INTRODUCTION

It is with great humility and pride that I received the Sumner J. Yaffe Lifetime Achievement award in Pediatric Pharmacology and Therapeutics from the Pediatric Pharmacy Advocacy Group. Dr Yaffe was one of my mentors, and his leadership and encouragement paved my way in what was then a new field. Witnessing now the hundreds of pharmacists in pediatric hospitals throughout North America dedicated to pediatric therapeutics is a major testament to Dr Yaffe’s legacy. The announcement that I had received this award came the day after Sumner’s death, and it signaled for me the strong need for continuation of his work and legacy. In this short essay, I will share with you an area of developmental therapeutics that I was very privileged to lead: drug exposure and response by the fetus.

Each year, numerous new medications enter the market. The official labeling for most of these does not contain safety data related to exposure in pregnancy; however, millions of women have conditions that need to be treated in pregnancy (e.g., urinary tract infections, diabetes, and morning sickness). The lack of knowledge regarding fetal safety of medications poses significant challenges for practitioners, places the mother at risk for inadequate treatment of her disease, and places the fetus at risk of toxicity.1

Since the thalidomide era, we practice as if any drug is unsafe to the fetus, leading physicians and expecting women to avoid the use of medications, even for the treatment of serious diseases. In acknowledging this situation, we founded the Motherisk program at the Hospital for Sick Children in order to conduct laboratory and clinical research, to translate the new knowledge to support decisions by women and their health professionals, and to affect policy.

Presently, the 75 members of Motherisk provide daily counseling to more than 200 women, families, and health professionals from Canada and internationally.2 With over 1000 peer-reviewed scientific papers, 2 regular columns for Canadian physicians, 12 medical books, and training physicians from over 35 countries, Motherisk is on the forefront of knowledge transfer, empowering the continuum between the laboratory, the patient, and the population.

In addition to monitoring for congenital malformations, Motherisk has created a research network collecting data on long-term child neurodevelopment after in utero exposure to drugs and chemicals. For example, in 1997 we published the first account on the long-term safety of fluoxetine (Prozac, Eli Lilly, Indianapolis, IN) during pregnancy, which led to major changes...
in practice worldwide and enabled physicians to treat pregnant women with this new class of medications.\(^3\)

Since its creation, Motherisk has worked to establish the fetal safety of numerous drugs (e.g., quinolones, rubella vaccine), while documenting fetal risks of other (e.g., solvents, corticosteroids, misoprostol). In parallel, our laboratory has developed novel hair and meconium tests, which quantify fetal exposure to drugs of abuse and alcohol that may have long-term devastating impacts on the unborn.\(^4\)

**MAJOR ACTIVITIES**

The Motherisk program directly impacts the management of thousands of women and their infants every year through the following activities:

1. The Motherisk team counsels over 200 women and health professionals each day. Contact occurs through the telephone, facsimile, and e-mail. An additional 10 to 20 women are seen in our weekly clinics.
2. Motherisk Web site (motherisk.org) is visited 34,000 times per month, with average monthly 150,000 page views (5 pages per visit). It is quoted in Google over 35,000 times. Our unique knowledge transfer feature, “electronic-learning,” is a series of videotaped lectures, which are widely accessed on our website.
3. In 1995, we began publishing a monthly column in *Canadian Family Physician*. Each month, the column answers a different question that has been posed by a practitioner. The column is received by every family physician in Canada and is listed in Medline and PubMed (National Center for Biotechnology Information, Bethesda, MD); the column can be retrieved freely on the Motherisk Web site, and hence accessed by thousands of health professionals worldwide. Physicians commonly report using these resources as the primary source of information in their practice. In addition, the Motherisk team publishes the “Motherisk Grand Rounds” in the journal of Society of Obstetrics and Gynaecology of Canada (SOGC) 4 times a year, which reaches every obstetrician in Canada.
4. The new knowledge developed by Motherisk is regularly communicated numerous times each year by members of our team through medical education activities related to this emerging field at all levels of education including lecturing to undergraduate medical students at Universities of Toronto and Western Ontario; frequent and regular lectures to residents in obstetrics, pediatrics, and medicine in both the University of Toronto and the University of Western Ontario; and lectures to undergraduate pharmacy students at the University of Toronto.\(^7\)
5. In order to address the leading cause of developmental disability in Canada, in 2001 we established the Fetal Alcohol-Canadian Expertise network. This initiative brings together hundreds of Canadian researchers, clinicians, parents, and policy makers in the area of fetal alcohol syndrome. To further extent the work of this group, in 2004 we founded the first scientific peer review journal, *Fetal Alcohol Research*. In order to ensure maximal exposure and knowledge transfer, this journal has free access (www.cjcp.com).
6. In 2005, I was invited by the CIHR-NIH to create the Summer Institute in Obstetric Pharmacology, which selects yearly 20 young clinicians and students for small group, interactive learning with top scientists from North America. The success of the first 8 institutes has been outstanding, with a substantial number of trainees establishing careers in this emerging field. Since the inception of Motherisk in 1985, we have also trained physicians and pharmacists from over 40 countries. Quite a few of them have subsequently established similar programs in their countries, helping millions of women worldwide. These include Israel (“Heriophone”), Japan (Motherisk), South Korea (Motherisk Korea), Australia (“MotherSafe”), and Brazil.

**IMPACT OF SPECIFIC KNOWLEDGE TRANSFER INITIATIVES**

Motherisk is multidimensional and has influenced a variety of areas. Several examples are provided below to demonstrate the impact of our programmatic initiatives.

1. In 2005, we described the first fatal case of a neonate who was poisoned by opioids delivered via breast milk. The mother was an
ultra rapid metabolizer of the 2D6 enzyme, leading her to transfer large amounts of morphine to the baby through her milk. This has led the US Food and Drug Administration and Health Canada to issue warnings related to codeine use during breastfeeding. Further research with support of Genome Canada and CIHR has led to develop guidelines for safe breastfeeding while treating post partum maternal pain (motherisk.org).

2. In 1988, we showed for the first time that fetal exposure to cocaine could be traced back by measuring the toxin in neonatal hair. This revolutionized neonatal diagnostic testing and was followed by analysis of numerous other drugs (e.g., methamphetamines, cannabinoids). In 1999, we showed that excessive maternal drinking could be traced by measuring fatty acid ethyl esters in neonatal meconium. Translational research, supported by CIHR in the Grey Bruce region of Ontario, has shown that 3% to 4% of newborns are exposed to excessive maternal alcohol consumption. This has led to the establishment of the meconium test, which is now used throughout Canada as a diagnostic test for fetal alcohol syndrome. The test has also been incorporation into the new Screening Guidelines of the Public Health Agency of Canada.

3. In 2005–2006, we conducted the first pharmacokinetic studies of folic acid in pregnancy, showing that an estimated 40% of Ontario women do not achieve sufficient systemic folate levels to prevent neural tube defects. With these findings, we initiated changes in the Society of Obstetrics and Gynecologists of Canada guidelines, facilitating more common use of 5 mg folate for women of reproductive age. These guidelines have had a major impact on practice in Canada and have led Canada to be the first country worldwide to produce a prenatal multivitamin containing 5-mg of folic acid.

4. Morning sickness, also called nausea and vomiting of pregnancy, is a condition that affects 80% of all pregnant women. Thalidomide was originally developed and prescribed as management for morning sickness in West Germany, but its use was discontinued when it was found to cause birth defects. Motherisk guidelines for the management of morning sickness have been adopted by both the Canadian (SOGC) and American associations of Obstetricians and Gynecologists.

5. We established the only Canadian laboratory and one of very few worldwide, to perform placental perfusion experiments of drugs and chemicals. This research has recently shown that glyburide, the oral hypoglycemic drug, is effluxed by the placenta from the fetal to the maternal circulation by the Breast Cancer Resistant Protein transporter, thus protecting the baby from hypoglycemia. Supported by CIHR, this research has led to increased use of glyburide as a first-line drug for gestational diabetes.

6. In 1995, we showed that the pain involved in neonatal circumcision is imprinted and remembered by the infant and results in augmented pain response to vaccination at 6 months of age. This work has changed the approach to neonatal pain and to its long-term effects.

7. The impact of Motherisk counseling on women and health professionals has been documented many times over. Due to space limitations, only 2 examples are presented. First, counseling women scheduled for pregnancy termination due to unjustified perception of teratogenic risk has been effective in preventing abortion in numerous cases. Second, counseling women on the need for folic acid supplementation has been shown to be very effective.

SUMMARY

Over the last 28 years, the Motherisk team has been committed to changing the science of maternal-fetal toxicology. Additionally, the team has been able to apply knowledge transfer to ensure that new information developed by the team affects practice and policy development. There is still much to do. Most critically, we must convince regulatory agencies worldwide that failure of pharmaceutical agencies to perform research of drug safety and effectiveness in pregnancy only produces therapeutic orphans of pregnant women. Ultimately, the lack of information may prevent the mother from receiving needed therapeutics modalities and may also cause unborn babies tremendous unacceptable risks.
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ABBREVIATIONS CIHR, Canadian Institutes of Health Research; NIH, National Institutes of Health; SOGC, Society of Obstetrics and Gynaecology of Canada

CORRESPONDENCE Gideon Koren, MD, Director, Motherisk Programs Clinical Pharmacology and Toxicology, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5X 1A8 email: gkoren@sickkids.ca

REFERENCES