Metformin treatment is effective in obese teenage girls with PCOS

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BACKGROUND: Polycystic ovary syndrome (PCOS) is the most frequent cause of menstrual disorders in teenage girls. Little information is available about the effects of metformin in adolescent girls with PCOS and its dose and its efficacy in regulating menstrual cyclicity and hyperandrogenic symptoms. We evaluated the effects of metformin treatment on ovulatory function, hirsutism, acne, hormonal patterns and body weight in adolescent girls with PCOS.

METHODS: Eighteen girls, ranging in age from 15 to 18 years, were enrolled in the study. Clinical diagnosis of PCOS was based on the consensus criteria for PCOS accepted in May 2003 at Rotterdam. All subjects received 1700 mg/day metformin as tablets continuously for 6 months. They were then followed up for 6 months.

RESULTS: Two patients complained of side effects for >2 weeks and interrupted treatment; they were not evaluated. All the others showed an improvement in menstrual cyclicity. Menstrual periods were ovulatory, with progesterone levels up to 6 ng/ml in luteal phase and a significant reduction in testosterone, androstenedione and free testosterone. BMI was restored within normal limits in all girls between 21 and 24 kg/m². Six months after the end of metformin treatment, menstrual cycles continued to be regular and ovulatory with normal BMI. Side effects were slight.

CONCLUSIONS: The present results confirm the positive effects of metformin on menstrual periods and show that the drug can be administered to young women to improve ovulation and hyperandrogenic symptoms such as hirsutism, acne and weight gain.

Key words: adolescents/androgens/hirsutism/metformin/obese/PCOS

Introduction

Polycystic ovary syndrome (PCOS) is the most frequent cause of menstrual disorders in teenage girls. After menarche, young women may show many initially minor or moderate symptoms that aggravate with time. These symptoms include menstrual irregularity, hirsutism, acne and obesity. Hormonal profile and ultrasound examination indicate PCOS. Insulin-resistance tests [homeostasis model assessment (HOMA) or oral glucose tolerance test (OGTT)] are now performed as well. Insulin resistance and consequent elevated plasma concentrations of insulin are reported to be associated with high androgen concentrations and related symptoms such as anovulation, oligomenorrhoea, hirsutism, acne and seborrhoea in adolescent girls with PCOS (Adams et al., 1986; Gilling-Smith and Franks, 1993).

More than 50% of girls with this syndrome are obese, and many develop type 2 diabetes in later life (Chang et al., 1983; Jalal et al., 1987). The clinical disorders and infertility have been ascribed to high levels of insulin and LH, high LH/FSH ratio and increased ovarian androgen production (Wajchenberg et al., 1986; Waldestreicher et al., 1988; De Leo et al., 2003). Hyperinsulinaemic insulin resistance and increased ovarian cytochrome P-450 and 17,20-lyase enzymatic activity, two features of PCOS, are pathogenically linked (La Marca et al., 2000). Insulin has been shown to stimulate the proliferation of thecal cells, increase LH-stimulated androgen secretion, increase P450c17mRNA levels, up-regulate LH receptors and up-regulate ovarian insulin-like growth factor-I (IGF-I) receptors (De Leo et al., 2003). In PCOS patients, high local androgen concentrations are responsible for anovulation by a direct effect on the ovary (Ehrmann et al., 1995).

In the last 10 years, insulin-lowering drugs have become widely used in the treatment of PCOS, particularly for the induction of ovulation. Many studies have demonstrated the efficacy of metformin, a biguanide normally used to treat non-insulin-dependent diabetes, in inducing ovulation in PCOS patients with insulin resistance (Nestler et al., 1998; De Leo et al., 1999). Metformin is the most thoroughly investigated insulin-lowering agent used to treat PCOS; it enhances insulin sensitivity in the liver, where it inhibits hepatic glucose production, and in muscle, where it improves glucose uptake and use (De Leo et al., 2003).

One of the main reasons PCOS patients seek medical advice is menstrual irregularity. Oligomenorrhoea and amenorrhoea are usually linked to the absence of ovulation. Available
studies indicate that 6 months of metformin therapy induces an improvement in menstrual regularity in at least 50% of patients (De Leo et al., 2003). Although confirmation is needed, it seems that responders have high insulin levels, low androgen levels and less severe menstrual abnormalities before therapy. This suggests that the best candidates for metformin therapy have oligomenorrhea rather than amenorrhea and are overweight rather than obese.

The relationship between PCOS, oligomenorrhea, hyperandrogenism and hyperinsulinism has been well documented in adults, but less in young women (Rosenfield et al., 2000; Van Hooff et al., 2000, 2004). Hyperinsulinaemia has been documented in a small group of oligomenorrheic adolescents with obesity (Apter et al., 1995) and in a group of lean anovulatory or oligo-ovulatory hyperandrogenic adolescents (Ibanez et al., 2001). Regarding medical treatment, little data are yet available about the effects of metformin in young women with PCOS, especially about its dose and ability to regulate menstrual cyclicity and hyperandrogenic symptoms.

In this study, we evaluated the effect of metformin treatment on ovulatory function, hirsutism, acne, hormone patterns and body weight in 18 girls with PCOS.

Materials and methods

Subjects

Eighteen obese girls with PCOS, ranging in age from 15 to 18 years, were enrolled in the study. The study was approved by the ethical committee of the University Medical School, and informed consent was obtained from each patient. The clinical diagnosis of PCOS was defined according to the consensus criteria for PCOS with the presence of clinical and biochemical signs of hyperandrogenism, chronic anovulation and/or oligomenorrhea and polycystic ovaries (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004). Hirsutism was evaluated by the modified Ferriman–Gallwey method (Hatch et al., 1981), and the mean score was 12 ± 2.5 (mean ± SD). Menstrual bleeding occurred every 45–60 days. All women were obese, with a BMI between 25.5 and 27 kg/m².

Insulin resistance was diagnosed by OGTT. The criteria for hyperinsulinemia were insulin basal levels >15 pmol/l and response >80 pmol/l at 90 min. All women had fasting insulin concentrations >15 pmol/l and cumulative insulin concentrations >48 000 pmol/min [area under the curve (AUC) insulin during a 2-h 75 g oral glucose test].

Basal hormone concentrations [LH, FSH, androstenedione, testosterone, free testosterone, estradiol (E₂), 17-hydroxyprogesterone (17-OHP), progesterone and sex hormone-binding globulin (SHBG)] were evaluated every 4 days from days 7 to 45 of the cycle, the month before metformin therapy was started and in the last month of therapy. Before treatment, basal hormone levels indicated anovulatory cycles, and androgens were at the upper limits of the normal range. All women were normoprolactinaemic and had normal thyroid function. None of the patients had virilization or congenital adrenal hyperplasia (on the basis of normal levels of 17-OHP).

A baseline ultrasound scan of uterus and ovaries was performed. The ultrasonographic diagnosis of PCOS was based on the presence of ≥10 follicles (2–10 mm in diameter) in one or both ovaries.

Study protocol

The patients entered the study on days 6–8 of induced menstrual bleeding. All received 1700 mg/day metformin (Metforal; Guidotti, Pisa, Italy) as tablets uninterruptedly for 6 months. Hirsutism was evaluated by a modified form of the Ferriman–Gallwey method that has been used in our clinic for many years. A score was assigned to patients before and after 6 months of metformin therapy. A score >8 is indicative of hirsutism. Patients were followed up for 6 months with plasma progesterone determinations on day 22 of the menstrual cycle.

Hormone assay

Plasma LH, FSH, E₂, testosterone, androstenedione, free testosterone, 17-OHP, progesterone and SHBG were measured by double-antibody radioimmunoassay using Radim Kits (Rome, Italy) for LH and FSH, Sorin Kits (Saluggia, Italy) for androstenedione, progesterone and testosterone, DPC Kits (Los Angeles, CA, USA) for SHBG, free testosterone and 17-OHP and Biodata Kits (Rome, Italy) for E₂. Free androgen index (FAI) was calculated as testosterone/SHBG × 100. Samples were assayed in duplicate at two dilutions. All samples from each subject were assayed together. Quality-control pools at low, medium and high hormone concentrations were included in each assay. The assay detection limits were 0.2 IU/l for LH, 0.18 IU/l for FSH, 18 pmol/l for E₂, 0.16 mmol/l for progesterone, 0.52 pmol/l for free testosterone, 277 pmol/l for testosterone, 104 pmol/l for androstenedione, 0.21 nmol/l for 17-OHP and 0.2 mmol/l for SHBG. The intra- and interassay variations were 7.8 and 8.2% for LH, 6.2 and 6.5% for FSH, 4.2 and 4.9% for E₂, 8.5 and 10.8% for progesterone, 3.4 and 4.6% for testosterone, 3.2 and 3.4% for free testosterone, 5.6 and 6.4% for androstenedione, 4 and 4.8% for 17-OHP and 6.9 and 13% for SHBG. Analytical methods were highly specific for each hormone with an extremely low cross-reactivity (<0.05%) to other naturally occurring hormones or therapeutic drugs that may be present in samples.

Statistical analysis

To assess responses to metformin therapy, we compared basal hormone concentrations, maximum increments (maximum rise above baseline) and AUC (cumulative rise above baseline) using the non-parametric Wilcoxon test. Differences were considered significant for P < 0.05.

Results

Clinical effects

The drug was well tolerated by all patients. Two patients who complained of side effects for >2 weeks and interrupted treatment were not evaluated. The others showed an improvement in menstrual cyclicity. After the first month of treatment, menstrual bleeding returned to once a month within 30 days of the start of the second month of therapy. Menstrual periods were ovulatory, with progesterone levels up to 6 ng/ml in luteal phase and a significant reduction in testosterone, androstenedione and free testosterone. The Ferriman–Gallwey score for hirsutism decreased significantly from 12 ± 2.5 to 7 ± 1.2 (mean ± SE) after 6 months of metformin treatment (Figure 1). In many girls, acne and/or seborrhoea were greatly alleviated after 6 months of treatment; only in 4 patients did mild acne persist, especially before menstrual bleeding. BMI was restored within normal limits in all girls between 21 and 24 kg/m². Six months after the end of metformin treatment, menstrual cycles continued to be regular and ovulatory with normal BMI (Table I).

Endocrine effects

Table II summarizes hormone concentrations during follicular phase before metformin therapy and at the sixth month of
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Treatment. Significant reduction \( (P < 0.01) \) in basal levels of LH, androstenedione, testosterone, free testosterone and LH/FSH ratio was observed. SHBG concentrations showed a significant increase in all women.

Figure 2 shows the patterns of plasma concentrations (medians and ranges) of LH and FSH measured every 4 days for 5 weeks before therapy and during the sixth month of treatment. Before metformin treatment, basal LH levels were high and without a peak, having a median value of 12.1 mIU/ml (range 16.2–7.5) for all cycles. During the sixth month of therapy, LH showed a reduction in basal levels and an ovulatory peak at days 13–15 in all women. FSH also showed a small increment in follicular phase during treatment with a small peak on the same days as LH. Before metformin treatment, the LH/FSH ratio was 2.23 (range 5.2–0.9). During therapy, LH showed a reduction in basal levels, and the LH/FSH ratio decreased.

Before metformin therapy, \( E_2 \) and progesterone showed constant patterns. During metformin therapy, \( E_2 \) and progesterone patterns reflected ovulatory cycles, with median luteal-phase progesterone levels of 6100±1400 pg/ml (Figure 3).

Plasma androgen levels were high before treatment. During metformin treatment, testosterone, free testosterone and androstenedione showed significant reductions in all women. The mean reduction was 22% for testosterone, 30% for free testosterone and 35% for androstenedione.

Fasting insulin levels and AUC insulin were low during metformin treatment with basal plasma levels <5 mIU/l.

Progesterone levels during follow-up (day 22 of the cycle) showed maintenance of ovulation with progesterone concentrations >5000 pg/ml in all women.

Discussion
The results of this study confirm the beneficial effects of metformin on ovulation in young women with PCOS and provide new information about the drug’s hormonal and clinical effects in this disorder.
Insulin resistance has long been recognized as a feature of PCOS (Chang et al., 1983; De Leo et al., 2003). Insulin resistance and elevated plasma levels of insulin are associated with high androgen concentrations in PCOS patients. There is evidence that insulin stimulates ovarian androgens *in vitro* (Poretsky et al., 1999). Insulin inhibits liver secretion of SHBG, increasing the availability of androgens (Preziosi et al., 1993). Another mechanism of action could be the inhibition of liver synthesis of IGF-1 in the ovary, directly influencing ovarian steroidogenesis through a specific receptor (Poretsky et al., 1999).

After menarche, adolescent women show a transient state of anovulation. This period is considered physiological within the ontogeny of fertility (Metcalf et al., 1983). However, in certain young women, regular menstrual cycles fail to occur within 2–3 years of menarche and the anovulatory condition persists. The prevalence of PCOS in women aged 18–25 years is 8% (Michelmore et al., 1999). However, studies suggest that PCOS begins in early puberty and evolves through adolescence into adulthood (Van Hooff et al., 2004).

The most common treatment in these patients worldwide is the contraceptive pill, especially those with anti-androgenic progestins (Lemay and Poulin, 2002; Wiegratz and Kuhl, 2002). The clinical outcome is good during therapy, but after termination, the symptoms recur and the young women undergo an increase in body weight.

Many articles have shown that metformin induces a significant improvement in insulin levels and menstrual cycles in oligo-menorrhoeic teenagers with PCOS (Ibanez et al., 2001). Six months of treatment was followed by significant reductions in serum lipids and hirsutism (Ibanez et al., 2000), indicating that insulin lowering has a normalizing effect on multiple aberrations in the endocrine metabolic profile of adolescents with ovarian hyperandrogenism. Metformin treatment of 15 obese adolescents with impaired glucose tolerance and PCOS for 6 months was found to be beneficial for glucose tolerance, insulin sensitivity, insulinemia and elevated androgen levels (Arslanian et al., 2002).

Our present study confirms the positive effects of metformin on menstrual periods and shows that the drug can be administered in young women to improve hyperandrogenic symptoms such as hirsutism and acne, as well as ovulation. The beneficial effect of metformin on acne and hirsutism in adolescents could therefore be due to the restoration of ovulation and the normalization of estrogens.

It is recognized that high insulin levels exert anabolic effects and modify fat distribution: our results showed a significant reduction in BMI to <25 kg/m². This weight reduction may be due to the normalization of plasma insulin resulting in reduced appetite. Our young women were therefore prescribed a low-carbohydrate high-protein diet to reduce BMI, restore ovulation and reduce acne and hirsutism. It has been shown that weight loss, accompanied by an increase in insulin sensitivity, can improve metabolic and hormonal abnormalities characteristic of the PCOS (Pasquili et al., 1989; Anderson et al., 1995).

Finally, early pharmacological intervention with metformin could possibly prevent manifestation of the complete spectrum of PCOS in young overweight girls. The persistence of regular ovulatory menstrual cycles in the 6 months after the end of treatment demonstrates that metformin treatment provides lasting benefits. All girls maintained a BMI <25 kg/m², and this can play a role in normal ovulation menstrual cycles. These patients are under follow-up for weight changes and to see how long normal menstrual cycles last.

This study shows the efficacy of metformin in adolescent women with anovulation and moderate obesity, confirming previous trials and contributing important information about the preventive effect of the drug on full manifestation of PCOS in young women. In these patients, metformin could well be a more appropriate treatment than estroprogestin pills.

### References


![Figure 3. Plasma estradiol (E₂) and progesterone levels in polycystic ovary syndrome (PCOS) patients before metformin therapy and during the sixth month of treatment.](image-url)


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