypertension was also diagnosed at a higher rate than the population at large but was highest among blacks at 22%, whites at 14%, and among the Asians and Hispanics at 14% and 12%, respectively.

Coney et al, in a review from Pittsburgh, evaluated the associations of African American women and PCOS as well as cardiovascular disease and the metabolic syndrome. The findings suggested that there was really no significant difference with regard to the baseline characteristics of metabolic factors by race.[16] However, African American women did show higher glucose level and abdominal circumferences, and tended to be more insulin resistant when measured by homeostatic testing. Interestingly, Asians had better metabolic profiles than African Americans and Caucasians.[16] Hispanics were not assessed in this study.

The available literature suggests that there is a significant increase in PCOS among Asian women, particularly those from the Indian subcontinent. In one study from Bangalore, India, 460 girls aged 15 to 18 from a residential college underwent clinical examinations.[17] Out of the 460 girls, 72 girls had oligomenorrhea and/or hirsutism and were invited for biochemical, hormonal, and ultrasonographic evaluation for the diagnosis of PCOS using the Rotterdam criteria. The study suggests that the prevalence of PCOS in Indian adolescents is approximately 9%, which is somewhat higher than the conventionally stated 5%. This is in contrast with Sri Lankans who appeared to have a 6% prevalence of PCOS and 2.4% among a well-sampled Chinese population.[18,19] It is also consistent with the findings that Indians appear to have a higher prevalence of diabetes overall. In another case–control study performed on women from the Indian subcontinent, 37 PCOS patients were evaluated using the Rotterdam criteria, age, family history of diabetes, acanthosis nigricans (AN), BMI, waist circumference, hypertension, total cholesterol, triglycerides, high-density lipoprotein cholesterol, and the presence of impaired glucose tolerance (IGT)/diabetes.[20] The study showed that women with family history of diabetes had a close to eightfold increase of the risk of insulin resistance. Moreover, subcutaneous fat was shown to be independently associated with insulin resistance. An evaluation of Sri Lankan women selected from a large database from a referral endocrine clinic showed that women tended to have significant increase in central obesity and one-third of the PCOS patients had the metabolic syndrome. Interestingly, the metabolic syndrome had no relationship to whether the women were hyperandrogenic. The study also showed that associations with the metabolic syndrome included advancing age, BMI greater than 25 kg/m^2, and AN.[21] ►**Table 1** summarizes these studies and their findings.

A review published in 2008 looked at the clinical, hormonal, and metabolic characteristics of PCOS women in a generalized Asian population.[22] The authors emphasized that it is important to identify the specific region and ethnicity of these women because parameters and possibly treatment modalities may be different from population to population. From the metabolic perspective, PCOS women from Japan were less obese and did not have hirsutism when compared with Western women with the disorder. Indian PCOS women had higher insulin response after an oral glucose tolerance test than Caucasian patients. The prevalence of IGT was approximately 20% in Chinese PCOS women, with 2% having developed non–insulin-dependent diabetes mellitus. Another study looked at women with PCOS from China and revealed that overweight was present in 30% of the population and the prevalence of insulin resistance was 12.8% using a glucose-to-insulin ratio, as compared with the 21.6% using the homeostasis model assessment.[23] The authors compared various parameters including follicle count, ovarian volume, and ovarian stromal flow among Chinese women with PCOS and found that PCOS ovarian morphology had little bearing on the presence of the metabolic syndrome.

Table 1 Summary of results on incidences of PCOS among different ethnic groups

Group	Incidence of PCOS (%)	Citation	Comment
Hispanic	6–13	13–14	Broad range may be associated with similar ethnicity but in different locations
African American	3–9	15, 28	Significant inference in first reference; second reference in ART population, which may be rarefied population
Asian	2–9	17–20	Broad range due to varying ethnicities associated with Asian descriptor

Abbreviations: ART, assisted reproductive technology; PCOS, polycystic ovary syndrome.

Treatment

The treatment of PCOS mainly depends on the therapeutic goals. Patients with PCOS commonly exhibit a broad range of symptoms and physical signs such as hirsutism, ovulatory dysfunction, obesity, insulin resistance, hyperandrogenism, and subfertility. For treating hirsutism, acne, and alopecia, the use of estrogen–progestin contraceptive, combined with antiandrogen such as spironolactone, has long been used to reduce androgen production and its end-organ effects.

As for subfertility and ovulatory dysfunction, lifestyle change, exercise, and diet control are often recommended for these patients and it is widely recognized that reductions in weight improve metabolic parameters and insulin sensitivity, with resulting improvement in ovulatory effort. Patients are frequently told that a reduction in weight of even 5 to 10% may result in improved ovulation and sensitivity to ovulation induction. Nestler and Jakubowicz showed that metformin significantly reduces the circulating insulin level in women with PCOS[24] and later showed that use of metformin improves ovulation in obese women, with and without clomiphene citrate.[25] The population studied was from Venezuela, Italy, and the United States, but he did not stratify these patients by ethnicity. Lord et al also showed in 2003 that metformin significantly increases the frequency of ovulation.[26] Unfortunately, the Pregnancy in Polycystic Ovary (PPCOS) trial that evaluated 626 infertile women with PCOS suggested that the combination of metformin and clomiphene can increase the cumulative ovulation rate, compared with the group with clomiphene alone. However, the live birth rates were not significantly different between the two groups.[27] In the trial, participants self-identified their ethnicity and could also select more than one category. Nevertheless, 26% were Hispanic, 17% were black, 2.7% were Asian, and 11.5% were Native American. The authors did not stratify pregnancy rates by racial or ethnic background. It is anticipated that the second phase of the study, known as PPCOS II trial that is now complete, will be able to stratify outcomes by ethnicity and will therefore contribute to the literature in this important area.

There have been numerous studies using the Society for Assisted Reproductive Technologies database to assess ethnic differences among patients from various backgrounds.[28–30] These data are compromised by poor reporting of ethnicity from the various centers, as this historically has not been a required field in the database and only two-thirds of reported cycles include this descriptor. Compared with white women, African Americans, Hispanics, and Asians had a significant decrease in the rate of clinical pregnancy and a higher rate of pregnancy loss. While success rates tend to be higher for ovulatory dysfunction patients, most of whom presumably have PCOS, the success rates by diagnosis and ethnic background are difficult to determine, since the studies do not stratify this way.

Nonreproductive health consequences of PCOS must also be addressed. Insulin resistance and the resulting hyperinsulinemia are estimated to affect 65 to 70% of women with PCOS.[31] Metformin has also been shown to be effective in treating obese adolescents with hyperandrogenemia and with IGT and type 2 diabetes as well as to reduce the incidence of type II diabetes in those patients vulnerable to the disorder.[32] In a multicenter trial, progression to diabetes was thwarted moderately effectively by the use of metformin and most effectively by an intense regimen of exercise and lifestyle intervention.[33] The study did stratify by ethnicity and effectively showed that regardless of background, all populations responded similarly to the intervention. However, it has been suggested by Marshall and Dunaif that since the severity of insulin varies by PCOS phenotype and some patients may only suffer from mild forms clinically, the administration of metformin should not be used in all women with PCOS.[34]

Future Directions

Much work needs to be done on the impact of PCOS on individuals from different ethnic backgrounds. It has been shown, however, that there are substantial variations in PCOS symptoms and prevalence among different ethnic backgrounds. However, the real difference may not be truly revealed in the previous studies due to limitations such as the appropriately defined ethnical background, culture/social factors, and the changing consensus on the diagnosis criteria for PCOS. Adequately powered, well-controlled studies should be conducted to determine the prevalence and phenotype among different ethnic and racial groups. In addition, genome-wide association study may provide a powerful tool in identifying novel susceptibility loci for PCOS and revealing single nucleotide polymorphisms variation among different racial and ethnical groups.

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