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Chapter 3

Ethnic variations in the expression of polycystic ovary syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine problem affecting women of reproductive age and is reported from many regions of the world.[1–4] Some reports indicate ethnic differences in its manifestation. This chapter examines the evidence for ethnic variation in the PCOS phenotype and explores the possible basis of this phenomenon.

Despite having a relatively recent ancestry, the species of modern *Homo sapiens sapiens* is a non-homogeneous group, as is evident from their differing physical, behavioural and social characteristics. Such variation has the potential to affect the prevalence and presentation of common diseases. Every human being has a unique inherited (genetic) make-up that can be affected by many environmental (non-genetic) influences during life that can modify external features and manifestations. Spielman *et al.*[5] demonstrated that the expression of some genes differs significantly among different ethnic group. Phenotypic variations in human populations may be caused by natural selection and adaptation to environmental conditions. Recent genome-wide studies have identified a few loci that contribute to differentiation of disease-related phenotypic diversity.[6]

Researchers studying PCOS in depth need to decipher any ethnic variations of its genotype and phenotype. This requires sound epidemiological evidence that can characterise risks, both at an individual and a population level, to enable effective planning of prevention and treatment strategies. Such an analysis must also consider variations in normal traits, risk factors for comorbidities, response to treatment and effects of pharmacological agents.[7]

Defining race and ethnicity

The word 'race' is attributed to an 18th century European outlook of a group of individuals with a common characteristic. 'Ethnicity' denotes a wider concept that

is based on one's history, language, religion and ancestral heritage and that is closely linked to geography, geo-politics and culture. Ethnicity encompasses culture, diet, religion, dress, customs, kinship systems and historical and territorial identity.[7,8] The accepted classification of ethnic groups in the USA for biomedical research includes black or African-American, white (Hispanic and non-Hispanic), Asian, Native Hawaiian or other Pacific Islander, American Indian and Alaskan Native, which are all mainly based on the geographic location of their ancestry.

Genetic differentiation depends on the degree and duration of geographic segregation of one's ancestors. Geographic isolation and inbreeding (endogamy) due to social and/or cultural forces over extended time periods create and enhance genetic differentiation, whereas migration and inter-mating reduce it. Numerous human population genetics studies have concluded that genetic differentiation is greatest when defined on a continental basis: African, Caucasian (Europe and Middle East), Asian, Pacific Islander (Australian, New Guinean and Melanesian) and Native American.[8,9] This does not take into account the diversity and vast differences that exist within specific groups or across the largest continent, Asia. For instance, a drawback of this classification is that South East Asians from countries east of India and south of China and South Asians predominantly from the Indian subcontinent are not distinctively identified. Another criticism is the distinction based on skin colour, which is superficial and makes no allowance for genetic interchange. Furthermore, genetics research that involves making broad comparisons between populations can inaccurately stereotype racial and ethnic groups by extrapolating findings of a section of the group to the entire group of individuals. This can have major implications on some sectors of the community by an overemphasis on health differences, which can shift attention away from established contributors to health disparities.[9]

An ethnic difference in the frequency of an aspect of the phenotype of a disease may be the first clue to its aetiology. Without suitable classification, the underlying factors may not be adequately investigated. To disentangle genetic from environmental causes, studies on the effects of migration are required. Assuming that the ethnic group being studied is homogeneous, migrant studies need to compare the frequency of a trait between people with the same ethnic origin who live in different environments.[8] A review of PCOS research published in the past three decades reveals that the main focus of its epidemiological, biomedical, genetic and social aspects are based on studies of predominantly Western women of white European origin, although more recent large studies carried out in predominantly mixed populations in the USA have attempted to identify the ethnic origin of subgroups. The link between insulin resistance and PCOS is strong and is a main determinant of the phenotypic presentation and response to management protocols. Recent epidemiological analysis of type 2 diabetes reveals its frequent detection in children and adolescents among American Indian and African-American people, and among Hispanic/Latino American people earlier than in non-Hispanic white people.[10] This disparity exists even after controlling for population age differences. However, the propensity for type 2 diabetes among young South Asian people is not reflected in these US-based studies, possibly owing to South Asian migrants forming a relatively insignificant proportion of the population. The effects of social determinants of health are also contingent upon ethnicity.[7] Given the known health consequences of obesity and recent trends towards increasing body mass in young women from some ethnic groups, the impact of ethnicity on disparities in phenotypic expression of PCOS requires in-depth study.

Evidence for ethnic variations in the expression of PCOS

Evaluating ethnic variations in the expression of PCOS requires systematic review of the strength of the evidence, preferably from population-based data or from large samples in the clinic setting. This includes studying the possible links with:

- racial determinants of manifestation
- cultural determinants of presentation and diagnosis
- body configuration and propensity to obesity, insulin resistance and metabolic risk.

This chapter evaluates reports of differing expression of hyperandrogenism, obesity, insulin resistance and metabolic manifestations. The reports discussed mainly comprise comparative and case–control studies providing level III evidence. Relevant research papers were identified from a literature search using MEDLINE, PubMed and BioMed Central using the keywords 'PCOS', 'phenotype', 'ethnicity', 'insulin resistance' and 'metabolic syndrome'.

PCOS is a polygenic disorder. Critical appraisal of epidemiological data therefore requires careful and uniform phenotyping, with the study of sufficiently large representative cohorts from differing backgrounds and populations. In view of the heterogeneity of the PCOS phenotype, such an appraisal must also evaluate possible links between the androgenic, reproductive and metabolic phenotypes of PCOS, together with the ovarian characteristics. To determine ethnic variation, phenotypic evidence of hyperandrogenism, oligomenorrhoea/amenorrhoea, infertility, age of manifestation, anthropometry, insulin resistance and the metabolic syndrome, family history, community prevalence and impact of migration must be determined.

The available data show variations in the PCOS phenotype among Caribbean Hispanic, Mexican American, Japanese, indigenous Chinese/Taiwanese, migrant versus indigenous South Asian, Thai, Malay, southern European, indigenous Canadian and migrant Arab women. Unpublished data of indigenous South Asian women that address some aspects of the phenotype, metabolic correlates, diagnostic criteria of polycystic ovaries, quality of life, health-seeking behaviour and new dimensions of metabolic problems will also be detailed. Finally, the effects of migration and urbanisation on type 2 diabetes and probable links to PCOS will be discussed.

Historical background

In 1992, Carmina and co-workers[11] studied women with hyperandrogenic anovulation from three distinct ethnic backgrounds, namely 25 Japanese women, 25 Italian women and 25 Hispanic American women, and compared them with normal women from each ethnic group (Table 3.1). The participants were characterised based on clinical features, endocrine status that included insulin sensitivity, and ovarian ultrasound scans. The Japanese women had less hirsutism but comparable hyperandrogenaemia, and lower body mass index (BMI) but a similar degree of insulin resistance when compared with white European women. Dunaif *et al.*[12] compared insulin sensitivity (determined by the euglycaemic clamp method) in Caribbean Hispanic and non-Hispanic white women with a control group of women matched for age, BMI and ethnicity.[12] They reported in 1993 that PCOS and ethnicity had an independent but additive effect, with the Caribbean Hispanic women with PCOS being the most insulin resistant. In 1995, Norman *et al.*[13] reported their comparison of glucose-induced insulin response in white and South Asian (Indian) women with and without PCOS in South Africa. A significantly greater insulin response was observed in the

Table 3.1 Ethnic variations of polycystic ovary syndrome reported among various ethnic groups in both migrant and indigenous settings

Source	Ethnic group(s) studied	Sample size, study design and study setting	Characteristics of comparison groups	Summary of findings
Multi-ethnic groups within and outside the USA				
Carmina *et al.* (1992)[11]	Japanese	$n=75$ (25 in each arm)	Italian and US-based white women	Japanese women were less hirsute but had similar androgen levels, and were less obese but had similar insulin resistance to white women
Dunaif *et al.* (1993)[12]	Caribbean Hispanic	PCOS: 13 vs 10; controls: 5 versus 8	Non-Hispanic white women; PCOS vs control groups	Normal Caribbean Hispanic women had greater insulin resistance than non-Hispanic white women and PCOS had an additive effect
Norman *et al.*(1995)[13]	South Africa: South Asian (Indian)	11 in each of 4 groups	White women; PCOS vs control groups	South Asian Indian women (PCOS and controls) had greater insulin response to glucose provocation than matched white women
Rodin *et al.* (1998)[14]	UK: South Asian	212 screened	Four groups with and without polycystic ovaries and/or type 2 diabetes, 12–15 women per group	Prevalence of polycystic ovaries in South Asian women was 52% (versus 20–33% in white women); insulin resistance of South Asian women with polycystic ovaries alone was the same as that of South Asian women with type 2 diabetes alone
Williamson *et al.* (2001)[15]	New Zealand: South Asian (Indian), Maori, Pacific Islander	$n=162$ (total)	Compared with 1996 census data	Infertility was more common among indigenous groups and they had higher BMI, insulin resistance and SBP but lower SHBG; they had less perception of obesity
Kauffman *et al.* (2002)[16]	Mexican American	PCOS $n=83$; controls $n=19$	37 Mexican Americans versus 65 white Europeans	Mexican American women had higher insulin resistance and BMI; insulin resistance was 73% in Mexican American women with PCOS versus 44% in white women with PCOS
Goodarzi *et al.* (2005)[17]	Mexican American	156 women screened	Selected group with family history of coronary artery disease	Greater prevalence (13%) of PCOS in Mexican American women; higher insulin resistance in women with PCOS

Source	Ethnic group(s) studied	Sample size, study design and study setting	Characteristics of comparison groups	Summary of findings
Kauffman *et al.* (2006)[18]	Mexican American	PCOS $n=50$	White women with PCOS $n=111$	Mexican American women had higher insulin resistance than white women but lower DHEAS; similar testosterone levels between groups
Wijeyaratne *et al.* 2002)[19]	UK: South Asian (Pakistani)	PCOS $n=47$; controls $n=11$	White women: PCOS $n=40$, controls $n=22$	South Asian women with PCOS presented at a younger age, had earlier symptoms, more infertility and acanthosis nigicans, greater insulin resistance and lower SHBG
Wijeyaratne *et al.* (2004)[20]	Sri Lanka: indigenous South Asian	PCOS $n=80$, mean age 26 years, mean BMI 26 kg/m²	British South Asian (Pakistani) women with PCOS $n=47$, mean age 26 years, mean BMI 30 kg/m²; hyperandrogenism in 66%	Lower BMI, more central obesity and acanthosis nigricans, higher insulin resistance, lower FG score, similar testosterone and lower SHBG; high homocysteine correlating with insulin resistance
Aruna *et al.* (2004)[21]	South Asian (Indian)	PCOS $n=50$		Lower BMI, more central obesity than white European women
Weerakiet *et al.* (2007)[22]	Indigenous Thai	PCOS $n=170$	Mean age 28.8 years, mean BMI 27 kg/m²	Metabolic syndrome in 35%
Charnvises *et al.* (2005)[23]	Indigenous Thai	PCOS $n=121$	Mean age 29 years, mean BMI 27 kg/m²	AGT in 42%, acanthosis nigricans was an important predictor
Saundararaman *et al.* (2003)[24]	South Asian (south Indian)	Case–control	PCOS BMI 26 kg/m² versus controls BMI 23 kg/m²	Greater insulin resistance and intima–media thickness in women with PCOS; insulin resistance correlated with waist circumference
Kalra *et al.* (2009)[25]	South Asian (Indian)	Body fat mass by MRI	Mean age 21 years, mean BMI 26 kg/m²	Total and subcutaneous fat volumes, not global obesity, measured by BMI; linked to family history of type 2 diabetes

Table 3.1 (*cont.*) Ethnic variations of polycystic ovary syndrome reported among various ethnic groups in both migrant and indigenous settings

Source	Ethnic group(s) studied	Sample size, study design and study setting	Characteristics of comparison groups	Summary of findings
US-based multi-ethnic groups				
Apridonidze *et al.* (2005)[32]	White $n=98$, African-American $n=8$	Retrospective cohort, $n=106$	Clinic-based, NCEP ATP III criteria	Metabolic syndrome in 43% (NIH criteria) of women with PCOS; acanthosis nigricans more frequent in women with the metabolic syndrome
Lo *et al.* (2006)[26]	White 34.2%, black 5%, Asian/Pacific 10%, Hispanic 12%, Other 3%, unknown 34.7%	PCOS $n=11\,035$, PCOS prevalence 2.6%, five age-matched controls selected for every case	Community-based, multi-ethnic, Kaiser Permanente	Women with PCOS, compared with white women: black and Hispanic women were more likely to be obese and Asian women less likely, Asian and Hispanic women were more likely to have diabetes, black women were more likely to have hypertension
Ehrmann *et al.* (2006)[27]	Clinic-based multi-ethnic groups	PCOS $n=394$, multicentre data	Metabolic syndrome in women with PCOS: white 34%, African-American 26%, Hispanic 31%, Asian 50%, mixed ancestry 43%	No statistically significant ethnic difference; African-American women had greater waist circumference and insulin resistance, and elevated triglycerides
Legro *et al.* (2006)[28]	Clinic-based multi-ethnic groups	Anovulatory PCOS $n=626$	Mean age 28 years, mean BMI 35.2 kg/m², polycystic ovaries in 90%	Asian women had a milder phenotype, and white and African-American women were similar
Welt *et al.* (2006)[29]	Clinic-based multi-ethnic groups	PCOS: Boston $n=262$, Iceland $n=105$	White women in both countries and, in Boston, African-American $n=44$, Hispanic $n=25$, Asian $n=21$	White women were taller; African-American women had greater BMI and type 2 diabetes; FG score and LH were lower in Icelandic women
Far East Asian groups				
Iwasa *et al.* (2007)[58]	Japanese	PCOS $n=46$, controls $n=50$; High LH diagnostic criterion (JSOG 1993)	Normal cycling, ovulatory, euthyroid women with normal prolactin and ovaries	Clinical and biochemical hyperandrogenism less prevalent at 10.2%; testosterone was not diagnostic
Lin *et al.* (2005)[59]	Taiwanese (Hoklo and Hakka)	PCOS $n=47$, controls $n=40$	Mean age 26 years, mean BMI 28 kg/m², acanthosis nigricans in 31%	AGT in 46.8%; both insulin resistance and AGT in more than 82%
Li *et al.* (2007)[60]	South China	PCOS $n=273$, retrospective clinic based	Mean age 24.8 years, mean BMI 22.2 kg/m², polycystic ovaries in 97%	Hyperandrogenism, obesity and insulin resistance were lower than in women from other races also with PCOS

Source	Ethnic group(s) studied	Sample size, study design and study setting	Characteristics of comparison groups	Summary of findings
Chen *et al.* (2008)[61]	South China	$n=915$, Guangzhou community	Mean age 30 years, FG score was 1–3, 7.5% were overweight, 1.3% were obese	Women with PCOS: prevalence was 2.2%; low rates of hirsutism; hyperandrogenism was age and BMI dependent
Yu Ng and Ho (2008)[62]	Asian (review)	Fertile Chinese women versus clinic-based infertile women	Polycystic ovaries in 5.6% versus 12.2%; women with PCOS had lower antral follicle counts	Women with polycystic ovaries: IGT in 20.5%; type 2 diabetes in 1.9%; 30% were overweight; insulin resistance in 12.8%
Other groups – Arab, Mediterranean and Eastern European				
Al-Fozan *et al.* (2005)[47]	Canada-based immigrant Arab women	PCOS $n=92$: white Europeans $n=41$, Arab (Middle Eastern) women $n=18$, others $n=33$	BMI-matched ethnic groups; insulin response to oral glucose tolerance test	Those of Middle Eastern origin had greatest response
Al-Ruhaily *et al.* (2008)[48]	Saudi Arab women	$n=101$ women with hirsutism: PCOS $n=83$, idiopathic hirsutism $n=11$; clinic based		79% of the women with PCOS were overweight or obese, 51% had BMI > 30 kg/m^2; no difference in metabolic phenotype (both groups high)
Schmid *et al.* (2004)[49]	Vienna-based Muslim immigrant women	PCOS $n=49$	Quality of life in terms of symptoms, compared with white women	Greater impact of infertility on health-related quality of life in Muslim immigrant women
Vural *et al.* (2005)[53]	Turkey	PCOS $n=43$, controls $n=43$	Mean age 21 years, mean BMI 23 kg/m^2	Women with PCOS: hyperandrogenism in 88%, median FG score 13; insulin resistance greater; carotid intima–media thickness greater
Vrbikova *et al.* (2003)[54]	Czech Republic-based	PCOS $n=69$, controls $n=73$	Age-matched controls, randomly selected	Women with PCOS: cardiovascular disease risk worse than women in the control group and not explained by obesity alone; IGT in 12%

AGT = abnormal glucose tolerance; BMI = body mass index; DHEAS = dehydroepiandrosterone sulfate; FG = Ferriman–Gallwey measure of hirsutism; IGT = impaired glucose tolerance; JCOG = Japan Society of Obstetrics and Gynecology; LH = luteinising hormone; MRI = magnetic resonance imaging; NCEP ATP = National Cholesterol Education Program Adult Treatment Panel; NIH = National Institutes of Health; PCOS = polycystic ovary syndrome; SBP = systolic blood pressure; SHBG = sex hormone-binding globulin

Indian women, both in the PCOS and the reference groups, compared with the white women. This highlighted the ethnic differences, particularly with regard to metabolic status, evident even among normal Indian women.

These reports prompted researchers in other regions of the world to study specific aspects of PCOS in different ethnic groups. They addressed variations in phenotypic manifestation, age of presentation, community prevalence and impact on quality of life linked to cultural and social issues.

Ethnic variations of obesity, insulin resistance and the metabolic syndrome in PCOS

Insulin resistance is central to the pathogenesis of PCOS and any ethnic variation is likely to be reflected in its manifestation among ethnic groups. Those studied so far include UK-based, New Zealand-based and indigenous South Asian women, and Maori, Pacific Islander, Mexican American and South East Asian women (Table 3.1).[14–25] A link between ethnicity and variation in the metabolic phenotype of PCOS (obesity, acanthosis nigricans and insulin resistance) has been identified and, to a lesser extent, between ethnicity and the androgenic phenotype.

The Asian perspective

A comparative study reported that more severe manifestations of PCOS occur in younger and more insulin-resistant UK-based South Asian women of Pakistani origin compared with white European women.[19] Others have suggested greater prevalences of polycystic ovaries among migrant South Asian women in the UK[14] and of PCOS among Mexican American women[17] that are probably linked to their ethnic propensity to insulin resistance.

No doubt such reports of ethnic variation could be confounded by heterogeneity of clinical presentation, controversies in diagnostic definitions that existed until 2004, inadequately powered samples, selection bias in recruitment from varying clinical settings, effects of migration, etc. Furthermore, accuracy of self-reported ancestry, ethnic variation in body configuration, propensity to obesity and insulin resistance, lack of standardised definitions of insulin resistance, equivocal family history and differing cultural perceptions of clinical manifestations are potential confounders. Some drawbacks were addressed in large multicentre national trials in the USA that identified geographically and ethnically diverse groups (Table 3.1).[26–29] However, migrant Asian women comprised fewer than 10% of each cohort, without details of their exact geographic origins within Asia. Constant features of Asian women with PCOS are that they are shorter, have lower BMI and have a 'milder' phenotype in terms of hyperandrogenism, but that they have the highest prevalence of the metabolic syndrome, affecting as much as 50% of one subgroup.[27] Another supporting feature of an ethnic basis is a family history of type 2 diabetes within groups that correlates with glucose intolerance of PCOS.

Consistent data indicate an earlier age of manifestation of PCOS among migrant and indigenous South Asian women (Table 3.1), which mirrors their ethnic propensity to insulin resistance and type 2 diabetes. South Asia is now identified as having an exponential increase of type 2 diabetes, with more young adults having the condition.[30] It is noteworthy that young South Asian women with PCOS consistently demonstrate a lower mean BMI of around 26 kg/m^2 but have greater insulin resistance and a higher prevalence of the metabolic syndrome than older and more obese white women.[20,24,25]

In fact, for South Asian women it is central obesity rather than BMI that correlates with insulin resistance and metabolic problems. This highlights the importance of measuring waist circumference of women from high-risk ethnic groups to help identify their risk of abnormal glucose tolerance (AGT), which should be specifically addressed at diagnosis and during follow-up. Furthermore, measuring total plasma testosterone alone is unlikely to identify an impact of ethnicity on hyperandrogenism, as sex hormone-binding globulin (SHBG), a surrogate marker of insulin resistance, is significantly lower in South Asian women than white women.[15,19,20] This supports the recommendation to measure plasma SHBG at initial evaluation of high-risk ethnic groups such as South Asian women and the need to emphasise lifestyle modification and weight reduction from diagnosis even though the women might have a 'lower' BMI. Greater awareness and application of ethnicity-specific BMI cut-off points is also recommended.[31]

It is noteworthy that indigenous Thai women with PCOS attending tertiary clinics with a mean age of 29 years had a higher mean BMI (27 kg/m^2) than South Asian women but had comparable prevalence of the metabolic syndrome.[22,23] A common clinical indicator of greater metabolic risk in South Asian and Thai women is acanthosis nigricans, although this is not included as a clinical marker in diagnosing PCOS. This supports the recommendation to adopt a policy of training primary health caregivers, particularly in resource-limited countries in South East Asia, on the need to evaluate young women complaining of irregular menses and hyperandrogenism, with or without infertility, for PCOS. This should be combined with risk assessment for metabolic disease by measuring waist circumference and blood pressure and identifying acanthosis nigricans to enable preventive care. It is interesting that US-based 'Asians' (not identified by geographic origin) with PCOS have a relatively large waist circumference despite smaller body configuration with similar risk for the metabolic syndrome that correlates with acanthosis nigricans[32] and family history of type 2 diabetes.[27]

Thus it is essential that a detailed family history of type 2 diabetes and assessment of cardiovascular risks is included in the baseline evaluation of young South Asian women with PCOS, and this should be linked to planning their long-term metabolic management. Their greater risk of gestational diabetes and premature type 2 diabetes should also be evaluated by incorporating baseline 75 g oral glucose tolerance testing, especially before ovulation induction.[33–35] Maintaining databases of high-risk ethnic groups for longitudinal follow-up of long-term cardiovascular and metabolic endpoints should be encouraged.

With regard to East Asian women, Chen *et al.*[36] reported AGT occurring in 22.4% of Chinese women with PCOS as opposed to the US figure of 38.5%.[28] However, in another study of 197 Chinese women diagnosed with PCOS by the Rotterdam criteria, with 125 having anovular hyperandrogenism (National Institutes of Health [NIH] criteria), and with a mean age of 26 years and median BMI of 26 kg/m^2, 60% had central obesity and 48% had insulin resistance, of whom more than two-thirds had AGT.[37] A larger study of 883 Chinese women with PCOS reported that hyperandrogenaemia, not hirsutism, was independently associated with the risk of type 2 diabetes (OR 5.7; $P = 0.028$).[38] Another study of 804 Chinese women with PCOS demonstrated hyperandrogenism-related metabolic syndrome, with its highest prevalence of 28.5% being in the well-characterised phenotype of PCOS.[39] However, an unpublised study of indigenous Sri Lankan women seeking treatment from an endocrine service ($n = 469$) found that the distribution of the four PCOS phenotypes by the Rotterdam criteria were:

- classical with hyperandrogenism, oligomenorrhoea and polycystic ovaries (H+O+P): 54.6%
- anovulatory and hyperandrogenism (O+H): 17.5%
- hyperandrogenism with polycystic ovaries (H+P) but with regular cycles: 7.7%
- anovulatory with polycystic ovaries but without hyperandrogenism (O+P): 20.3%.

The median BMI was 25 kg/m^2 but the group of women with normal cycles had a significantly lower median BMI of 21 kg/m^2 ($P<0.001$). However, the prevalence of the metabolic syndrome (National Cholesterol Education Program [NCEP] criteria) within each phenotype showed no significant difference ($\chi^2 = 0.394$):

- H+O+P: 34.7%
- O+H: 31.7%
- H+P: 20.0%
- O+P: 23.5%.

This observation in South Asian women is different to the relationship between hyperandrogenism and the metabolic syndrome evident in white European[40–42] and Chinese women.[43] This suggests a South Asian propensity to the metabolic syndrome that is independent of the hyperandrogenism of PCOS. Another insight into metabolic manifestations of PCOS in this South Asian cohort was that non-alcoholic hepatic steatosis affected about 52% of a consecutive series of 110 women, of mean age 25 years, attending the clinic (unpublished data).

Non-Asians

In contrast, a US-based study[40] of 258 women with PCOS whose ethnic origins, although not detailed, had a family history of type 2 diabetes of more than 47% reported a higher prevalence of metabolic syndrome, about 40%, in hyperandrogenic women versus 20% in normoandrogenic women, and AGT in one-fifth of hyperandrogenic women. Their mean age was 29 years, and BMI above 30 kg/m^2 was associated with the metabolic syndrome. African-American women with PCOS generally have higher BMI and blood pressure than US-based Asian women,[26–29] although their degree of insulin resistance does not mirror this difference. Compared with other racial groups, African-American women bear a disproportionate burden of cardiovascular disease risk factors of hypertension, obesity and the metabolic syndrome, which is reflected in their greater age-adjusted death rates than white women.[40,44] Consistent data demonstrate that African-American women with and without PCOS are more obese than other racial groups, with a higher likelihood of hypertension. However, their clinical manifestation of PCOS is reported to be similar to that of white women[45] in age, hyperandrogenism and infertility, despite greater body weight, central obesity and insulin resistance. Interestingly, African-American and white women with PCOS appeared to have a worse metabolic phenotype than US-based Asian women with PCOS.[28] Ehrmann *et al.*[27] reported no significant racial/ethnic differences but larger waist circumference among the African-American women, which was linked to their greater insulin resistance. Nevertheless, their low prevalence of elevated fasting triglycerides remains unexplained.[27,46] This brings into focus possible genetic- or ethnic-based variations in manifesting PCOS among African-American women that might be due to genetic modification over generations. Unfortunately, there are no published reports from their indigenous counterparts residing in their countries of origin.

There are sparse reports of PCOS in Arab women, although the few available suggest a similarity to South Asian women. There are reports of an even greater prevalence of metabolic problems among clinic-based Arab women with PCOS, although not different from those with idiopathic hirsutism.[47–49] White European women with PCOS manifest symptoms and seek medical help at an older age than South Asian women and have less acanthosis nigricans and less insulin resistance based on fasting plasma glucose and insulin measurements, despite a higher mean BMI (30 kg/m^2).[19] The prevalence of the metabolic syndrome among white women with PCOS shows wide variation: 43–47% in the USA,[32,50,51] 28% in Brazilian women,[41] 2–8% among Turkish, Czech and southern Italian women[53–55] and 16% in Dutch women,[41] with a 12% rate of impaired glucose tolerance among Czech women.[54] Furthermore, white women with PCOS living in Iceland differ from their Boston-based counterparts by having lower high-density lipoprotein (HDL) cholesterol and less severe hirsutism and acne.[29] Migration, different environments, cultures and lifestyles, and diet-induced genetic modifications might explain such wide variation within this group with a supposedly common ancestry. Further study is thus recommended to determine any variation of the metabolic syndrome among white Europeans living in different geographic locations.

Ethnic variation of hyperandrogenism in PCOS

Hirsutism, the main hyperandrogenism feature of PCOS, is a function of the individual's genetically determined response to circulating androgens. Testosterone acts on the pilosebaceous unit through androgen receptors responsive to the active metabolite dihydrotestosterone formed by 5α-reductase-driven conversion of testosterone in hair follicles. Reports on the degree of hyperandrogenism in PCOS in women from different regions of the world are varied, as they are based on various diagnostic criteria, clinical settings, age and ethnic origins.

East Asians

East Asian people are typically less hairy than European people despite having no major differences in androgen concentration.[56,57] Chinese and Japanese women have a lower prevalence of hirsutism despite fulfilling the diagnostic criteria of PCOS (Table 3.2).[58–62] This may be explained by low 5α-reductase activity in their skin. Such an ethnic difference will also have an effect on the diagnosing of PCOS, particularly when NIH diagnostic criteria are applied. Lam *et al.*[63] found that the Rotterdam criteria for diagnosing PCOS are more applicable to Hong Kong Chinese women than the NIH criteria, since fewer than half those with PCOS had clinical or biochemical hyperandrogenism. Chen *et al.*[61] reported the mean modified Ferriman–Gallwey hirsutism score in southern Chinese women with PCOS as 3–4 and only 63% of Chinese women with PCOS diagnosed by the Rotterdam criteria fulfilled the NIH criteria. Moreover, Hsu *et al.*[43] reported that Taiwanese Chinese women with hyperandrogenism had more severe metabolic problems of PCOS, with dyslipideamia affecting more than 50%. Thus hyperandrogenism manifesting in Chinese women with PCOS appears to be particularly severe.

I have rephrased this further – OK?

The exact pathophysiology of the interrelationship between obesity/insulin resistance and androgenic problems of PCOS remains unresolved. Obesity, which is reported in 40% of Taiwanese women with PCOS, correlates with testosterone concentration. Hence, using obesity as the Asian 'cut-off' rather than hyperandrogenism to identify the more severe form of PCOS should be encouraged. However, the BMI of Taiwanese

Table 3.2 Ethnic variations of hyperandrogenism and metabolic problems in polycystic ovary syndrome

Source	Ethnicity	Number of women with PCOS	Findings
Hyperandrogenic manifestations in Far East Asian women with PCOS			
Lam *et al.* (2005)[63]	Hong Kong Chinese	90	Clinical or biochemical hyperandrogenism in 48.9%
Li *et al.* (2007)[60]	Southern Han Chinese	273	Hirsutism in 34%, acne in 45%
Iwasa *et al.* (2007)[58]	Japanese	46	Hirsutism only in 10%; need to rely on luteinising hormone and testosterone concentrations
Chen *et al.* (2008)[61]	South Chinese	2.2% of 915	Mild hirsutism; FG score low (≤ 3)
Welt *et al.* (2006)[29]	Boston-based Asian	21 Asian women of 262	Hirsutism in 66%, far less than in white and African-American women
Legro *et al.* (2006)[28]	US-based Asian	2.7% Asian of 626	Milder phenotype and testosterone lower than in white European women
Obesity, insulin resistance and abnormal glucose tolerance in women with PCOS			
Carmina *et al.* (1992)[55]	Japanese	25	Less obese but similar insulin resistance compared with Italian and US white women
Lam *et al.* (2005)[63]	Hong Kong Chinese	90	Insulin resistance in 40%
Welt *et al.* (2006)[29]	Boston-based Asian	21 Asian of 262	Shorter; mean BMI 26 kg/m² versus ≥ 30 kg/m² in others; waist circumference less; waist–hip ratio similar; insulin resistance/IGT less common than in white and Hispanic women
Lo *et al.* (2006)[26]	California-based Asian/ Pacific Islander	10% Asian/Pacific Islander of 11 035	Type 2 diabetes in 12%; BMI > 30 in 45% versus 67.5% in white, 80% in black and 74% in Hispanic women
Chen *et al.* (2006)[36]	Guangdong Chinese	102	IGT and type 2 diabetes in 22%; not BMI related
Li *et al.* (2007)[60]	Southern Han Chinese	273	Insulin resistance in 12.8–21.6%; BMI > 25 in 30%
Charnvises *et al.* (2005)[23]	Thai	121	Mean BMI 27 kg/m²; IGT and IFG in 33.9%; type 2 diabetes in 9.1%; acanthosis nigricans was an independent predictor
Weerakiet *et al.* (2007)[22]	Thai	170	Mean BMI 27 kg/m²; the metabolic syndrome (IDF definition) in 35%
Wijeyaratne *et al.* (unpublished)	South Asian (Sri Lankan)	460, clinic setting	Mean age 25 years; mean BMI 26 kg/m²; the metabolic syndrome (NCEP definition) in 38%
Kumarapeli *et al.* (unpublished)	South Asian (Sri Lankan)	170, community setting	Mean age 23 years; median BMI 24 kg/m²

AGT = abnormal glucose tolerance; BMI = body mass index; IDF = International Diabetes Federation; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; FG = Ferriman–Gallwey measure of hirsutism; NCEP = National Cholesterol Education Program; PCOS = polycystic ovary syndrome

women with simple obesity also correlates with the concentration of androgens[64] but shows negative correlation with luteinising hormone, which remains unexplained.

Other ethnic groups

A parallel difference – greater metabolic risk in those with hyperandrogenism – was observed among white women in the USA,[40] Bulgarian women[42] and Dutch women.[41] Women with PCOS in US clinics, except for Asian women, had hirsutism in 60–70% of cases, without major differences between black and white women.[28] Interestingly, white women showed a difference in the degree of hirsutism based on residence in Iceland or in Boston: the Icelandic women were less androgenic with lower luteinising hormone concentrations and a taller body frame.[29] Further variations have been shown in that only 10.4% of selected Greek women[2] and 7.1% of unselected Spanish women had hyperandrogenism,[3] while 88% of clinic-based young Turkish women with PCOS were hyperandrogenic.[3] These differences do appear to mirror the variation in the metabolic syndrome.

I have inserted "with PCOS" – OK?

In contrast, among the 6.3% of young Sri Lankan women with confirmed PCOS in a randomly selected community-based study[65] of 3030 women (of whom 2915 responded to the questionnaire), only 53% had hyperandrogenism, although this was significantly more than among the women without PCOS. These newly diagnosed women had a higher prevalence of the metabolic syndrome (32% versus 17%; $P = 0.002$), hypertension (11% versus 4%; $P = 0.02$) and central obesity (waist–hip ratio more than 0.85) (57% versus 41%; $P = 0.01$) than age-matched women without PCOS from the same community. Their BMI and waist circumference correlated positively with insulin resistance, triglycerides and low-density lipoprotein (LDL) cholesterol ($P < 0.001$), and negatively with SHBG and HDL cholesterol ($P < 0.01$). The newly diagnosed women ($n = 147$) were then compared with clinic attendees ($n = 460$) from the same province (unpublished data). This revealed a graded increase in severity of manifestations from community to clinic, with hyperandrogenism-related symptoms rather than metabolic problems being the main determinant for seeking medical help. Seventy-three percent of this series of 460 women with PCOS, referred to earlier, had hyperandrogenism but there was a low prevalence of infertility as they were a predominantly (60%) unmarried group.

I asked: I have rephrased this sentence considerably for clarity and logic – OK? (The original sentence was: "In contrast, among randomly selected community-based young Sri Lankans (n=3030) of whom 6.3% had PCOS, only 53% had HA (65) although significantly more than in controls."
You responded: Best for it to remain the way it was originally as this was randomised community study and reflects the prevalence as well as the occurrence of HA
FOLLOW-UP QUERY: I still think my rephrased sentence contains all your original facts (as well as including the response rate) and is somewhat clearer to understand. Please reconsider whether it is acceptable to you. Also, we can't refer to women as "controls" in RCOG house style, which is why I changed that to "among the women without PCOS".

Ethnic interrelationships of metabolic problems and hyperandrogenism manifestations of PCOS

The correlation between metabolic problems of PCOS and hyperandrogenism and infertility is based on the concept that insulin resistance plays a central role in its pathogenesis and manifestations. Therefore any ethnic variation in insulin resistance is deemed to be the main determinant of the severity of manifestations, in particular hyperandrogenism. The question arises as to the role of obesity in hyperandrogenism, independently of PCOS.

It is interesting that 73% of Chinese women with PCOS in Taiwan (mean age 26.7 years) who met the Rotterdam criteria had oligo-ovulation/anovulation and 78% had hyperandrogenism, but only 28% had significant hirsutism, with 48% manifesting acne.[66] Liou *et al.*[66] reported that 93% of those women diagnosed by the Rotterdam criteria had polycystic ovaries and women with obesity had no significant difference in hirsutism when compared with lean women, despite having higher total testosterone. A discrepancy between body weight and hyperandrogenism in PCOS is further supported

by affected Taiwanese women with obesity having significantly less acne than their non-obese counterparts (38% versus 54%; $P=0.009$).[64] Liou *et al.*[66] highlighted this, which parallels a report by Lin *et al.* in the Chinese language of nearly 200 Chinese women with PCOS who showed no significant difference in hirsutism between obese and non-obese subgroups. Such a discrepancy may be confined to East Asian women.

Interestingly, a study[67] of young Mediterranean women with PCOS revealed that AGT affected about 19%, which is lower than US and Asian figures, with hyperandrogenism being linked to insulin resistance and AGT, but with paradoxical skin manifestations like in Taiwanese women. Acne was more prevalent in normoglycaemic women with PCOS, at 25% in the obese subgroup and 58% in the non-obese subgroup.[67] This supports an ethnic difference in skin response to androgen stimulation that is independent of obesity and insulin resistance.[64] Liou *et al.*[66] suggested an explanation whereby an obesity-associated difference in androgen clearance might explain this relative 'ineffectiveness' of circulating androgens. An association between adipose tissue and the elevated testosterone of PCOS and a correlation between hyperandrogenism and metabolic complications have led to the hypothesis of androgen excess contributing to the development of insulin resistance, the metabolic syndrome and type 2 diabetes in PCOS.[68] However, ethnic diversity in manifesting hyperandrogenism and obesity, particularly in East Asian women, disallows direct comparison of data without making suitable adjustment for the ethnic origins of cohorts. Hence, it is recommended that any translation of these concepts to clinical practice should include awareness of an ethnic variation.

Additionally, differences in plasma homocysteine and other markers of premature atherosclerosis have been reported in South Asian women with PCOS,[20,24] as well as differing responses to ovarian stimulation that suggest a lower fertilisation capacity.[69] Such ethnic differences are mirrored by greater insulin resistance in South Asian children living in Britain,[70,71] which might be partly explained by their lower physical activity,[72] although greater insulin resistance with endothelial dysfunction and lipid abnormality in brothers of South Asian women with PCOS supports a genetic basis.[73] Such ethnic propensity to metabolic problems is also reflected in the rising prevalence of gestational diabetes in Asia,[74] with reports from the UK,[35] Thailand[34] and Sri Lanka[33] of gestational diabetes in Asian women being linked to PCOS. This favours a role for epigenetics in the development of PCOS.

Epidemiological variations of insulin resistance and the prevalence of PCOS – are they in parallel?

Epidemiological variations in obesity-related insulin resistance and metabolic disease are greater in non-white populations, who also appear to have more complications of diabetes. However, this might be due to confounding variables such as migration and socio-cultural disparities in health and disease management. Furthermore, Misra and Ganda[75] clearly demonstrated a step-wise increase in risks of the metabolic syndrome and type 2 diabetes in people from rural India (8.4%) to urban India (13.6%) to US-based Indian people (17.4%).[75] Heterogeneity of coronary artery disease risks within the South Asian group has also been noted, in that, despite being metabolically a disadvantaged group in comparison with white European people, Indian, Pakistani and Bangladeshi people differ in their individual coronary artery disease risk factors. The differences observed in manifestations of PCOS between Pakistani[19] and Sri Lankan[20] women support this. Therefore, pooling all South Asian data might prove misleading and should be discouraged.[76]

It would also be interesting to determine any ethnic variation in the prevalence of PCOS. Community prevalence in Sri Lanka using the Rotterdam criteria was found to be 6.3% (95% CI 5.9–6.8%) in women aged 15–39 years.[65] Other ethnic groups had similar results: 6.8% in white women in Greece,[2] 6.5% in white women in Spain[3] and 4.6% in white and black women in south-eastern USA (Table 3.3).[77] However, these prevalence rates are not directly comparable owing to different diagnostic criteria, methodologies and sampling. The Sri Lankan study conducted random sampling of a defined community of a younger age group. Other community-based assessments include a southern China report of 2% prevalence in a young population[61] and 5% in Thai women,[78] while a retrospective birth cohort of presumably diverse ethnicity from Australia suggests a higher prevalence of 11%.[79] Hence, the currently available data are inadequate to identify ethnic diversity in the prevalence of PCOS.

Ethnic differences in diagnostic thresholds for polycystic ovaries

In a review of the Rotterdam diagnostic criteria for polycystic ovaries, Jonard *et al.*[80] found that the best threshold for ovarian volume in white European women was 10 cm^3 rather than 7 cm^3, and they recommended follicle number greater than 12 to be the best diagnostic criterion to define polycystic ovaries. An endocrine clinic in Sri Lanka that performed early follicular ultrasound by a blinded single observer (one of the current authors, SCY) in consecutive women with classical PCOS ($n = 337$) and women in a control group ($n = 205$) found that the best cut-off value for ovarian volume was 6 cm^3 or more (sensitivity and specificity by receiver operating characteristic curves of 72% and 69%, respectively) and for follicles measuring 0.2–0.9 cm in diameter was 10 (sensitivity and specificity of 90% and 70%, respectively) (unpublished data). Chinese women with PCOS have also been reported to have significantly lower ovarian stromal volume and vascularity than white women with PCOS.[81] These variations suggest possible ethnic differences in ovarian volume and follicle number in polycystic ovaries that needs further study.

Ethnic differences in quality of life

PCOS causes significant psychological distress and leads to poor health-related quality of life as a result of physical changes in appearance, infertility, menstrual irregularity and obesity. Most published studies are on PCOS in Western women. An unpublished case–control study of newly diagnosed Sri Lankan women with PCOS revealed significant effects on their physical, psychological and social relationships-related quality of life when compared with women in an age-matched control group ($P = 0.01$). Their psychological distress was based mainly on the severity of physical change, with one-third of the women being affected. It was their Ferriman–Gallwey hirsutism score and not obesity that emerged as the most significant predictor of their distress, which is different from the data in Western women with PCOS. Immigrant Arab women rated menstrual irregularities, infertility and hirsutism as bigger problems than being overweight,[49] suggesting that obesity might be considered unattractive only in Western cultures and when dressed in Western attire, while Eastern cultures might perceive obesity as a sign of prosperity. The Sri Lankan study also revealed that only 20% of women with PCOS who had psychological distress perceived that they had excess body weight, which supports this hypothesis. Hence, the impact of PCOS on psychological wellbeing appears to be determined by ethnicity and cultural backgrounds, and requires further study.

Table 3.3 Prevalence and specific features of polycystic ovary syndrome (PCOS) among various ethnic groups

Country and source	Method of selection	Ethnic group	Prevalence of PCOS	Findings
Greece; Diamanti-Kandarakis *et al.*(1999)[2]	Selected invitees	White	6.8%	Hyperandrogenism in 10.4%
Spain; Asuncion *et al.* (2000)[3]	Blood donors	White	6.5%	Hirsutism in 71%
USA; Knochenhauer *et al.* (1998)[77]	Pre-employment	White and black	3.4% and 4.7%, respectively	Black women were more obese
China; Chen *et al.* (2008)[61]	Community based	South Chinese	2%	Younger
USA; Goodarzi *et al.* (2005)[17]	Self-reporting	Mexican American	13%	Symptoms and insulin resistance greater
Sri Lanka; Kumarapeli *et al.* (2008)[65]	Community based, random selection	South Asian	6.3%	Younger; less insulin resistance than clinic-based women with PCOS; only half sought help; oligomenorrhoea/ amenorrhoea was the predominant feature

Summary and conclusion

Ethnic variation in PCOS does occur and appears to be linked to differing expression of hyperandrogenism and insulin resistance. Possible explanations include genetic and ethnic propensities to obesity and metabolic problems, possibly compounded by environmental and/or cultural factors. A variation within Asia is also evident. The variations have implications for screening and diagnosis, management priorities and response to intervention that indicate the need for ethnicity-specific guidelines where appropriate.

The variations of PCOS among different ethnic groups needs further assessment by larger studies of community prevalence among indigenous groups residing in their countries of origin, long-term follow up of ethnic cohorts and the study of the role of genetics, environmental factors and medication such as insulin sensitisers in such groups with a view to improving the health status of women from all regions and in all settings.

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