Pregnancy Labeling for US Drug Products

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“It’s not as easy as A,B,C, (or 1,2,3, or do-re-mi for that matter!”

Objectives
1. Discuss the FDA pregnancy category system (i.e., the A,B,C,D,X system).
2. Discuss the shortcomings and limitations of the this system.
3. Discuss the proposed changes to the current pregnancy category system

Introduction
- Prescribing drugs during pregnancy and lactation
  - Ultimate example of balancing benefits to risks
- Current pregnancy category system
  - Lacks adequate detail to quantify risk
  - Forced to look outside current labeling
Background

Thalidomide tragedy in early 1960’s
- Prior to 1979
  - “The safety of this drug during pregnancy is unknown; benefits should be weighed against the risks”
- After 1979, implement current A,B,C,D,X category system

Comorbidities and Pregnancy
- HIV-AIDS
- Hypertension
- Migraine
- Psychiatric disorders
- Diabetes
- Gestational diabetes

All drugs might be suitable when we weigh the benefit of adequate treatment versus the risk of morbidity to mother and baby

Drugs and Pregnancy
- Most drugs will cross the placenta
- Beneficial vs undesirable
  - Zidovudine, Nevirapine in HIV
  - SVT and complete heart block
- Quantify risk to mother and baby
  - β-hemolytic strep infection vs penicillin
  - Chlamydia STD vs erythromycin

Official Labeling for hydralazine - PDR 1975

Use MAO inhibitors with caution in patients receiving PRACTOR.

Usage in Pregnancy

The drug should be used in pregnancy only when, in the judgment of the physician, it is deemed essential to the welfare of the patient.

Precautions: Myocardial stimulation produced by Apraclonidine can cause arrhythmias and ECG changes of myocardial ischemia. The drug has been implicated in the production of myocardial infarction. It must, therefore, be used with caution in patients with suspected coronary artery disease.

The “hyperdynamic” circulation caused by
The Grim Reminder of Thalidomide

Thalidomide: Like the Phoenix Rising out of the Ashes

Thalidomide

The Phoenix

The A,B,C,D,X System

- Implemented in 1979
- Announced with great fanfare
  - “by Nov. 1984 almost all Rx drugs will carry this information” (FDA)
- In reality, the system has been a big disappointment
The A,B,C,D,X System

- Category A

Controlled studies show no risk.
Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester of pregnancy.

Adequate, well-controlled studies in humans

- 3 drugs carry category A labeling in U.S.
  - Thyroid hormones
  - Folic acid
  - Prenatal vitamins

The A,B,C,D,X System

- Category B

No Evidence of Risk in Humans.
Adequate, well-controlled studies in pregnant women have not shown increased risk of fetal abnormalities despite adverse findings in animals, or in the absence of adequate human studies, animals studies show no fetal risk. The fetal risk is remote, but remains a possibility.

The A,B,C,D,X System

- Category B: Terbutaline

Teratogenic Effects – Pregnancy Category B
A reproduction study in Sprague-Dawley rats revealed terbutaline sulfate was not teratogenic when administered at oral doses of 50 mg/kg (approximately 25 times the maximum recommended daily oral dose for adults on a mg/m² basis). A reproduction study in New Zealand white rabbits revealed terbutaline sulfate was not teratogenic when administered at oral doses up to 50 mg/kg (approximately 50 times the maximum recommended daily oral dose for adults on a mg/m² basis). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See PRECAUTIONS / Teratogenesis).
The A,B,C,D,X System

**Category C**
Risk Cannot be Ruled Out.

Adequate, well-controlled human studies are lacking, and animal studies have shown a risk to the fetus or are lacking as well.

There is a chance of fetal harm if the drug is administered during pregnancy, but the potential benefits may outweigh the potential risks.

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Official Labeling for hydralazine - *PDR 1997*

Pregnancy Category C: Animal studies indicate that hydralazine is teratogenic in rats at 20-30 times the maximum daily human dose of 80-200 mg and possibly in rabbits at 10-15 times the maximum human dose, but that it is nanteratogenic in rats. Teratogenic effects observed were cleft palate and malleformations of feet and cranial bones. There are no adequate and well-controlled studies in pregnant women. Although clinical experience does not include any positive evidence of adverse effects on the human fetus, hydralazine should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

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What Does the Literature Say?

**RESULTS:** Twenty trials were included (1637 women) and 19 were excluded. There were ten different comparisons. Hydralazine was the most common drug for others to be evaluated against.

**REVIEWER’S CONCLUSIONS:** Until better evidence is available, the choice of antihypertensive should depend on the experience and familiarity of an individual clinician with a particular drug, and on what is known about adverse maternal and fetal side-effects.

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The A,B,C,D,X System

**Category D**
Positive Evidence of Risk.

Studies in humans, or investigational or post-marketing data, have demonstrated fetal risk. Nevertheless, potential benefits from the use of the drug may outweigh the potential risk.

For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.
**The A,B,C,D,X System**

**Category X**
**Contraindicated in Pregnancy.**

Studies in animals or humans, or investigational or post-marketing reports, have demonstrated positive evidence of fetal abnormalities or risk which clearly outweighs any possible benefit to the patient.

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**Category X**

- Human Teratogen
- No justification

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**Problems with A,B,C,D,X System**

- Timing of drug exposure
  - Days 31 to 72 post conception
- ACE inhibitors, NSAIDS, Tetracycline
- Pharmacokinetic changes
  - Vd, Albumin, GFR
- Lactation not addressed
The A,B,C,D,X System

- Categories B, C, and D drugs
  - Based on animal studies
  - Why is this a problem?
    - DOES NOT ALWAYS PREDICT HUMAN RISK
      - Thalidomide
  - How does a drug get to be category C?
    - Unfavorable animal data
    - No data in humans

What does the practitioner want?

- A clear directive about prescribing a drug for his pregnant or lactating patient
- Safe or not?
- YES or NO?

Implications of Inadequate Labeling

- “Therapeutic nihilism”
- Risk assessment
  - 1*, 2*, 3* literature
  - PDR not enough
    - Briggs, Teris, Reprotox, Shepards, Drugdex
    - Condense vast amounts of data

How do we change the system?

- FDA Pregnancy Labeling Task Force
  - Revise
  - Develop a new label
  - Implement and utilize registries
  - Update practitioners

What has the FDA proposed?

- More reliance on human data
- No letter categories to describe risks
  - Replace categorical model with narrative
- Distinguish clinical considerations from risk information
- Different levels of information for different levels of practice


FDAs Proposal

Pregnancy Labeling Initiative: Goal

A label that adequately imparts the information necessary to prescribe for and counsel a pregnant patient

New Label

- Three Categories
  - Fertility
  - Pregnancy
  - Lactation
- Subdivided into three components
  - Clinical considerations
  - Summary risk assessment
  - Discussion of Data

FDAs Proposal

Revise Regulations to Require a New Labeling

- Distinguish clinical advice from risk information
- Different levels of information
- Narrative text not letter categories
FDAs Proposal

New Model Format

- Clinical Considerations
  - What clinicians need to consider to link RA to practical applications
- Summary Risk Assessment
  - Incorporates human & animal data and clearly states factors considered
  - Standardized risk statements
- Data
  - Brief, but conveys body of science
  - Animal separate from human

FDAs Proposal

Problem: Lack of Data on Drug Use in Pregnancy

- Pregnant women rarely included in Clinical trials
- Animal data usually all that is available
- Must rely on postmarketing data

FDAs Proposal

Pregnancy Registries are One Tool to Improve Safety Information

- The most practical means to collect information on safety and experience during pregnancy

FDAs Proposal

A Pregnancy Registry is ...

- A pregnancy drug exposure follow-up study
- A prospective epidemiologic study that actively collects information on medical product exposure & associated infant outcomes when exposure occurred during pregnancy
FDAs Proposal

Key Elements
- Addressed timing of exposure
- Described numbers of exposure
- Targeted likely concerns of clinicians and patients
  - congenital defects
  - congenital rubella
- Honest about limits of data & residual uncertainty

Conclusions
- Good science must underlie regulatory/public health decisions related to drug use in pregnancy.
- The pregnant patient brings us into an area of medicine where the most certainty is desired, but there is least data upon which to assess risk.

Criticism of New Label
- Clinical Considerations Section
- Data needs to be specific
- Summary risk assessment
  - Still based on animal data
- Discussion of data
  - Not helpful clinically

Implementation
- FDA will mandate these changes
- Time intensive and expensive
- First target:
  - Drugs likely used in pregnant women
  - Narrow therapeutic index
  - Suspected adverse effects
  - Required for all new drugs

http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3601t1a1c00 transcripts/3601t1c00, accessed December 15, 2000.
What was old is new again

- “The safety of this drug during pregnancy is unknown; benefits should be weighed against the risks”
  - PDR, 1979

- “If this drug is administered to a woman of reproductive potential, the patient should be apprised of the potential hazard to the fetus”
  - 21 CFR Part 201, Physician's Labeling Proposal

Conclusions ... (or more questions??)

- Systems strive for clinical usefulness
  - Reliance on human data from registries
  - Clinical usefulness of new label unknown
  - Any ideas?