



MotherToBaby
UTAH

Medications & More During Pregnancy & Breastfeeding
Ask The Experts



HEALTH
UNIVERSITY OF UTAH

Problems with the FDA Categories

Why change is desperately
needed

FDA Categories

- ABCD&X

- BOGUS!!!!!!



TERATOLOGY FOR THE CLINICIAN

ASSESSING RISK



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UTAH'S TERATOLOGY
INFORMATION SERVICE

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MotherToBaby

- ESTABLISHED IN 1984
- FOUNDING MEMBER OF THE ORGANIZATION OF TERATOLOGY INFORMATION SPECIALISTS (OTIS)
- TELEPHONE RESOURCE FOR HEALTH CARE PROVIDERS AND THE PUBLIC THROUGHOUT UTAH
- RECEIVES NEARLY 10,000 CALLS/YEAR

MotherToBaby **SERVICES**

- TELEPHONE SERVICES
- CONTINUING MEDICAL EDUCATION AND TERATOGEN UPDATES
- MEDICAL & PHARMACY STUDENT ROTATIONS
- POST-MARKETING DRUG RESEARCH
- COMMUNITY EDUCATION



TERATOGEN

- ANY AGENT EXTERNAL TO THE FETAL GENOME THAT INDUCES STRUCTURAL AND/OR FUNCTIONAL ALTERATIONS DURING PRENATAL DEVELOPMENT.

BACKGROUND RISK

- ALL PREGNANCIES CARRY A 3-5% RISK FOR PRODUCING A CHILD WITH A **MAJOR** BIRTH DEFECT,
- A 10-15% RISK FOR A **MINOR** DEFECT,
- A 15-50% RISK FOR MISCARRIAGE AND
- A 5-25% RISK FOR DEVELOPMENTAL DELAY OR LEARNING PROBLEMS

CAUSES OF BIRTH DEFECTS

- SINGLE GENE DISORDERS 20%
 - CYSTIC FIBROSIS, ACHONDROPLASIA
- CHROMOSOME DISORDERS 10%
 - TRISOMIES 13, 18, 21
- TERATOGENS 5%
 - DRUGS, CHEMICALS, INFECTIONS
- UNKNOWN CAUSES 65%

TERATOGENIC CAUSES

- MATERNAL STATES
 - UNCONTROLLED DIABETES 2.5%
- ILLNESSES & INFECTIONS 1.5%
- DRUGS, CHEMICALS, ETC. 1.0%

ASSESSING RISK/ APPROACH TO THE LITERATURE

The
MotherToBaby Utah
Teratology Risk
Assessment
MODEL

ASSESSING RISK



Control Group

Out of Control Group

EPIDEMIOLOGY

- CASE REPORTS (Astute Clinician)
- CASE SERIES (Astute Clinicians)
- REGISTRIES AND OBSERVATIONAL STUDIES (Case Series' Combined)
- CASE/CONTROL (Outcome to Exposure)
- COHORT (Exposure to Outcome)
- METANALYSES (C/C and Cohort Studies Combined)

PRINCIPLES OF TERATOLOGY

- DOSE
- ROUTE
- TIMING
- DURATION
- CONFOUNDERS
- PLACENTAL ISSUES
- SPECIES SUSCEPTIBILITY
- MATERNAL METABOLISM
- FETAL METABOLISM
- CLINICAL CONSISTENCY

DOSE

- ALL HUMAN TERATOGENS HAVE A PROVEN ***THRESHOLD***, ABOVE WHICH TERATOGENICITY OCCURS.
- FOR INSTANCE: CHEMICAL EXPOSURES IN WHICH NO MATERNAL SIGNS OF TOXICITY OCCUR HAVE NOT BEEN FOUND TO BE TERATOGENIC IN HUMANS.
- METHOTREXATE

ROUTE OF ADMINISTRATION

- THE MEANS BY WHICH AN AGENT ENTERS THE BODY IMPACTS THE *DOSE*.
- INHALED V. INJECTED
- SUBCUTANEOUS/MOLECULAR WEIGHT

TIMING AND DURATION

- TIMING REALLY *IS* EVERYTHING
- ALL OR NONE PERIOD
 - FIRST TWO EMBRYONIC WEEKS
- EMBRYOGENESIS/STRUCTURAL DEVELOPMENT
 - EMBRYONIC WEEKS THREE THROUGH 10
- FETAL/FUNCTIONAL DEVELOPMENT
 - FETAL WEEKS 10 THROUGH TERM

CONFOUNDING EXPOSURES

- NO PREGNANT WOMAN IS EXPOSED TO *ONLY* ONE THING.
- TO ASSIGN CAUSATION, CONFOUNDERS MUST BE CAREFULLY ACCOUNTED FOR.



STEPHANIE KLEIN-DAVIS | The Roanoke Times

Mellisa Williamson, 35, a Bullitt Avenue resident, worries about the effect on her unborn child from the sound of jackhammers.

PLACENTAL ISSUES

- PASSAGE
- METABOLISM
- LATE PREGNANCY AND THE PLACENTA

SPECIES SUSCEPTIBILITY

- ANIMAL MODELS HAVE **NEVER** PREDICTED HUMAN TERATOGENICITY

TERATOGEN

- ANY AGENT THAT, WHEN GIVEN TO A PREGNANT RAT, INDUCES A SCIENTIFIC PAPER.

MATERNAL METABOLISM PHARMACOGENOMICS

- ONLY ONE HUMAN TERATOGEN AFFECTS MORE THAN HALF OF EXPOSED FETUSES. MOST AFFECT LESS THAN 10% OF EXPOSED.
- INDIVIDUAL METABOLIC DIFFERENCES ARE COMMON.

FETAL PHARMACOGENOMICS

- LITTLE IS KNOWN AND RESEARCH IS ONLY BEGINNING IN HUMANS

CLINICAL CONSISTENCY

- ALL HUMAN TERATOGENS AFFECT THE **SAME** DEVELOPMENTAL PROCESSES FROM ONE INDIVIDUAL TO ANOTHER.
- TERATOGENS CREATE **SYNDROMES**, NOT ISOLATED CONGENITAL ANOMALIES.



FDA PREGNANCY CATEGORIES



Category A:

- Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

Category B:

- Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

Category C:

- Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Category D:

- There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Category X:

- Studies in animals *or* human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, **and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit.** The drug is contraindicated in women who are or may become pregnant.

FDA TASK FORCE

- As of early 2008 there were:
- Cat A 21 (2%)
- Cat B 172 (18%)
- Cat C 544 (57%)
- Cat D 155 (16%)
- Cat X 66 (7%)
 - 80% of drugs are categorized as concerning, *but* 80% of them should be As or Bs according to the FDA Task Force
 - Of the Cat X drugs, only 14 have definitive human data indicating they are teratogens. Of the Cat D drugs, human experience is the basis for the category in less than half of them.
 - Briggs, GG, *Drugs in Pregnancy & Lactation* 8th Edition 2008

FDA TASK FORCE

- One of the Task Force Members observed that "...a new pharmaceutical causing as many fetal deaths (abortions of wanted pregnancies) as are caused by the FDA pregnancy categories would never be allowed on the market." (Scialli,1992).

Limitations of the FDA Pregnancy Categories

- The Category is assigned to the drug and included in the package insert upon first marketing, but very seldom is it changed. FDA regulations require package inserts be updated when adverse events are reported, but there is no requirement to update when studies showing **no** adverse fetal effects are accomplished.

Limitations of the FDA Pregnancy Categories

- The Category provides information on the *quantity* of studies and whether they are performed in humans or animals, but doesn't comment on the *quality* nor the *appropriateness* of the studies.



Limitations of the FDA Pregnancy Categories

- Endpoints other than structural birth defects are not accounted for in the categories. Drugs that have been associated with fetal problems in late pregnancy (i.e., drug accumulation and toxicity as well as prematurity) are often not appropriately categorized.

Limitations of the FDA Pregnancy Categories

- Rather than simply assigning a single risk letter or number to a drug, the circumstances required for the drug to be teratogenic (timing of use in pregnancy, dose necessary to cause problems, etc.) should be fully discussed.



Limitations of the FDA Pregnancy Categories

- Understanding the impact of the teratogenic condition (minor v. major malformations, developmental delay, tooth staining, lethal defects, etc.) is vital for care providers or patients and their families to make better decisions about their pregnancy care.

Limitations of the FDA Pregnancy Categories

- It is also helpful to understand the level of risk (how often teratogenicity occurs after maternal use of a drug) to the fetus when a drug is used at the concerning time in pregnancy. No drug affects most fetuses after maternal use in pregnancy.

Limitations of the FDA Pregnancy Categories

- While the Categories rely heavily (almost exclusively) on animal studies, these types of studies have ***never*** been found to be predictive of teratogenicity in humans.

Limitations of the FDA Pregnancy Categories

- The American College of Obstetrics and Gynecology, the American Academy of Pediatrics, the Teratology Society and other medical societies have repeatedly called for changes in the Pregnancy Categories because of the above issues as well as the confusing language utilized in the current categorization system.