Use of diuretics during pregnancy

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ABSTRACT

QUESTION Several of my pregnant patients use diuretics for hypertension. I have heard that diuretics cannot be used in pregnancy because of the reduction of plasma volume and the potential for decreasing placental perfusion, as well as a possible diabetogenic effect.

ANSWER Many studies—including a meta-analysis of almost 7000 neonates exposed to diuretics during pregnancy—did not find an increased risk of adverse effects, such as birth defects, fetal growth restriction, thrombocytopenia, or diabetes, among neonates exposed to diuretics in utero.

RÉSUMÉ

QUESTION Quelques-unes de mes patientes prennent des diurétiques pour l'hypertension. J'ai entendu dire qu'il ne fallait pas prendre de diurétiques durant la grossesse en raison de la réduction du volume plasmatique et de la possibilité de réduction de la perfusion placentaire, sans compter un effet diabétogène possible.

RÉPONSE De nombreuses études, dont une méta-analyse portant sur près de 7 000 nouveau-nés exposés aux diurétiques durant la grossesse, n'ont trouvé aucune augmentation du risque d'effets indésirables, comme des anomalies à la naissance, une réduction de la croissance du fœtus, la thrombocytopénie ou le diabète, chez les nouveau-nés exposés aux diurétiques *in utero*.

Hypertensive disorders are the most common medical disorders during pregnancy. These disorders are a major cause of maternal and perinatal mortality and morbidity.[1] Diuretics are commonly prescribed in essential hypertension before conception and are used during pregnancy for treating hypertension and cardiac disease.[2]

The mechanism of action of diuretics responsible for lowering blood pressure is not completely understood. The initial hypotensive response is mediated by a simple reduction in plasma volume and cardiac output. Long-term effect of low blood pressure is associated with partial reversal of the initial hemodynamic changes; the plasma volume and cardiac output partially rise toward the baseline level, while the systemic vascular resistance falls.[3]

Until recently, blood pressure in pregnancy was often managed using methyldopa, which was not always effective. Drugs such as prazosin and nifedipine have been introduced, and adding diuretics can potentiate the actions of all 3 drugs. In addition, methyldopa and prazosin can cause fluid retention, which can be prevented by using diuretics.[4]

Studies

Theoretically, diuretics can be associated with potential harmful effects owing to the reduction of plasma volume, cardiac output, and uteroplacental perfusion.[5] In 1975, Gant and colleagues[6] demonstrated that the dehydroisoandrosterone sulfate clearance, as a measure of uteroplacental perfusion, decreased by 18% when short-term use of furosemide was employed in chronic hypertensive patients and returned to baseline once the medication was stopped. Sibai et al[7] raised the concern that diuretic therapy in pregnant women with chronic hypertension was associated with a lower-than-normal degree of plasma volume expansion, which can be detrimental to fetal growth. In a subsequent randomized, prospective study, Sibai and colleagues demonstrated that plasma volume expansion was minimal in the diuretic-treated group (mean increase of 18%), whereas it was normal in the diuretic-discontinued group (mean increase of 52%). No difference was observed in perinatal outcome between the 2 groups.[8] These results suggest that in hypertensive pregnancies, diuretics prevent normal plasma volume expansion without influencing perinatal outcome.

In a meta-analysis of 9 randomized trials that compared diuretics with no therapy in 7000 pregnant women, Collins et al[9] found no difference in adverse outcomes. When the data on perinatal death were reviewed, little difference was seen in postnatal survival. The incidence of stillbirths was reduced by about one-third with treatment; however, perhaps because of small numbers (only 37 stillbirths), the difference was not statistically significant. In addition, the authors concluded that these randomized trials failed to provide reliable evidence of either the presence or absence of any worthwhile effects of treatment with diuretics on perinatal mortality.

In that same meta-analysis, there was also no evidence that diuretics could have adverse effects in pregnancy,

such as neonatal thrombocytopenia, jaundice, maternal pancreatitis, hypokalemia, and hyponatremia.

In a study conducted to examine the effect of diuretics on birth weight and preterm delivery, 2 population-based follow-up studies based on the Northern Jutland Prescription Database (NJPD) in Denmark and the Medicines Monitoring Unit's Database (MEMO) in Scotland reported that Danish women who purchased prescription loop diuretics during pregnancy gave birth to infants with higher birth weights than women who did not use diuretics, with a mean difference of 104.7 g (95% confidence interval [CI] 2.6 to 206.9 g). However, the authors believed this difference was most likely due to the high prevalence of diabetes (10.3%) among Danish women who used loop diuretics during pregnancy and who normally give birth to larger babies anyway. The authors also reported that women who purchased prescription diuretics during their pregnancies were at increased risk of preterm delivery (<37 completed weeks): NJPD (1.8 odds ratio [OR], CI 1.2 to 2.7); MEMO (1.9 OR, CI 0.9 to 4.3). The proportion of women with hypertension among those who purchased prescription thiazides was 15.8%, and the risk of having an infant with a birth weight of <2500 g was increased: NJPD, 2.6 OR, (CI 1.4 to 5.0); MEMO, 2.4 OR (CI 0.8 to 7.8). From this study, it could be concluded that prescribing diuretics during pregnancy was associated with differences in birth weight and incidence of preterm delivery, but confounding by indication can explain the findings.[10]

The National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy in Canada concluded that pregnancy does not preclude the use of diuretic drugs to reduce or control blood pressure in women whose hypertension predates conception (if an attempt is made to lower the dose) or the combinination of diuretic drugs with other agents, especially for women deemed likely to have salt-sensitive hypertension.[11]

Conclusion

Hydrochlorothiazide, triamterene, and amiloride are not teratogenic according to a small number of case reports. Some older studies raise concerns that thiazide diuretics might cause neonatal thrombocytopenia, but subsequent studies have shown that there is no increase in these events among neonates who were exposed to diuretics in utero. In addition, although diuretics do affect the plasma volume expansion of normal pregnancy, this has not been correlated with a negative effect on fetal growth.

Competing interests
None declared

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MOTHERISK

Motherisk questions are prepared by the **Motherisk Team** at the Hospital for Sick Children in Toronto, Ont. **Mr Al-Balas** is a doctoral candidate in the Faculty of Pharmacy at the University of Toronto. **Ms Bozzo** is a member and **Ms Einarson** is Assistant Director of the Motherisk Program.

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