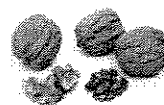




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IN A NUTSHELL



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The Perils of the Pregnancy Label

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You are a specialist in reproductive medicine. Your patients and your colleagues look to you as an expert on fertility, pregnancy, and lactation. But, if you're like most practicing Ob-Gyns, questions about medications during pregnancy send you right to the product label.

Most physicians use the PDR, a collection of product labels for many marketed drugs. Pharmaceutical companies pay to have their labels reproduced in the PDR. Other sources of product labels are the Internet sites of drug companies or of the FDA.

Regardless of the source, it's the same product label, written by the manufacturer and approved by the FDA. If you call a drug company with a question about the effects of a medication in pregnancy, you are going to get the same information that is in the label.

Product labels are divided into sections, and the section of greatest interest to Ob-Gyns is the pregnancy section. By regulation, this section contains a standardized rating system for pregnancy effects that involves five categories, each of which is given a letter (A, B, C, D, and X). The categories were introduced by the FDA in 1979 to make pregnancy information easier to understand by practitioners with no training in developmental toxicology. However, the categories have been a dismal failure.

Why doesn't the system work?

The category system doesn't help practitioners because it doesn't communicate accurately what is

known about the effects of a medication on pregnancy, nor does it tell practitioners or patients what action to take. To test your knowledge of the category system, take this simple true/false quiz:

1. The categories represent a gradation of risk: A is safer than B, which is safer than C, and so on. (True/False)
2. Category D drugs have been shown to cause birth defects in humans. (True/False)
3. Category X drugs have been shown to cause birth defects in humans. (True/False)
4. A drug can only get into Category X with human studies. (True/False)
5. Category X drugs cause birth defects more often than Category D drugs (True/False)

All the answers are False. Here is why you might have gotten tricked by the Categories.

Codes are for spies

The first problem is the use of codes. In communication, the use of code requires that the person sending and the person receiving both attach the same meaning to the code element. For example, in Morse code, everyone on the sending and receiving end of the message understands that dot-dot-dot means S. With the FDA code, the people on the sending end and the people on the receiving end may attach different meanings to the code elements. Try this game: get a bunch of residents together and

have them write down a definition for A, B, C, D, and X. Then compare the definitions with one another. Then compare the definitions with the standard FDA definitions (sidebar next page). Repeat the game the next day. You'll find that even just one day after hearing what the real FDA definitions are, intelligent people still show that they don't have the code quite right.

Gradation of risk?

If you look closely at the definitions, you can see why the gradation-of-risk idea doesn't work. Category B might be assigned to a drug that has not been adequately tested in experimental animals, rather than a drug that has been shown to be safe. Category X might be assigned to a drug that does not cause birth defects but simply has no conceivable use during pregnancy. Birth control pills are a great example of a Category X drug that has been shown not to increase the risk of birth defects. Birth control pills have been much better tested than some drugs in Category B or C and are likely to be much safer than some drugs in Category B or C. Oral contraceptives are in Category X only because there is no reason to take birth control pills during pregnancy.

Severity of effect

Just as the categories do not describe a gradation of risk, severity of effect is not indicated by the category level. For example,

Sidebar: The categories

Category A is the easiest, because virtually nothing is Category A. Category A means that adequate controlled studies in women have failed to show a risk to the fetus.

Category B means either (1) experimental animal studies show risk but human studies do not, or (2) experimental animal studies are negative and adequate human studies do not exist.

Category C means either (1) experimental animal studies show fetal risk or (2) there is no information one way or the other.

Category D means that there is evidence of risk to the human fetus (not necessarily from human studies, by the way), but that the benefit may outweigh the risk.

Category X means either (1) that there is evidence of risk to the human fetus, but the benefit would never outweigh the risk or (2) the drug has no conceivable utility in pregnancy.

Category B is a funny one, because if part (1) is fulfilled (adequate human studies do not show fetal risk), why is the drug not Category A? If part (2) is fulfilled, you have to wonder whether the experimental animal studies were adequately done. The way experimental animal studies are performed, a selection of doses is used in pregnant rodents or rabbits; the highest dose tested is supposed to result in some degree of maternal toxicity. Usually the top dose results in impairment of weight gain by the pregnant animal. In the face of impaired maternal weight gain during pregnancy, there ought to be an effect on the offspring (often a parallel impairment of offspring weight gain). This effect on offspring should count as fetal toxicity.

phenytoin, a Category D drug, is associated with birth defects in something like 10% of exposed pregnancies, while lovastatin, a Category X drug, is associated with birth defects in about 0% of exposed pregnancies. The difference between D and X may be simply whether the label-writer felt there could be a reason to prescribe the drug during pregnancy, in spite of the presumed risk.

Human data?

The last time I checked the list of Category X drugs, I found human data for only about 60% of the drugs. In other words, the Category X listing was awarded for presumed risk based on experimental animal studies plus a lack of a reason to ever use the medication during pregnancy. In some cases, human data exist but show the opposite of what the category implies. The best example is birth control pills, which do not increase the risk of malformation. Benzodiazepines (Category D) are another example. These medications may be associated with withdrawal symptoms in newborns after pregnancy exposure, but do not increase birth defects.

Missing advice

Knowing a drug's category status doesn't necessarily give you information about what to do. Certainly, if you are counseling a pregnant woman about a drug she is considering, you might want to avoid medications that are known to increase the risk of fetal harm, but what if you are counseling a woman who has been inadvertently exposed? A woman who has been on alprazolam finds out she is 4 weeks pregnant. The label says Category D. Now what? Of course, we have just seen how the Category D designation for benzodiazepines is misleading. This woman can be told to relax and enjoy her pregnancy. But what about a Category D designation that is not so misleading, like valproic acid? Valproic acid is associated with a 1 to 2% incidence of lumbar meningomyelocele; the Category D designation is not misleading, but it is incomplete.

As a well-trained Ob-Gyn, you know that maternal serum or amniotic fluid alpha-fetoprotein in conjunction with targeted ultrasound is an effective way to evaluate fetuses for lumbar men-

ingomyelocele, but most patients don't know what you know. What happens to the pregnant woman who learns that valproic acid is a Category D drug without knowing that 98 to 99% of exposed fetuses are unaffected and without knowing what can be done about assessing the risk to her fetus?

Are The Categories Dangerous?

In 1994, the Teratology Society issued a recommendation that the Category system be abandoned in favor of a plain-text explanation of the available information on reproduction. Society members viewed the Categories as hazardous to the fetus in potentially causing the abortion of wanted pregnancies through inaccurate and incomplete information. The Society was not taking an anti-abortion stance; rather, the Society's view was that women who wanted to have a baby should not be tricked into terminating their pregnancies because of faulty labels.

Anxiety about liability may cause a health care provider to rely on the Categories (which may have the appearance of official government pronouncements), but the Categories don't help with liability:

1. The labels may not be up-to-date. Although the PDR appears each year with a new date on its cover, many of the labels have *never* been updated.

2. The manufacturer, not the FDA, owns the label. The FDA approves the label when it is issued but the label cannot be regarded as either an official government document or as a peer-reviewed source.

3. Bad advice is bad advice, no matter what the source. A doctor was sued for recommending

abortion to a woman who was inadvertently exposed to birth control pills. The woman lost her uterus secondary to a procedure-related injury. The doctor's defense that the product label said Category X was not successful given the substantial literature showing that there is no increase in birth defects with oral contraceptive exposure.

4. The label may be a tool of the drug company to limit its own liability.

5. Withholding important medication because of pregnancy fears may result in an adverse outcome due to untreated maternal illness. Without necessary medication, epileptics can have seizures and asthmatics can become hypoxemic. These outcomes are not good for either the mother or the baby.

In providing the best care for our patients, there is no substitute for good information—single letter codes just don't work.

REPROTOX® in a Nutshell is a supplement to the REPROTOX program for residents. Make sure all your colleagues have registered for their free access to REPROTOX. Contact Tony Scialli (ascialli@sciences.com).

In future issues:

How can I interpret experimental animal studies?

What's so important about dose-response relationships?

How do birth defects occur?

What about workplace exposures?

We would love to hear your ideas for articles—send Dr. Scialli an email.