

## PERSONAL VIEW

## Polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in women of reproductive age. The classical symptoms are those of hyperandrogenism (hirsutism, persistent acne, androgen dependent alopecia) together with symptoms of anovulation (infertility, amenorrhoea, irregular dysfunctional uterine bleeding).<sup>1</sup> In the last 10 to 15 years, the use of high resolution pelvic ultrasonography has greatly facilitated identification of polycystic ovaries in women with hirsutism or menstrual disturbance. It is now clear that the range of presenting symptoms of women with polycystic ovaries includes not only non-hirsute women with oligomenorrhoea or amenorrhoea but also hirsute subjects with regular, ovulatory cycles. PCOS occurs in nearly 75% of cases of anovulatory infertility and over 80% of subjects with hirsutism.<sup>1</sup> The typical biochemical features of PCOS include hyperandrogenaemia and an increase of serum luteinising hormone (LH) (with normal follicle stimulating hormone) but PCOS is also associated with a characteristic metabolic syndrome that includes hyperinsulinaemia, insulin resistance, and dyslipidaemia.<sup>1–4</sup> These features are linked to a significantly increased risk of type II (non-insulin-dependent) diabetes in later life and women with PCOS may also have a greater chance of developing premature cardiovascular disease.<sup>3, 5, 6</sup>

### Polycystic ovaries and PCOS

The presence of polycystic ovaries is necessary for the development of the syndrome but not all women with polycystic ovaries have PCOS. The typical polycystic morphology is present in about 20% of the normal female population many of whom are non-hirsute, have regular menses, and normal serum concentrations of testosterone and gonadotrophins.<sup>7</sup> Nevertheless, as a group, women with polycystic ovaries in this normal population have slightly raised serum testosterone and LH compared with subjects with normal ovarian morphology.<sup>7</sup> In other words there appears to be a broad but single spectrum of clinical and biochemical features which link subjects with polycystic ovaries.<sup>1, 7</sup> The aetiology of polycystic ovaries and PCOS remains unclear but there is increasing evidence for a major genetic component. Familial clustering of cases is well recognised with a high prevalence among siblings (around 50% are affected).<sup>8</sup> An autosomal dominant mode of

inheritance has been suggested but PCOS is more likely to represent a complex trait in which a small number of major genes interact with environmental and other genetic factors to account for the heterogeneity. Recent molecular genetic studies point to the insulin gene minisatellite and the P450 cholesterol side chain cleavage gene (CYP11a) as major susceptibility loci.<sup>9, 10</sup> It seems probable that other genes involved in steroidogenesis and in insulin secretion or action may be implicated. The observation that the insulin gene may be related to the aetiology of PCOS emphasises the emerging importance of the role of insulin and particularly hyperinsulinaemia—whether genetically or nutritionally determined (or both)—in the pathogenesis of PCOS. Significantly, hyperinsulinaemia and insulin resistance appear to be features of anovulatory women with polycystic ovaries and not of equally hyperandrogenaemic subjects with regular cycles.<sup>1</sup> Indeed, there is evidence that hyperinsulinaemia may be involved in the mechanism of anovulation in PCOS.<sup>11</sup>

### PCOS in adolescent girls

The symptoms of PCOS often date from adolescence and it is no surprise that polycystic ovaries are commonly found in teenagers with menstrual disturbances and/or hirsutism. The typical biochemical abnormalities are often present but it is important to be aware that, as in adults, serum concentrations of LH or testosterone (even in hirsute subjects) may be normal and should not prohibit the diagnosis of PCOS, which is made, primarily, on clinical and ultrasonographic criteria. Polycystic ovaries can be identified on ultrasound, even in prepubertal children. The prevalence of polycystic ovaries increases throughout puberty, reaching 26% by the age of 15.<sup>12</sup> Full expression of clinical and endocrine features of polycystic ovary syndrome depends on the maturational changes in the hypothalamic-pituitary-ovarian axis which occur during normal puberty, notably the influence of gonadotrophins on ovarian steroidogenesis. The presence of polycystic ovaries before the onset of puberty suggests that the origin of the syndrome depends on ‘programming’ of ovarian morphology and function at a much earlier stage of development—perhaps in utero when the newly differentiated ovary begins to secrete steroids under the influence of human chorionic gonadotrophin. Normal developmental

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changes in LH secretion might be expected to 'unmask' hypersecretion of androgens in adolescent girls with polycystic ovaries. An increase of serum LH may compound the problem and abnormal patterns of LH secretion have indeed been observed in teenage girls with symptoms of PCOS. The abnormalities observed include high amplitude LH pulses with an aberrant sleep related pattern, which suggested a primary hypothalamic disturbance of gonadotrophin regulation.<sup>13</sup> Interestingly, however, a similar pattern of abnormal LH pulses was noted during pulsatile gonadotrophin releasing hormone treatment of a hypogonadotrophic girl with polycystic ovaries.<sup>14</sup> This emphasises the overriding importance of ovarian derived feedback signals in the control of tonic secretion of LH.<sup>1</sup> Expression of PCOS during adolescence may also be affected by metabolic changes that are closely related to changes in body fat topography. There is a steady increase in serum concentrations of fasting insulin through normal puberty and adolescence.<sup>15</sup> This is accompanied by a reciprocal fall in sex hormone binding globulin that amplifies the effects of sex steroids. Furthermore, insulin has a direct gonadotrophic action on ovarian steroidogenesis.<sup>11</sup> This phenomenon may be regarded as one mechanism by which nutritional status can influence reproductive development. In girls with polycystic ovaries, the *physiological* hyperinsulinaemia of puberty may affect the genesis of both ovarian hyperandrogenaemia and anovulation. Higher than normal insulin concentrations, whether due to a genetic predisposition or excessive weight gain (or both), would be expected to exaggerate these potentially adverse effects.

#### Management of PCOS in adolescent girls

The management of PCOS in teenage girls, like that in older women, is essentially symptomatic.<sup>1</sup> Amenorrhoea or anovulatory menses should be treated by either cyclical progestagens or a combined oral contraceptive (preferably one containing a non-androgenic progestagen). Hirsutism is a particularly distressing symptom in young women and needs sympathetic and effective treatment. This includes advice about cosmetic measures and the early use, if necessary, of antiandrogen therapy. Cyproterone acetate is widely and

successfully used. In most cases this can be given at a dose of 2 mg for 21 days in 28, with ethinyl oestradiol 35 µg (Dianette, Schering). In overweight girls, weight reduction is a very important aspect of management, particularly in view of the possible long term sequelae of the attendant metabolic disturbance. Energy restriction reduces plasma insulin concentrations and improves cyclical ovarian function but effective dietary management usually involves input from an endocrinologist, dietitian, and psychological counsellor or therapist.

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