Polycystic ovary syndrome in adolescence—a therapeutic conundrum

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The polycystic ovary syndrome (PCOS) often presents in adolescence with menstrual disorders, acne and hirsutism. The early diagnostic signs are sometimes dismissed as ‘normal’ changes of adolescence, and the opportunity to save the teenager from the stigmata of the syndrome is missed. The finding that the metabolic syndrome is a possible long-term sequela of PCOS now presents a challenge to make an early diagnosis, educate patients regarding the importance of weight control and exercise, and treat accordingly both symptomatically and prophylactically. The use of long-term insulin sensitizers, particularly metformin, for these purposes in adolescents is now the subject of an inter-disciplinary debate. Good, hard supportive data are not yet forthcoming but, as in the adult, the establishment of metformin treatment for the hyperinsulinaemic adolescent with PCOS may precede the evidence.

Key words: adolescence/hyperandrogenism/menstrual disturbance/metformin/PCOS

Introduction

The lot of an adolescent girl is not always a happy one and may involve some turbulent times. If this period in life is complicated further by the emergence of polycystic ovary syndrome (PCOS), which very often presents at this stage, it is often a cause of worry and strife as there is little that can be more devastating to a young woman than the stigmata of hyperandrogenism. Hirsutism and acne are there for all to see and they may have an often disturbing effect on the psychosocial make-up of a teenager. Absent or infrequent menstruation is also a cause for worry, often combined with lingering doubts about future fertility potential. Adolescents are much less concerned about, and probably unaware of, the long-term sequelae of hyperandrogenism, often accompanied by hyperinsulinaemia, which are now coming to light and may threaten their general health over the age of 40 years.

Although the pathogenesis of this heterogeneous syndrome is still incompletely determined, the symptomatic management in adult women has been investigated intensively and is now fairly well determined, documented and relatively successful. The management of PCOS in adolescents, however, leaves many questions unanswered, such as: Are we sufficiently aware of the signs and symptoms of PCOS at this age? How often are we missing or ignoring the diagnosis? Even when the diagnosis of PCOS has been well established, should the condition be managed symptomatically, prophylactically or passively, at such a young age? Are those to whom the adolescent is referred, whether gynaecologist, endocrinologist or, particularly, dermatologist, sufficiently aware of the importance of lifestyle intervention for the symptoms and possible sequelae of the syndrome?

More specifically, the main subject of this debate, is there a place for long-term treatment with insulin sensitizers starting in adolescence?

Diagnosis

As some of the accepted symptoms of PCOS (menstrual irregularities, acne) have been associated with a ‘normal’ adolescence, definitive diagnostic criteria have been blurred. Oligomenorrhoea in adolescents has been regarded widely as a stage in the physiological maturation of the hypothalamic-pituitary-ovarian axis. However, today, following close investigation of oligomenorrhoeic adolescents, it seems that a very large proportion of these have biochemical markers typical of PCOS and eventually develop the further clinical features of the syndrome. For example, 57% of 52 oligomenorrhoeic 15 year olds had LH and testosterone levels above the 95th percentile of girls with regular menstrual cycles (van Hooff et al., 1999). In a longitudinal study, adolescents with oligomenorrhoea but normal plasma LH concentrations ~2 years post-menarche had a better chance of ovulating spontaneously within the following 40 months than those who had high LH concentrations (Venturoli et al., 1992). Clinically obvious hirsutism was found in 32% of adolescents with oligomenorrhoea (Siegberg et al., 1986) and 21% had acne (Apter and Vihko, 1990). If the oligomenorrhoea of adolescence does ‘correct itself’, it is most likely to do so in the first 2
years post-menarche. After this time, oligomenorrhea may be regarded as a possible early clinical sign of PCOS and is worth investigating.

Acne vulgaris is basically caused by increased activity in sebaceous glands which is a manifestation of cutaneous androgenization. It often appears in the teenage years, induced by the burst of pubertal androgenic activity, but, if persistent, particularly severe or of late onset, it is commonly associated with PCOS.

The earliest recognized sign of PCOS is a premature pubarche. Girls who present in mid-childhood with premature growth of pubic hair, elevated dehydroepiandrosterone (DHEA) levels and hyperinsulinaemia are at high risk for developing the full PCOS phenotype, including ovarian hyperandrogenism and chronic anovulation (Rosenfield et al., 2000). Paradoxically, a very large study from our group (Sadrzadeh et al., 2003) found that PCOS patients were significantly older at menarche.

Biochemical features such as increased androgen and insulin secretion, typical of PCOS, are also often a feature of a normal adolescence. Additionally, the biochemical markers for PCOS are inconsistent so that the basis of the diagnosis should be clinical, preferably employing the criteria adopted by the Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group (2004). The typical morphological features of the polycystic ovary can be seen on ultrasound examination, even though this examination will be trans-abdominal rather than trans-vaginal in the majority of adolescents. On the first examination of a group of adolescents with menstrual irregularities, 41% had polycystic ovaries but, when examined 2–7 years later, the number had risen to almost 70%. Enlarged ovaries, polycystic structure, hyperandrogenaemia and high LH concentrations were strongly linked, even in the absence of signs of hyperandrogenism (Venturoli et al., 1995). The main use of laboratory examinations should be to rule out a suspicion of other diagnoses such as androgen-secreting tumours (total testosterone), congenital adrenal hyperplasia (17-hydroxyprogesterone) and standard examinations for Cushing’s syndrome, if suspected.

While insulin resistance and impaired glucose intolerance are not essential features of the diagnosis, their unveiling may be important at an early stage for the prevention of future health hazards, especially in the obese. Overweight [body mass index (BMI) 26–30 kg/m²], and frank obesity (BMI ≥30 kg/m²) are associated features in ~40% of adults with PCOS but are less common and less pronounced in adolescents. Screening can be performed relatively easily, by employing a fasting glucose:insulin ratio of <7 as a useful index of insulin sensitivity in adolescents (Kent and Legro, 2002). Periodic checks with a 2 h oral glucose challenge test and fasting lipid profiles should be contemplated for obese, hyperinsulinaemic patients, but are not really necessary for the non-obese.

Management

The management options in adolescent PCOS are numerous, usually symptomatic and, possibly, preventative. Weight loss for the obese and treatment with some anti-androgens are well established in adults, but data on their possible beneficial effects in adolescents are scarce. Moreover, the use of insulin sensitizers for adolescents with PCOS is still a debatable topic.

As excessive androgens fuel the development of acne, seborrhoea and hirsutism, anti-androgens are today the cornerstone of treatment. Although banned in North America, cyproterone acetate (CPA) is probably the most widely used anti-androgen when combined with ethinyl estradiol (EE). The combination of CPA (2 mg/day) and EE (35 μg/day) given cyclically has proved very effective in the treatment of hirsutism and acne as well as serving as an excellent contraceptive (Golland and Elstein, 1993). A reduction of >50% in the hirsutism score has been demonstrated after 9 months of treatment (Sarih et al., 2001), and acne has been treated successfully in almost 100% of cases using this minimal dose (van Waygen and van den Ende, 1995). The addition of CPA in a dose of 10–100 mg/day on the first 10 days of the combined medication has proved effective for more severe cases. Success rates in reversing or severely diminishing symptoms and maintaining improvement with minimal side effects are high, but patients need to be informed that this treatment is not ‘instant’ and that at least 4–9 months are needed to see an improvement in hirsutism and 3–5 months for acne. Acne will be cleared in 60% of patients in 6 months and, after 12 months, 95% should be free of acne.

What is now becoming clear is that the longer the duration of treatment (at least with CPA/EE) the less chance of relapse within a given time. Following the cessation of long-term treatment with CPA (25–50 mg/day) and EE (0.01–0.02 mg/day) in a reverse sequential regimen, hirsutism was absent for 6 months in all patients (Flagmini et al., 1988). After 12 months without treatment, 28% had worsened and, after 24 months, 44% were still showing an improvement on the original hirsutism score.

As untreated PCOS may be regarded as a progressive syndrome, at least up to the age of 40 years, it is reasonable to assume that treatment with this combination of EE and CPA, which markedly reduces androgen concentrations and their untoward effects, will put the syndrome ‘on hold’, thus improving the prospects of success of fertility treatment when it is discontinued. All other cyclically administered contraceptive pills will of course regularize the cycle.

Other anti-androgen agents, spironolactone, flutamide and finestrilde, are also being employed, mainly in North America, where CPA is unavailable, but they are not well established as therapeutic options in PCOS.

While traditional treatments with oral contraceptives or CPA combined with EE correct menstrual irregularity and hyperandrogenaemia and, consequently, acne and hirsutism, they do not seem to positively affect hyperinsulinaemia and its consequences. However, the predicted deterioration in the metabolic profile due to CPA/EE administration does not seem to have materialized. In a comparative study of the effect on hirsutism of CPA/EE and metformin, in the CPA/EE group, over 1 year, there was no increase in any of the insulin parameters measured and even an insignificant decrease in cholesterol, triglycerides and low-density lipoprotein (LDL)
Weight loss and lifestyle changes

For the adolescent who is overweight or frankly obese, the first line of treatment should be a serious attempt to lose weight. Central obesity exacerbates insulin resistance, and, if a more normal body weight can be maintained by correct diet and exercise instruction, it is equally as successful as metformin in correcting the stigmata of hyperinsulinism. A reduction of 5–10% in body weight can, for example, improve hirsutism in 40–55% within 6 months of weight reduction (Pasquali et al., 1989). This is good strategy in order to achieve short-term goals such as reduction in hirsutism, acne and regular menstruation, and long-term goals such as return of ovulation, consequent conception and, almost certainly, a decreased prevalence of cardiovascular disease, hypertension and diabetes mellitus in later life. Weight loss has the undoubted advantages of being effective and cheap with no negative side effects, and does not involve long-term medication.

Insulin-sensitizing agents

Metformin is an oral biguanide, well established for the treatment of diabetes as it is an anti-hyperglycaemic which inhibits hepatic glucose production and increases the number of insulin receptors. Insulin concentrations are therefore decreased as a secondary phenomenon with a resulting decrease in androgen and LH concentrations and increase in sex hormone-binding globulin. Metformin may also have a direct action on theca cells, reducing androgen production. There are now many reports of clinical improvement with metformin in, mostly obese, adult women with PCOS (Moghetti et al., 2000; Pasquali et al., 2000). A recent meta-analysis (Lord et al., 2003) revealed a very positive effect of metformin regarding restoration of ovulation and also some benefit on parameters of the metabolic syndrome. In doses of 1500–2550 mg/day for adults, gastrointestinal side effects have proved troublesome and common but serious side effects have not been reported in an adolescent population (Legro, 1998).

While adolescents with PCOS will inevitably be disturbed by the obvious and blatant stigmata of acne and hirsutism, and be worried by menstrual irregularity or absence of menstruation, the long-term sequelae of the syndrome are of less immediate concern to them. A debate has now evolved regarding the use of insulin-sensitizing agents, notably metformin, in this age group (Jamieson, 2002). Theoretically, this treatment, as evidenced in adults, will reduce hyperandrogenism and therefore will improve hirsutism, acne and ovulatory dysfunction in the short to medium term. In the long term, it would hypothetically help to prevent the onset of type II diabetes, β cell exhaustion and perhaps cardiovascular disease after the age of 40 years, by eliminating persistent hyperinsulinaemia. Oral contraceptives and anti-androgens alone do not positively affect hyperinsulinaemia and its consequences.

The decision of whether to employ metformin as part of the therapeutic armamentarium in adolescent PCOS is a difficult one based on today’s knowledge. There are no large, randomized, controlled trials in adolescents. A handful of studies, short term and with small numbers, have shown a distinct improvement in obese and non-obese adolescents with PCOS in restoring menstrual regularity and improving androgen concentrations. Glueck et al. (2001) gave metformin for a mean of 10 months to 11 oligo- or amenorrhoeic adolescents with PCOS. Ten responded by resuming regular, ovulatory cycles. Although this sounds encouraging, the results are confounded by a concomitant diet-induced weight reduction. Ibanez et al. (2001) gave metformin for 6 months to 18 non-obese girls with anovulatory, hyperinsulinaemic hyperandrogenism with success, in that 14 started ovulating regularly and no serious side effects were noted. A recent study by the same team (Ibanez et al., 2003) examined the effects of a low-dose combination of flutamide and metformin on 30 teenagers who had hyperinsulinaemic hyperandrogenism. Hirsutism, serum androgens, insulin sensitivity, lipid profile, abdominal fat and ovulation rate all showed marked improvement on this treatment. This synergy between an anti-androgen and an insulin sensitizer seems a common sense combination and should be examined further.

Several questions still remain unanswered. Will metformin be effective in preventing the long-term sequelae of the syndrome? Will it prove as completely safe and effective in the long term as present data suggest? How troublesome will the infrequent gastrointestinal side effects prove to be for the adolescent? What will be the effect of committing a teenager to maybe 20 years of medication? Time and well-controlled, randomized, long-term trials are needed to answer these questions. Hopefully, these will not be too long in coming as they would give credence to the belief that we have a real opportunity to improve not only symptoms in the short term but also, and perhaps more importantly, the long term consequences of hyperinsulinism.

In the meantime, adolescents with PCOS are probably best treated according to the presenting symptom. Regularization of menstruation and amelioration of symptoms of hyperandrogenism can be achieved relatively painlessly, while insulin sensitizers should probably be reserved, at this stage, for those demonstrating hyperinsulinaemia who, if overweight, have failed to lose weight.

It should be remembered that a correct diet and lifestyle have already proven to be of value in the prevention of diabetes, hypertension and cardiovascular disease in adults. Notably, the Diabetes Prevention Programme Research Group (Knowler et al., 2002) found that lifestyle intervention was significantly more effective than metformin in reducing the incidence of diabetes. If this education could be impressed upon adolescent girls with PCOS and continued into the reproductive years, there is much to be gained.

References

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