Motherisk Update

Metformin use during the first trimester of pregnancy

Is it safe?

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ABSTRACT

QUESTION A pregnant patient with polycystic ovary syndrome asked me whether continuing metformin, which she was taking to treat infertility before her pregnancy, is safe for her fetus. She has heard that metformin is a "drug for diabetes." How safe is it to take metformin during the first trimester of pregnancy and beyond?

ANSWER Despite the traditional response that all oral hypoglycemic agents are absolutely contraindicated during pregnancy,[1-3] evidence that metformin is probably safe during the first trimester of pregnancy and beyond is accumulating. Results of a recent meta-analysis by the Motherisk Program showed no increase in incidence of major malformations and a potential protective effect in this patient population.

RÉSUMÉ

QUESTION Une de mes patientes enceintes ayant le syndrome des ovaires polykystiques m'a demandé s'il était sans danger pour son fœtus de continuer la metformine qu'elle prenait pour traiter l'infertilité avant sa grossesse. Elle a entendu dire que la metformine était un «médicament contre le diabète». Dans quelle mesure est-ce sécuritaire de prendre de la metformine durant le premier trimestre de la grossesse et au-delà?

RÉPONSE Malgré la réponse traditionnelle voulant que les agents hypoglycémiants par voie orale soient contre-indiqués durant la grossesse[1-3], les preuves scientifiques qui soutiennent que la metformine est probablement sécuritaire durant le premier trimestre et au-delà se font de plus en plus nombreuses. Les résultats d'une récente méta-analyse réalisée par le Programme Motherisk n'ont démontré aucune augmentation de l'incidence des malformations majeures et ont cerné un effet protecteur potentiel dans cette population de patientes.

Polycystic ovary syndrome (PCOS) is defined by the presence of oligo-ovulation or anovulation in combination with hyperandrogenism. Between 5% and 7% of women of reproductive age have PCOS,[4] making it the most common cause of anovulatory infertility.[5]

Metformin is currently approved by the United States Food and Drug Administration for treatment of type 2 diabetes.[6] The most current product monograph still lists pregnancy as a contraindication to use of metformin; however, in both Canada and the United States, its off-label use in treatment of infertility caused by PCOS is growing.

Metformin is known to facilitate conception in women who have oligomenorrhoea and PCOS.[7,8] Recent studies have suggested that metformin use during pregnancy decreases the high incidence of spontaneous abortion associated with PCOS (30% to 50%)[9] and with gestational diabetes (31% in untreated women vs 3% in treated women).[10]

Animal studies

Whether metformin causes teratogenicity in animals is controversial. Some animal studies found no evidence of teratogenicity at doses as high as 600 mg/kg daily.[11] One study showed that metformin at doses similar to clinical in vivo levels had no direct toxic effects on mouse embryo development.[12] Another study showed that, although exposure to both biguanides, phenformin and metformin,

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were associated with embryo death, phenformin has greater toxicity in mouse whole embryo culture, suggesting that metformin might be safer to use during pregnancy.[13] Other studies, however, have suggested that metformin induces a low incidence of malformations in rats.[14] For women taking metformin for PCOS, the question of teratogenicity remains challenging because it is difficult to clarify whether the teratogenic potential is subsequent to poor glycemic control or subsequent to the direct actions of the oral hypoglycemic drug itself.

First-trimester exposure

The Motherisk Program recently conducted a retrospective cohort study on pregnancy outcome among women with PCOS[15] and a meta-analysis of all published studies with data on pregnancy outcomes with respect to major malformations.[16] In the retrospective cohort study, 72 PCOS patients exposed to metformin were compared with 48 PCOS patients who conceived without metformin in five different fertility clinics. The prevalence of major malformations was similar in the two groups. The metformin group had a higher prevalence of multiple pregnancies and prematurity. Prematurity is a substantial confounder of concomitant use of other fertility drugs.[15]

Results of the meta-analysis are encouraging. In the five studies included in the statistical analysis, there was no increase in the rate of major malformations, and in fact, metformin might actually have a protective effect in women with PCOS. In the treated group, there were three malformations among 172 babies (1.7%); in the control group, there were 17 malformations among 235 babies (7.2%). The odds ratio was 0.50 in favour of treatment.[16]

In summary, no evidence currently in the literature shows that use of metformin in women with PCOS is associated with increased risk of malformations. Most of the studies applicable to PCOS restricted exposure to the first trimester, ie, metformin was discontinued as soon as pregnancy was diagnosed. Evidence beyond the first trimester is anecdotal at this point. Large well-controlled studies of humans are needed. For women with non–insulin-dependent diabetes mellitus, insulin is still considered the treatment of choice during pregnancy, although glyburide has been shown not to cross the human placenta.[17,18]

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MOTHERISK

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Do you have questions about the safety of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at 416 813-7562; they will be addressed in future Motherisk Updates.

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