Review paper

Polycystic ovary syndrome (PCOS): the physician's point of view

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Introduction

Polycystic ovary syndrome (PCOS) is the commonest endocrine disturbance in women of reproductive years, and affects 5-10% of women of this age group[1]. The symptoms include: hirsutism and acne as evidence of excess androgen production, obesity, menstrual disturbances, and consequently anovulation, and infertility. Symptoms often appear around menarche, while the biochemical abnormalities may be present around adrenarche[2]. PCOS is the commonest cause of anovulatory infertility and hirsutism worldwide[3]. However, the clinical presentation can vary widely; from an asymptomatic woman with the incidental diagnosis of polycystic ovaries on ultrasound, to that which was first described by Stein and Leventhal[4], an obese, hirsute, infertile woman with amenorrhoea and enlarged polycystic ovaries. Approximately 50% are obese, with significant central fat accumulation. A high fasting blood glucose associated with hyperinsulinaemia and insulin resistance occurs independent of the obesity in PCOS; all of which confer an increased risk of glucose intolerance[5]. The range of biochemical abnormalities of PCOS include: hypersecretion of luteinizing hormone (LH), hyperandrogenaemia, acyclic oestrogen production, decreased sex hormone binding globulin (SHBG) concentrations and hyperinsulinaemia[6].

Insulin resistance, accompanied by obesity, is an important risk factor for the development of long-term metabolic disease as described in the Metabolic Syndrome[7]. Recognized complications of PCOS are pregnancy associated diabetes mellitus and hypertension, and "non reproductive" consequences such as, type 2 diabetes mellitus, hypertension, dyslipidaemia, and endometrial cancer in those not treated appropriately[8]. Hence, PCOS must be considered a major women's health issue, with ramifications well beyond the gynaecological and dermatological abnormalities that usually bring affected women to seek medical attention[2]. Indeed, significant health risks remain after the reproductive dysfunction has been treated by hormonal therapy or disappear with the menopause.

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Historical perspective

Stein and Leventhal first described the polycystic ovary syndrome in 1935[4]. Its management included wedge resection of ovaries to restore regular menstruation and fertility. In the 1950s, the first insight into its biochemical derangement, i.e. elevated urinary LH level, was made. In the 1960s, increased androgen production as its cardinal feature and excess oestrogen causing endometrial hyperplasia, were noted. In the 1970s, the advent of radioimmunoassay shifted the diagnostic emphasis to biochemical markers. It was not until the 1980s, that metabolic derangement was identified as an important feature of PCOS[5,6]. At the turn of the millennium, the focus of research is to try to decipher its aetiology, with particular emphasis on the molecular genetics[2,3].

Clinical characterization

Follicular maturational arrest and the resulting accumulation of small subcortical cysts, with an increased ovarian stromal volume are identified as the polycystic ovary (PCO), usually by transvaginal ultrasound[9]. However, the presence of polycystic ovaries alone does not confer a diagnosis of the endocrine *syndrome*. PCOS lacks a universal definition, with neither a consistent clinical marker nor a unique phenotype. The more expansive the diagnostic criteria, the more heterogeneous the disorder becomes (Figure 1). Other causes of hyperandrogenism also manifest similarly, including insulin resistant states and non-classical congenital adrenal hyperplasia. In 1990, the National Institute of Child Health and Human Development (NICHD) conference on PCOS concluded, that the diagnosis of PCOS requires hyperandrogenism and/or hyperandrogenaemia, oligo-ovulation regardless of ovarian scan appearance, and the exclusion of congenital adrenal hyperplasia, hyperprolactinaemia and Cushing's syndrome[10]. In the United Kingdom, the diagnosis of PCOS is based upon ultrasound evidence of PCO, combined with one or more associated clinical and/or biochemical characteristics[1].

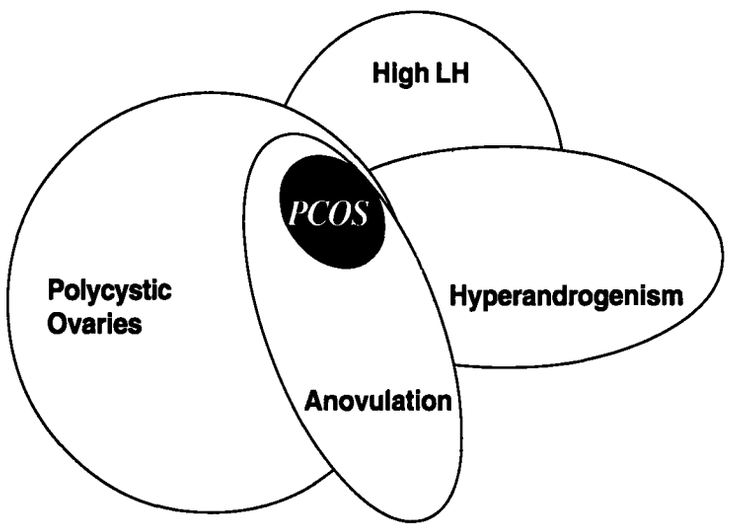

Figure 1. Proposed phenotypic traits in the polycystic ovary syndrome.
PCO = polycystic ovary by ultrasound; High LH = inappropriately high LH = Hypeandrogenism = acne, hirsutism;

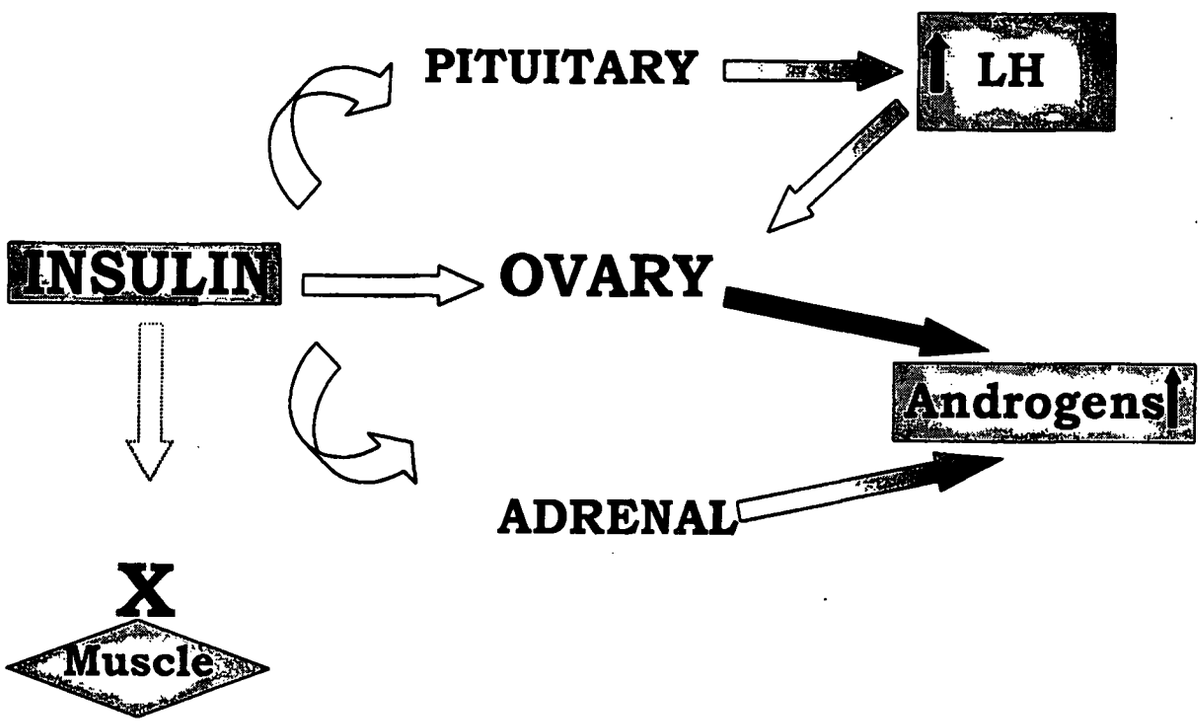

Figure 2. Schematic representation of the peripheral insulin resistance in PCOS (confined to skeletal muscle & adipose tissue) causing hyperinsulinaemia, which leads to ovarian androgen excess by direct action, and to a smaller degree via excess LH production from the anterior pituitary, and via adrenal androgen production.

Pathophysiology

The polycystic ovary produces an excess of androgens (androstenedione and testosterone) caused partly by altered ovarian insulin and insulin like growth factor 1 (IGF1) activity in the theca cells[11]. PCOS is the commonest disorder in which insulin resistance and ovarian dysfunction are linked[12]. Women with PCOS have peripheral insulin resistance involving skeletal muscles and adipose tissue, resulting in a compensatory hyperinsulinaemia (Figure 2). The polycystic ovary remains insulin sensitive, thus producing excess androgens.

Complications of PCOS

Long term metabolic risks of PCOS (Table 1)

Type 2 diabetes mellitus Glucose intolerance is the commonest complication. Studies on cohorts of women with well-characterized PCOS report an increased prevalence of type 2 diabetes between 7-15%, and of impaired glucose tolerance around 30%, significantly higher than age and weight matched normal women[3,5,8,13].

Hypercholesterolaemia Affected women have high circulating total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride, and lower levels of high density lipoprotein 2 (HDL2). Long term follow-up data is yet lacking[8].

Hypertension Despite reports of higher systolic and diastolic blood pressures in women with PCOS compared to normal age matched women the difference was not significant after correction for BMI. Hypertension being rare in young women would not necessarily imply that differences would not emerge in later life[8].

Cardiovascular disease The risk of coronary artery disease (CAD) is increased threefold in women with type 2 diabetes mellitus, twofold in women with hypertension, and is directly proportional to total and LDL cholesterol and triglycerides, and inversely proportional to HDL levels. Obesity and increased waist: hip ratios are independent risks for CAD in women. Based on these facts, it is reasonable to conclude that women with PCOS are at increased risk of cardiovascular disease, although there is no current epidemiological data to support this[14].

Pregnancy complications When women with PCOS become pregnant, they have an increased risk of developing gestational diabetes mellitus and pregnancy-induced hypertension.

Gestational diabetes mellitus (GDM) Physiological insulin resistance of pregnancy in a woman with PCOS makes gestational diabetes a very likely complication. Prospective data support this, showing a higher than population-based-expected rate of GDM (8%-38%), although in small samples without matched controls[15].

Pregnancy-induced hypertension Obesity, insulin resistance and glucose intolerance are risk factors for pregnancy-induced hypertension. In a study of 81 patients with PCOS and matched controls, the risk for pre-eclampsia was significantly greater among those with PCOS (14% versus 2.5%)[16].

Cancer PCOS is associated with a high risk of developing endometrial cancer[8,17]. High and unopposed levels of endogenous oestrogens and hyperinsulinaemia are the proposed mechanisms. Although endometrial cancer is a disease of older women, the reported age of afflicted women with PCOS is much younger[8]. Currently available data does not support a higher risk of breast cancer nor ovarian cancer in PCOS.

Table 1. Risk stratification of the long-term complications of PCOS

An increased risk

Type 2 diabetes mellitus
Dyslipidaemia
Endometrial cancer

Probable risk

Hypertension
Cardiovascular disease
Gestational diabetes mellitus
Pregnancy-induced hypertension
Ovarian cancer

Remote risk

Breast cancer

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