Metformin in pregnancy and lactation

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Summary

Metformin improves insulin sensitivity and reduces hepatic glucose output in patients with diabetes. It offers potential benefits for pregnant women with gestational or type 2 diabetes because both conditions are associated with increased insulin resistance. Some cohort data are available and randomised trials are currently in progress to compare metformin with insulin, but strong evidence is not yet available to guide management. There are no long-term follow-up data to provide reassurance about the safety of metformin, given its passage across the placenta, although recent evidence suggests that there is no significant risk of teratogenesis. Limited amounts of metformin are transferred into breast milk, but the risk of neonatal hypoglycaemia is negligible.

Key words: birth defects, gestational diabetes, hypoglycaemic drugs, insulin.

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Introduction

Oral hypoglycaemic drugs have been viewed with suspicion for many years in the management of women with diabetes during pregnancy or breastfeeding. Pregnant women with type 2 diabetes are often switched to insulin. However, there is long experience with use of the biguanide metformin in pregnant women in South Africa. Metformin increases insulin sensitivity, reduces hepatic glucose release and is associated with a tendency to lose weight.[1]

Increasingly metformin is being used in the management of women with polycystic ovary syndrome, as the syndrome is associated with insulin resistance. Metformin reduces hyperandrogenaemia and, as it allows more effective ovulation to occur, it is now widely used in the management of infertility.[2] If a woman with polycystic ovary syndrome becomes pregnant while taking metformin, a decision has to be made whether to continue treatment.

Teratogenicity

Caution is needed when using metformin in pregnancy. In the Australian categorisation of risk metformin is in category C. The product information recommends switching to insulin during pregnancy. It is important for any changeover to insulin to be done under specialist supervision to maintain optimum glucose control and reduce the risk of congenital anomaly from maternal hyperglycaemia.

Limited data are available about the pharmacokinetics of metformin during pregnancy. In one small study of seven women, the clearance of metformin increased with gestation and the associated increased renal elimination.[3] More data are required to clarify the possible need for dose adjustment as pregnancy proceeds. Studies of the passage of metformin across the placenta suggest that there is a rapid transfer of metformin into the fetal circulation.[4]

Recent data provide some reassurance about the safety of metformin in respect of lack of teratogenicity when taken in early pregnancy, although no long-term follow-up data are available.[5] Properly conducted randomised trials are required, as well as a large enough database to exclude rare unanticipated adverse outcomes, such as birth defects.

Outcomes

It is not known if continuation of metformin in early pregnancy provides any better outcome than either ceasing the drug (in women with polycystic ovary syndrome) or changing to insulin (in women with type 2 diabetes). In some circumstances, use of metformin may be preferred, but patients should be individually advised of the harms and benefits.[6] Ideally they should be recruited into appropriately designed studies.

Non-randomised data from New Zealand, where a number of pregnant women with type 2 diabetes have been treated with metformin, suggest that there may be no difference in outcomes when compared with similar women treated with insulin.[7] A small randomised trial in Australia showed no difference in fetal beta cell activity, as measured by cord C-peptide concentrations at delivery, between the babies of women with gestational diabetes treated with metformin and the babies of women treated with insulin.[8]

The randomised Metformin in Gestational Diabetes trial is currently underway to establish the efficacy of metformin compared with insulin, using neonatal outcome as a primary end point. The results may be available soon. After reviewing the results from 600 women, the independent data monitoring committee recommended that the trial continue as there was no indication for early closure.

Metformin improves plasma concentrations of some markers of endothelial activation in people with impaired glucose tolerance,

unrelated to changes in glycaemia, lipids, weight or insulin sensitivity.[9] This is a potential benefit for pregnant women with diabetes, as they are at increased risk of problems associated with endothelial activation, such as pre-eclampsia. Few data are currently available to assess the outcome of such therapy. A secondary outcome in a small randomised placebo-controlled trial in 38 pregnant women with polycystic ovary syndrome was significantly fewer severe pregnancy complications in the women taking metformin.[10]

Any potential benefit of metformin on future childhood obesity and later development of diabetes is hypothetical. Long-term follow-up data from the current studies are required.

Lactation

There are three published studies of metformin in breast milk. The milk:serum or milk:plasma ratio varied between 0.18 and 1.00, while the estimated mean infant dose as a percentage of the mother's weight-adjusted dose varied between 0.18% and 1.08%. This dose is much less than the usual 10% level of concern.[11] Women can be reassured that it is unlikely that there will be any significant effect on their babies. In particular, there is no risk of neonatal hypoglycaemia, in contrast to the use of drugs stimulating insulin release, such as the sulfonylureas. Maintenance of maternal euglycaemia during lactation remains an important principle to reduce the risk of subsequent obesity in the child.[12]

Conclusion

Evidence is emerging that metformin may improve insulin sensitivity during pregnancy. This may be of benefit in gestational diabetes, but further evidence is required. Metformin can be used by women who are breastfeeding.

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[R] randomised controlled trial

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 83)

3. Women with polycystic ovary syndrome who are planning pregnancy should not take metformin.
4. Metformin is contraindicated in breastfeeding because of the risk of neonatal hypoglycaemia.

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