

## Use of hypoglycemic drugs during lactation

Miguel Marcelo Glatstein MD   Nada Djokanovic MD MSc   Facundo Garcia-Bournissen MD  
Yaron Finkelstein MD   Gideon Koren MD FRCPC FACMT

### ABSTRACT

**QUESTION** My patient was taking glipizide (an oral sulfonylurea) for type 2 diabetes. Now she is pregnant and taking insulin instead. She is very anxious to return to her previous treatment immediately after delivery because of the pain and hurdles associated with the administration of insulin. Can sulfonylureas cross into human milk and, if so, is it safe for her to breastfeed her infant?

**ANSWER** The exposure of infants to second-generation sulfonylureas (eg, glipizide, glyburide) through breast milk is expected to be minimal, based on the limited data available. Women with type 2 diabetes treated with sulfonylureas should not be discouraged from breastfeeding. The benefits of breastfeeding greatly outweigh the risks of these medications, if any. The baby should, however, be monitored for signs of hypoglycemia.

### RÉSUMÉ

**QUESTION** Ma patiente prenait du glipizide (sulfonylurée par voie orale) pour un diabète de type 2. Elle est maintenant enceinte et prend plutôt de l'insuline. Elle a bien hâte de revenir à son ancien traitement et veut le faire immédiatement après l'accouchement à cause de la douleur et des embarras associés à l'administration d'insuline. Est-ce que les sulfonylurées peuvent passer dans le lait maternel et, dans l'affirmative, est-il sécuritaire pour elle d'allaiter son nourrisson?

**RÉPONSE** Selon les données limitées à notre disposition, on pourrait s'attendre à ce que l'exposition du nourrisson aux sulfonylurées de deuxième génération (p. ex., glipizide, glyburide) par l'intermédiaire du lait maternel soit minimale. Il ne faudrait pas décourager les femmes ayant un diabète de type 2 et traitées aux sulfonylurées d'allaiter leur enfant. Les avantages de l'allaitement dépassent largement les risques de ces médicaments, s'il en est. Il faudrait par ailleurs surveiller chez le bébé tout signe d'hypoglycémie.

Sulfonylureas are oral hypoglycemics commonly prescribed for type 2 diabetes mellitus, as they stimulate the release of insulin from the pancreas.<sup>1</sup> These drugs are classified into first-generation (eg, chlorpropamide, tolbutamide) and second-generation agents (eg, glyburide, glipizide, glimepiride, and gliclazide). First-generation sulfonylureas are rarely used nowadays owing to a high incidence of adverse reactions. Second-generation drugs possess better safety profiles and are more potent than the older agents.<sup>2</sup> Sulfonylureas act on the sulfonylurea receptor, an adenosine triphosphate-dependent potassium channel, stimulating the depolarization of pancreatic  $\beta$  cells and triggering insulin secretion via exocytosis.<sup>3</sup> Sulfonylureas also inhibit hepatic clearance of insulin.<sup>4</sup>

Sulfonylureas are absorbed through the gastrointestinal tract quickly; they appear in blood within 15 minutes of ingestion but have a prolonged duration of action,<sup>4</sup> especially the extended-release preparations. Sulfonylureas are mostly metabolized in the liver to metabolites excreted renally.<sup>5</sup> Peak plasma concentrations of second-generation sulfonylureas occur within

2 to 4 hours of therapeutic doses.<sup>6</sup> Duration of action is 12 to 24 hours.<sup>6,7</sup>

First-generation sulfonylureas have, to a limited extent, been shown to cross into breast milk. Tolbutamide is excreted into breast milk in small amounts (less than 0.5% of the maternal weight-adjusted dose). A 500-mg dose of tolbutamide twice daily produced milk levels of 3 and 18  $\mu\text{g}/\text{mL}$  in 2 patients, with milk-to-plasma ratios of 0.09 and 0.40, respectively.<sup>8</sup> In 1 patient, chlorpropamide was found in breast milk at concentrations of 5  $\mu\text{g}/\text{mL}$  (approximately 10% of the maternal weight-adjusted dose) after a 500-mg maternal oral dose.<sup>9</sup> No clinical effects to the exposed infants were reported.

Transfer of second-generation sulfonylureas into breast milk has been studied, with similar results. A Motherisk study examining the transfer of glyburide and glipizide into breast milk failed to detect these drugs in breast milk.<sup>10</sup> In a recent study,<sup>8</sup> mothers who had recently delivered were given a single dose of glyburide, 5 mg ( $n=6$ ) or 10 mg ( $n=2$ ), and maternal blood and milk were tested at 8 hours after the dose. The

authors estimated that the maximum dose that a fully breastfed infant would receive with maternal 5- and 10-mg daily doses would be below 1.5% of the maternal weight-adjusted dose.<sup>10</sup> Another group of mothers (N=5) received daily doses of glyburide (nonmicronized 5 mg) or glipizide (immediate-release 5 mg). Neither glyburide nor glipizide could be detected in breast milk. Blood glucose levels were normal in all 3 infants who were exclusively breastfed (glyburide [n=1], glipizide [n=2]). Based on these data, maternal exposure to these drugs seems unlikely to exert any clinically significant pharmacologic action on breastfed infants.

Extensive binding of glyburide and glipizide to plasma proteins has been postulated as the reason for the observed lack of transfer of these drugs into breast milk.<sup>10</sup>

Sulfonylureas offer substantial therapeutic benefits to women with type 2 diabetes mellitus, and an expanding number of pregnant women are taking these medications for the treatment of gestational diabetes or type 2 diabetes during pregnancy.<sup>11</sup> The benefits provided by these medications seem to outweigh the small theoretical risk posed by the minimal (if any) excretion of these drugs into breast milk. These medications are likely compatible with breastfeeding, provided that monitoring the baby for signs of hypoglycemia is feasible.<sup>12</sup>

### Metformin with breastfeeding

Metformin is a widely used oral, biguanide hypoglycemic drug for the management of type 2 diabetes. Metformin stimulates glucose uptake in the liver and peripheral tissues and decreases hepatic glucose production. These actions are the result of an enhanced tissue response to insulin and therefore require the presence of insulin. Metformin is not expected to cause hypoglycemia.<sup>13</sup>

Three studies have evaluated the transfer of metformin into breast milk. In one study, 5 women taking a median dose of 1500 mg/d of metformin had average breast milk levels of 0.27 mg/L, amounting to an estimated 0.28% of the maternal weight-adjusted dose ingested by the infant. Very low or undetectable concentrations of metformin were observed in the plasma of the 4 babies studied.<sup>14</sup> A second study looking at breast milk transfer of metformin enrolled 7 women who took 1000 mg/d of the drug. The milk concentrations observed were similar to those of the previous study, with estimated doses ingested by the infants below 1% of the maternal weight-adjusted dose.<sup>15</sup> Another study involving 8 women (3 at steady state and 5 after single 500-mg doses of metformin) estimated that nursing infants would ingest about 0.11% to 0.25% of the maternal weight-adjusted dose.<sup>16</sup>

A recent prospective study followed 61 breastfed and 50 formula-fed infants born to 92 mothers with


polycystic ovary syndrome taking 1.5 to 2.55 g of metformin daily throughout pregnancy and lactation.<sup>17</sup> The authors concluded that metformin use during lactation had no adverse effects on breastfed infants' growth, motor-social development, or intercurrent illnesses, compared with formula-fed infants.

Metformin is considered a first-line agent for the treatment of type 2 diabetes,<sup>13</sup> and has also been proposed as a useful drug for the management of gestational diabetes.<sup>18</sup> The very limited amounts of metformin observed in breast milk are highly unlikely to lead to substantial exposure in the breastfed baby. Metformin can be considered a safe medication for the treatment of type 2 diabetes in a breastfeeding mother.

### Conclusion

The available data suggest that the levels of glyburide and glipizide in milk are negligible and would not be expected to cause adverse effects in breastfed infants; however, as data are based on a single study with a limited sample size, monitoring of the breastfed infant for signs of hypoglycemia is advisable during maternal therapy with any of these agents.

Treatment with metformin during lactation is unlikely to lead to toxicity in the breastfed infant. Given the safety profile of metformin, as compared with sulfonylureas, it is advisable to consider metformin as first-line treatment during lactation if this drug is appropriate for the particular patient. Nevertheless, second-generation sulfonylureas are also likely to be safe during lactation.

Other oral medications currently used for the treatment of type 2 diabetes, such as the thiazolidinediones and acarbose, have not been studied in the lactation period. 

#### Acknowledgment

Dr Garcia-Bournissen has received funding from the Clinician Scientist Training Program. This program is funded, fully or in part, by the Ontario

## MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. Drs Glatstein, Djokanovic, Garcia-Bournissen, and Finkelstein are members and Dr Koren is Director of the Motherisk Program. Dr Koren is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation. He holds the Ivey Chair in Molecular Toxicology in the Department of Medicine at the University of Western Ontario in London.

Do you have questions about the effects 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 *Canadian Family Physician* website ([www.cfp.ca](http://www.cfp.ca)) and also on the Motherisk website ([www.motherisk.org](http://www.motherisk.org)).

Student Opportunity Trust Fund—Hospital for Sick Children Foundation Student Scholarship Program.

#### Competing interests

None declared

#### References

- Nathan DM, Rousell A, Godine JE. Glyburide or insulin form metabolic control in non-insulin-dependent diabetes mellitus. A randomized, double-blind study. *Ann Intern Med* 1988;108(3):334-40.
- Rumboldt Z, Bota B. Favorable effects of glibenclamide in a patient exhibiting idiosyncratic hepatotoxic reactions to both chlorpropamide and tolbutamide. *Acta Diabetol Lat* 1984;21(4):387-91.
- Gerich JE. Oral hypoglycemic agents. *N Engl J Med* 1989;321(18):1231-45.
- Harrigan RA, Nathan MS, Beattie P. Oral agents for the treatment of type 2 diabetes mellitus: pharmacology, toxicity, and treatment. *Ann Emerg Med* 2001;38(1):68-78.
- Matteucci MJ. One pill can kill: assessing the potential for fatal poisoning in children. *Pediatr Ann* 2005;34(12):964-8.
- Sulphonylureas. In: *AHFS drug information*. Bethesda, MD: American Society of Health-System Pharmacists; 1998. p. 2595-7.
- Hussain K, Mundy H, Aynsley-Green A, Champion M. A child presenting with disordered consciousness, hallucinations, screaming episodes and abdominal pain. *Eur J Pediatr* 2002;161(2):127-9.
- Moiel RH, Ryan JR. Tolbutamide orinase in human breast milk. *Clin Pediatr (Phila)* 1967;6(8):480.
- Briggs GG, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation*. 8th ed. Philadelphia, PA: Lippincott William & Wilkins; 2008. p. 331.
- Feig DS, Briggs GG, Kraemer JM, Ambrose PJ, Moskovitz DN, Nageotte M, et al. Transfer of glyburide and glipizide into breast milk. *Diabetes Care* 2005;28(8):1851-5.
- Moretti ME, Rezvani M, Koren G. Safety of glyburide for gestational diabetes: a meta-analysis of pregnancy outcomes. *Ann Pharmacother* 2008;42(4):483-90.
- Feig DS, Briggs GG, Koren G. Oral antidiabetic agents in pregnancy and lactation: a paradigm shift? *Ann Pharmacother* 2007;41(7):1174-80. Epub 2007 May 29.
- Setter SM, Iltz JL, Thams J, Campbell RK. Metformin hydrochloride in the treatment of type 2 diabetes mellitus: a clinical review with a focus on dual therapy. *Clin Ther* 2003;25(12):2991-3026.
- Hale TW, Kristensen JH, Hackett LP, Kohan R, Ilett KF. Transfer of metformin into human milk. *Diabetologia* 2002;45(11):1509-14. Epub 2002 Sep 25.
- Briggs GG, Ambrose PJ, Nageotte MP, Padilla G, Wan S. Excretion of metformin into breast milk and the effect on nursing infants. *Obstet Gynecol* 2005;105(6):1437-41.
- Gardiner SJ, Kirkpatrick CM, Begg EJ, Zhang M, Moore MP, Saville DJ. Transfer of metformin into human milk. *Clin Pharmacol Ther* 2003;73(1):71-7.
- Glueck CJ, Salehi M, Sieve L, Wang P. Growth, motor, and social development in breast- and formula-fed infants of metformin-treated women with polycystic ovary syndrome. *J Pediatr* 2006;148(5):628-32.
- Rowan JA, Hague WM, Gao W, Battin MR, Moore MP; MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med* 2008;358(19):2003-15.

