Article

Metformin monotherapy in lean women with polycystic ovary syndrome

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Abstract

This study was carried out to compare ovulation and pregnancy rates in response to metformin therapy in lean and obese women with polycystic ovary syndrome (PCOS). A total of 34 (17 lean and 17 obese) women with PCOS were treated with 500 mg metformin 3 times daily for 12 weeks. In the lean and obese groups, the mean body mass index was 24 and 36, and the mean fasting insulin concentrations were 12 and 21 mIU/l respectively. There was no difference between the two groups as regarding age, DHEA-S, androstenedione, 17-OH progesterone and LH concentrations. In the lean and obese groups 15/17 women (88%) and 5/17 women (29%) ovulated while 11/17 women (65%) and 3/17 women (18%) conceived respectively. Comparison between the groups was found to be statistically significant. Metformin monotherapy is very effective in improving ovulation and pregnancy rates in lean women with PCOS as compared with obese women.

Keywords: *body mass index, lean women, metformin, obese women, PCOS*

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder that affects women of reproductive age, and is characterized by oligomenorrhoea, hyperandrogenism, anovulation, and more often than not obesity. Although the exact aetiology of PCOS is unknown, current research supports insulin resistance and hyperinsulinaemia as playing a pivotal role in the pathogenesis of this disease (Burghen *et al*., 1980; Nestler and Strauss, 1991).

Insulin is thought to possess true gonadotrophic activity, directly increasing androgen production by the theca cells of the ovary (Gambineri, 2002). Insulin has also been shown to augment the activity of p450-c 17α, the rate-limiting enzyme in the production of testosterone from ovarian thecal cells (Iuorno and Nestler, 2001). It has also been shown to increase LH-mediated androgen synthesis from the ovary. Effects of insulin on the hypothalamic–pituitary axis in increasing LH concentrations and on ovary, causing premature follicular atresia, have been suggested, but remain to be proven (Franks, 1995).

At least 50–60% of PCOS patients are obese or overweight, and hyperinsulinaemia is the usual accompaniment in these women. The pathogenesis in the remaining 25–30% who are lean has been suggested to be due to a defect in the hypothalamo–pituitary axis, resulting in increased LH production, and insulin appears to play no role in the disease process in this subset of PCOS patients (Grulet *et al*., 1993). This theory has been substantiated by the finding of near-normal insulin values in these women (Date *et al*., 1992). However, subsequent research has demonstrated that these women, although they have lower insulin concentrations when compared with obese PCOS patients, are definitely hyperinsulinaemic and insulin resistant when compared with their healthy counterparts (Dunaif *et al*., 1992). Insulin sensitizers are being tested extensively in the treatment of PCOS women. Metformin (MTF) is the most widely employed insulin-sensitizing agent used in ovulation induction regimes, and also to improve outcome in 'coasted' patients with PCOS undergoing IVF (Stadtmauer *et al*., 2002). It improves insulin sensitivity in the liver, reducing gluconeogenesis, and improves uptake and utilization of glucose in the peripheral

tissue, thereby reducing insulin concentrations. Thirteen studies to date have evaluated the efficacy of MTF monotherapy on restoration of regular menstrual cycles. However, almost all of these studies were performed in obese PCOS women with an average body mass index (BMI) of 31.3 (Costello and Eden, 2003). Only one study included lean adolescent PCOS patients with BMI of <25; menstrual cyclicity was restored in all 18 girls after 6 months of MTF treatment (Ibanez *et al*., 2001).

During initial efforts to normalize insulin concentrations using MTF alone in PCOS women, some lean women became pregnant before initiating clomiphene therapy. With this experience, a prospective study was conducted to determine the differences in response as regards restoration of normal cycles and pregnancy rates between lean and obese PCOS women. A meta-analysis (Lord *et al*., 2003) of 13 randomized controlled trials (RCT) evaluating the efficacy of MTF monotherapy, comprising 428 participants, showed a 4-fold increase in ovulation rate, with the number needed to treat being 4.4. Based on these numbers, it was calculated that a sample size of 34 women (17 in each group) would have sufficient power to address this question.

Materials and methods

Thirty-four consecutive new PCOS patients attending outpatient clinics at the Al-Mafraq Hospital, Abu Dhabi, United Arab Emirates were the study subjects. A diagnosis of PCOS was made if either of the following two criteria was met: oligomenorrhoea (fewer than six cycles during the last year) or amenorrhoea, clinical features of androgen excess such as hirsutism with Ferriman–Gallwey score >7, acne and alopecia or biochemical evidence of androgen excess such as elevated free testosterone, androstenedione and dehydroepiandrosterone sulphate (DHEAS). Congenital adrenal hyperplasia, Cushing's syndrome, thyroid disorders and hyperprolactinaemia were excluded by appropriate tests. The presence of multiple subcapsular follicles on days 1–3 of a spontaneous cycle was considered suggestive of PCOS. All these women had infertility of at least 2 years duration. None of them had been on any medication during the past 3 months preceding the study. Male factor and tubo–uterine factors were excluded by semen analysis and hysterosalpingogram or laparoscopy. Diabetes with a fasting blood sugar (FBS) of <120 mg/dl was excluded. Seventeen women had a BMI <25 and the other 17 belonged to the obese group with BMI >30.

All women were recruited during the follicular phase of the cycle. They presented to the hospital after 12 h of overnight fasting. Their height and weight were recorded and blood samples were drawn for FSH, LH, insulin, fasting glucose and androgen profile (testosterone, androstenedione, DHEA-S and 17-hydroxyprogesterone). The protocol was to administer MTF alone at a dose of 500 mg, three times daily, to all PCOS women for a period of 3 months. At the end of 10–12 weeks of MTF treatment or immediately after the missed period (whichever was first), blood samples were taken and hormonal profile and fasting glucose were repeated. If conception did not occur within 3 months, clomiphene was added to MTF. After the commencement of MTF, all these women were tested by ultrasound for evidence of ovulation. Follicular rupture, presence of free fluid in the pouch of Douglas and endometrial thickness of >7.5 were considered as evidence of ovulation.

Laboratory measurements

Fasting blood samples were collected from the subjects. The samples were centrifuged at 200 *g* for 10 min and sera were separated and stored at –20°C until measurement. FSH, LH, total testosterone and prolactin concentrations were quantitatively measured by the Abbott ARCHITECT Immuno-analyser (Abbott Laboratories; from GmbH Diagnostics, Wiesbaden-Delkenheim, Germany). Hormonal measurements were also carried out in all patients in the lean and obese groups after MTF therapy. The sensitivity of the ARCHITECT System was calculated to be better than 0.07 mIU/ml for LH and 0.05 mIU/ml for FSH. The functional sensitivity of the ARCHITECT testosterone assay was calculated to be 0.14 ng/ml (95% confidence interval of 0.11–0.17 ng/ml). Concentrations of DHEA-S and insulin were measured by electrochemiluminescence immunoassay on Roche Elecsys 2010 (Roche Diagnostics; GmbH, Mannheim, Germany). The lower detection limits of DHEA–S and insulin immunoassay were 0.0003 µmol/l and 0.20 µIU/ml respectively. 17-Hydroxy-progesterone and androstenedione were measured by RIA using Coat-a-Count kits supplied by Diagnostic Products Corporation (Los Angeles, CA, USA). Analytical sensitivities of radioimmunoassay for the detection of androstenedione and 17-hydroxyprogesterone were 0.04 and 0.07 ng/ml respectively. The normal values for 17-OH progesterone measured by RIA with the Coat-a-Count kits supplied by Diagnostic Products Corporation ranged between 0.27 and 4.9 ng/ml.

Glucose concentrations were measured by the glucose oxidase method (Boehringer Ingleheim GmbH, Ingleheim, Germany).

Intra- and interassay coefficients of variation (CV) for hormonal measurements were as follows: androstenedione (3.2 and 5.6%); DHEA-S (2.4 and 4.7%); testosterone (4.5 and 8%); 17-hydroxy progesterone (7.1 and 7.3%); LH (3 and 3.6%); FSH (3.3 and 4.2%); insulin (1.9 and 2.8%).

Data analysis

Statistical analysis of the data was performed using Microsoft Excel. Inter-group differences were compared by Student's *t*-test and $P < 0.05$ was considered as statistically significant.

Results

The baseline characters of 17 lean women and 17 obese women are shown in **Table 1**. The mean age in both groups was 25.9 and 24.3 respectively. The mean BMI of the obese group was 36, which was significantly higher ($P < 0.001$) as compared with the lean group (BMI = 24). None had an FBS above 120 mg%. Three women in the obese group and none in the lean group had impaired glucose tolerance on a 75 g oral GTT. The common side effects noted with MTF were nausea and dizziness, but not severe enough to stop treatment. **Table 2** demonstrates the differences in response between lean and obese PCOS women to MTF therapy. Resumption of menstrual cyclicity, ovulation and pregnancy rates were significantly higher in the lean PCOS group as compared with the obese group. In one out of 11 women in the lean group, and in all three in the obese group who conceived on MTF, pregnancy ended in a first trimester miscarriage.

Results of hormonal measurements pre- and post-MTF therapy are shown in **Table 3**. Significant reductions were noted in serum