American Academy of Pediatrics Webinar

Medication Prescribing for Pregnant and Childbearing-aged Women: Resources for the Practicing Clinician

January 26, 2016

Cheryl S. Broussard, PhD
Division of Birth Defects and Developmental Disabilities
National Center on Birth Defects Defects and Developmental Disabilities
Centers for Disease Control and and Prevention

Christina Chambers, PhD, MPH
Department of Pediatrics
School of Medicine
University of California, San Diego

Learning Objectives

- Recognize medications that are known teratogens
- Recognize the importance of discussing medication use with women who are or could become pregnant
- Access resources available through MotherToBaby affiliates and other relevant organizations to help counsel women regarding treatment decisions before and during pregnancy

Part 1: Preventing Teratogenic Exposures

Cheryl S. Broussard, PhD

Division of Birth Defects and Developmental Disabilities

January 26, 2016

National Birth Defects Prevention Month 2016

- Theme:

  Making Healthy Choices to Prevent Birth Defects –

  Make a **PACT** for Prevention

  Plan ahead

  Avoid harmful substances

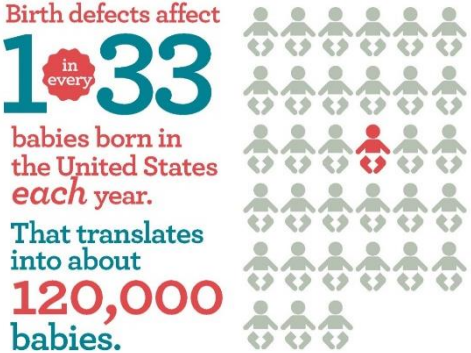
  Choose a healthy lifestyle

  Talk with your healthcare provider

- #LivingMyPACT

Birth Defects

- Birth defects are common, costly, and critical
- 1 in every 33 babies are born with a birth defect in the United States
- Preconception health is key



HOW SOME MEDICATIONS CAN BE HARMFUL

Birth defects

Pregnancy loss

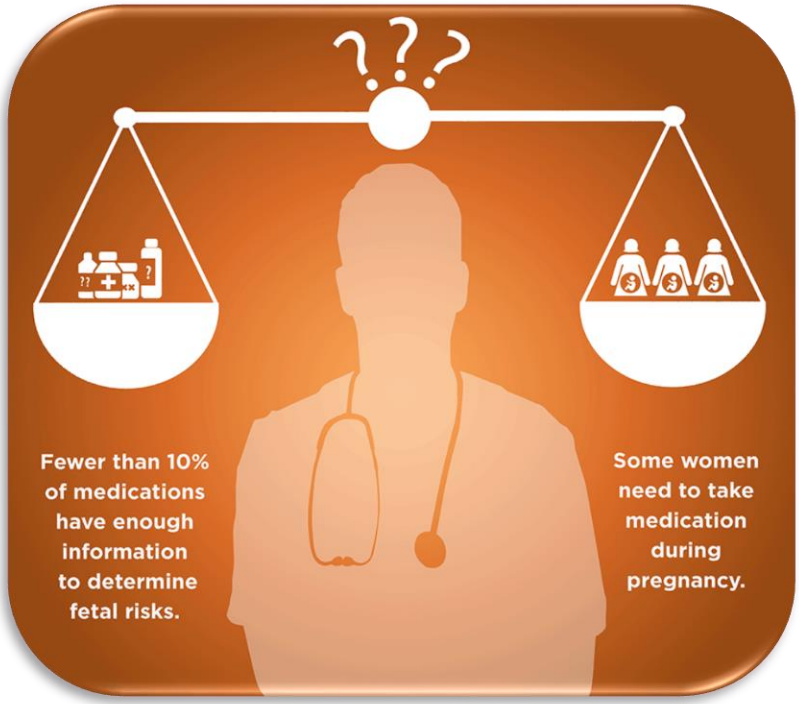
Prematurity

Infant death

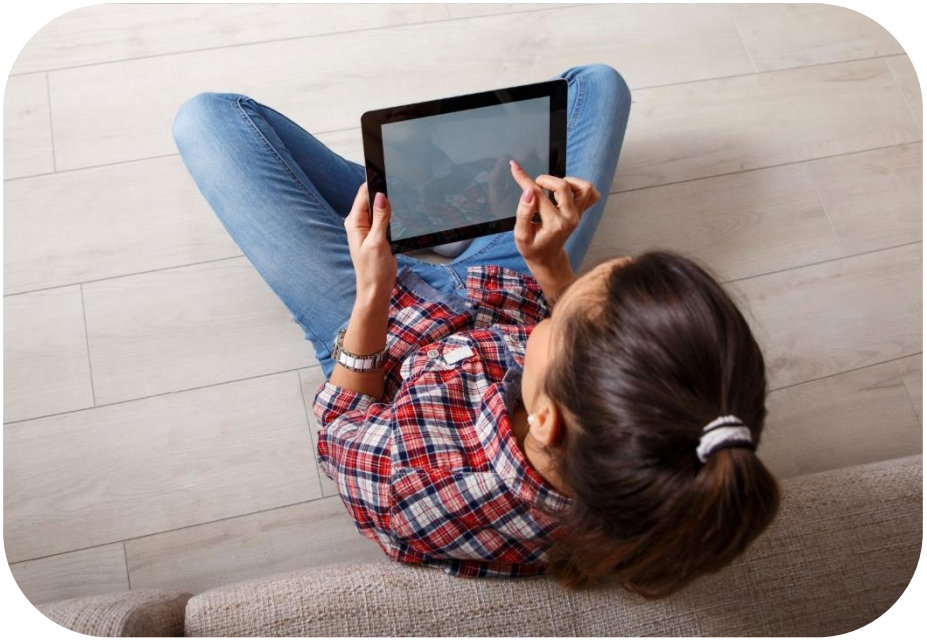
Developmental disabilities

Unknown outcomes

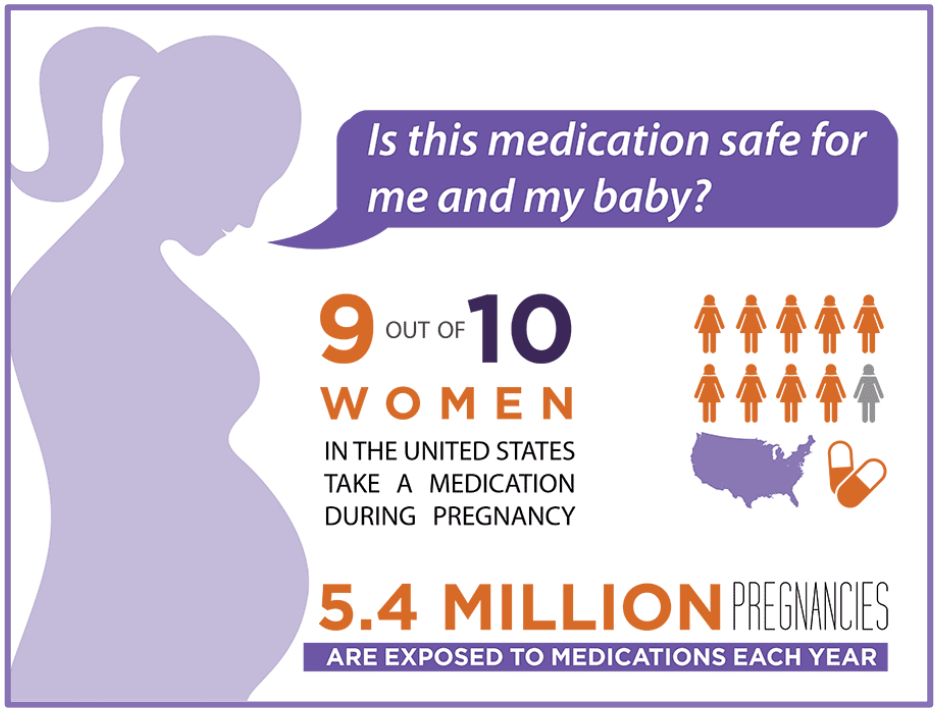
Medication Safety Information is Lacking



Misinformation is Abundant



Medication Use in Pregnancy is Common



TREATING X for TWO

How Do We Study Medication Use in Pregnancy?

- Animal toxicology
- Exclusion of pregnant women from clinical drug trials due to ethical concerns places heavy reliance on observational studies
- Prospective studies are usually not feasible for rare outcomes such as birth defects
- Retrospective studies are the only realistic options
  - Cohort
  - Case-control
- Methodological challenges exist for both types

How Do We Recognize Teratogenic Exposures?

- Teratogens are agents that act to irreversibly alter growth, structure or function of the developing embryo or fetus
- Only way to know with certainty that a prenatal medication is teratogenic in humans is to observe birth defects in babies
- Which study designs were responsible for producing the first signals for subsequent recognition of 17 teratogens?

Friedman JM. ABCDXXX: The obscenity of postmarketing surveillance for teratogenic effects. *Birth Defects Res Part A Clin Molec Teratol* 2012 (OTIS Special Issue)

Sources of Information about Potential Teratogens

- Case reports*/ case series
- Pregnancy registries*
- Birth defects surveillance systems
- Epidemiologic studies
  - Cohort
  - Case-control
- FDA adverse event reporting system

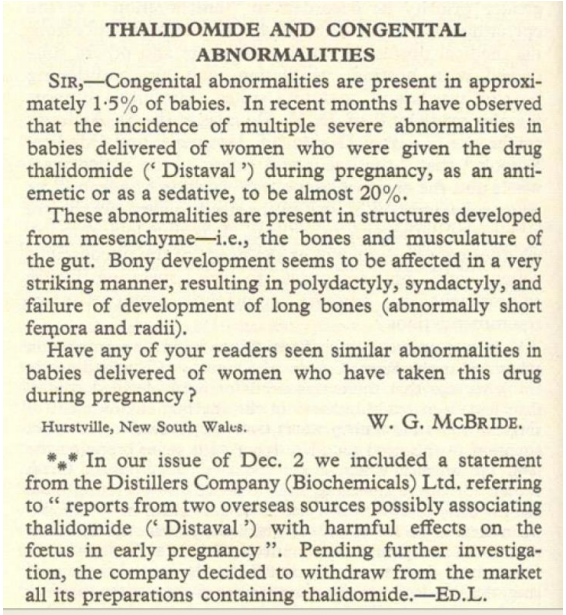
***first-line sources**

Rasmussen S, et al. Emerging infections and pregnancy: Assessing the impact on the embryo or fetus. *Am J Med Genet A* 2007.

Sources of Information about Potential Teratogens

- Case reports*/ case series 11
- Pregnancy registries* 5
- Birth defects surveillance systems
- Epidemiologic studies
  - Cohort 3
  - Case-control 1
- FDA adverse event reporting system 1

*first-line sources



THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (' Distaval ') during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales. W. G. MCBRIDE.

*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to " reports from two overseas sources possibly associating thalidomide (' Distaval ') with harmful effects on the fœtus in early pregnancy ". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.—ED.L.

Papers that shaped pharmacoepidemiology:

#1

McBride WG (1961). Thalidomide and congenital abnormalities. *Lancet* 2:1358

Tribute:
Frances Oldham Kelsey, who Saved U.S. Babies from Thalidomide, Dies at 101 – *The New York Times*

Frances O. Kelsey received the President's Award for Distinguished Federal Civilian Service from President John F. Kennedy, 1962

National Library of Medicine, Images from the History of Medicine, A018057

'Heroine' of FDA Keeps Bad Drug Off Market

By Morton Mintz
Washington Post Staff Writer
July 15, 1962

This is the story of how the skepticism and stubbornness of a Government physician prevented what could have been an appalling American tragedy, the birth of hundreds or indeed thousands of armless and legless children…

Thalidomide-associated phocomelia – 1960s

http://toxipedia.org/display/toxipedia/Thalidomide

Teratogenic Exposures

Medication	Description	Pregnancy Outcomes
Thalidomide	Sedative/ antiemetic	Thalidomide embryopathy (including phocomelia)
Isotretinoin	Severe cystic acne	Isotretinoin embryopathy (craniofacial, ears, heart, CNS)
Methotrexate	Ectopic pregnancy, some autoimmune diseases, malignancies	Fetal methotrexate/ aminopterin syndrome (CNS and palate)
Warfarin	Anticoagulant	Warfarin embryopathy (hypoplastic nose, limb, CNS, eye, spontaneous abortion)

Običan & Scialli. Teratogenic exposures. *Am J Med Genet Part C Semin Med Genet* 2011;157:150–169.

Teratogenic Exposures – Antiepileptic Drugs (AEDs)

Medication	Pregnancy Outcomes
Valproic acid	Spina bifida, atrial septal defect, cleft palate, hypospadias
Carbamazepine	Anticonvulsant embryopathy (spina bifida)
Phenobarbital	Anticonvulsant embryopathy (dysmorphic facial features and distal limb defects)
Phenytoin	Anticonvulsant embryopathy (IUGR, dysmorphic facial features, CNS anomalies, cleft lip/palate, and distal limb defects)
Lamotrigine	Facial clefts
Topiramate	Facial clefts

Običan & Scialli. Teratogenic exposures. *Am J Med Genet Part C Semin Med Genet* 2011;157:150–169.

Teratogenicity of AEDs

- Exposure to AEDs during pregnancy has been consistently associated with increased risk for birth defects overall

Monotherapy Treatment	Prevalence of Birth Defects (%)
Women without epilepsy	3.3 (1.4-5.2)
Lamotrigine	2.9 (2.0-3.8)
Carbamazepine	4.6 (3.5-5.8)
Phenobarbital	4.9 (3.2-6.6)
Phenytoin	7.4 (3.6-11.1)
Valproic Acid	**10.7 (8.1-13.3)**

*Adapted from: Meador et al. 2008. Pregnancy outcomes in women with epilepsy: A systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Research* 81:1-13

Current Treatment Guidelines (AAN and AES*)

- Optimize treatment prior to conception
- Choose the most effective AED for seizure type and syndrome
- If possible, avoid valproic acid and AED polytherapy during the first trimester (and throughout pregnancy)
- Use monotherapy and lowest effective dose
- Supplement with folic acid (0.4 mg = recommendation for all women)

*AAN: American Academy of Neurology; AES: American Epilepsy Society

Teratogenic Exposures

Medication	Description	Pregnancy Outcomes
Misoprostol	Prevent gastric ulcers, abortifacient	Mobius syndrome (skull, cranial nerves), limbs (clubfoot)
Methimazole	Antithyroid	Aplasia cutus of the scalp
Mycophenolate	Immunosuppressant	Mycophenolate embryopathy (ear, facial clefts, conotruncal heart defects)
Lithium	Antimanic	Ebstein anomaly (rare heart defect)
Penicillamine	Treatment for Wilson disease, rheumatoid arthritis, cystinuria	Connective tissue disorder resembling cutis laxa

Običan & Scialli. Teratogenic exposures. *Am J Med Genet Part C Semin Med Genet* 2011;157:150–169.

Teratogenic Exposures

Medication	Description	Exposure	Pregnancy Outcomes
ACE inhibitors (Angiotensin converting enzyme)	Antihypertensive	2nd and 3rd trimesters of pregnancy	Fetal renal failure, renal dysplasia, hypocalvaria (skull), fetal death
DES (Diethylstilbestrol)	Prevent pregnancy complications	During pregnancy	Vaginal adenocarcinoma in young women

Običan & Scialli. Teratogenic exposures. *Am J Med Genet Part C Semin Med Genet* 2011;157:150–169.

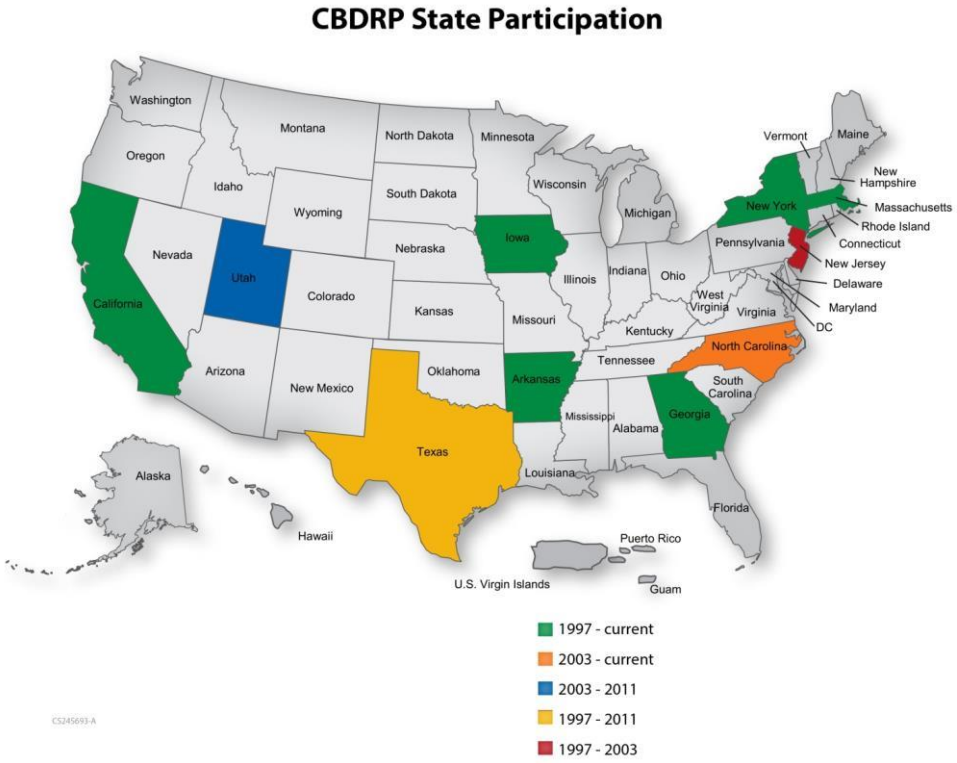
Medication Safety

- Medications not mentioned today as teratogenic exposures are not necessarily “safe”!

- Many commonly used medications require further study
  - Prescription medications
    - Antidepressants
    - Opioid analgesics
    - Antibacterials
    - Others
  - Over-the-counter medications
  - Herbal products

Research Study Sites across the US

Centers for Birth Defects Research and Prevention



CDC Messages

Key Messages:

Women: Pregnant or thinking about pregnancy? Don't stop or start taking any medications without first talking with a healthcare provider.

Healthcare Providers: Discuss the potential risks and benefits of [xyz] medication use with women of reproductive age, prior to prescribing. You might be treating for two.

Visit: **www.cdc.gov/treatingfortwo**

Contact: **cbroussard@cdc.gov**

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Part 2: When & How to Assess & Advise

Christina Chambers, PhD, MPH
Department of Pediatrics
University of California, San Diego
La Jolla CA

MotherToBaby
Medications & More During Pregnancy & Breastfeeding
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Prevention of Risky Exposure in Pregnancy and Lactation

- Therapeutic and safety goals
  - Best (most effective) medication for treatment of mother
  - Among choices of medications and based on best-quality evidence, safest treatment for both mother and baby
  - Prevention of exposure to teratogenic medications at critical times in gestation if possible
  - Reassurance for mother that lack of treatment or inappropriate/under-treatment may be harmful for mother and baby

When to Assess and Advise

- Most pregnancies are unplanned
- Exposures to potentially harmful medications can easily take place in the first few weeks of embryonic development when many mothers do not yet know they are pregnant

When and How to Assess and Advise

- Routine health visits for women with the potential to become pregnant even if not planning to do so
- At dispensing of a known teratogen or medication that may pose risks during lactation to a female of reproductive age
  - Assess current medication use and any risks associated with the underlying condition being treated if the woman were to become pregnant
  - Review plans for pregnancy and contraceptive practices as appropriate

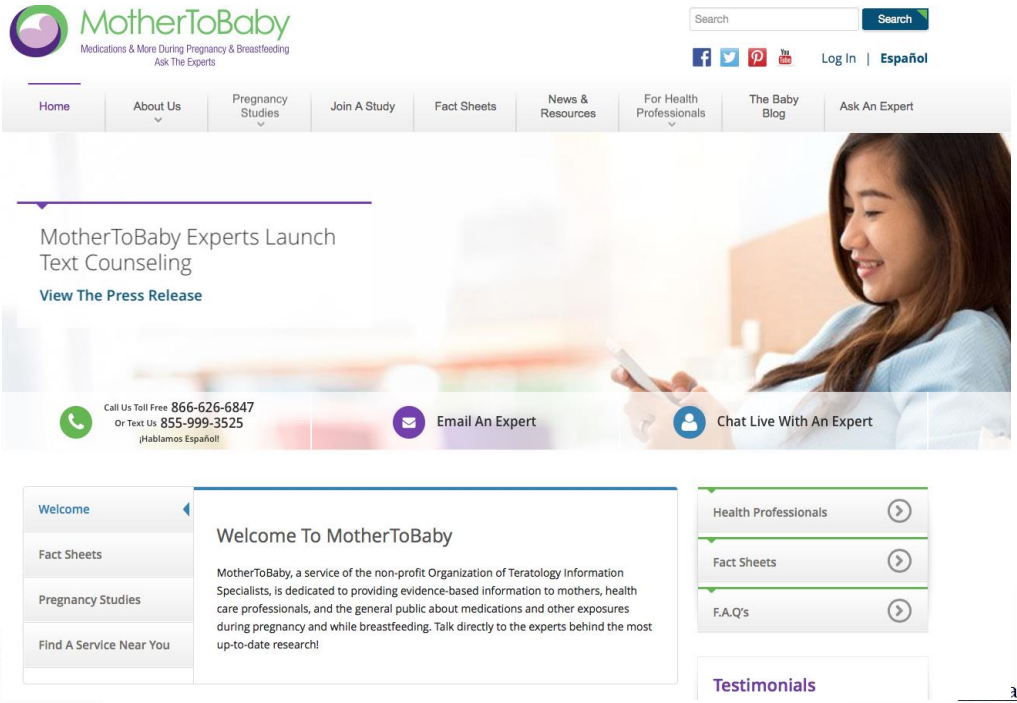
When and How to Assess and Advise

- Upon first positive pregnancy test
- When discussing plans for breastfeeding
- Postpartum visit
- Inter-pregnancy/pediatric visits

Resources for Information on What and How to Advise

- Even with known teratogens, often not an easy yes/no answer
- Choice of medications often made in the context of inadequate safety data for any of the available options
- Timing, dose and route of administration matter
- Can require assistance with accessing the most current reliable data
- Can require assistance in interpretation and communication of the information

Sources of information for clinicians
http://mothertobaby.org
866-626-6847 phone; 855-999-3525 text



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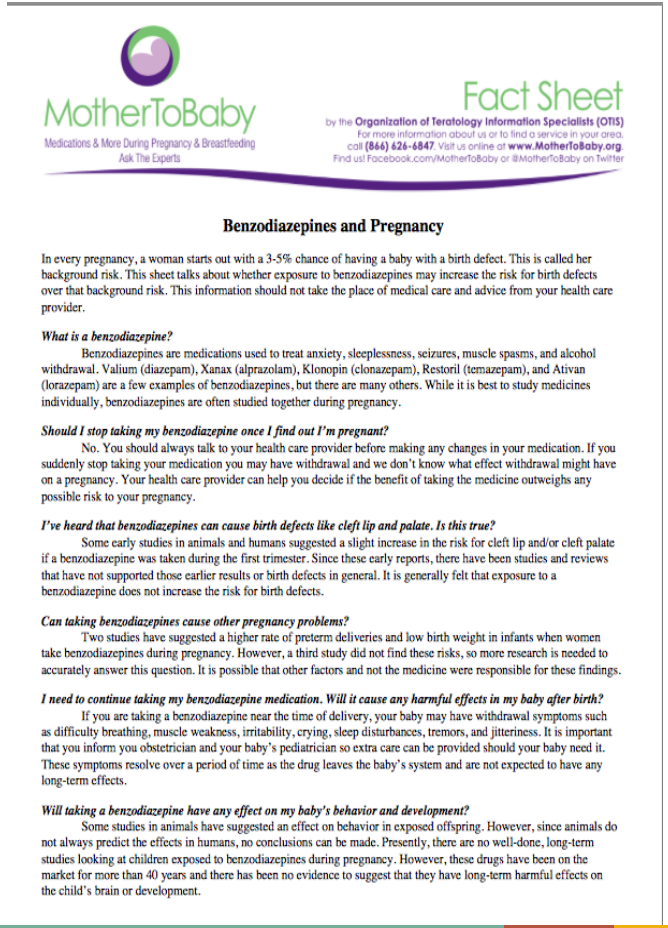
MotherToBaby: Patient-Oriented Fact Sheets



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Fact Sheet
by the Organization of Teratology Information Specialists (OTIS)
For more information about us or to find a service in your area, call (866) 626-6847. Visit us online at www.MotherToBaby.org.
Find us! Facebook.com/MotherToBaby or @MotherToBaby on Twitter

Benzodiazepines and Pregnancy

In every pregnancy, a woman starts out with a 3-5% chance of having a baby with a birth defect. This is called her background risk. This sheet talks about whether exposure to benzodiazepines may increase the risk for birth defects over that background risk. This information should not take the place of medical care and advice from your health care provider.

What is a benzodiazepine?

Benzodiazepines are medications used to treat anxiety, sleeplessness, seizures, muscle spasms, and alcohol withdrawal. Valium (diazepam), Xanax (alprazolam), Klonopin (clonazepam), Restoril (temazepam), and Ativan (lorazepam) are a few examples of benzodiazepines, but there are many others. While it is best to study medicines individually, benzodiazepines are often studied together during pregnancy.

Should I stop taking my benzodiazepine once I find out I'm pregnant?

No. You should always talk to your health care provider before making any changes in your medication. If you suddenly stop taking your medication you may have withdrawal and we don't know what effect withdrawal might have on a pregnancy. Your health care provider can help you decide if the benefit of taking the medicine outweighs any possible risk to your pregnancy.

I've heard that benzodiazepines can cause birth defects like cleft lip and palate. Is this true?

Some early studies in animals and humans suggested a slight increase in the risk for cleft lip and/or cleft palate if a benzodiazepine was taken during the first trimester. Since these early reports, there have been studies and reviews that have not supported those earlier results or birth defects in general. It is generally felt that exposure to a benzodiazepine does not increase the risk for birth defects.

Can taking benzodiazepines cause other pregnancy problems?

Two studies have suggested a higher rate of preterm deliveries and low birth weight in infants when women take benzodiazepines during pregnancy. However, a third study did not find these risks, so more research is needed to accurately answer this question. It is possible that other factors and not the medicine were responsible for these findings.

I need to continue taking my benzodiazepine medication. Will it cause any harmful effects in my baby after birth?

If you are taking a benzodiazepine near the time of delivery, your baby may have withdrawal symptoms such as difficulty breathing, muscle weakness, irritability, crying, sleep disturbances, tremors, and jitteriness. It is important that you inform you obstetrician and your baby's pediatrician so extra care can be provided should your baby need it. These symptoms resolve over a period of time as the drug leaves the baby's system and are not expected to have any long-term effects.

Will taking a benzodiazepine have any effect on my baby's behavior and development?

Some studies in animals have suggested an effect on behavior in exposed offspring. However, since animals do not always predict the effects in humans, no conclusions can be made. Presently, there are no well-done, long-term studies looking at children exposed to benzodiazepines during pregnancy. However, these drugs have been on the market for more than 40 years and there has been no evidence to suggest that they have long-term harmful effects on the child's brain or development.

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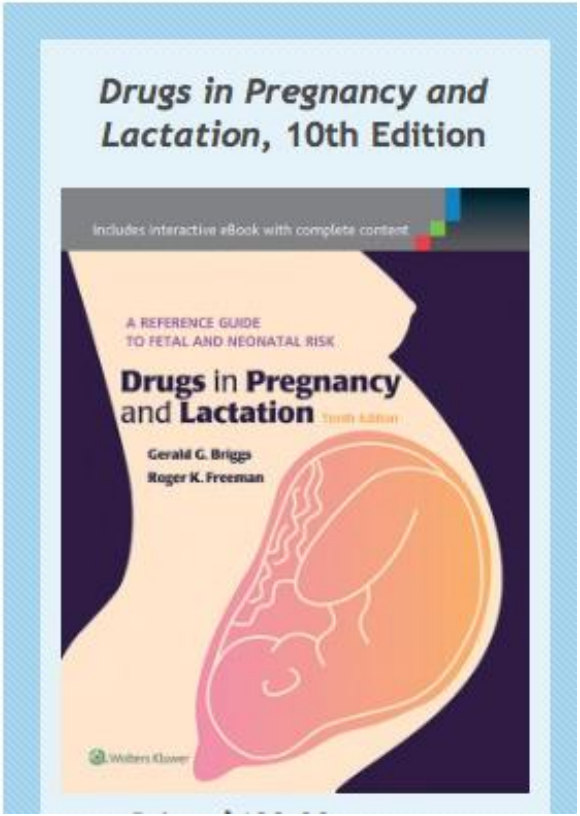
Briggs Drugs in Pregnancy & Lactation



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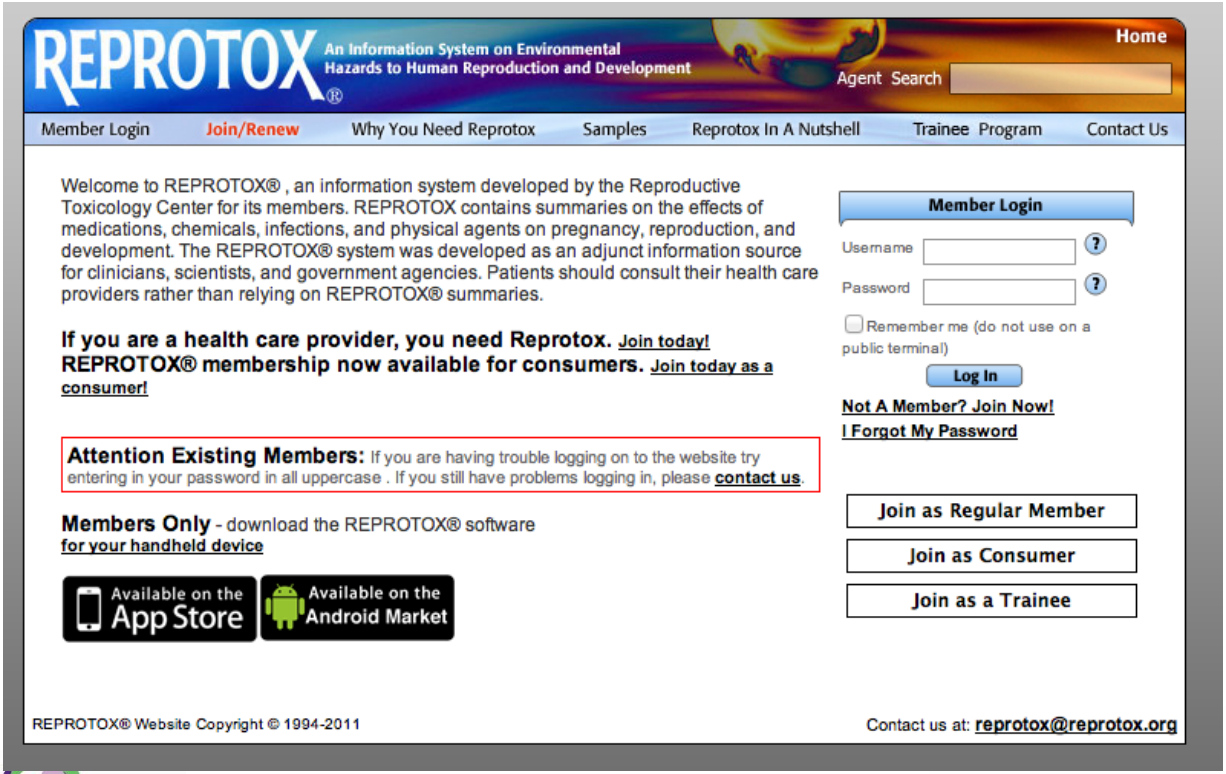
Reprotox – On-Line Subscription Service/App



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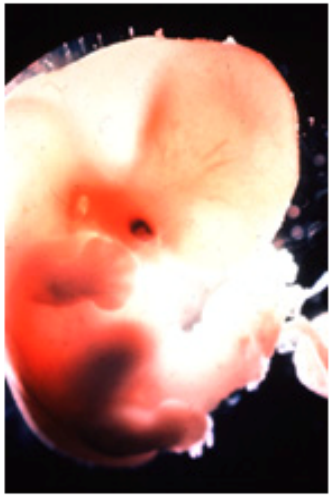
TERIS – On-Line Subscription Service



Teratogen Information System

and the on-line version of

Shepard's Catalog of Teratogenic Agents

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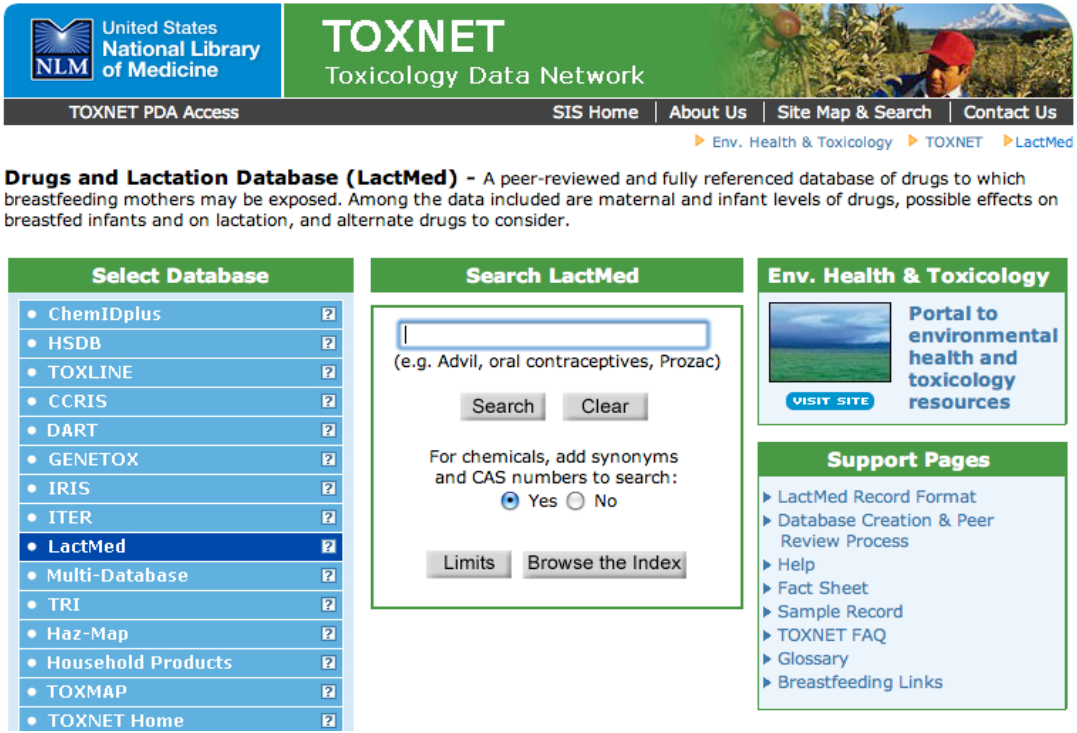
LactMed – On-Line NLM resource/App



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Revised Pregnancy and Lactation Labeling

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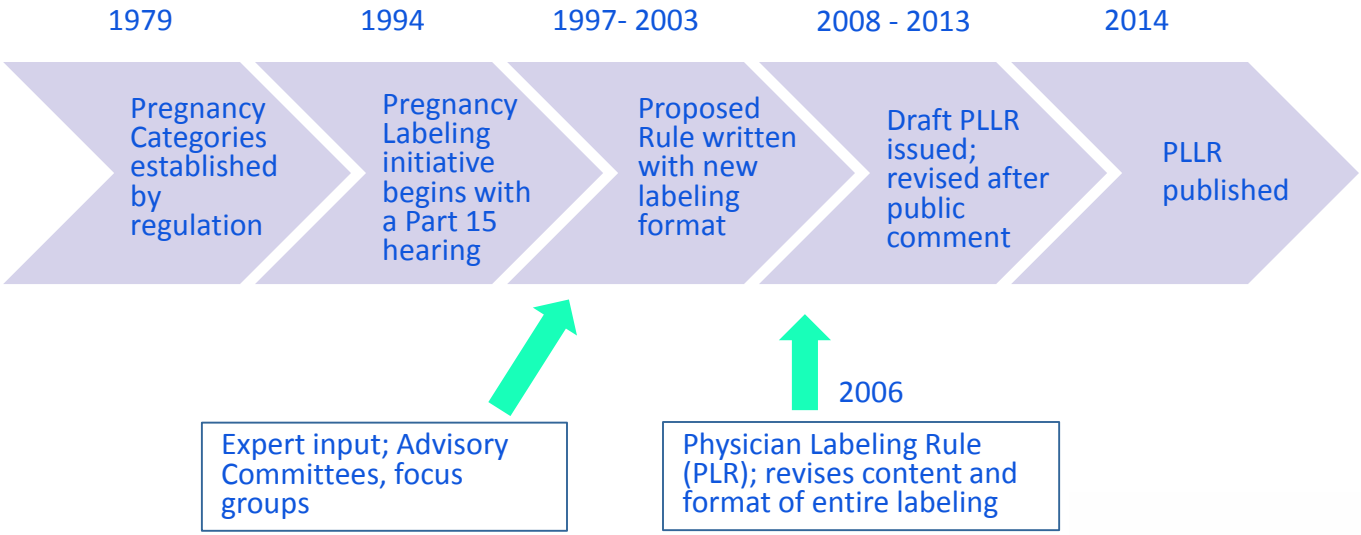
The Pregnancy and Lactation Labeling Rule (PLLR) December 4, 2014

- Addresses long standing problems with pregnancy and lactation labeling
- Amends the Physician Labeling Rule (PLR)
  - Pregnancy and Lactation labeling subsection revisions were deferred when PLR was published in 2006

Pregnancy Categories

A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
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, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

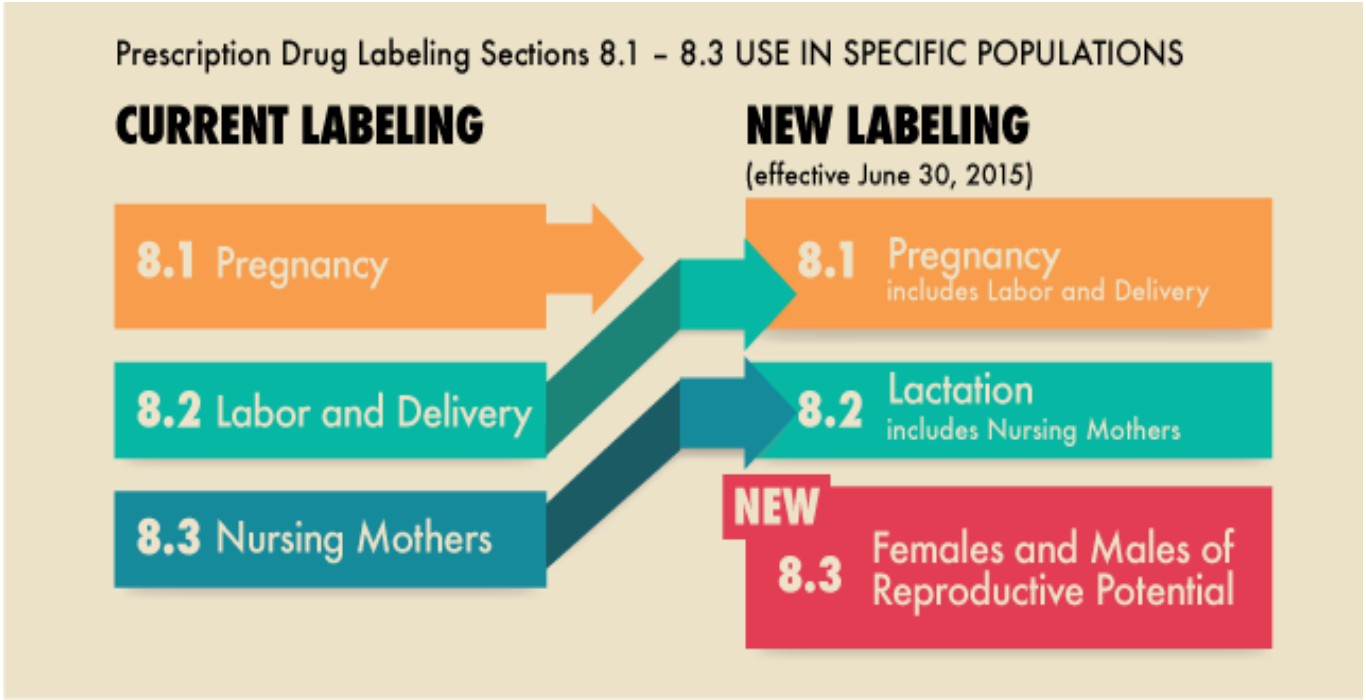
PLLR: a brief history



Pregnancy and Lactation Labeling Rule

- Published on December 4, 2014
- Amends the Physician Labeling Rule (PLR)
  - Pregnancy and Lactation labeling subsection revisions were deferred when PLR was published in 2006
- All prescription drugs approved on or after June 30, 2001 must revise content and format of the Pregnancy and Nursing Mothers (Lactation) subsections of labeling
  - Pregnancy letter categories are replaced with an integrated Risk Summary
- **ALL** prescription drugs are required to remove pregnancy letter categories
- Staggered implementation over 3-5 years

Labeling Changes with PLLR



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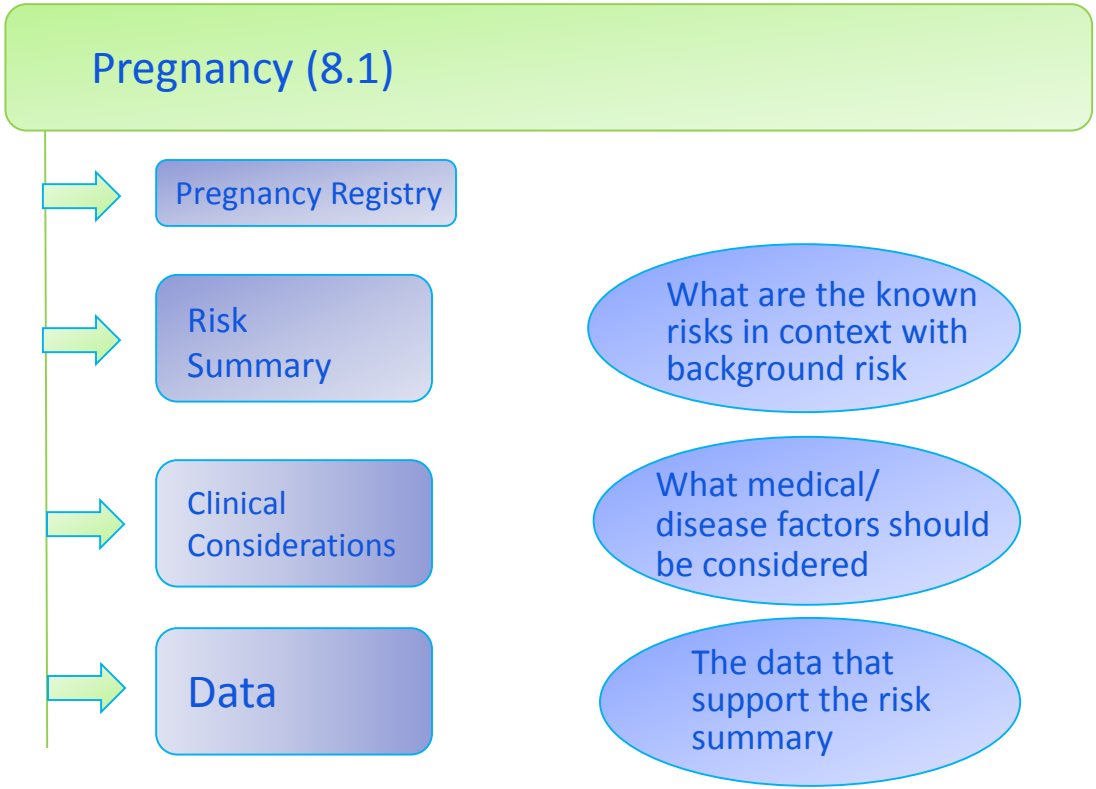
Revised Format



Required Labeling Elements

Pregnancy Exposure Registry*

> *"There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to (name of drug) during pregnancy."*

- Contact information listed

The availability of a pregnancy registry is also noted in the PATIENT COUNSLEING INFORMATION section.

* Is not included if there is no available registry

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Required Labeling Elements

Risk Summary*

- Risk statement based on human data
- Risk statement based on animal data
- Risk statement based on pharmacology **
- Background risk information in general population
- Background risk information in disease population**

* required heading

** is not included if there is no risk information

Pregnancy – Risk Summary

Drugs systematically absorbed:

- When use of a drug is contraindicated during pregnancy, this information must be stated first in the Risk Summary
- Human data:
  - A summary of the available human data or a statement there are no available human data to establish a drug-associated risk
- Background Risk:
  - A statement about the estimated background risk of major birth defects and miscarriage in the US general population or the estimated background risk in the diseased population.

Pregnancy – Risk Summary (2)

- Animal data:
  - A summary of the available animal data; a statement if studies do not meet current standards; a statement when no data exist
- Pharmacology:
  - A statement regarding the mechanism of action and potential associated risks when the drug has a well-understood MOA

Pregnancy – Risk Summary (3)

- No drug systemic absorption:
  - If drug is not systemically absorbed, Risk Summary will only contain the following statement:

"[Drug name] is not absorbed systemically following (route of administration) and maternal use is not expected to result in fetal exposure to the drug."

Pregnancy – Clinical Considerations

Clinical Considerations: provides information to further inform prescribing and risk-benefit counseling (Five subheadings)*

- Disease-Associated Maternal and/or Embryo/Fetal Risk
- Dose Adjustments during Pregnancy and the Post-Partum Period
- Maternal Adverse Reactions
- Fetal/Neonatal Adverse Reactions
- Labor or Delivery

* Heading and subheadings are optional; use when needed to convey information

Examples of Clinical Considerations

Clinical Considerations

Disease-Associated Maternal and Fetal Risk

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight and small for gestational age for the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Dose Adjustments during Pregnancy and the Postpartum Period

Dosage adjustments of TRADENAME are necessary for pregnant women to maintain adequate drug plasma concentrations *[see Dosage and Administration (2.x) and Clinical Pharmacology (12.3)].*

Pregnancy - Data

Data: Description of the data that provide the scientific basis for the summary information presented in the Risk Summary and Clinical Considerations headings*

- Human Data
  - Description of the studies includes type of study, number of subjects, study duration, exposure information and limitations of the data
- Animal Data
  - Description of the studies includes, type of study, species studied, animal doses and the basis for the exposures described in terms of the human dose or exposure, duration and timing of exposure, study findings, presence (or absence) of maternal toxicity, limitations of the data.

PLLR Implementation Schedule

	NDAs, BLA, ESs	Required Submission Date of PLLR Format
New Applications (prospective cohort)	Submitted on or after 6/30/2015	At time of submission
Start (6/30/15) ----------		
Older Approved Applications (retrospective cohort)	Approved 6/30/2001 to 6/29/2002 Approved 6/30/2005 to 6/29/2007	6/30/2018
	Approved 6/30/2007 to 6/29/2015 or pending on 6/30/2015	6/30/2019
	Approved 6/30/2002 to 6/29/2005	6/30/2020
	For applications approved prior to 6/30/2001 in old format labeling	Not required to be in PLLR format. However, must remove Pregnancy Category by 6/29/2018

Older Labeling

- Drugs approved before June 30, 2001 are required to remove the pregnancy letter category by June 30, 2018 (3 yrs after PLLR goes into effect)
- But, the labeling for these drugs is not required to conform to the Physician Labeling Rule (PLR)
  - Consequently are not required to revise the Pregnancy and Nursing Mothers sections under PLLR
- Efforts underway to encourage conversion of the older labeling to the PLR (and PLLR) format

Development & Approval Process (Drugs)

Development Resources

Labeling

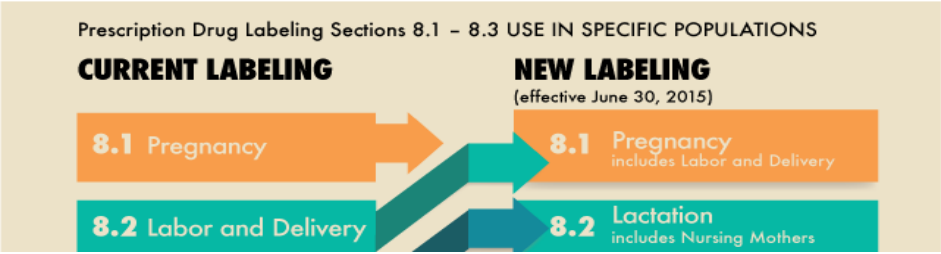
Pregnancy and Lactation Labeling Final Rule

Pregnancy and Lactation Labeling Final Rule

[12/3/14] The FDA published the *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, referred to as the "Pregnancy and Lactation Labeling Rule" (PLLR or final rule).

The PLLR requires changes to the content and format for information presented in prescription drug labeling in the Physician Labeling Rule (PLR) format to assist health care providers in assessing benefit versus risk and in subsequent counseling of pregnant women and nursing mothers who need to take medication, thus allowing them to make informed and educated decisions for themselves and their children. The PLLR removes pregnancy letter categories – A, B, C, D and X. The PLLR also requires the label to be updated when information becomes outdated.

Below is a comparison of the current prescription drug labeling with the new PLLR labeling requirements.



Questions & Answers

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