Polycystic ovarian syndrome: the metabolic syndrome comes to gynaecology

Abstract:
Polycystic ovarian syndrome, a common form of infertility, may be the result of an insulin resistance which comes from what is known as metabolic syndrome. In addition to the insulin resistance, the syndrome generally includes a tendency toward lipid imbalances and later-life cardiovascular disease. Viewing the non-ovulation as metabolic rather than gynecological changes the attitude of management and allows new possibilities for prevention as well as new approaches to treatment.

Full Text:
Polycystic ovarian syndrome is the most common form of anovulatory infertility.[1] Its association with menstrual disturbance and altered hormonal parameters leads many affected women of reproductive age to attend a gynaecology or infertility clinic. The aetiology of the condition is unknown, but recent evidence suggests that the principal underlying disorder is one of insulin resistance, with the resultant hyperinsulinaemia stimulating excess ovarian androgen production. Associated with the prevalent insulin resistance, these women exhibit a characteristic dyslipidaemia and a predisposition to non-insulin dependent diabetes and cardiovascular disease in later life. Thus, polycystic ovarian syndrome seems to have many of the hallmarks of the metabolic syndrome.[2-4] This article focuses on the recent change in attitudes to polycystic ovarian syndrome arising from the link with insulin resistance--a concept that not only has major implications for the health of affected women but also offers a potential for new treatments.

Methods

This article is derived from a review of recent publications in the relevant subjects of endocrinology, reproductive medicine, and gynaecology. In addition, we conducted a Medline search of "polycystic ovarian syndrome" and "metabolic syndrome in women." Our clinical experience and that of colleagues in relevant specialties further supplemented this review.

Diagnostic parameters

Diagnostic clinical features of polycystic ovarian syndrome include menstrual disturbance secondary to chronic anovulation or oligoovulation, and hirsutism or acne due to hyperandrogenaemia. Despite this classic concept, it is a heterogeneous disorder and exact diagnostic criteria remain contentious (see box). Hence, along with racial variations, the prevalence of the condition can only be estimated at between 5% and 10% of women of reproductive age.[5]

Elevated free testosterone activity, defined by the free androgen index, represents the most sensitive biochemical marker supporting the diagnosis. A raised luteinising hormone concentration, although a useful marker of the syndrome, is now less favoured as a diagnostic tool.[5] Most, but not all, subjects show a characteristic ultrasound appearance of enlarged ovaries and an increased echo dense stroma surrounded by multiple, small, peripherally situated follicles.[5] Exclusion of other possible aetiologies that may present in a similar fashion--such as late onset congenital adrenal hyperplasia, thyroid disease, hyperprolactinaemia, and androgen secreting tumours--is essential.

Aetiology

The aetiology of polycystic ovarian syndrome is uncertain. There is some evidence of autosomal transmission related to strong familial clustering. Potentially, a gene or series of genes renders the ovaries susceptible to insulin stimulation of androgen secretion while blocking follicular maturation? This genetic predisposition may be expressed as premature balding in men.[7]

The onset may occur in late childhood since many of the metabolic and endocrine features of the disorder mimic puberty.[8] Insulin resistance increases dramatically at the onset of puberty and then declines in early adulthood. Associated with this are increases in the pulse amplitude of luteinising hormone, increasing androgen concentrations, and irregular menses. Multiple, small ovarian cysts

are seen on ultrasound examination and are a common and normal feature of puberty. It is therefore possible that women genetically predisposed to polycystic ovarian syndrome fail to resume normal insulin sensitivity and continue to express metabolic and endocrine features usually confined to puberty.[8]

Pathophysiology

Good evidence supports the hypothesis that decreased peripheral insulin sensitivity and consequent hyperinsulinaemia are pivotal in the pathogenesis of polycystic ovarian syndrome.[5] Peripheral insulin resistance is most evident in overweight patients: obesity and polycystic ovarian syndrome each seem to have a separate and synergistic relation with insulin resistance.[5] The exact mechanism(s) for insulin resistance is uncertain, but a post-receptor defect in adipose tissue has been identitied.[5] Despite insulin resistance in adipose and skeletal muscle, the ovary remains relatively sensitive to insulin, and both insulin and insulin-like growth factor 1 have stimulatory effects on thecal androgen production? In fact, some lean women with polycystic ovarian syndrome, who may not have insulin resistance and therefore hyperinsulinaemia, may show enhanced ovarian sensitivity to insulin. Figure 1 shows how the relative excess of insulin or enhanced ovarian sensitivity to insulin, in combination with an elevated luteinising hormone concentration, brings about thecal hyperplasia, increased androgen secretion, arrest of follicular development, and therefore anovulation along with menstrual disturbance.

Insulin also acts on the liver to inhibit the production of sex hormone binding globulin and insulin-like growth factor 1 binding protein. A reduction in sex hormone binding globulin leads to an increase in the biologically available free testosterone. Thus, insulin resistance not only increases secretion of ovarian androgens but also promotes an increase in the proportion of free (active) hormone. Similarly, inhibition of production of insulin-like growth factor 1 binding protein results in an increased concentration of circulating free insulin-like growth factor 1, further enhancing ovarian androgen production.[10]

Current consensus suggests that the ovary is the principal site of excess androgen production, but some women with polycystic ovarian syndrome may have an adrenal contribution to the increased androgen production. The mechanisms for this remain obscure and are almost certainly multifactorial.[11]

Metabolism and health implications

Figure 2 shows the principal features of the polycystic ovarian syndrome. It is well recognised that visceral distribution of body fat, common in the syndrome, is of greater consequence to the metabolic effects of insulin resistance than obesity per se).[12 13] Central obesity and insulin resistance lead to an altered lipolytic response to insulin, with impaired suppression of release of free fatty acids from adipose tissue. An increased flux of free fatty acids from central sites enters the portal circulation, increasing the availability of substrate to the liver for triglyceride production. Furthermore, women with the syndrome exhibit increased activity of hepatic lipase, an enzyme responsible for the conversion of large lipoprotein particles to smaller, more atherogenic species. This explains the findings of reduced concentrations of high density lipoprotein cholesterol and increased levels of atherogenic, small, low density lipoprotein.[14]

The combination of raised triglyceride and decreased high density lipoprotein is strongly linked with cardiovascular disease.[15] Discrepancies in these lipid parameters between patients with polycystic ovarian syndrome and controls matched for age and weight are evident at an early age.[2] Hence, an increased risk of cardiovascular disease due to lipid perturbances will present in early adult life. Women with polycystic ovarian syndrome also show elevated concentrations of plasminogen activator inhibitor[1,16 17] a potent inhibitor of fibrinolysis, which have been shown to predict the occurrence of myocardial infarction. Suppression of hyperandrogenaemia by use of gonadotrophin releasing hormone analogues has little effect on the insulin resistance or the dyslipidaemia, suggesting that the abnormal lipid profile is independent of the raised androgen concentrations.[5]

Important retrospective studies provide evidence of increased risk of cardiovascular disorders. A study of women thought to have polycystic ovarian syndrome who were treated with ovarian wedge resection 20-30 years earlier showed that they were four times more likely to be receiving treatment for hypertension than age and weight matched controls and seven times more likely to have a diagnosis of diabetes.[18] Studies of women undergoing coronary angiography for evaluation of chest pain found a disproportionately large number with polycystic ovaries on ultrasound scan.[19] Furthermore, on multiple linear regression analysis the presence of polycystic ovaries was independently associated with the severity of the coronary vascular disease. Models using triglyceride concentrations, waist to hip ratio, non-insulin dependent diabetes, and elevated blood pressure in women with polycystic ovarian syndrome indicate a 7.4-fold increased risk of myocardial infarction compared with age matched referents.[3] Clearly, comprehensive longitudinal studies are required if the long term implications of the syndrome for cardiovascular health are to be fully appreciated.

Current and future treatments

Women with polycystic ovarian syndrome are currently treated according to their presenting features-irregular menses, hirsutism, or infertility (table).

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Current and potential treatments for polycystic ovarian syndrome Treatment Problems addressed Current treatments Oral
contraceptives Menstrual disturbance Clomiphene Ovarian diathermy or laser treatment Anovulatory infertility Assisted
conception techniques Cyproterone acetate+ ethinyloestradiol Hirsutism and acne Spironolactone Weight loss Menstrual
disturbance and anovulatory infertility, but also improvement of metabolic perturbances and thus risk of coronary heart
disease Potential treatments Insulin sensitising agents (such as metformin) Obesity and central obesity Androgen excess
Menstrual disturbance Anovulatory infertility Metabolic perturbances
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Irregular menses--The combined oral contraceptive pill is commonly used to regulate menses. By increasing levels of sex hormone binding globulin while decreasing androgen secretion, it reduces the circulating free testosterone activity. However, the combined pill exacerbates insulin resistance, and, since many patients are overweight and obesity is a relative contraindication, this treatment may be unsuitable.[20]

Hirsutism may be addressed by the use of the antiandrogens cyproterone acetate or spironolactone (the former used in combination with ethinyloestradiol).[21] Their principal mode of action is the inhibition of the binding of dihydrotestosterone to its receptor at the hair follicle. Beneficial effects can be seen after three months, but excessive hair growth returns soon after cessation of treatment. Cyproterone acetate may exacerbate irregularity of the menstrual cycle, and both drugs are unsuitable for use in those trying to conceive.

Infertility--For patients wishing to become pregnant, domiphene citrate may be successful in stimulating ovulation but carries an increased risk of multiple pregnancy.[22] By inhibiting the oestrogen mediated negative feedback loop at the hypothalamus, it enhances secretion of follicle stimulating hormone. Guidelines suggest that the duration of clomiphene treatment should not exceed six months because of the potential increased risk of ovarian cancer.[23] Those failing to conceive after clomiphene treatment usually respond to exogenous gonadotrophins, but this requires intensive monitoring to reduce the risk of multiple conceptions.

Alternatives to medical treatment include laser or electrocautery of the ovary. This is often used as a last resort, is not available in all centres, and is difficult with obese patients. Although effective in aiding ovulation and regulating menses, its beneficial effects are usually short term.

Insulin resistance

As the principal underlying defect in polycystic ovarian syndrome seems to be insulin resistance, the most appropriate treatment for all clinical presentations may be one that specifically addresses this problem.

Weight reduction has multiple benefits for obese women with polycystic ovarian syndrome.[24] The resultant reduction in insulin resistance corrects the hormonal imbalance, promotes ovulation and regular menses, and improves the metabolic consequences of the disorder. Weight loss should therefore be encouraged, but it seems to be hard to achieve for this group of patients.

Insulin sensitising agents--Recent trials have investigated the effect of such agents on polycystic ovarian syndrome.[16 17 24-33] Metformin, a biguanide often used in non-insulin dependent diabetes, has been the most commonly used. Troglitazone, a thiazolidinedione that improves muscle insulin sensitivity, has also been studied[17 27] but has recently been removed from the market because of adverse effects on hepatic function. Trials to date have included only small numbers of subjects, but results have been promising, with most showing reductions in concentrations of fasting serum insulin, androgen, and luteinising hormone)[16 17 26 28 29 31-33] In addition, circulating concentrations of sex hormone binding globulin increased, resulting in less bioactively available testosterone. Preliminary evidence indicates that treatment of obese women with polycystic ovarian syndrome with metformin restores regular menstrual cycles and ovulation[26 30-32] Whether insulin sensitising agents can modify the vascular risk factors associated with the syndrome remains to be seen, but reductions in Lp (a) lipoprotein and plasminogen activator inhibitor 1 have been observed.[16 17] Additionally, some studies have reported that treated subjects have shown some weight loss despite continuation of their normal diet and lifestyle,[16 26] and others have demonstrated a reduction in central obesity[16 29 33]

Thus, treatments targeting the key factor in the disorder may not only resolve the gynaecological problems with which the syndrome presents, but also reduce the risk of vascular disease in later life. There is now an urgent need for randomised, placebo controlled trials to assess the potential benefits of these treatments for women's health.

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RELATED ARTICLE: Summary points

It is evident that polycystic ovarian syndrome should no longer be considered a purely gynaecological disorder

Affected women seem m have subclinical insulin resistance and a form of the metabolic syndrome that manifests itself in early adult life with gynaecological symptoms

They may therefore gain particular benefit from early screening for cardiovascular risk factors, particularly glucose intolerance

Intervention with insulin sensitising agents, such as metformin, may play a major role in the future treatment of this condition, with the potential capacity to improve both endocrine and metabolic disturbances and reduce the risk of vascular disease

This approach may replace therapies used to treat individual components of polycystic ovarian syndrome such as hirsutism which may reflect a "downstream" feature of dais complex metabolic syndrome

RELATED ARTICLE: Diagnostic criteria of polycystic ovarian syndrome

Diagnosis is based on the presence of some or all of the common clinical features, confirmed by biochemical evidence of endocrine abnormality and exclusion of other possible aetiologies

Clinical features

* Oligomenorrhoea or dysfunctional uterine bleeding Anovulatory infertility

* Hirsutism or acne, or both

* Central obesity

Endocrine abnormalities

* Increased testosterone activity (often expressed as raised free androgen index)

* Elevated luteinising hormone concentration with normal follicle stimulating hormone concentration

* Insulin resistance with compensatory hyperinsulinaemia

RELATED ARTICLE: One hundred years ago

Hogarth's paintings at St. Bartolomew's Hospital

The paintings by Hogarth, to which a brief reference was made in the British Medical Journal of October 8th, ornament two of the walls of the grand staircase which leads to the Great Hall in the north wing of the hospital. The subjects are "The Good Samaritan" and "The Pool of Bethesda." They were painted gratuitously in 1736 by Hogarth, who was thereupon elected a life-governor of the charity. The pictures are well worthy of the careful treatment to which they have lately been subjected, for the painter in his autobiographical sketch says that they were his first efforts in the grand style. "Before I had done anything of much consequence in this walk," he says (thatis, the painting and engraving of modern moral subjects) "I entertained some hopes of succeeding in what the puffers in books call `the great literary style of history painting' so that without having done a stroke of this grand business before I quitted small portraits and familiar conversations, and with a smile at my own temerity commenced history painter, and on a great staircase at St. Bartholomew's Hospital painted two Scripture stories, `The Pool of Bethesda' and `The Good Samaritan, with figures 7 feet high." Both paintings were engraved in 1772, and impressions of the plates appear in Boydell's edition of Hogarth's works. (BMJ 1898;ii:1186)

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Source Citation (MLA 9th Edition)

Hopkinson, Zoe E.C., et al. "Polycystic ovarian syndrome: the metabolic syndrome comes to gynaecology." *British Medical Journal*, vol. 317, no. 7154, 1 Aug. 1998, pp. 329+. *Gale Academic OneFile*, link.gale.com/apps/doc/A21023725/AONE?u=cuny_centraloff&sid=bookmark-AONE&xid=3f24339e. Accessed 23 Mar. 2023.

Gale Document Number: GALE|A21023725