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Metformin in diabetic pregnancy

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ABSTRACT An ever-increasing number of women with Type 2 diabetes mellitus (DM) are going through pregnancy and, with the current epidemic of obesity, more women are being diagnosed with gestational diabetes mellitus (GDM). Insulin has traditionally been the gold standard in diabetic pregnancy because of its efficacy and the fact that it does not cross the placenta. However, recent data from well-designed trials and meta-analysis on the use of oral agents in gestational diabetes may mark a significant shift in clinical practice. Evidence for metformin use in GDM has been enhanced by the MiG trial, but a randomised controlled trial in women with Type 2 DM in pregnancy is required. No long-term follow-up data for offspring of mothers receiving metformin have been published, apart from reassuring findings in one study with an 18-month follow-up period. The aim of this article is to review the safety, efficacy and future of metformin in diabetic pregnancy.

KEYWORDS Diabetes, metformin, pregnancy

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INTRODUCTION

The Confidential Enquiry into Maternal and Child Health (CEMACH) reported that women with diabetes mellitus (DM) have five times the risk of stillbirth, three times the risk of neonatal death and twice the risk of a major congenital anomaly than women in the general population.[1] These outcomes were similar for women with Type 2 and Type 1 DM. There is therefore major interest in improving pregnancy outcomes in females with Type 2 DM and gestational diabetes mellitus (GDM).

Metformin is a dimethylbiguanide first described in scientific literature in 1957.[2] This compound originates from the French lilac (*Galega officinalis*), a plant known for several centuries to ameliorate the symptoms of DM.[3] Metformin has a diverse mechanism of action, comprising decreasing hepatic glucose output,[4,5] increasing insulin sensitivity and insulin-mediated glucose use in the peripheral tissues (muscle and liver),[6] lowering serum-free fatty acid concentration through an anti-lipolytic effect[7] and increasing intestinal glucose use.[8] The activation of the enzyme AMP-mediated protein kinase seems to be an important mechanism by which metformin lowers the blood glucose levels.[9]

These effects of metformin make it an attractive option in diabetic pregnancy as it decreases peripheral insulin resistance, does not cause hypoglycaemia nor increase insulin secretion. Patients are also likely to prefer tablets over injections. However, there has always been a reluctance to use metformin in diabetic pregnancy due to a lack of large-scale randomised studies, fear of congenital abnormalities and uncertainty over its effectiveness in this subgroup. In 1998, the Australasian Diabetes in Pregnancy Society included a statement in the guidelines for the management of GDM which stated that 'oral agents have no place in the treatment of GDM under normal circumstances'. So, what has changed over a decade that may influence a shift in clinical practice?

SAFETY

Metformin is a category B drug, indicating that there is no evidence of fetal or animal teratogenicity,[10] but there are legitimate concerns about metformin use in pregnancy. Metformin readily crosses the placenta[11] and hence there is concern regarding possible adverse effects on the fetus. Metformin-induced lactic acidosis is rare, with no reported cases using therapeutic doses where the renal function is normal. In pregnancy it has been reported in a patient where metformin was taken as an overdose.[12] Despite these valid concerns, there have been clinical reports of metformin use in diabetic pregnancy since 1966.[13–16] In those earlier studies, mainly from South Africa, the authors conclude that metformin 'appears' to be safe for use in GDM and that the perinatal mortality rate in such women taking metformin until approximately 24 hours predelivery was 'acceptable'.

Metformin use has increased in women with polycystic ovarian syndrome as it has potential benefits of regulating menstrual cycles and ovulation induction. Evidence for

the safety and efficacy of metformin in pregnancy has come from the increasing number of such women who have gone on to conceive on metformin. A pilot study of continuing metformin use throughout pregnancy in women with polycystic ovarian syndrome showed that metformin therapy was not teratogenic and reduced the otherwise high rate of first trimester abortion seen among women not receiving this treatment.[17] A systematic review and meta-analysis of eight small and non-blinded studies relating to pregnancy outcomes after first trimester exposure to metformin in women with polycystic ovarian syndrome, from 1966 to 2004, showed no evidence of increased risk of major malformations.[18] Based on studies in Type 2 DM, the prevalence of malformations in the metformin group was 1.7%,[19] which was within the rate for the general population. Apart from a lack of harmful effects, metformin use in the context of polycystic ovarian syndrome may have beneficial effects in pregnancy by causing a ten-fold reduction in GDM.[20]

One non-randomised and non-blinded study showed a significantly increased rate of perinatal mortality (11.6% vs 1.3% using insulin, p<0.02) and pre-eclampsia (32% vs 10%, p<0.001) in pregnant women with GDM or Type 2 DM taking metformin.[16] However, these patients were more obese than the patients on insulin, and obesity per se is a major risk factor for late fetal death[21] and pre-eclampsia.[22,23] Two of the still births in this study occurred in infants of 'poorly regulated non-compliant obese women', and mothers of two other infants with still births had polyhydraminos and pre-eclampsia. Therefore, it is extremely unlikely that the perinatal mortalities in this study were directly attributable to metformin. Against this study, in a retrospective audit of 214 pregnant women with Type 2 DM[24] of which 93 were on metformin, there were no significant differences in the rate of pre-eclampsia, perinatal loss, neonatal morbidity, neonatal admissions, respiratory distress or treatment with intravenous dextrose between metformin and the control group. It has to be noted that women in the metformin group had more risk factors for adverse pregnancy outcomes in this study.

It is clear from the above discussion that randomised trials to assess the safety and efficacy of metformin in women with GDM or Type 2 DM have been lacking. The recently published MiG (Metformin versus insulin for the treatment of Gestational diabetes) study has gone some way in addressing this issue.[25] This randomised, open-label trial involving 751 women with GDM (single fetus) at 20–33 weeks of pregnancy tested for non-inferiority a comparison of metformin (with supplemental insulin if needed) with insulin. Of the 363 women on metformin who completed the study, the rate of primary outcome (a composite of neonatal complications: neonatal hypoglycaemia, respiratory distress, need for phototherapy, birth trauma, 5 min Apgar score below 7 or premature birth) did not differ significantly from the insulin group (32 % versus 32.2% in the insulin group). Of the outcomes recorded, severe hypoglycaemia (glucose level <1.6 mmol/l) was less common in the metformin than in the insulin group (p=0.008). There were no significant differences between the metformin and insulin groups in terms of maternal hypertensive complications or glycaemic control, although it has to be pointed out that supplemental insulin was used in 46.3% of women in the metformin group. There were no serious adverse events associated with metformin, and more women preferred metformin to insulin treatment.

The premature delivery rate was significantly higher in the metformin group (12.1% vs 7.6%, p=0.04). The authors stated that this difference was associated with a greater frequency of spontaneous (rather than iatrogenic) preterm births that could be due to chance or an unrecognised effect of metformin on the labour process. The increased rate of preterm birth was not associated with a higher rate of other complications, probably because the difference between the two groups in mean gestational age was clinically insignificant. This will require further investigation in future studies. The authors concluded that metformin, alone or with supplemental insulin, is an effective and safe treatment option for women with GDM. Follow-up data on the offsprings from this trial should be available in the near future, but data on 126 infants of women with polycystic ovarian syndrome treated with metformin throughout the whole of pregnancy showed normal growth and motor development when followed up to 18 months.[26]

In a further study presented at the European Association for Diabetes in Rome in September 2008, a comparison was made of maternal and neonatal outcomes in women with GDM.[27] Eighty women were treated exclusively with metformin, and a similar number, matched for body mass index and ethnicity, were treated with basal bolus human insulin. The metformin dose was titrated from a starting one of 500 mg twice daily up to a maximum of 2,500 mg daily to achieve target home blood glucose monitoring values of fasting <6 mmol/l, one hour postprandial <8 mmol/l and two hour postprandial <7 mmol/l. Women treated with metformin gained less weight compared with those on insulin (mean standard error weight gain in kg: 0.3 ± 0.03 vs 1.4 ± 0.15, p< 0.01), with no significant differences in the occurrences of hypertension or pre-eclampsia. Neonatal morbidity was significantly improved in the metformin group, with less prematurity (0% vs 11%; p<0.01). There were no significant differences in the rate of caesarean section, birth weight, number of babies with macrosomia, shoulder dystocia at delivery, congenital malformations or abnormalities in the postnatal glucose tolerance test. The authors felt that metformin is of benefit in managing GDM and may offer advantages over insulin. However, the numbers in this study were small and it has as yet only been published in abstract form.

Metformin appears to be 'safe' during lactation[28] as the mean infant exposure to the drug was found to be only 0.28% of the weight-normalised maternal dose, although the patient numbers in these studies[29, 30] were small (n=7). The manufacturer advises against the use of metformin during breastfeeding, while the recent National Institute for Health and Clinical Excellence (NICE) guidance has endorsed the use of metformin in breastfeeding mothers with pre-existing Type 2 DM.[31] Reassuringly, there was no difference in weight, height or motor-social development between breastfed and formula milk-fed infants of metformin-treated mothers with polycystic ovarian syndrome when followed up for the first six months of infancy.[32]

EFFICACY

It is important to note that the question is not whether metformin is efficacious, but whether it is suitable for use in pregnancy with the tighter glycaemic targets and shorter timescale to achieve the targets. A review of the efficacy of metformin is also fraught with problems as a substantial number of patients in all the studies have had supplemental insulin added to the regime. Initial data on the efficacy of metformin comes from Coetzee's study in the late 1970s of 160 treated patients with established insulin-independent diabetes.[14] In this study, 14% of patients were able to maintain good glycaemic control, as defined by a fasting glucose of 5.5 mmol/l and a post-prandial value below 6.7 mmol/l on a combination of diet and metformin, compared with about 26% of women who needed insulin. In another retrospective study of 93 pregnant women exposed to metformin, women in the metformin group had a higher mean HbA1c in the first trimester compared with the control group (8.3% vs 7.5%), who were mostly on insulin, but the patients in the metformin group had a significantly greater body mass index than control subjects.[24] Throughout pregnancy, 95% of patients in the metformin group needed supplemental insulin, and during the second and third trimesters the HbA1c was comparable in both groups.

In a small randomised study, women with gestational diabetes not controlled with diet and exercise were randomised to metformin (n=32) or insulin (n=31).[33] There were no significant differences in fasting or postprandial glucoses between the two groups. In the MiG trial, of the 363 women assigned to metformin, 92.6% continued to receive metformin until delivery and 46.3% received supplemental insulin.[25] Therefore metformin may have an adjunct role to insulin which may be important in those pregnant females with marked insulin resistance and who require very large insulin doses. In terms of glycaemic control from randomisation to delivery, there were no significant differences in the fasting capillary glucose level between the metformin (± supplemental insulin) and the insulin groups. Interestingly, the overall mean maternal two-hour postprandial glucose levels were slightly lower in the metformin group, but these values did not differ significantly in the two weeks preceding the delivery.

ALTERNATIVE ORAL HYPOGLYCAEMIC AGENTS IN PREGNANCY

First-generation sulphonylureas have been avoided in pregnancy because of transplacental passage leading to fetal hyperinsulinemia, but glyburide (glibenclamide) appears to have minimal transplacental transfer.[34] In a randomised controlled trial of glyburide versus insulin (n=404) in gestational diabetes, there were no significant differences in perinatal or neonatal outcomes, nor maternal glycaemic control and fetal anomalies between both the groups.[34] In the glyburide group, 4% of patients needed insulin therapy. In addition, glyburide was not detected in the cord serum of any of the infants in this group. Metformin was associated with similar outcomes in the MiG trial,[25] although 46% of women in the metformin group needed supplemental insulin. It is not clear whether there were any significant differences in the patient population between the two studies to explain the differences in the need for supplemental insulin. Similar to metformin, a retrospective cohort study[35] did find an increased incidence of pre-eclampsia in the glyburide group compared with the insulin group (12% vs 6%, p=0.02), but this association was not found in the prospective, randomised controlled trial. There are no direct trials comparing metformin with glyburide. This may be important as it would be useful to know whether metformin is better or worse than glyburide, as evidence until now suggests more need for supplemental insulin and transplacental transfer with metformin compared with glyburide.

The NICE guidance for England and Wales has stated that the treatment of diabetes in pregnancy should be 'tailored to the glycaemic profile and acceptability to the individual woman' and 'may include insulin and/or hypoglycaemic agents (metformin and glibenclamide)'.[31] This advice is starting to have an important impact on clinical practice, especially for metformin.

THE FUTURE

In a commentary on the 2008 NICE guideline,[31] Mathiesen and Damm from Copenhagen stated that they 'would be reluctant to advise the use of metformin before information from follow-up studies on children is available'.[36] This comment highlights the continuing debate with regard to those against[37] and those in favour[38] of metformin use in pregnancy. A ten-year retrospective analysis of pregnancy outcome in pre-gestational Type 2 DM comparing insulin and oral glucose-lowering agents showed no evidence of teratogenicity with metformin.[39] However, follow-up of children born to mothers exposed to metformin has not

been done on a systematic basis, but has only been assessed in one study after 18 months following delivery with no reported adverse consequences[26] and is ongoing in the follow-up of the MiG study.[25] Metformin is licensed for use in children with Type 2 DM from 10 years and upwards.[40] Several studies have examined the use of metformin as a weight-reducing agent in non-diabetic children and adolescents, with no reported behavioural consequences.[41,42]

Metformin is an attractive treatment option for GDM and Type 2 DM women who get pregnant. It improves insulin sensitivity, does not cause hypoglycaemia or weight gain, is more convenient to use compared with insulin and seems to be a safe and effective option, alone or with supplemental insulin. While there has always been a reluctance to use metformin during pregnancy, the data from the recently published MiG trial is greatly reassuring for the use of metformin in GDM, but more evidence from randomised controlled trials with insulin is required in Type 2 DM pregnancies.[43] We believe that the accumulating evidence will increasingly lead to a shift in clinical practice towards using metformin in diabetic pregnancy in women who meet the criteria for starting insulin, changing the notion that 'oral agents should never be used in gestational diabetes under normal circumstances'. This will also be of particular relevance to the developing world, where rates of diabetes are greatly increasing, cultural beliefs may be at odds with insulin injections and the cost of insulin may be prohibitive. Further follow-up offspring data available in the next few years will add to the debate for using metformin in diabetic pregnancy.

Not directly related to the use of metformin in pregnancy are the findings of three recently published papers that suggest that the pleiotrophic effects of metformin in preventing cardiovascular events in women with a history of gestational diabetes may stimulate further discussion of metformin use. The first study, from Canada, describes an increased risk of cardiovascular disease (HR=1.71, 1.08–2.69) following GDM with a median follow-up of 11.5 years.[44] The second publication shows that metformin, like intensive lifestyle measures, is highly effective in reducing by about 50% over a three-year period the development of Type 2 DM in women with a history of GDM.[45] These findings are part of the Diabetes Prevention Program (DPP) in the USA. The third study in Type 2 DM is from the UK Prospective Diabetes Study (UKPDS). The original study regarding metformin, published in 1998, showed that this drug offered cardiovascular protection in a ten-year follow-up of Type 2 DM patients.[46] The new data for metformin relates to a further ten-year follow-up (giving a median follow-up of about 17 years) and shows continuing benefit for metformin therapy with sustained significant reduction in cardiovascular events.[47]

These studies widen the discussion of the use of metformin to include the routine management of GDM patients who continue to show impaired glucose tolerance following delivery. Benefits include the reduced risk of conversion to frank Type 2 DM and the potential for reduced cardiovascular risk recognised in those with a history of GDM. These issues will be subject to further studies.

KEY POINTS

- Gestational diabetes mellitus and pregnancy in women with Type 2 diabetes are on the rise.
- Insulin has been the gold standard for establishing optimal glucose control in diabetic pregnancy.
- Recent evidence indicates that metformin is a safe and effective alternative in women with GDM and those with Type 2 diabetes who become pregnant.
- Further long-term outcome data on the offspring of 'metformin mothers' will add to the debate of using metformin in diabetic pregnancy.

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