Drugs in Pregnancy

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The first reaction of many of us when we hear "thalidomide" is to think "birth defects," or perhaps "phocomelia" if we are old enough. The thalidomide story is one of the saddest stories of modern medicine, and is an illustration of how rigorous the regulation of medication use must be. The affected survivors of intrauterine exposure to thalidomide (or any teratogenic agent, for that matter) deserve our sympathy and full support. It is heartening that, two months ago, the federal Minister of Health announced a commitment by the federal government to provide immediate and continuing financial aid for Canadian survivors of the teratogenic effects of thalidomide.[1] This was welcome news, but astonishingly delayed.

It was in December 1961 that William McBride, an obstetrician working in Sydney, Australia, made public his concern about the teratogenic effects of thalidomide in a letter published in *The Lancet*.[2] His observations were just that; thalidomide had been marketed in Australia for some years and had been prescribed enthusiastically for nausea and insomnia in pregnant women. Curiously, at that time it was widely believed that drugs ingested by the mother did not cross the placenta if they did not harm the mother. During a short time span, McBride had delivered a group of newborns with limb and bowel deformities, and in searching for links in the prenatal management of these babies he had identified maternal use of thalidomide as a potential contributing factor. His letter to the editor of *The Lancet* reflected the communication style of the day: he reported that almost 20% of women in his practice who had taken thalidomide prenatally had delivered babies with multiple severe abnormalities affecting "the bones and musculature of the gut," and he asked the editor if any *Lancet* readers had seen similar abnormalities. As it turned out, they had. Multiple reports led to the withdrawal of thalidomide from the global market, although not as quickly as might have been expected; it was withdrawn from the West German market in November 1961 and the United Kingdom in December 1961, but remained available in Canada for another three months. Since thalidomide was never approved for use by the Food and Drug Administration, there has not been a corresponding thalidomide story in the United States.

The thalidomide story led to an enormous change in how medications are prescribed for pregnant women. It is not an exaggeration to say that since the early 1960s every drug has been assumed to be potentially teratogenic. Clinical trials of new medications have expressly excluded involvement of women who are (or even might be) pregnant. This caution has been entirely valid, but it has become impossible for the most part to prove that any relatively new drug is *not* either teratogenic or capable of producing some fetal abnormality; safety is proven only by widespread use without consequences over a very long period. Perhaps the most insidious effect of the thalidomide story has been to instil in women the fear that *any* medication that they take during pregnancy will have a harmful effect on the fetus. Because many women will take medication before they learn that they are pregnant, their intentions to avoid any medication during pregnancy will be thwarted at the outset.

Newly pregnant women who have taken medication and who are worried that they have harmed their fetus will seek reassurance from their obstetric caregiver. But their caregiver is often not able to give informed advice. In fact, no single medical specialist is likely to be in a position to do so. Clinical pharmacologists can give partial reassurance; medical geneticists or toxicologists might also be able to reassure to some extent. The best advice, however, will come from a multidisciplinary entity such as Motherisk, whose focus is the safety of medication in pregnancy.

Motherisk was established in 1985 at the Hospital for Sick Children in Toronto to counsel women and health care professionals. The counsel that the organization provides is based on their continuous evaluation of reproductive

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toxicology literature and on their own clinical and laboratory research. The work of Motherisk, directed by Gideon Koren, has been widely recognized, most recently in 2011 when the Motherisk team became one of the two highest ranked winners of the CIHR/CMAJ competition for Top Achievements in Health Research.[3]

Such recognition is well-deserved, although Dr Koren and colleagues will surely acknowledge that their professional high point came in 2005, when the Motherisk team was invited to contribute a quarterly review article related to drug use in pregnancy to this journal. To date, Dr Koren and colleagues have contributed 40 evidence-based, peer-reviewed "Motherisk Rounds" articles to JOGC. Over the course of 10 years, the Motherisk team has reviewed a wide range of subjects, and unsurprisingly they have been both timely and topical. Contributions have included reviews of H1N1 influenza in pregnancy, and subsequently H1N1 vaccination during pregnancy; the use of antidepressants in pregnancy, from fetal, neonatal, maternal, and clinical pregnancy perspectives; and discussions of hypothyroidism in pregnancy, the safety of methimazole and propylthiouracil in pregnancy, and fetal thyroid disorders. They have reviewed cocaine abuse during pregnancy and the safety of conscious sedation during pregnancy. They have reviewed the effects of diagnostic radiation and the use of probiotics. Just about every timely and significant subject has been covered in the series, and we look forward to continuing evidence-based coverage of critical topics.

The Motherisk team has a long-standing interest in maternal folate levels, folic acid supplementation, and the prevention of neural tube defects.[4] In the May issue of the journal, they provided a systematic review of the association between use of oral contraceptives and folate status,[5] and in the present issue they review the effectiveness of folate-fortified oral contraceptive preparations in maintaining optimal folate levels in users.[6] This is important to ensure maximal protection against neural tube defects when users of these preparations discontinue use in order to conceive. So long as women continue to have unplanned or unexpected pregnancies, they risk playing "catch-up" to achieve the optimally protective folate levels.

As Editor-in-Chief, I felt vicarious pride when hearing at a meeting in Europe that a Motherisk review in JOGC (it happened to be on nicotine replacement during pregnancy[7]) had contributed to a speaker's change in practice. I value and appreciate our relationship with Motherisk, and am very grateful for their continuing contributions. And I still think they have the snappiest name of any such program!

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