Metformin therapy and diabetes in pregnancy

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ABSTRACT

- No adverse pregnancy outcomes with metformin use have been reported, except in one unmatched study. Otherwise, the studies are small and non-randomised, with the exception of one prospective, randomised controlled trial, currently under way, comparing metformin with insulin in women with gestational diabetes mellitus (the MiG trial). No long-term follow-up data for offspring of mothers receiving metformin have been published.
- Any woman with diabetes should be as close to euglycaemia as possible before pregnancy.
- In some circumstances (eg, severe insulin resistance), metformin therapy during pregnancy may be warranted.
- When metformin treatment is being considered, the individual risks and benefits need to be discussed with the patient so that an appropriate decision can be reached.

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IN 1998, the Australasian Diabetes in Pregnancy Society (ADIPS) published guidelines for the management of gestational diabetes mellitus (GDM), which included a statement that "oral hypoglycaemic agents have no place in the treatment of GDM under normal circumstances".[1] Since then, there have been several published reports of the use of metformin during pregnancy, predominantly in women with polycystic ovary syndrome (PCOS).[2-5] In addition, with the current epidemic of obesity and type 2 diabetes mellitus, an increasing number of women with diabetes are entering pregnancy and continuing to take metformin.[6] GDM is also a common pregnancy complication in Australia, with a reported incidence in detailed surveys ranging from 5.5% to 8.8%.[7]

Doctors caring for women with diabetes in pregnancy are often asked about the safety and potential role of metformin treatment in pregnancy. ADIPS was asked to comment on this issue, so an ad hoc working party was formed and its recommendations circulated to the ADIPS committee, whose members represent the range of disciplines involved in the management of diabetes in pregnancy. The work involved a MEDLINE search (undertaken on 16 January 2004), using the terms "metformin" and "pregnancy". Only human studies among women with diabetes were included.

Search results

Recent published data on metformin treatment in pregnancy are mostly based on small cohort studies in women with PCOS, in whom it has been used to assist fertility.[2-5] These studies have suggested:

- Reduced rates of spontaneous abortion with normal morbidity and mortality rates in women continuing to taking metformin in the first trimester or throughout pregnancy;[2,3]
- A reduced subsequent risk of GDM with continued use of metformin during pregnancy;[4] and
- Favourable pregnancy outcomes,[5,8] and normal growth and development of the offspring with use of metformin before and during pregnancy.[9]

Although these studies add to existing data reported from South Africa (where metformin has been used for 30 years),[10-12] they do not formally assess safety and effectiveness. Currently, metformin is classified as a Class C drug. This means that, while there is no evidence of teratogenesis or adverse fetal effects, insufficient data exist to state that harm does not occur.[13] Metformin does cross the placenta, prompting a cautious approach to its use in pregnancy.[14] Further, one retrospective study from 1970 reported an increase in perinatal losses and pre-eclampsia in a small cohort of metformin-treated women compared with women taking insulin or a sulfonylurea.[15] However, the groups were not matched, with the metformin group mostly treated in the third trimester and having increased risk factors for pre-eclampsia. Thus, the perinatal losses may not have been related to metformin treatment. Perinatal deaths, unrelated to either malformation or extreme prematurity, occurred only in metformin-treated women who were also obese and either non-compliant with treatment or treated with metformin for only 2 weeks. The prospective study of Glueck et al showed no relationship between metformin use and pre-eclampsia.[8]

Australasian research

Over the past 5 years, several groups in Australasia have been using metformin in selected women during pregnancy.

A report from an Australasian Diabetes in Pregnancy Society Ad Hoc Working Party

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An audit of metformin use in Auckland has not shown any increase in perinatal mortality or pre-eclampsia in treated women.[16] A prospective, randomised controlled trial comparing metformin with insulin in women with GDM (the MiG trial) has now commenced in New Zealand and Australia. This trial aims to recruit 750 women over the next 2 years. In a small pilot study, in which 30 women were allocated at random to metformin or insulin therapy, there was no difference in cord C-peptide levels or neonatal outcomes.[17] In MiG, so far over 70 women have been recruited, and no serious adverse events have occurred in the metformin arm. An interim analysis of the first 200 recruits is planned for June 2004.

Women who may be using metformin

Women with PCOS — possible undiagnosed diabetes?

It is not the role of ADIPS to comment on the use of metformin for non-diabetic women with PCOS. However, it is important to remember that women with PCOS are at increased risk of developing type 2 diabetes mellitus, and current National Health and Medical Research Council guidelines recommend that they should be screened for type 2 diabetes and offered treatment when necessary.[18] Should undiagnosed type 2 diabetes be present, there are increased risks of congenital anomaly in the fetus, correlated with the degree of hyperglycaemia during early pregnancy.[19] This should be explained to women so they can work towards achieving euglycaemia. The use of effective and suitable contraception should be recommended during this time.

The usual recommendation for folic acid intake also applies to all women with pre-gestational diabetes. Folic acid probably reduces the rate of neural tube defect in infants of women with diabetes, as it does in normal women.[20]

Women with type 2 diabetes planning pregnancy or in early pregnancy

As explained above, optimal glycaemic control in the preconceptional period and early pregnancy is of paramount importance. If metformin-treated women become pregnant, it is important to ensure that any change in therapy occurs without deterioration in glycaemic control. Stopping metformin may result in greater teratogenic risk by exposing the fetus to increasing levels of hyperglycaemia. Many women with type 2 diabetes require insulin during pregnancy to achieve optimal glycaemic control. Currently, most women switch from oral agents to insulin. It appears reasonable for some women to continue metformin (eg, if they refuse insulin therapy), or add metformin (eg, if they are very insulin resistant), when the likely benefits from improved glycaemic control outweigh the potential for harm. While there are no hard data in this setting, metformin has been used clinically to achieve optimal glycaemic control with lower insulin doses.

Recommendations for pre-pregnancy

- Women with type 2 diabetes should be offered preconceptional counselling (as should any woman with preexisting diabetes). Such pre-conceptional care should include consultation with an endocrinologist or physician experienced in the care of women with diabetes before and during pregnancy. Should glycaemic control be suboptimal, women should be counselled regarding the risks of pregnancy and, in particular, the risks of fetal malformation. Contraception should be continued until glycaemic control is considered adequate (ie, HbA_{1c} level is as close to normal as possible for that individual).
- Folic acid supplements should be prescribed.
- The data regarding metformin use in pregnancy should be discussed with the woman and a decision made, on an individual basis, regarding ongoing treatment.

Recommendations for pregnancy

- If a woman with type 2 diabetes taking metformin presents already pregnant, she should be reassured that there is no evidence of teratogenesis with metformin use.
- The relevant diabetes-in-pregnancy team should be contacted and an appointment made within 1 week. If appropriate, advice should be sought regarding management before the appointment. The woman should be advised to continue taking metformin until ongoing treatment options are discussed.
- Metformin use may be considered as an adjunct or alternative to insulin therapy when the likely benefits from improved glycaemic control outweigh the potential for harm.

Women with type 2 diabetes beyond early pregnancy or women with GDM

There are an increasing number of women with GDM. This increase is associated with the rising prevalence of obesity and type 2 diabetes, more older women undergoing pregnancy, and greater ethnic diversity.[7] The ADIPS guidelines for GDM recommend dietary therapy for these women, supplemented by insulin therapy if the degree of hyperglycaemia warrants this.[1] While there are a range of theoretical and practical benefits from using metformin in lieu of insulin therapy in later pregnancy, at this stage the data are inadequate to support metformin therapy as routine management. As above, women who refuse insulin or who are very insulin resistant have sometimes been treated with metformin. Again, after discussion, this may be appropriate for certain individuals.

Recommendations

- Metformin therapy is not to be used routinely in women with pregnancies complicated by diabetes.
- When the potential harm from metformin therapy is likely to be outweighed by the benefits of metformin use, metformin therapy should be considered after discussion. Such situations include a requirement for large doses of insulin, and refusal of the patient to use insulin.

Breastfeeding

Metformin is not currently recommended for use in lactation. However, there is no evidence of harm for the infant from the small dose of metformin that enters breast milk.[21,22] Use should only occur after obtaining the mother's informed consent. If the decision that the potential benefit of drug use outweighs any possible risk, infant exposure to metformin can be minimised by breast feeding just before taking the dose and avoiding feeding for a minimum of 2 to 3 hours after taking the dose.[23]

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Competing interests

None identified.

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