Polycystic ovary syndrome and its relevance to women from south Asia

The syndrome has vast epidemiological, socio-economic and health care delivery implications for south Asia

Introduction

Polycystic ovary syndrome (PCOS) is the commonest endocrine disturbance in women of reproductive years, and its aetiology remains unclear (1). Its clinical features include hyperandrogenism, obesity, menstrual irregularity and anovular infertility, but the clinical presentation can vary. PCOS in the commonest cause of anovulatory infertility and hirsutism world-wide (2). PCOS is associated with insulin resistance and hyperinsulinaemia, with a risk of glucose intolerance (3). A wide range of biochemical abnormalities occurs in PCOS (4) that form the basis of its clinical features and associated disease risks (Table 1). PCOS is familial and thought to be the morphological manifestation of a genetically determined disorder, whereas its heterogeneity is believed to result from interaction with environmental factors (2).

Defining the polycystic ovary (PCO) and polycystic ovary syndrome

The diagnosis of PCO, based on transvaginal ultrasound, requires the presence of 15 cysts of 2 to 10 mm diameter arranged in a single plane (5). The presence of polycystic ovaries alone does not diagnose the endocrine syndrome. PCOS lacks a universal definition. Other causes of hyperandrogenism manifest similarly, eg. late onset congenital adrenal hyperplasia (CAH), and syndromes of extreme insulin resistance (eg. leprechaunism, Rabson-Mendenhall syndrome, Type A syndrome) (3,4). In the USA the diagnosis of PCOS requires the presence of hyperandrogenism, hyperandrogenaemia, oligo-ovulation regardless of ovarian scan appearance, and the exclusion of CAH, hyperprolactinaemia and Cushing's syndrome (1,6,7). In Europe its diagnosis is based on ultrasound evidence of PCO, combined with one or more associated clinical or biochemical characteristics, in the absence of adrenal or pituitary disease (1,8,9,10).

The role of insulin resistance in PCOS

Ovarian hyperandrogenism

All women with PCO, including the asymptomatic, have elevated serum androstenedione and testosterone. The bulk of evidence points to the ovary being their source. The theca cells in PCOS hyper-respond to luteinising hormone (LH) and produce excess androgens, caused partly by altered cytochrome P450c17 action in steroidogenesis, and partly by altered ovarian insulin and insulin like growth factor 1 (IGF 1) activity (11). Increased levels of oestradiol result from peripheral aromatisation of excess androgens, and from follicle stimulating hormone (FSH) induced ovarian follicular secretion. Plasma inhibin-B is elevated in women with PCOS; inhibin stimulating androgen production and androgens in turn stimulating

Table 1. Biochemical abnormalities, associated clinical features, complications and risks in PCOS

Biochemical derangement	*Associated clinical features*	*Resulting complications*	*Risk stratification*
High testosterone/ androstenedione Decreased sex hormone binding globulin	Hirsutism Frontal balding Acne Hydradenitis suppurativa	Anovular infertility	Increased risk
Acyclic oestrogen excess	Menstrual irregularity/ oligomenorrhoea	Endometrial cancer Ovarian cancer Breast cancer	Increased risk Probable risk Remote risk
Insulin resistance and hyperinsulinaemia	Acanthosis nigricans Obesity	Diabetes mellitus Gestational diabetes Hypertension Pregnancy induced hypertension	Increased risk Increased risk Probable risk Probable risk
Dyslipidaemia		Coronary artery disease	Probable risk

inhibin secretion, thus establishing a vicious circle within the ovary that inhibits ovulation. Although ovarian follicle recruitment and growth remain unaffected, the selection of a dominant preovulatory follicle does not occur in PCOS (11). In summary, ovarian insulin, IGF1 and inhibin act on the LH driven theca cell to produce excess androgens by altered cytochrome activity, and the androgens in turn with insulin and IGF1, act on the FSH driven granulosa cell causing anovulation and increased oestrogens.

Insulin resistance, obesity and PCOS

PCOS is perhaps the commonest disorder in which an association between insulin resistance and altered ovarian function are improtant (3,12). Insulin acts on the normal ovary by a receptor mediated stimulation of steroidogenesis. Ovarian effects of increased insulin are described in women with diabetes mellitus, obesity, syndromes of extreme insulin resistance and PCOS (12). The efficacy of insulin sensitising agents such as metformin in the treatment of PCOS supports this hypothesis (13). Women with PCOS have peripheral insulin resistance affecting skeletal muscle and adipose tissue, although insulin resistance does not effect the ovary, thus enabling the excess insulin to cause ovarian androgen hypersecretion (12,14). Obese women with PCOS are more insulin resistant than non-obese controls, suggesting that obesity and PCOS exert independent effects on insulin resistance. But weight loss restores insulin sensitivity only in some, and insulin resistance is described also in non-obese PCOS subjects (12). Insulin resistance in PCOS is more prominent in anovular women than equally hyperandrogenaemic women with regular menses (3,14). *In vitro* studies of insulin action on granulosa cells from PCO show that hyperinsulinaemia causes premature arrest of follicular growth and amplifies thecal androgen production (15). Obese and non-obese women with PCOS have exaggerated insulin secretion following a glucose load that is inadequate relative to their degree of insulin resistance (16). Women with PCOS have "android obesity", with fat deposition confined to the upper two-thirds of the body, and a waist-hip ratio exceding 0.85. Increased waist-hip ratio occurs independent of body mass index, and correlates with dyslipidaemia and insulin resistance (17).

Birth weight, PCOS, and their link to adult type 2 diabetes

The existence of specific prenatal risks for the post-pubertal expression of PCOS remains under scrutiny. The relationship between intrauterine growth retardation and adult insulin resistance and glucose intolerance is well established (18). Polycystic ovaries may reflect fetal programming, for a retrospective analysis reported that obese, hirsute, hyperandrogenic women with PCO were born large for gestational age (19).

Natural progression of PCOS

The onset of symptoms of PCOS is linked to menarche, and puberty is accompanied by a physiological insulin resistance (20). Menstrual disturbance is the earliest manifestation, and hirsutism and infertility become apparent later. The evolution of symptoms with age appears to be associated with increase of adiposity (21). Androgen excess occurs in more than 70% of those affected, infertility results from anovulation, and excess LH is associated with a high rate of miscarriage in PCOS (21).

Genetics of PCOS and the link to type 2 diabetes

Family studies of PCOS There is a high incidence of PCOS in first degree relatives of the affected, and most studies suggest a dominant inheritance (22-28). All studies reported so far have been of families of white European descent, with none from those of south Asian descent (Table 2).

Male phenotype Many male phenotypes have been proposed (Table 2) (22-26,28). Increased prevalence of frontal baldness in male relatives was first reported in 1979 (24), to which hyperinsulinaemia was later included (28).

Twin studies in PCOS The only large study in twins revealed an incidence of 50% for PCO in monozygotic and dizygotic twins, but with strong discordance. These data suggest a complex inheritance pattern, perhaps polygenic, which is linked to insulin resistance (29).

Affected sisters with PCOS On average, the occurrence of hirsutism and oligomenorrhoea among sisters of the proband is about 50% (22,24,25,28), of PCO 73%, or hyperandrogenaemia 87% and of hyperinsulinaemia 66% (7,28). A recent report of a large number of sisters of affected women showed that 22% of sisters had well characterised PCOS, and another 24% had hyperandrogenaemia with regular cycles (7). Several phenotypes of PCOS are reported to occur within a given family, which supports a heterogeneous genetic basis with variable expression of a monogenic trait or an oligogenic trait (7,30).

Molecular genetic studies in PCOS Making no assumption of the mode of inheritance, a search was carried out for candidate genes in the androgen biosynthetic pathway, and in the secretion and action of insulin (30). The genetic association and linkage with PCOS reported so far include: a) the *CYP11a* gene, which converts cholesterol to pregnenolone, a rate-limiting step in androgen biosynthesis (31); b) insulin gene variable number of tandem repeats (VNTR) polymorphism, particularly class I and III alleles, linked to an increased susceptibility to type 2 diabetes and high birth weight (32); c) a microsatellite located outside the insulin receptor (INSR) gene possibly influencing INSR gene expression in the ovary (33); d) follistatin gene (which has not been substantiated by other workers) (34), and e) AccI polymorphism in the FSH β gene (35). All these studies were predominantly on women of white European descent, except for the FSH β gene tested in affected south Asians and Chinese women resident in Singapore.

Table 2. Review of family studies in PCOS and proposed male phenotypes and modes of inheritance

Reference number	*Phenotypic criteria of PCOS*	*Sample characteristics*	*Proposed male phenotype*	*Proposed mode of inheritance*
22	Menstrual irregularity Hirsutism PCO (by culdoscopy)	Small cohort of PCOS First degree relatives + Control group +	Increased pilosity	AD
23	Menstrual irregularity Hirsutism PCO (by surgery)	Few kindreds of several generations	Testicular dysfunction	? X-linked dominant
24	Menstrual irregularity PCO (by gynaecography)	Large cohort of PCOS, First/second degree relatives + Controls +	Premature balding	Dominant
25	Symptoms of PCOS PCO (at wedge resection)	Large cohort of PCOS, First/second degree relatives + Controls +	Increased pilosity Premature balding	?AD
26	Symptoms of PCOS PCO (by ultrasound)	PCOS cohort CAH cohort + Controls +	-	AD
27	PCO (by ultrasound)	Several kindreds	Premature balding	AD
28	Elevated androgens Decreased SHBG PCO by ultrasound	Few kindreds	Insulin resistance	Not stated

(PCO = polycystic ovaries; PCOS = polycystic ovary syndrome; CAH = congenital adrenal hyperplasia; AD = autosomal dominant)

Epidemiology of PCOS and its relevance to south Asian women

The prevalence of PCOS is variable due to lack of a universal definition (36). Population studies of randomly selected normal white European women of reproductive age report the prevalence of PCO to be 20 to 22% (9), and 33% in the post-menarcheal group (10). Using the USA criteria, the prevalence of PCOS in population based studies was 5% to 11.2% in Alabama (37), 9% in Greece (38) and 6.5% in Spain (39). The highest reported prevalence of PCO in a community survey was 52% in south Asian immigrants in Britain, of whom 49% had menstrual irregularity (40). There is a paucity of data on the prevalence of PCO and PCOS in south Asian women.

Ethnic differences in the prevalence of PCOS have not been explored (36). An increased rate of PCOS was reported among Caribbean Hispanics (41), but is similar between black and white women (3.4% versus 4.7%) (37). There may be ethnic variation in overt features of PCOS despite similar biochemical manifestations across races, since affected Japanese women are less obese and hirsute than Caucasians although with similar androgen excess and insulin resistance (42).

Epidemiology of type 2 diabetes mellitus in south Asian women and its implications on PCOS

Type 2 diabetes mellitus shows strong familial aggregation in populations with insulin resistance (43). The south Asian subcontinent has a high prevalence of type 2 diabetes, with central obesity strongly associated with diabetes in women (44). The prevalence of diabetes in urban and rural women in Pakistan is reported to be 10.6% and 4.8% respectively, and of impaired glucose tolerance 14.3% and 13%, values higher than in Caucasians (45). Similar trends in both genders are reported from India (46), and Sri Lanka (47). The largest projected number of diabetics by year 2025 is in India (57 million), among younger age groups and greater numbers of women (48). The high prevalence in south Asia is in striking contrast to that in white Europeans (49). It is postulated, based on data among Caucasians alone, that PCOS contributes to 10% of glucose intolerance in premenopausal women (50). Hence the implications of PCOS on diabetes in south Asian women would be of great importance.

Abnormal fetal growth and low birth weight are linked to a higher prevalence of glucose intolerance, hypertension and vascular disease caused by insulin resistance in

adult life (18,51). Such a "fetal origins" hypothesis proposes that fetal adaptation to an adverse intrauterine environment effects lifelong physiological changes in neuroendocrine development, even affecting the hypothalamo-pituitary-adrenal axis (52). Low birth weight has a high incidence in south Asia, including Sri Lanka (47,49). Hence such a mechanism of hormonal alteration could link insulin resistance of PCOS with type 2 diabetes in south Asian women. Reports of a high prevalence of type 2 diabetes mellitus in native south Asian women, the highest recorded prevalence of PCO being in migrant women of south Asian descent, suggest a possible common genetic or fetal origin.

The insulin response to a glucose challenge in a small group of PCOS women of Indian and white European origin based in Australia reported that Indian women have significantly higher insulin response (53), which confirms that the ethnic background of subjects with PCOS needs consideration. A review of the "metabolic syndrome" (which links adult insulin resistance with hypertension, dyslipidaemia, type 2 diabetes and coronary heart disease), confirms the genetic and ethnic influence in its development (54).

To summarise, (a) PCOS in young women, rather than being limited to gynaecological or dermatological problems, has much wider and long term metabolic implications; (b) insulin resistance is central to its pathogenesis, with a strong genetic basis, and important implications to its management; (c) the majority of research on PCOS has been in those of white European descent, and the only report on the prevalence of PCO in a migrant south Asian population in England has found it to be strikingly higher than in Caucasians; (d) type 2 diabetes, which is preceded by insulin resistance, is an emerging problem in women of indigenous populations in south Asia; and (e) the prevalence of PCOS in native south Asian women needs to be resolved by large epidemiological studies, and the degree of insulin resistance in affected south Asians also needs quantification.

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