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# DRUGS IN PREGNANCY AND LACTATION SYMPOSIUM

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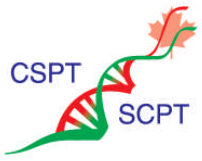


Canadian Society of Pharmacology and Therapeutics
La Société canadienne de Pharmacologie Therapeutique

# Drugs in Pregnancy – The Issues for 2010

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## ABSTRACT

A Motherisk symposium on establishing benchmarks for the evaluation of medications during pregnancy, was held on May 10, 2006, under the auspices of the Canadian Society of Pharmacology and Therapeutics.[1] From that symposium came a consensus on the need for collection and analysis of data on fetal safety and ongoing post-marketing surveillance, which in turn led to the establishment of CaseMed-Pregnancy – the Canadian Alliance for Safe and Effective Medication During Pregnancy and Breastfeeding.

CaseMed-Pregnancy subsequently changed its name to Pregmedic, whose mission it is to advocate for the safe and effective use of medications in pregnancy and lactation. The organization's goals are to increase awareness of pregnancy issues at Health Canada and among Canadian practitioners; to require standard labelling of medicines for use in pregnancy and lactation, providing practitioners and patients access to current and reliable information for decision making; and to advocate for the development of patient registries or surveillance programs for medications used during pregnancy and breastfeeding.

During pregnancy, there are a number of considerations as regards medication disposition and effectiveness. These include:

- Changes in total body weight and body fat,
- Delayed gastric emptying and prolonged GI transit,
- Increased extracellular fluid and total body water,
- Increased cardiac output,
- Increased stroke volume and elevated maternal heart rate,
- Decreased albumin concentration with reduced protein binding,
- Increased blood flow to organs,
- Increased glomerular filtration rate,
- Changed hepatic enzyme activity.

Many drugs are used in pregnancy and lactation to treat chronic and pregnancy-induced conditions, such as hypertension, which can occur *de novo* during pregnancy or can be exacerbated by pregnancy. Few drugs are studied for use during pregnancy and lactation and little guidance is available to physicians and patients, thus most medications are used "off label" in pregnancy. Most product monographs advise that drugs should not be used during pregnancy or breastfeeding, yet two-thirds of women who deliver a baby have taken at least one prescription medication during pregnancy; many more have taken non-prescription medications. In North America, 45-50% of pregnancies are unintended, so that many women who are on medications prior to conception continue taking them not knowing they are pregnant.

For reasons such as cost and litigation, pharmaceutical companies do not address pregnancy. Information on the disposition of drugs during this state is usually obtained post-approval and through voluntary adverse drug reaction (ADR) reporting. There do exist some pregnancy exposure registries, retrospective birth defect registries, and case controlled studies; however, registry information is difficult to access, is not widely disseminated or publicized, and is not in one repository where we can gain access and provide practitioners and patients with useful information. Overall, healthcare professionals are left with the burden of evaluating the risk/benefit of using a medication during pregnancy or breastfeeding. An article from the journal Obstetrics and Gynecology notes: "many labels are outdated". For example, two recent randomized controlled trials examined outcomes in pregnant women exposed to metformin, with numerous clinically relevant endpoints. This information would help inform clinician prescribing and patient counseling; however, the metformin label contains data from neither study. Current regulations do not require drug manufacturers to include these postmarketing published data in the drug label. For an individual clinician, searching and reviewing the medical literature is labor-intensive, not always feasible, and requires an ability to discern a study's quality and power to detect risks.[2]

Looking to what is happening in other countries we find that the U.S. Food and Drug Administration (FDA) in the United States require labelling according to preset categories, using letter codes:

A: Controlled studies in humans,
B: Human data is reassuring (animal positive) OR animal studies show no risk,
C: Human data is lacking; animal studies are positive; OR not done,
D: Human data show risk, benefit may outweigh risk,
X: Animal or human data positive.

One would assume that "A" would be the safest and "X", the most worrisome. But, again from the Obstetrics and Gynecology article, "the letter categories are limited in their scope at best and misunderstood at worst". Despite common misperception, the current system is not a gradation of risk from A to X in which a category C drug affords less risk than a category D drug. In fact, categories C, D, and X are based on risk weighed against benefit. For example, oral contraceptives are labeled X, not because they are inherently riskier than category C drugs, but because they afford no benefit during pregnancy.[2]

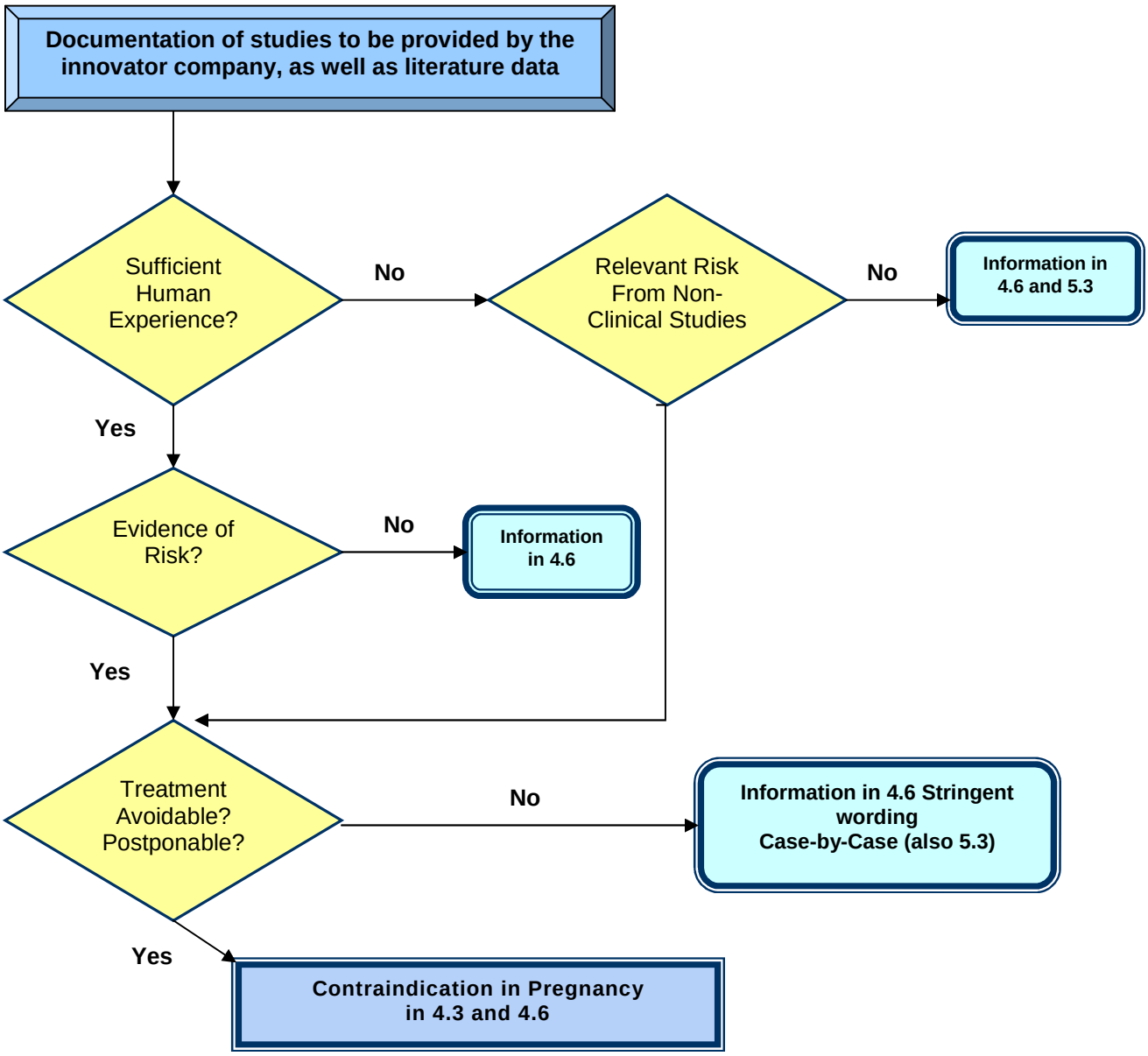
There is a move to revise these categories, and on May 28, 2008, the FDA proposed to amend its regulations for labelling and move pregnancy information from the "Contraindications" section to the section "Use in Specific Populations". Prescription drug labelling would require pregnancy exposure registry information (if applicable); a general statement about the background risk of fetal developmental abnormalities, a fetal risk summary; clinical considerations; and a data component. Very recently, on December 30, 2009, the FDA announced that it will collaborate with other researchers in a new study called the *Medication Exposure in Pregnancy Risk Evaluation Program*. Data will be used from 11 health plan-affiliated research sites.

In Europe, the European Medicines Agency (EMA) has published the Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-authorization Data. There is also the Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling, effective January 2009.

The following are acceptable statements for use in the PREGNANCY section of a product monograph, which the EMA has developed:

- Based on human experience (specify), Drug X is suspected to cause congenital malformation (specify) when administered during pregnancy.
- Drug X should not be used during pregnancy (specify trimester) unless the clinical condition of the woman requires treatment with Drug X.
- A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicates no malformative or feto/neonatal toxicity for Drug X.
- No effects during pregnancy are anticipated, since systemic exposure to Drug X is negligible.

**FIG. 1** Decision Scheme - Contraindication in Pregnancy




From the European Medicines Agency. Evaluation of Medicines for Human Use.[3]

Such statements allow the clinician or practitioner to counsel patients and provide them with relevant information about the risks and benefits of a medication taken during pregnancy so that they can make an informed decision.

Outlined in Figure 1 is the approach taken by the EMA for arriving at a recommendation *against* a medication being used in pregnancy.[3] The process looks largely at human experience and whether or not there is sufficient data available from clinical assessments; if not, it then looks to non-clinical studies which can help to shape the types of recommendations to be made.

In Canada, Pregmedic has drafted the Guideline for Inclusion of Pregnant Women in Pharmacokinetic Studies presented to Health Canada in June 2009, and has identified the following priorities; to advocate for the adoption by Health Canada of the European (EMA) Labelling Requirements for Pregnancy and Lactation, and to request the creation of registries of women who need to take drugs during pregnancy and of post-market surveillance studies.

Pregmedic has worked with the Society of Obstetricians and Gynecologists of Canada and is in the process of developing a Policy Statement and patient education pamphlets for practitioners as well as for pregnant or nursing women. The intent is to undertake presentations at CME events, for example, regarding Natural Health Products and vitamins—to present the value of these in adolescent women, in women deciding on pregnancy, and in pregnancy and lactation. Pregmedic is pleased to be associated with Motherisk and, of course, the Canadian Society of Pharmacology and Therapeutics (CSPT/SCPT).

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