Women with polycystic ovary syndrome (PCOS) often undergo protracted treatment with metformin and are disinclined to stop: indications for a change in licensing arrangements?

Sabine Muth, Jane Norman, Naveed Sattar and Richard Fleming

University Department of Obstetrics and Gynaecology, Royal Infirmary, Glasgow, G31 2ER, UK

1To whom correspondence should be addressed: University Department of Obstetrics and Gynaecology, Level 3 Q.E. Building, Royal Infirmary, Glasgow, G31 2ER, UK. E-mail: gqta13@udcf.gla.ac.uk

Women with polycystic ovary syndrome (PCOS) are increasingly being treated with metformin as an insulin sensitizing agent to reduce symptoms of hyperandrogenism and promote fertility. Indications such as hirsutism and cycle regulation require long term treatment. The drug is also being used through pregnancy. It is not licensed for any indication specific to PCOS, which means that much of this prescribing is taking place in an environment short of reliable information concerning safety. We describe the failure of recruitment to a study undertaken to explore the effects of metformin treatment discontinuation in women with PCOS, to provide both clinical and aetiological information. The study failed because the patients did not wish to stop treatment, and it illustrates the problems facing doctors working in this area. To achieve a safer prescribing environment, we recommend that action be taken by the manufacturer of metformin to work with regulatory agencies on a European base to extend prescribing indications for metformin to women with PCOS.

Key words: license/metformin/polycystic ovary syndrome

Background: PCOS and the use of metformin
It is now understood that the principle underlying feature of the common endocrinopathy, polycystic ovary syndrome (PCOS), is relative insulin resistance and compensatory hyperinsulinaemia (Dunaif, 1997). Women with PCOS are at risk of increased diabetes in later life (Solomon et al., 2001), and those who conceive may have an increased incidence of gestational diabetes. The absolute aetiology and evolution of the disorder are not clearly understood, but reduction of insulin resistance and related hyperinsulinaemia has been shown to improve many of the symptoms (Ehrman et al., 1997). In clinical trials, treatment of women with PCOS with insulin sensitizing agents such as metformin leads to reduction in circulating insulin concentrations, reduction in circulating androgens, improvements in ovarian function, and also improvements in circulating lipid profiles and hirsutism (Harborne et al., 2003a; Lord et al., 2003).

The use of metformin for the management of type 2 diabetes is evidence based, but in recent years, treatment is becoming widespread in clinical practice for the treatment of PCOS-associated symptoms such as infertility, hirsutism and acne, and cycle regulation. Evidence supporting these practices is exciting, but generally based upon small patient numbers in very different environments. Particular concerns may be expressed over the use of metformin during pregnancy in women with PCOS, where little controlled evidence exists confirming its efficacy and safety (Norman et al., 2004). In the UK, metformin is recommended in the guidelines on fertility treatment published by the National Institute of Clinical Excellence (NICE, 2004), despite this being a non-licensed indication. In fact, metformin is not licensed for any of the PCOS indications. This situation means that there is no advice network for prescribing practice (starting therapy, doses, influence of other factors or treatments), and that there is an ad hoc treatment environment based on no guideline base and a shortage of contra-indication information.

Duration of metformin treatment
The use of metformin in infertility treatment is a relatively short term procedure, although continuing treatment through pregnancy to reduce the incidence of gestational diabetes (Glueck et al., 2004) adds an extra dimension to this programme. Increasing numbers of patients are being treated with the drug on a protracted basis, for such indications as hirsutism (Harborne et al., 2003b), acne and cycle regulation. These conditions demand upwards of 1 year to
establish benefit, and possibly longer to prevent recurrence. There is also a proposition that protracted treatment of adolescents with symptoms common to PCOS (acne, hirsutism and menstrual irregularity) may show long term benefit (Homburg and Lambalk, 2004). However, there is no information available to answer the questions: how long should treatment be continued? Who is likely to derive benefit from treatment? What happens when treatment is discontinued? We intended to address this latter issue with a study of changes associated with treatment discontinuation supported by the CSO Grant CZG/1/92 (Scottish Executive). The planned recruitment period was from mid 2003 to early 2004.

Study design and recruitment

Eligible patients were asked to volunteer to undergo investigations limited to a physical examination, including hirsutism assessment, an ultrasound scan and fasting blood sample before stopping metformin treatment, each repeated after 1, 2 and 3 months with no treatment. Inclusion criteria were: original diagnosis of PCOS, no evidence of glucose intolerance, BMI < 39 kg/m², being on daily metformin treatment for at least 6 months and being prepared to discontinue metformin for a period of at least 13 consecutive weeks, as well as the exclusion of pregnancy. During the 6 months of recruitment, 62 women fulfilling the study criteria were identified from case notes, of whom 26 (42%) failed to. The remaining 36 patients were interviewed and exclusion criteria reduced the cohort to 22. Seventeen (77%) of the 22 women declined participation in the programme, on the grounds that they did not want to cease treatment, even for a short period of time, as they all considered that the treatment was effective, and they enjoyed the benefits. Two women (9%) wished not to get involved in research projects. Seven patients (31%) were initially interested in the study and were given Patient Information leaflets at the time of their return clinic visit. Three of these seven, after reflection, preferred to continue metformin, and two withdrew due to personal reasons. One woman undertook the study.

Discussion

The figures reported above indicate that the majority of women with PCOS taking metformin consider that they derive benefit, and few individuals are willing to discontinue the treatment; even for a short time. This has implications for (i) the validity of any research studying the effects of treatment discontinuation, and more importantly, (ii) medical practitioners considering prescribing the drug for long-term use. The outcome serves mainly to illuminate the difficulties facing clinicians working in this area, and it suggests even more complex problems for practitioners whose patients are demanding ad hoc treatment.

Patients who receive metformin at the Glasgow Royal Infirmary are made aware that this drug is not licensed for the use in PCOS and as such remains a ‘research tool’, or they are prescribed on an individual patient basis after detailed discussion of the implications of ‘off-label’ use. Although we believe metformin to be a safe drug even in prolonged use, as revealed by studies in patients with type 2 diabetes (UKPDS, 1998) or at increased risk for diabetes (Knowler et al., 2002), we do not know of potential long-term sequelae affecting women with PCOS, who generally do not show evidence of glucose intolerance, and are generally younger than patients with glucose intolerance and type 2 diabetes. Furthermore, we cannot predict outcome and chronology of events once treatment is discontinued. This leaves all in a state of ignorance.

The widespread use of any drug in an unlicensed environment is not desirable. Whilst NICE guidelines support its use in infertility associated with clomiphene citrate, no protocol is available to assist patient selection or management issues. Furthermore, there are no guidelines for its use in other PCOS related symptoms, and ‘metformin in PCOS’ is likely to remain in this situation for some time with many important issues unresolved. Few of the important questions have been answered to a satisfactory degree of certainty, and we suggest that much research remains to be carried out in this field.

To achieve a safer prescribing environment, we recommend that action be taken by the manufacturer of metformin (Merck Pharmaceuticals) to work with regulatory agencies (such as the MHRA) to extend prescribing indications for metformin, on a European base. This would aid national professional bodies to draw up guidelines for the use of metformin, and help establish the framework for future work to establish best practice. We propose that this issue be debated by practitioners within Europe to determine whether there is a consensus amongst gynaecologists and physicians, and whether and how progress can be made towards the licensing of metformin for treatment of women with PCOS.

References


Submitted on April 16, 2004; resubmitted on May 26, 2004; accepted on August 26, 2004