Polycystic ovarian disease: heritability and heterogeneity

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The polycystic appearance of the ovary is the distinguishing characteristic of polycystic ovary syndrome (PCOS) but there is a wide range of other clinical and biochemical features, e.g. elevated serum concentrations of androgens, insulin, LH and decreased insulin sensitivity. The high prevalence of affected individuals and the wide range of related phenotypes can be explained by the interaction of a small number of key genes with environmental factors. Heritability of PCOS has been inferred from studies of the syndrome in various populations (ethnic groups, twins and PCOS families). The data suggest that the condition is passed down through either sex, according to an autosomal dominant model of genetic transmission. To date, specific gene mutations affecting androgen synthesis, insulin secretion and insulin activity explain most of the endocrine and metabolic symptoms, while environmental risk factors (either during prenatal or post-natal life), seem to convert an occult PCOS into a clinically manifest syndrome.

Key words: anovulation/hirsutism/insulin resistance/obesity/polycystic ovarian disease

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Polycystic ovarian disease

Polycystic ovaries are often seen in healthy women but are more frequent in women with abnormal cycles and hyperandrogenism (Figure 1). The polycystic appearance of the ovary is the distinguishing sign of polycystic ovary syndrome (PCOS) but there is a wide range of clinical and biochemical features, e.g. elevated serum concentrations of androgens, insulin, LH and decreased insulin sensitivity. These conditions are frequently associated with obesity. Since insulin resistance in PCOS patients is predominantly extra-splanchnic (Dunaif et al., 1992), the fasting blood sugar is normal.

According to another group (Franks et al., 1997), ovarian morphology is the essential marker of the syndrome and the wide range of related phenotypes can be explained by the interaction of a small number of key genes with environmental factors.

Since these symptoms are found in up to 10% of young women, PCOS is certainly the most frequent endocrine disorder diagnosed in these subjects. Despite the high prevalence of isolated polycystic ovarian morphology (22%), the syndrome may be accompanied by minimal clinical manifestations and, in particular, no uniformly deleterious effect on fertility has been reported (Clayton et al., 1992). A controlled comparative study of patients undergoing an IVF programme found no significant difference in pregnancy and live birth rates between women with and without polycystic ovaries (MacDougall et al., 1993). Nevertheless, in a large group of PCOS patients, a high prevalence of primary (46%) and secondary (26%) infertility was found (Balen et al., 1995), while another group (Regan et al., 1990) found an elevated rate of miscarriages in patients with raised LH concentrations in which PCOS was inferred.

PCOS phenotypes in various populations

In view of the high prevalence of affected individuals, a genetic cause of the syndrome was suggested 30 years ago (Cooper et al., 1968). This has been investigated in several studies on PCOS phenotypes in different populations.

Ethnic groups

PCOS women (n = 75) from three different ethnic groups were studied (Carmina et al., 1992) and it was concluded that although obesity and hirsutism varied with genetic and environmental factors, the prevalence of adrenal androgen excess and insulin resistance appeared fairly uniform. More recent studies, however, found that ethnicity and PCOS were associated with independent and additive defects of insulin action in Caribbean–Hispanic women (Dunaif et al., 1992). There were also differences in

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insulin and glucose responses to glucose provocation tests between white and Indian women with the syndrome (Norman et al., 1995). Other authors (Legro et al., 1999) suggest that PCOS is a more important risk factor than ethnicity or race for glucose intolerance in young women.

**Twins**

PCOS has been occasionally reported in identical twins (McDonough et al., 1972; Hutton and Clark, 1984). An Australian study found a 50% incidence of PCOS in 34 female twin pairs studied. The high degree of discordance in sonographic ovarian imaging between twins suggests a complex inheritance pathway and/or an important role of environmental factors in the genetic transmission mechanism (Jahnfar et al., 1995). These authors suggest that the high prevalence of PCOS among twins may be explained by factors acting in prenatal life.

**Families**

Ovarian morphology, menstrual irregularities and signs of hyperandrogenism were the main symptoms investigated by studies on the familial clustering of PCOS cases, and premature balding was the male phenotype frequently found in the male relatives. All the studies showed a substantially increased risk of PCOS in first-degree female relatives of PCOS patients (Table I). Two additional studies on PCOS pedigrees (Franks et al., 1997; Govind et al., 1999), suggest the condition is passed down through either sex according to an autosomal dominant model of genetic transmission (Tables II and III).

**Mechanism of heritability**

**Ovarian steroidogenesis**

Although the secretion of androgens by the adrenal glands may be increased, the main source of androgen excess in PCOS is the ovary (Franks et al., 1989). Oestrogen production may be linked either to abnormal stimulation of the ovary or to an intrinsic defect of ovarian steroidogenesis or increased extraovarian conversion of androgen in fat tissue.

**Abnormal ovarian stimulation**

Sensitive immunoassay systems have revealed the existence of microheterogeneity of human LH in a large population (Pettersson and Soderholm, 1991; Pettersson et al., 1992). Analysis of the structure of the \( \text{LH}^\beta \) gene in women with immunologically anomalous LH revealed two nucleotide substitutions in codons 8. This common genetic variant induces higher LH bioactivity than the wild form (Haavisto et al., 1995). While abnormal LH secretion may cause anovulation and luteal insufficiency, leading to PCOS, the frequency of LH mutations in women with PCOS is not different from that in healthy women, so the presence of the variant does not explain the abnormal steroidogenesis in polycystic ovaries (Elter et al., 1999).

Follistatin binds to activin and affects its stimulatory activity on FSH secretion. A follistatin gene mutation in PCOS patients may play a role in the functional impairment of the FSH–granulosa cell axis. While evidence for such a link between the follistatin gene and PCOS has been found in a large study (Urbanek et al., 1999), the association of PCOS with a polymorphism of the gene encoding follistatin was not confirmed by another recent study (Liao et al., 2000).

**Intrinsic ovarian defects**

It is well known that there is a primary abnormality in the theca cells of PCOS patients leading to excessive production of progesterone and androgen (Gilling-Smith et al., 1994, 1997). Therefore the abnormal steroidogenesis observed in

![Figure 1. Prevalence of the polycystic appearance of the ovary in different groups of women. Data taken from (1) Adams et al. (1986); (2) Clayton et al. (1992); and (3) O’Driscoll et al. (1994).](image)

**Table I. Familial clustering of polycystic ovarian syndrome (PCOS)**

<table>
<thead>
<tr>
<th>Publication</th>
<th>Population studied (n)</th>
<th>Inherited symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferriman and Purdie (1979)</td>
<td>Hirsute women (284) Oligomenorrhoeic with enlarged ovary (45)</td>
<td>Compared with controls (179): higher prevalence of hirsutism oligomenorrhoea and infertility in first-degree female relatives</td>
</tr>
<tr>
<td>Lunde et al. (1989)</td>
<td>Women with polycystic ovaries after wedge resection (132)</td>
<td>Polycystic ovary phenotype in 31.4% of first-degree relatives (3.2% in the controls)</td>
</tr>
<tr>
<td>Carey et al. (1993)</td>
<td>PCOS: family pedigrees (10)</td>
<td>67% of mothers and 87% of sisters affected.</td>
</tr>
</tbody>
</table>
PCOS is related to an intrinsic abnormality of the theca cells rather than to abnormal gonadotrophin stimulation (Ibañez et al., 1996).

This finding prompted a study of the cholesterol side chain cleavage gene (CYP11a) as a possible cause of the deranged steroidogenesis. The segregation of CYP11a in 20 PCOS families was studied (Gharani et al., 1997). The most common polymorphism of the gene (indicated as 216–) was significantly associated with PCOS families. A non-parametric linkage (NPL) analysis using polymorphic markers in that region similarly suggested that the steroid synthesis gene CYP11a is a very important locus for the genetic susceptibility of PCOS hyperandrogenism (NPL score 3.03, P = 0.003) (Gharani et al., 1997).

**Adrenal and ovarian hyperandrogenism**

The increased ovarian and adrenal steroidogenic activity in PCOS can also be caused by enhanced lyase activity, exclusively by the cytochrome P450 C17α. Serine phosphorylation of this enzyme system selectively increases its enzymatic activity, leading to hypersecretion of ovarian and adrenal androgen, with no rise in adrenocorticotropic hormone (ACTH) or other steroidogenic activity (Zhang et al., 1995).

**Insulin resistance**

Insulin resistance is another common feature in women with PCOS. The cause is still unknown. Interestingly only women with an endocrine syndrome of hyperandrogenism and chronic anovulation appear to be insulin resistant and at high risk of glucose intolerance (Dunaif et al., 1987; Robinson et al., 1993).

There appears to be a genetic target cell defect as a cause of the metabolic condition (Holte, 1996).

The same hyperphosphorylation process described for cytochrome P450 C17α lyase activity, leading to adrenal and ovarian hyperandrogenism, has been implicated as the cause of a specific post-receptor defect of transduction of the insulin signal in fibroblasts (Dunaif et al., 1995). In these patients, autophosphorylation of the serine (rather than tyrosine) residue impairs insulin signal transduction and contributes to the 50% insulin resistance observed. Thus a single molecular defect leading to the activation of a serine kinase might explain the two main biochemical disturbances in these patients: hirsutism and insulin resistance.

**Abnormal insulin secretion**

Hyperinsulinaemia has been reported in patients with PCOS and the syndrome is one of the major risk factors for non-insulin-dependent diabetes mellitus (NIDDM) (Holte et al., 1995). The β cell dysfunction is not obesity-dependent and in the majority of PCOS women is not associated with glucose intolerance (Dunaif and Finegood, 1996).

The direct role of the insulin gene in the aetiology of hyperinsulinaemia was investigated in three groups of PCOS patients (one of which included 17 families with several affected individuals). All three populations showed an association between class III alleles at the variable number of tandem repeats (VNTR) 5’ to the insulin gene and PCOS (Bennet et al., 1995). The association was stronger in anovulatory patients, who more frequently have hyperinsulinaemia. A non-parametric linkage analysis in the PCOS families showed excess allele sharing at the same locus (NPL score 3.250, P = 0.002) (Waterworth et al., 1997). The authors concluded that the VNTR 5’ region to the insulin gene is a major locus for PCOS-associated hyperinsulinaemia. Table IV summarizes the pathophysiology for inherited susceptibility.

### Table II. Clinical findings in sisters with and without polycystic ovaries (PCO) from proband families (Govind et al. 1999)

<table>
<thead>
<tr>
<th></th>
<th>PCO (n=35)</th>
<th>no PCO (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual cycle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>16 (46%)</td>
<td>15 (84%)*</td>
</tr>
<tr>
<td>Oligomenorrhoea</td>
<td>19 (54%)</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>Ovarian volume (mm³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>6.7 (3.2–24)</td>
<td>5.2 (2.4–7.7)**</td>
</tr>
<tr>
<td>Left</td>
<td>6.9 (2.9–23)</td>
<td>4.5 (1.2–7.1)**</td>
</tr>
</tbody>
</table>

*PCO versus no PCO (P < 0.02).
**PCO versus no PCO (P < 0.001).

### Table III. Premature male-pattern baldness in polycystic ovarian syndrome (PCOS) and control families (Govind et al., 1999)

<table>
<thead>
<tr>
<th></th>
<th>PCOS</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable men</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>Men with premature male-pattern baldness</td>
<td>10 (22%)</td>
<td>1 (5%)*</td>
</tr>
</tbody>
</table>

*P = 0.006.

### Table IV. Polycystic ovarian syndrome (PCOS): pathophysiology for the inheritable susceptibilities

<table>
<thead>
<tr>
<th>Gene</th>
<th>Molecular lesion</th>
<th>Target</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 11a locus (gene coding cholesterol side chain cleavage)</td>
<td>216 genotype</td>
<td>Ovarian theca cells</td>
<td>Hyperandrogenism</td>
</tr>
<tr>
<td>Autosomal dominant gene</td>
<td>Point mutation encoding serine hyperphosphorylation</td>
<td>Adrenal and ovarian P450 C17αLYASE Activated insulin receptor</td>
<td>Hyperandrogenism Insulin resistance</td>
</tr>
<tr>
<td>11 p 15.5 locus (insulin gene)</td>
<td>Class III alleles at VNTR</td>
<td>Pancreatic β cells</td>
<td>Hyperinsulinaemia</td>
</tr>
</tbody>
</table>

VNTR = variable number of tandem repeats.
PCOS: environmental risk factors

Prenatal life
Following a retrospective study on PCOS patients (Cresswell et al., 1997), the existence of specific prenatal risk factors for the post-pubertal expression of the PCOS phenotype was suggested. These authors found two distinct groups of patients with polycystic ovaries: (i) those who had above-average birthweight and (ii) those born to overweight mothers. The second group comprised women of normal weight who had high plasma LH, but normal testosterone, concentrations. These women were born after term (40 weeks gestation). On the basis of these findings, the authors suggest that the two forms of PCOS have different origins in intrauterine life. Obese, hirsute women with polycystic ovaries have higher than normal ovarian secretion of androgens, associated with high birthweight and maternal obesity. Thin women with polycystic ovaries have altered hypothalamic control of LH release resulting from prolonged gestation.

Postnatal risk factors

Chronic anovulation
The role of chronic anovulation as an environmental risk factor for PCOS is suggested by several pathophysiological mechanisms where androgen, LH and sex hormone binding globulin (SHBG) play key roles. A subgroup of patients with PCO and hypogonadotrophic anovulation has also been described (Shoham et al., 1992).

Obesity
Obesity is an independent risk factor for chronic anovulation (Grodstein et al., 1994) and body fat distribution (waist to hip ratio) seems more important than weight itself (Zaadstra et al., 1993). In obese women, the two main mechanisms leading to anovulation are similar to those in patients with PCOS: (i) excess of LH and androgen secretion; and (ii) hyperinsulinemia and insulin resistance. In fact, short-term fasting reduces LH secretion in normal weight women (Olson et al., 1995). In overweight women, calorific restriction lowers insulin concentrations and raises SHBG concentrations (Kiddy et al., 1992), while in severely obese patients post-gastrectomy recovery of ideal weight restores normal glucose and insulin metabolism (Letiexhe et al., 1995).

In contrast, in women with PCOS, obesity worsens the syndrome; in these patients insulin resistance appears to be directly related to the body mass index (BMI) (Pasquali et al., 1986), while weight reduction in obese women with PCOS lowers LH hypersecretion and reverses insulin insensitivity (Kiddy et al., 1990; Bützow et al., 1996). Experimental data suggest there may be some genetic control of appetite, body weight and reproductive function (Friedman, 1997).

Conclusions
PCOS can be considered a complex, heterogeneous metabolic syndrome triggered or maintained by the combined effect of inheritable genetic susceptibilities and environmental risk factors. The complicated panel of genetic and post-conceptional mechanisms leading to PCOS is still poorly understood.

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