DRUG INFORMATION
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QUESTION:
What is the safety of metformin for treatment of polycystic ovary syndrome (PCOS) in pregnancy?

ANSWER:
PREGNANCY:
BACKGROUND: Major malformations affect 2-4% of all live births. The cause is not identifiable in most cases and exogenous factors such as drugs may account for only 1-5% of all malformations (ie. affecting < 0.2% of all live births) [1]. However, as drug-induced malformations are often preventable, they remain an important consideration. The risk of foetal malformations is greatest during organogenesis (18 to 55 days post conception) [2,3]. The foetus is reported to have relative resistance to the toxic effects of drugs in the initial few weeks of pregnancy (until about day 17 post-conception) [3]. This is because there is either failed implantation with early abortion, or normal foetal development (ie. an 'all or nothing response'). Drug exposure before the 17th day post-conception would not be expected to pose risk of teratogenicity unless the drug has a long half-life and persists in maternal circulation beyond this period.

METFORMIN AND DIABETES: Most of the few studies on metformin in pregnancy come from the setting of diabetes. These studies are difficult to interpret because of factors such as small number of exposures, retrospective data collection, and the association of diabetes with a 2- to 5-fold increased risk of malformations [3,4]. The latter is believed to be mainly due to poor glycaemic control so insulin is the preferred choice for pregnant women with diabetes as it often enables better control of maternal glucose concentrations than alternative treatments. Further, it is safe for the foetus as it is one of the few drugs that are too large to cross the placenta. However, treatment with insulin is complex and in some countries (eg. South Africa) metformin is often used preferentially [3].
In general, the published data on outcomes with metformin in pregnancy are reassuring [5-8] and support low teratogenicity potential. Some studies have associated metformin with an increased risk of problems such as pre-eclampsia [9]. However, the findings are inconsistent across studies and confounding factors are likely to be present. For example, a recent case review conducted in New Zealand did not demonstrate any difference in the rate of pre-eclampsia, perinatal loss or neonatal morbidity amongst women with type 2 diabetes who took metformin and had more risk factors for adverse pregnancy outcomes (eg. hypertension) than controls [10].

METFORMIN AND PCOS: Metformin appears to improve conception rates in some chronically infertile women with PCOS. While further discussion on this topic is beyond the scope of this report, the published studies offer valuable information on pregnancy outcomes. Many of the women documented to have taken metformin to improve the chance of conception discontinued the drug on attainment of a positive pregnancy test. In these cases, there appeared to be no adverse sequelae for the infant, although again, the

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number of documented exposures is small [3,11,12]. Some other studies provide data on a small number of women who have continued the drug throughout pregnancy. For example, one prospective study included 19 women who took metformin throughout pregnancy and produced 11 (58%) normal babies without malformations. Two of the 19 women (11%) had first-trimester miscarriages and 6 (32%) had ongoing pregnancies deemed to be 'normal' via sonographic assessment at the time of publication. A further three women stopped metformin at 4 – 6 weeks' gestation and produced two live births (one with patent foramen ovale) and one miscarriage [13]. Another study prospectively monitored growth, motor and social development for the first 18 months of life in 126 live births (122 pregnancies) to 109 women with PCOS who took metformin throughout pregnancy. There were two birth defects (1.6%), which is a rate comparable to the 2 – 4% seen in the general population. The rate of pre-eclampsia did not differ from control pregnancies, and metformin did not appear to adversely affect growth or motor-social development score [14].

BREASTFEEDING: Three studies show that maternal use of metformin in breastfeeding results in very low exposure for the sucking infant. The infant dose is less than 1% of the maternal dose, corrected for the difference in body weight [15-17]. This is substantially below our (fairly) arbitrary cut-off of 10% which guides drug safety in breastfeeding, and will be much lower than in utero exposure.

CONCLUSION

The safety of metformin in pregnancy is difficult to assess as congenital malformations may occur as a result of poorly controlled diabetes. From the limited information in the first-trimester, metformin does not appear to be overtly teratogenic. However, as tight glycaemic control is essential during pregnancy, insulin is generally considered to be the drug of choice for the management of diabetes in pregnancy. If management with insulin is inadequate, it might be warranted to consider the addition of metformin after assessment of the risks and benefits.

Metformin is also being trialed for use in women with PCOS, primarily to increase the chance of conceiving. Again, the data in this population are limited to very small numbers, meaning that the possibility of an association with foetal malformations cannot be excluded. Ideally, all forms of drug exposure should be completely avoided in the first trimester of pregnancy, although it is recognised that metformin may carry considerable benefits for patients with PCOS in terms of maternal morbidity, and restoration of normal menstrual cycles. Risk:benefit assessment is required.

We do not expect the use of metformin during breastfeeding to be problematical due to low infant exposure. However, it should be noted that infant exposure may be greater in some circumstances such as prematurity or renal dysfunction. Under these circumstances we would advise seeking further advice.

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