FDA pregnancy risk categories and the *CPS*

Do they help or are they a hindrance?

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ABSTRACT

QUESTION My patient is taking a medication for a chronic condition and has just found out that she is 6 weeks pregnant. The US Food and Drug Administration (FDA) has assigned this medication to pregnancy risk category D, and the *Compendium of Pharmaceuticals and Specialties* provides no additional data. How should I interpret this information, and how does the Motherisk Program evaluate the safety or risks of drug use in pregnancy?

ANSWER Pregnancy safety data provided by the FDA pregnancy risk categories and the *Compendium of Pharmaceuticals and Specialties* are insufficient to guide clinical decisions on how to proceed with a pregnancy following exposure to a category D medication. The Motherisk Program creates peer-reviewed statements derived from the primary literature, and we examine fetal outcomes as well as the risk-benefit profile of maternal treatment when evaluating the safety of medication use in pregnancy. The FDA announced in May 2008 that it is dropping its pregnancy risk categories and adopting a method similar to the one we use at Motherisk.

RÉSUMÉ

QUESTION Une de mes patientes prend des médicaments pour une maladie chronique et vient d'apprendre qu'elle est enceinte de 6 semaines. La Food and Drug Administration (FDA) des États-Unis a classé ce médicament dans la catégorie D de risque durant la grossesse, et le Compendium des produits et spécialités pharmaceutiques ne donne aucune autre information additionnelle. Comment devrais-je interpréter ces renseignements et comment le programme Motherisk évalue-t-il l'innocuité ou le risque des médicaments utilisés durant la grossesse?

RÉPONSE Les données sur la sécurité durant la grossesse fournies par les catégories de risque attribuées par la FDA et le Compendium des produits et spécialités pharmaceutiques ne suffisent pas pour guider les décisions cliniques sur la façon de procéder dans le cas d' une grossesse après une exposition à des médicaments de catégorie D. Le programme Motherisk produit des déclarations révisées par des pairs se fondant sur les ouvrages scientifiques primaires. Nous examinons les résultats chez le fœtus ainsi qu'un profil risques-avantages du traitement maternel quand nous évaluons la sécurité de l'usage d'un médicament durant la grossesse. La FDA a annoncé, en mai 2008, qu'elle abandonnait ses catégories de risque durant la grossesse et qu'elle adoptait une méthode semblable à celle que nous utilisons à Motherisk.

The National Longitudinal Survey of Children and Youth reported that between 1984 and 2003, up to 33% of Canadian women took medications during their pregnancies.[1] Some women have chronic conditions that require treatment throughout pregnancy, and 50% of pregnancies are unplanned.[2] Physicians require accurate and meaningful teratogenic information to assist their patients in making informed decisions on the management of maternal medical conditions and fetal drug exposure. One study reported that 91% of medications approved by the US Food and Drug Administration (FDA) between 1980 and 2000 were classified as "undetermined" in terms of safety of use in pregnancy.[3] Consequently, physicians are faced with the difficult and complicated task of assessing the safety of medication use in pregnancy and counseling their patients accordingly, with only limited human data.

The FDA pregnancy risk categories

In response to the thalidomide tragedy, the FDA implemented labeling requirements in 1979 with the aim of providing evidence-based information about use of medication in pregnancy. Each drug is classified into 1 of 5 categories based on the absence or presence of data on the safety of its use during pregnancy, the type of study subjects, and the study results (**Table 1**). Each category has designated sentences to be included in the drug label. The FDA categories are intended to guide drug choice before fetal exposure, rather than provide information on how to manage the pregnancy following exposure.[4] Critics of the FDA classification pointed out that, although the system is easy to use, it might oversimplify the complexity of weighing risks to the fetus against the need to adequately manage maternal medical conditions. The system does not fully address the

Table 1. Definitions and management strategies from the US Food and Drug Administration categories for drugs taken during pregnancy

CATEGORY	DEFINITION	MANAGEMENT STRATEGY
A	Adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy.	Because studies are not able to rule out the possibility of harm, (name of drug) should be used during pregnancy only if clearly indicated.
B	Animal reproduction studies have failed to demonstrate a risk to the fetus, but there are no adequate and well-controlled studies of pregnant women. *Or* animal studies demonstrate a risk, and adequate and well-controlled studies in pregnant women have not been done during the first trimester.	Because the studies of humans cannot rule out the possibility of harm, (name of drug) should be used during pregnancy only if clearly needed.
C	Animal reproduction studies have shown an adverse effect on the fetus, but there are no adequate and well-controlled studies of humans. The benefits from the use of the drug in pregnant women might be acceptable despite its potential risks. *Or* animal studies have not been conducted and there are no adequate and well-controlled studies of humans.	(Name of drug) should be given to pregnant women only if clearly needed.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies of humans, but the potential benefits from the use of the drug in pregnant women might be acceptable despite its potential risks.	If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
X	Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both. The risk involved in the use of the drug in pregnant women clearly outweighs any possible benefits.	(Name of drug) is contraindicated in women who are or might become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

fact that the benefits of treatment of some conditions (eg, diabetes, asthma, pregnancy-induced hypertension, and psychiatric conditions) might outweigh the risk of fetal drug exposure.[5]

There is also a misunderstanding that the successive categories represent increasing severity of malformation and that all medications in the same category have the same risk and type of malformations. Furthermore, this system does not make a distinction between the sources of data for medications within the same risk category. For example, a medication can be listed as class B based on the failure of animal studies to show fetal risk but without well-controlled human studies; or based on the failure of animal studies to show fetal risk but with adequate and well-controlled human studies demonstrating safety in pregnancy. Classifying these 2 types of data in the same category implies that both have the same rigour of safety information in human pregnancy, when the most important data should always be derived from human studies.[6] There are also concerns that the generic statements provide insufficient information for clinicians to properly counsel pregnant patients in the event of inadvertent fetal drug exposures.[5]

In response to these concerns, the FDA made an announcement in May 2008, stating that they will replace the A, B, C, D, and X classification system with a narrative framework consisting of 3 sections. The new labeling information will contain a risk summary section that incorporates human and animal data and a clinical consideration section that addresses risk assessment and how to handle inadvertent fetal drug exposure. In addition, there will be therapeutic alternatives and a data section summarizing the evidence discussed in the other 2 sections.[7] However, to date, the pregnancy risk categories are still in effect and are still being used by physicians.

Compendium of Pharmaceuticals and Specialties

The *Compendium of Pharmaceuticals and Specialties* (*CPS*) is the most frequently used reference for evaluating safety when prescribing medication to pregnant women in Canada.[8] However, its contents are legal product monographs provided by the manufacturers and are not designed for physicians to advise pregnant women about the safety of medication use in pregnancy. Therefore, information obtained from the *CPS* might provide the physician with incomplete or misleading information with regards to safety. For example, to date, there have been many studies involving thousands of women exposed to fluoxetine during pregnancy, which have reported reassuring information.[9-11] However, the product monograph for fluoxetine (Prozac) in the 2009 *CPS* edition states the following:

"Safe use of fluoxetine during pregnancy has not been established. Therefore PROZAC should not be administered to women of childbearing potential unless, in the opinion of the treating physician, the expected benefits to the patient markedly outweigh the possible hazards to the fetus or the child."[12] Consequently, after reading this statement in the *CPS*, it is not surprising that physicians are hesitant to advise their pregnant patients to take this drug during pregnancy, even if their conditions warrant its use.

Motherisk approach

Owing to the limitations of the current FDA pregnancy risk classification system and pregnancy information contained in the *CPS*, additional resources are required to assess the safety of medication use in pregnancy. Counselors at the Motherisk Program use peer-reviewed, in-house statements prepared from published primary literature, including materials such as abstracts from meetings. The strengths and limitations of the various types of study designs are discussed in a paper by a Motherisk team member,[13] as it is important to understand how studies are conducted in order to critically evaluate the literature.

When evaluating the literature there are many considerations to be made about the risk-benefit profile of taking a drug during pregnancy. In addition to congenital malformations, other neonatal outcomes, such as prematurity, low birth weight, abnormal neurodevelopment, functional abnormalities, miscarriage, and stillbirth, are also important and might affect the physician's and patient's decisions on how to proceed with the pregnancy. As well, items such as timing of exposure are important to know, as some drugs might be safe for use in one trimester and contraindicated in another.

Some women and their health care providers, overestimate the teratogenic risk associated with drug use during pregnancy, resulting in unnecessary termination of a wanted pregnancy or not using needed medications to manage serious maternal conditions.[14] In addition, in some cases, such as depression and bipolar disorder, inadequate maternal treatment might lead to poor pregnancy outcomes and negatively affect maternal-infant interaction.[15]

Conclusion

Physicians frequently rely upon the FDA pregnancy risk category system and the *CPS* to evaluate the safety of medications in pregnancy; however, both the FDA classification system and the product monographs of the *CPS* are inadequate to address the complexity of weighing the benefits of treatment against the possible risk of drug exposure. The Motherisk Program is a reliable source for physicians to receive evidence-based, unambiguous information, assisting physicians in counseling their pregnant patients and ensuring appropriate treatment of the mother while at the same time protecting her unborn child. For more information, please visit **www.motherisk.org**.

Competing interests
None declared

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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**.

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