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, making it the most common cause of anovulatory infertility. Metformin is currently approved by the United States Food and Drug Administration for treatment of type 2 diabetes. 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 oligomenorrhea and PCOS. Recent studies have suggested that metformin use during pregnancy decreases the high incidence of spontaneous abortion associated with PCOS (30% to 50%) and with gestational diabetes (31% in untreated women vs 3% in treated women).

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. One study showed that metformin at doses similar to clinical in vivo levels had no direct toxic effects on mouse embryo development. Another study showed that, although exposure to both biguanides, phenformin and metformin,
were associated with embryonic death, phenformin has greater toxicity in mouse whole embryo culture, suggesting that metformin might be safer to use during pregnancy. Other studies, however, have suggested that metformin induces a low incidence of malformations in rats. 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 and a meta-analysis of all published studies with data on pregnancy outcomes with respect to major malformations. 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.

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.

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.

**References**


**MOTHERISK**

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. Dr Koren is Director and Mr Gilbert and Dr Valois are members of the Motherisk Program. Dr Koren is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation and, in part, by a grant from the Canadian Institutes of Health Research. He holds the Ivey Chair in Molecular Toxicology at the University of Western Ontario in London.

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.

Published Motherisk Updates are available on the College of Family Physicians of Canada website (www.cfpc.ca) and also on the Motherisk website (www.motherisk.org).