

Review Article

GENETIC AND NON-GENETIC THEORIES ON THE ETIOLOGY OF POLYCYSTIC OVARY SYNDROME: A REVIEW

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INTRODUCTION

Polycystic ovary syndrome (PCOS) may be defined as a multifaceted disorder characterized by ovulatory dysfunction, hyperandrogenism and gonadotropin abnormality with cystic changes in the ovary. PCOS is a spectrum of clinical, biochemical and anatomical findings. However, it should be mentioned that not all women with polycystic ovaries suffer from PCOS. In his paper of 1935, Stein stated that in his opinion, PCOS was not the result of a congenital, inflammatory or degenerative disease but from a definite endocrine disturbance.¹ Nearly sixty years later, the precise causes of this disturbance still remain unknown.

The pathophysiology of PCOS has been described using different paradigms. Some investigators have used the "primary-secondary" concept to explain the abnormal secretion of LH, FSH and their relationship to serum androgens.² Others have used an anatomical approach, attributing the etiology of PCO to the adrenal,³ ovary,⁴ skin,⁵ or the immune system.⁶ Lately, PCOS has been considered as an inherited disease that occurs as a result of a single gene defect,⁷ or a

combination of several genes producing a relatively unique phenotype.⁸ Non-genetic hypotheses may be classified as "intrauterine" and "childhood and puberty" theories.

INTRAUTERINE THEORIES

Case studies have reported cystic changes within neonatal ovaries.^{9,10} Excess androgen production in the pregnant mother is sometimes associated with fetal virilization suggesting that excessive maternal androgen may alter the fetal ovary.⁹ Mulaikal and colleagues suggested that prenatal or neonatal exposure to androgen may lead to a congenital masculinization of the hypothalamus that in turn results in impaired GnRH pulsation.¹¹ Insler suggested that the synaptic function and post-synaptic membrane structure could be disturbed during intrauterine life, altering the fetal endocrine system.¹²

Impaired glucose tolerance in adult life is associated with a low birth weight.¹³ It has been suggested that this association reflects the long-term effect of reduced growth of the pancreas *in utero*. It has also been postulated that this immature endocrine system may lead to impaired glucose tolerance and an insulin profile which in turn is responsible for endocrine changes of PCOS. Recently we measured the level of fasting serum insulin in a group of female-female twins and found that only a small subgroup of subjects with PCO had high levels of insulin. Also, twin analysis showed that insulin is under genetic control.¹⁴

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CHILDHOOD AND PUBERTY

Kazer hypothesized that PCO may be due to an altered feeding behaviour early in life.¹⁵ He reasoned that IGF-1 might directly influence ovarian steroidogenesis. In young rats, maternal protein deprivation during the period before weaning can induce permanent alterations in the growth hormone-IGF-1 axis. He then adds that in the case of PCOS women, a period of "protein loading" during infancy might increase the serum level of IGF-1, altering steroidogenesis.

Factors such as gestational diabetes, childhood obesity and abnormal adrenal function during the pre- and peri-puberty period may also play important roles in the etiology of PCOS. Mechanick postulated that PCOS is the result of an aberrant puberty resulting from abnormal development of the brain.¹⁶ Insler further suggested that increased adrenal production during puberty may result in elevated androgen function.¹² Some of these androgens are converted into estrogens in fat or brain tissues. The excessive estrogen levels may then alter the synaptology type and post-synaptic membrane function of the arcuate nucleus and possibly other centers in the brain resulting in abnormal LH secretion.

The hormonal and ovarian abnormalities of PCOS are common in patients with eating disorders such as Briquer's disorder¹⁷ or bulimia nervosa.^{18,19} Also, puberty is a risk factor for the development of eating disorders.²⁰ From the above premises it may be concluded that PCO may occur as the result of an eating behaviour that tends to be amplified by puberty.

Yen proposed that the initiating event in the genesis of PCO could be due to an exaggerated adrenarche.²¹ Dewailly hypothesized that the female puberty system offers a physiological model to explain the gonadotropic action of insulin.²² He stated that in patients with insulin resistance, hyperandrogenemia could induce a state of "hyperpuberty", leading to the development of PCOS during adolescence.

Finally, it has been hypothesized that there may be a progressive nature to the syndrome.²³ This progress may need a considerable length of time and it is likely that in many females who subsequently develop PCOS, changes in ovarian morphology started somewhere before or during puberty.

INTRA-OVARIAN FACTORS

Ovarian enlargement is known to be associated with excessive androgen production and disturbances of the menstrual cycle in PCOS.²⁴ The ovary is the major

source of circulating T and androstenedione in PCO subjects.²⁵ An abnormal response of women with oligomenorrhea, hirsutism or acne to GnRH agonists such as nafarelin suggests an ovarian cause of androgen excess.^{26,27} Above all, the existence of unilateral polycystic ovaries would suggest that intra-ovarian factors can cause primary PCOS.²⁸

Recent studies showed that insulin-like growth factors (IGFS) play an important and complex role in ovarian physiology. Hammond and colleagues²⁹ were the first to demonstrate the ovarian secretion of IGFS. Insulin-like growth factor 1 (IGF-1) can actively induce insulin resistance and increase adrenal androgen secretion.¹⁵ It is likely that IGF-1 stimulates E2 production by a combination of granulosa cell proliferation and stimulation of the aromatase complex.³⁰ It may also act as an amplifier of FSH action by interacting with the FSH transduction signal at multiple cellular sites.³¹ *In vitro* experiments with PCO granulosa cells show that physiological concentrations of IGF-1 and FSH act synergistically to control E2 production.³²

IGF-2 of theca-interstitial cell origin may also play an autocrine role in patients with PCO. In addition, it may serve as one of several signals through which androgen producing cells may communicate in a paracrine fashion with the adjacent granulosa cell compartment.³³ IGF-1 can also stimulate the LH-induced androgen production, and the accumulation of androgens in the ovary.³⁴

In addition of IGF-1 and IGF-2, their binding proteins in follicular fluid are important modulators of the IGF autocrine/paracrine system in the ovary.³⁵ A third of PCOS subjects have low levels of insulin-like growth factor binding protein 1 (IGFBP-1). These groups have a tendency to be more obese and hirsute.³⁶ Conway and colleagues showed that serum insulin concentration in lean women with PCOS correlated positively with serum IGF-1 and negatively with IGFBP-1 concentrations.³⁷ This association was also described by Pekonen.³⁸ He found that the lack of 34k IGFBP-1 increased the IGF-1 receptor binding in the ovary, thereby enhancing androgen production by thecal-interstitial and stromal cells.

IGFBP-2 is also present in FF of PCOS patients as atretic follicles from normally cycling women in a greater amount, compared to levels in FF from healthy, developing, estrogenic follicles. IGFBP-2 may also bind IGFS in FF, inhibiting IGF action on the granulosa during normal folliculogenesis.³⁹

Epidermal growth factor (EGF) and transforming growth factor (TGF) also exert an inhibitory action on aromatase activity of granulosa cells.⁴⁰ Mason has shown that EGF is a potent inhibitor of E2 secretion in

granulosa cells taken from normal and polycystic ovaries.⁴¹

The role of growth factor (GH) in stimulating ovarian androgen production has also been studied. Anaplitou et al. reported that the basal circulating levels of GH were elevated in PCOS subjects.⁴² However, the increased basal levels of GH did not reflect differences in the circulating levels of T or androstenedione. On the other hand, according to Insler et al.,⁴³ proposing a model for non-obese PCOS subjects, a relative increase of GH concentration stimulates excessive ovarian IGF-1 production. This increase then leads to excessive androgen production which in turn may cause changes in brain centers and disturbance in gonadotropin secretion leading to the typical changes of PCOS. Other studies revealed no abnormality in the basal circulating levels of GH among PCOS patients. For instance, Chang could not demonstrate an alteration in the basal circulating levels of GH in non-obese PCOS subjects.⁴⁴ Similar conclusions were reached by Lanzone who measured both GH and IGF-1 levels in PCOS and control subjects.⁴⁵

In contrast, some studies have suggested a deficit in GH secretion among women with PCOS. In one such study, the basal circulating level of GH was found to be lower in PCOS subjects when compared with obese controls.⁴⁶ Urdle raised the possibility that a primary elevation of IGF-1 is responsible for the GH deficit.⁴⁷ Overall, the role of GH in PCOS remains speculative. Improved understanding must await carefully controlled data for the effects of obesity and detailed analysis of pulsatile release of GH.

GENETICS

The genetic basis for Stein-Leventhal syndrome was suggested by Cooper and colleagues in 1968.⁴⁸ They studied 18 families in which the syndrome appeared in a pattern consistent with a dominant mode of inheritance. However, they were unable to differentiate between autosomal dominant and X-linked dominant inheritance on the basis of the data. Later, in the 1970s Givens studied a group of patients with hyperthecosis, oligomenorrhea and/or hirsutism and concluded that PCO was inherited in X-linked dominant fashion.⁴⁹ Wilroy reported that these presentations in families appear to be in more than one generation.⁵⁰ Wilroy noted that 47% of female offspring of affected females were considered to be also affected and 89% of daughters of offsprings of males having elevated levels of LH were also affected.⁵⁰ The pattern of inheritance in the last group was considered as X-linked dominant inheritance. In 1988, Givens reported the observation

that occurrences of acanthosis nigricans, insulin resistance and hypertension were present in many family members.⁵¹

Ferriman and Purdie studied 381 women with hirsutism and/or oligomenorrhea diagnosed as having polycystic ovaries, detected by gynecography.⁵² The incidence of oligomenorrhea and infertility was found in less than 50% of female relatives. In contrast to the Givens study, baldness proved to be significantly more frequent in relatives of hirsute women than in relatives of nonhirsute subjects. Lunde in a more recent study showed that 19.7% of first-degree male relatives of affected subjects had early baldness or excessive hairiness.⁵³ For female first-degree relatives, the percentage affected was 31.4%. Autosomal dominant inheritance could be excluded as an explanation for PCO in their whole data set but their findings were consistent with this mode of inheritance for a sizable fraction of families. This study also discarded the possibility of X-linked inheritance.

Hague et al. performed a study which relied upon ultrasound diagnosis of PCO and suggested that 67% of mothers of probands (with PCOS) and 87% of sisters of probands were affected.⁵⁴ Overall, 80.5% of female relatives in all sibships were recognized as affected. The high familial incidence of PCO in the last study was not compatible with either autosomal dominant or X-linked dominant modes of inheritance.

Only a small number of case studies of twins have been published. Goldzieher and Jeffcoate reported the occurrence of concordantly affected identical twin sisters (one pair in each study).^{55,56} McDonough and colleagues compared a pair of identical twins at age of 16 years, with a "normal" 18 year old sibling.⁷⁵ PCO was documented by laparoscopy. Both twin sisters had amenorrhea and moderate hirsutism. A similar pattern of steroid secretion in the identical twins associated with inappropriate gonadotropin secretion and ovulatory failure existed. It was suggested that some genetically determined difference in sensitivity of receptor sites may be involved in gonadotropin control. The author further showed that no correlative data was found between the MZ twin pair and the normal sibling, and suggested that it was difficult to study PCOS in individuals with diverse genetic background. Lee and colleagues studied a pair of MZ twins with a history of premature pubarche, postpubertal hirsutism and amenorrhea.⁵⁸ Biochemical screening suggested that the subjects were affected by an attenuated form of congenital adrenal hyperplasia. He concluded that the disorder was not due to a mild 21-hydroxylase deficiency but rather was an inherited condition which could be expressed as an autosomal or X-linked dominant trait.

Some studies have analyzed karyotype reports in subjects with PCOS. Parker and colleagues performed chromosomal analysis on a group of 189 cases of PCO.⁵⁹ A normal karyotype was found in 179, but a variety of sex chromosomal anomalies were found in 13. The diversities of the karyotype anomalies lead to the conclusion that no typical chromosomal anomaly is associated with PCOS. However, there are several reports in the literature describing an association between PCOS and chromosomal abnormalities. Turner's syndrome with a 45X karyotype or mosaicism appearances of genotypes like 45X/46XX have been reported in women with PCOS.^{49,60,61} Other reports have described subjects with PCO who have also had karyotypic abnormalities but without the Turner phenotype,^{62,63} including X chromosome mosaicism and pseudodiploidy with trisomy. Given the above cases, it seems that in some cases an autosomal anomaly may lead to PCO.

The above studies represent different approaches to assess the role of heritability in PCOS. Franks suggested that high familial incidence of PCO makes it possible to conclude that this disorder is genetically determined. Moreover, these studies imply that PCOS is a permanent state. Failure to improve the ovulatory response in PCOS after suppression of the HPO-axis may reflect the presence of an inherent defect.^{15,65,66} Dewailly postulated that the likely genetic origin of insulin resistance which accompanies some cases of PCOS could explain, at least in part, the genetic predisposition to this disease.²² Deficiency of 17-ketosteroid reductase enzyme which results in the excess level of androstenedione and estrone has been suggested as another candidate for the genetic theory.⁶⁷ It is worthy to note that although PCO is a familiar condition, it does not necessarily mean that it is genetic. A learned behaviour such as eating habits or exercise pattern could also cause the condition.

Since PCOS is a heterogeneous disorder, it seems unlikely that it is caused by a single gene defect. In contrast, polygenic inheritance or a combination of genetic and environmental factors may better explain the complex nature of PCOS. Twin studies have been used to elucidate the influence of genetic and environmental factors in the etiology of PCOS. If PCO is inherited via a single gene defect, monozygotic (MZ) twins who are genetically identical should be similarly affected. On the other hand, dizygotic (DZ) twins who are no more alike than siblings, may have a 50% chance of being affected by this condition. Using ultrasound and/or biochemistry as the diagnostic tools, we recently examined the incidence of PCOS in a group of MZ and DZ twins. Twin model-fitting analysis was also applied to investigate the role of genetic or environmental

factors in the etiology of PCO. The result suggested that PCOS is not the result of a single autosomal genetic defect. This result was also confirmed by the existence of 11 pairs of scan-discordant twins, one of whom had scan evidence of PCO and the other had scan normal ovaries. Rather, PCOS may be an X-linked disorder with non-random X-chromosome inactivation.¹⁴ This has been described previously for X-linked disorders such as (Hunter's) mucopolysaccharidosis type II.⁶⁸ Molecular studies of such disorders have shown that the affected twin shows non-random X-inactivation, while the normal twin demonstrates equal usage of both X chromosomes. Winchester and colleagues have suggested that twinning may be strongly associated with non-random X-inactivation and that it is not specific to the properties of the genetic disease. Several theoretical explanations for the discordant expression of phenotype in MZ twins have been offered.⁶⁹ If events that occur after twinning are excluded, the most likely explanation is that at twinning the cell mass that gives rise to the affected twin consists predominantly of cells in which the normal allele has been inactivated. This segregation of the 2-cell mass may be a statistical artefact resulting from splitting the cell mass into two and the affected twin may only be the extreme example of the normal variability of phenotype observed in women heterozygous for an X-linked trait.

Winchester argues that asymmetric splitting in twinning could lead to a birth weight discrepancy in the twins and consequently an extreme X-inactivation in a twin with a lower birth weight. He states that MZ twins are not, in general, half the size of singletons. If the number of precursor cells after the deviation is not equal, an extreme X-inactivation profile is more likely in the twin arising from the fewest cells. Inner cell masses that contain fewer cells would be expected to have shown a greater amount of catch-up growth during embryonic life that results in doubling of cell number at some time during their prenatal development. These catch-up divisions would be expected to lead to an increase in the number of cells with an inactivated X-chromosome. Another theory that could explain the process of inactivation in the X-chromosome is the possibility of an aberration in the twinning process itself which causes selective inactivation of the normal allele in one twin and not in the other.

PCO may also be the result of an intra-uterine event such as anomalous placental site or function, or an abnormality of fetal growth, their vascular supply, a nutritional factor or an endocrine event. Further studies on birth details including birth weight, the number of placentas, amniotic layers, placenta site and size may provide more information on the intra-uterine situation of subjects. The results from our twin analysis are also

consistent with PCO being the result of an interaction between genetic and environmental elements during childhood, puberty and adulthood.^{60,61}

In conclusion, PCO is more likely to be influenced by a polygenic complex, an interaction between genetic and environmental factors or an X-linked condition which is associated with non-random X-inactivation. Further studies on monoamniotic MZ twins who were reared apart may improve our understanding of the etiology and pathophysiology of PCO.

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