

## CIHR/CMAJ: TOP ACHIEVEMENTS IN HEALTH RESEARCH

## Essay for the 2011 CIHR/CMAJ award: Motherisk — caring for mothers, protecting the unborn

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The two highest-ranking winners of the 2011 CIHR/CMAJ competition for Top Achievements in Health Research are Daniel Drucker, and Gideon Koren and colleagues for the Motherisk team. In the following essay, Dr. Koren and colleagues describe the work of the Motherisk team in the area of fetal–maternal toxicity. The essay by Dr. Drucker and synopses of the other four winning achievements are available at [www.cmaj.ca](http://www.cmaj.ca).

Every year, scores of new medications enter the market, and few of them have safety data concerning fetal exposure during pregnancy. With half of all pregnancies unplanned, and with large numbers of women who have conditions requiring treatment during pregnancy (e.g., epilepsy, morning sickness), there is a serious knowledge gap as to which medications are safe for the unborn baby and which should be avoided.

Since the thalidomide disaster of 1958–1961, medicine is practised as if any drug is a potential human teratogen, leading physicians and pregnant women to avoid using medications — even for life-threatening conditions — or to terminate otherwise wanted pregnancies after exposure to safe drugs perceived as being risky.<sup>1</sup> Acknowledging this gap, the Motherisk program was founded at the Hospital for Sick Children in 1985 to counsel women and health professionals, to conduct large-scale laboratory and clinical research, and to translate this new knowledge to counselling.<sup>2</sup> With continuous research support from the Canadian Institutes of Health Research (CIHR), National Institutes of Health, Genome Canada, March of Dimes, Physicians' Services Incorporated Foundation and the pharmaceutical industry, Motherisk has revolutionized the area of medication safety in pregnancy and affected the way women are cared for during pregnancy in Canada and around the world.

### Major activities of the program

With over 800 peer-reviewed scientific papers, two regular columns for Canadian physicians, 12 medical books and training programs for physicians from over 40 countries, Motherisk is at the forefront of knowledge translation, empowering the continuity between the laboratory, the patient and the population. By telephone, fax, email or in person, the team (currently 75 members) counsels over 200 women and health professionals daily, directly affecting the care of thousands of Canadian women and their infants each year, in addition to numerous international cases. The Motherisk website ([www.motherisk.org](http://www.motherisk.org)), which includes a series of videorecorded lectures for health professionals, is visited 54 000 times each month.

Since 1995, the Motherisk team has published a monthly column in *Canadian Family Physician*. Indexed in MEDLINE and available free on the websites of both the journal and Motherisk, these articles are accessed by thousands of health professionals worldwide. Physicians commonly report using these columns as their main source of information on the effects of different drugs during pregnancy. In addition, the Moth-

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Gideon Koren has received grants from Astra Zeneca, Novartis, Bayer, Duchesnay and Wyeth Ayerst. Irena Nulman has received grants from Wyeth. Adrienne Einarson has received a grant from Eli Lilly. Shinya Ito is a member of the board of the American Society for Clinical Pharmacology and Therapeutics, and he receives a fee as an associate editor for their journal; he has received grants from Astra Zeneca and the World Health Organisation. No other competing interests were declared.

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### KEY POINTS

- There is a serious knowledge gap concerning which medications are safe for unborn babies and which should be avoided during pregnancy.
- The Motherisk program at the Hospital for Sick Children was established to counsel women and health professionals on fetal–maternal toxicity, to conduct large-scale laboratory and clinical research and to translate this new knowledge to counselling.
- Motherisk has established a program for long-term follow-up of infants exposed to drugs in utero.
- The Motherisk team has shown that fetal exposure to illicit drugs can be detected in neonatal hair and meconium, and reported the first case of neonatal death from opioid toxicity after breastfeeding as a result of ultrarapid metabolism of codeine by the mother.

risk team publishes a quarterly column in the *Journal of Obstetrics and Gynaecology Canada*, which reaches every Canadian obstetrician. Recent advances in knowledge developed by the Motherisk team are also communicated through regular lectures to medical students, pharmacy students, midwives and residents, in addition to professional development activities for family physicians, obstetricians and pharmacists.

In 2001, Motherisk established Fetal Alcohol Canadian Expertise (FACE), a network of Canadian researchers, clinicians, parents and policy-makers actively engaged in preventing and treating fetal alcohol spectrum disorder, the leading cause of developmental disability in Canada. In 2004, we founded the first peer-reviewed scientific journal on this subject, *Fetal Alcohol Research*, with open access to ensure maximal knowledge transfer (available at [www.motherisk.org/FAR](http://www.motherisk.org/FAR)).

Since its inception in 1985, the Motherisk team has trained health care professionals from over 40 countries, facilitating large-scale knowledge transfer of novel Canadian science to other countries. As a consequence, programs like Motherisk have been established in countries such as Israel, Australia, Japan, South Korea, Brazil and Hong Kong, helping millions of women worldwide.

## Changes in practise, policy and decision-making

The work of the Motherisk team has changed policy and practise in the care of pregnant women and their babies. The Motherisk team discovered that fetal exposure to illicit drugs can be detected in neonatal hair and meconium. In 1989, the laboratory showed that fetal exposure to cocaine can be traced by measuring both the toxin itself and its major metabolite, benzoylecgonine, in neonatal hair.<sup>3</sup> This breakthrough revolutionized neonatal diagnostic testing and was followed by similar findings for other drugs (e.g., methamphetamines, cannabinoids).<sup>4</sup> In 1999, the laboratory found that excessive maternal drinking can be traced by measuring fatty acid ethyl esters in neonatal meconium,<sup>4</sup> leading to the establishment of a diagnostic test for fetal alcohol spectrum disorder throughout Canada and its incorporation into the new screening guidelines of the Public Health Agency of Canada.<sup>5</sup>

In 2005, Motherisk researchers described the first-ever fatal case of an infant poisoned by opioids ingested through breastmilk from a mother taking codeine who was an ultrarapid metabolizer of the drug owing to overexpression of the cytochrome P450 2D6 enzyme.<sup>6</sup> This and subse-

quent findings by Motherisk led the US Food and Drug Administration and Health Canada to issue warnings related to the use of codeine during breastfeeding. Further research supported by Genome BC, Genome Canada and CIHR has resulted in new guidelines for breastfeeding (available at [www.motherisk.org](http://www.motherisk.org)) while treating maternal pain postpartum.

In 1995, Dr. Koren and colleagues showed that the pain involved in neonatal circumcision is remembered by the infant and results in augmented pain response to vaccination at six months of age.<sup>7</sup> This work, cited in over 500 scientific papers, has led to major changes in the approach to neonatal pain and its long-term effects.

Motherisk's work has helped establish the fetal safety of numerous drugs (e.g., quinolones, rubella vaccine),<sup>8</sup> while documenting the fetal risks of other substances and medications (e.g., organic solvents, corticosteroids, misoprostol).<sup>9,10</sup> In addition, the team has established a program for the long-term follow-up of infants exposed to drugs in utero. This program has shown, for example, the long-term safety of fluoxetine.

In 2005–2006, Motherisk documented that about 40% of women in Ontario do not achieve sufficient systemic folate levels to prevent neural tube defects.<sup>11</sup> This finding resulted in changes in Canadian guidelines for folate intake during pregnancy<sup>12</sup>, and Canada was the first country to produce prenatal vitamins containing 5 mg of folate. The management of morning sickness has also been changed by the work of the Motherisk team, with their guideline (available at [www.motherisk.org](http://www.motherisk.org)) adopted by both the Canadian and American associations of obstetricians and gynecologists.

The impact of Motherisk's counselling for women and health professionals has been documented many times. For example, effective counselling for women planning pregnancy substantially increased adherence to supplementation with folic acid.<sup>13</sup> Counselling women booked for pregnancy termination because of unjustified perceptions of teratogenic risks has also been effective in preventing abortion.<sup>14</sup>

Over the past 25 years, the Motherisk team has revolutionized the field of maternal–fetal toxicology by effectively applying knowledge translation to ensure that new knowledge developed by the team affects practise and policy.

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