

Spontaneous singleton and twin pregnancy in two patients with polycystic ovary syndrome and type 2 diabetes following treatment with metformin combined with rosiglitazone

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Polycystic ovary syndrome (PCOS) is a complex disorder affecting about 5% to 15% of women in the reproductive age group and accounting for 75% of cases of anovulatory infertility.¹ Women with PCOS have a significant degree of insulin resistance and compensatory hyperinsulinemia² and a high prevalence of type 2 diabetes has been documented in these women.³ Hyperinsulinaemia in PCOS has been observed to lead to hyperandrogenism, which creates a hostile hormonal milieu for ovulatory cycles and for conception to occur.⁴ Thus, targeting insulin resistance and hyperinsulinemia can favourably alter the hormonal environment allowing ovulation and conception. There is some evidence to suggest that the thiazolidinediones may alter the intra-ovarian hormonal milieu of women with PCOS. Aziz et al⁵ reported that troglitazone improves defects in insulin action, insulin secretion and ovarian steroidogenesis in women with PCOS. Rosiglitazone has been reported to improve insulin sensitivity, and improve the menstrual pattern,⁶ decrease ovarian androgen production and improve ovulatory cycles in women with PCOS.⁷ The use of rosiglitazone in a young woman with PCOS has ameliorated insulin resistance, lowered androgen levels and helped spontaneous conception.⁸ Recently Vaughan and Bell reported a 46-year-old woman with PCOS who conceived spontaneously following the use of rosiglitazone to treat supervening diabetes.⁹ We report two women with PCOS and longstanding primary infertility, where the addition of rosiglitazone to metformin to treat type 2 diabetes resulted in spontaneous pregnancy with a viable singleton baby in the first woman and twin babies in the second case.

Case 1

A 30-year-old Saudi female, diagnosed as suffering from PCOS since her teenage years, had been followed and managed for years in another hospital. The diagnosis was based on a clinical profile of obesity, mild hirsutism and irregular cycles as well as polycystic ovaries on pelvic ultrasound. She had been trying for pregnancy since age 20, had received several courses of clomiphene citrate, and eventually had a total of three trials of in vitro fertilization (IVF), but with no success. At age 25 she developed type 2 diabetes, following presentation with frank osmotic symptoms, hyperglycaemic malaise and a random blood glucose of 15 mmol/L. There was no ketonuria or profound weight loss. She was treated initially with metformin at a dose of 500 mg twice daily, later increased to 2 g daily. For the last 4 years she had been followed in our diabetic clinic, and continued to have significant obesity

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(height 160 cm, weight 87 kg, BMI 34 kg/m²), and erratic menstrual cycle and mild hirsutism. Despite encouragement for physical exercise and dieting, her metabolic control failed to improve with HbA1c remaining elevated >8.5% (normal reference non-diabetic range, 4.5% to 6%). In early 2003, rosiglitazone maleate at a dose of 4 mg was added to achieve better glycaemic control. The patient noticed some changes in the pattern of her menstruation, but overall they remained erratic, occurring every 2 to 3 months. She put on more weight, an average of 3-5 kg since the start of rosiglitazone, but her HbA1c dropped to 6.6% in June 2003. In July 2003, she had persistent symptoms of nausea and vomiting occurring early in the morning, and by then she was 4-months amenorrhoeic. Pregnancy was suspected and a subsequent pregnancy test was found to be positive. Ultrasonography confirmed a viable 17-week-old fetus. Metformin and rosiglitazone were both stopped and twice-daily pre-mixture insulin was started to control glycaemia. Pregnancy progressed well with no complications and the baby was delivered at 37 weeks by elective caesarean delivery due to fetal macrosomia. A healthy male baby weighing 4 kgs was born who had no neonatal complications and achieved normal developmental milestones on regular follow up.

Case 2

A 41-year-old British woman of Caucasian descent had PCOS with a longstanding history of primary infertility for which she underwent extensive investigations at a fertility clinic from 1984 to 1992. She received several treatment modalities for ovulation induction, including two long courses of clomiphene citrate, and laparoscopic ovarian electrocautery with no successful outcome. She was finally offered the option of IVF, which she was not too keen to pursue. In 1997, by then age 35 years, she was diagnosed with type 2 diabetes, following symptoms of hyperglycaemia and a random blood glucose of 14 mmol/L and HbA1c of 8.8% (normal 4.5-5.6%). On initial assessment she was noted to be morbidly obese with a body mass index (BMI) of 46 kg/m², a normal blood pressure and significant hirsutism with a Ferrimen-Galleway score of 13. She had normal renal, hepatic, calcium and lipid profiles. She was started on metformin 500 mg three times daily, given dietary advice and encouraged to adopt a more active life style with a view toward weight loss. On follow up in the subsequent year she managed to lose about 6 kg of body weight, and her menstrual cycles improved to

some extent but remained erratic. Her diabetes control, however, remained poor with HbA1c running >10%. At this stage acarbose 50mg three times daily was introduced to achieve a better diabetic control. By October 2000, her diabetes control was still unsatisfactory, so rosiglitazone maleate 4 mg was added and later increased to 8 mg by early 2001. During this time she was noted to have hypertension, so perindopril at a dose of 2.5 mg was started and later felodipine 5 mg was added. With the above regimen her glycaemic control improved with the HbA1c dropping to 6% by the end of 2001. Also she realised that her menstruation showed some improvement, despite that she had gained an average of 5 kg in weight over the preceding 12 months.

In August 2002, now older than 40 years of age, she visited her general practitioner with symptoms of breast fullness and tenderness. By then, she was amenorrhoeic for seven months but was not particularly bothered about it, as this could be quite normal for her. Her primary care physician suspected that she might be pregnant but the patient denied any symptoms of pregnancy. A pregnancy test turned out to be positive, so she was referred to our joint antenatal-diabetic clinic where ultrasonographic examination confirmed pregnancy with twins with an estimated gestational age of 27 weeks. Both metformin and rosiglitazone were discontinued, and the ACE inhibitor was substituted for labetalol 200 mcg/d. The pregnancy progressed well in subsequent weeks, with diet only to control her diabetes, and her blood sugar series were running within the target range for our clinic. By 32 weeks she had premature rupture of the membranes for which she was admitted to hospital and managed conservatively with beclomethasone. Following this her glycaemic control deteriorated significantly necessitating insulin therapy. Two weeks later she delivered two healthy male babies by elective caesarean delivery. The babies spent a few weeks in a special care baby unit, were breastfed, and later discharged in good health. On follow up both babies were well and healthy and achieving normal developmental milestones.

Discussion

Insulin resistance and compensatory hyperinsulinemia are established as the central pathophysiologic mechanisms in women with PCOS. There is a mounting body of evidence to suggest that tackling insulin resistance either via physical exercise, weight loss or by use of insulin sensitizers can improve the menstrual pattern and aid conception in these wom-

en.^{10,11} One might argue that the successful conception in our cases occurred by sheer chance and has nothing to do with the medication, as spontaneous conception can occur in women with PCOS and longstanding infertility. However, we argue that the use of the two drugs (to treat diabetes) has resulted in ovulation induction and spontaneous conception. Metformin acts primarily by decreasing hepatic glucose output and enhancing peripheral glucose uptake and has in addition an insulin sensitizing effect. It has been shown to be helpful in restoring a normal menstrual cycle,¹² improving ovulation rate,¹³ and enhancing the conception rate when used alone¹⁴ or in combination with clomiphene citrate in women with PCOS.¹⁵ Moghetti et al,¹⁶ in a randomised placebo controlled trial, showed that long-term metformin treatment in obese PCOS women reduces hyperinsulinemia and hyperandrogenaemia independently of changes in body weight and improved menstrual abnormality.

The thiazolidinediones directly target insulin resistance by increasing insulin sensitivity and glucose uptake in the muscle and to some extent in the liver via their action on the peroxisome proliferator-activator receptor gamma.¹⁷ This direct effect on insulin resistance could influence the intra-ovarian hormonal milieu in PCOS similar to that achieved with metformin. Troglitazone, the first of the thiazolidinedione group was shown in a few studies to increase the number of ovulatory cycles when used alone or in combination with clomiphene citrate.^{5,18} The newer members, rosiglitazone and pioglitazone can potentially produce the same beneficial effects in PCOS but there are limited data to support their use in ovulation induction. Shobokshi and Shaarawy¹⁹ reported an improvement of insulin sensitivity via reducing IGF-1 bioavailability following combined use of rosiglitazone with clomiphene citrate, a finding confirmed by Ghazeeri et al.²⁰ Recently Yilmaz et al demonstrated that both metformin and rosiglitazone improve androgen profile, menstrual cyclicity and the hirsutism score with somewhat superior effect of rosiglitazone over metformin.²¹ The same group later reported that both agents also improve insulin sensitivity and serum androgen level in lean and obese women with PCOS.²² In a study involving non-obese women with PCOS, the frequency of ovulation following treatment with rosiglitazone improved significantly, though the combination of rosiglitazone with metformin was not superior over

metformin alone.²³ However the combination of pioglitazone and metformin was superior to metformin alone in ameliorating insulin resistance, hyperandrogenism and improving menstruation in women with PCOS.²⁴ On the other hand, metformin alone has been shown to be less effective in obese women with PCOS.¹³ Our two patients had been on metformin for some time, with some beneficial effects upon their menstrual cycles. We hypothesise that the addition of rosiglitazone to metformin to improve diabetes control resulted in unexpected ovulation and conception. It is plausible that the two drugs in combination have corrected the metabolic defect(s) that were responsible for their longstanding infertility and paved the way for successful conception. Our report compliments the observation of Vaughan and Bell where the addition of rosiglitazone to metformin resulted in spontaneous conception in a perimenopausal woman with PCOS.⁹ Arlt et al²⁵ demonstrated that the thiazolidinedione class of drugs have a direct inhibitory effect on the steroidogenic enzymes P450c17 and 3 β HSD. Metformin has been recently reported to possess similar property.²⁶

Those cases highlight that women with PCOS and type 2 diabetes may conceive spontaneously following the use of this combination, and this fact should be pointed out to them and they should be counselled for such an outcome. Furthermore the safety issue of the use of the thiazolidinediones, including potential teratogenicity, should not be forgotten, despite the fact that there is some anecdotal evidence of its safety in pregnancy.^{9,27,28} Therefore, these women should be warned about such a possibility and where appropriate contraceptive measures should be advised.

In conclusion, these case series highlight the need for patient awareness of the possible effect of the thiazolidinediones, either alone or in combination with metformin on fertility in women with PCOS. Taking into account their direct insulin-sensitising effect, these agents may be capable in solo in initiating ovulation and aid conception in women with PCOS. This may prove more attractive as a new therapeutic armamentarium to treat infertility in these women. However, proof awaits the completion of randomised controlled trials. In the meantime, women should be counselled and where appropriate contraceptive measures offered.

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