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The Pregnancy and Lactation Labeling Rule (PLLR)

Joint Meeting NASOM and Rocky Mountain GIM
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The speaker has nothing to disclose

Pregnancy and Medication Use

- Six million pregnancies in US every year
- 50% of pregnant women reported taking at least one medication
- Pregnant women take an average of 2.6 medications at any time during pregnancy
- First trimester use of prescription medications has increased by more than 60%
- Use of 4 or more medications in the first trimester has tripled (9.9% to 27.6%)

Mitchell AA, Gilboa SM, Werler MM, et al., Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol. 2011;205(1):51.e1-8.

Medication use in pregnancy

- Only a small percentage of drugs are contraindicated for use in pregnancy or while breast feeding.
  - e.g., isotretinoin, mycophenolates
- For the majority of drugs, labeling should provide what is known in a way that enables decisions for treatment.

The question is HOW?

The Problem with Letters

- Pregnancy letter category system was overly simplistic
- Misinterpreted as a grading system
- A drug with adverse information in animals could be labeled as the same category as a drug with no animal information
- Pregnancy Category C

  - Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, BUT the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks

  - Studies in pregnant women and animals are not available

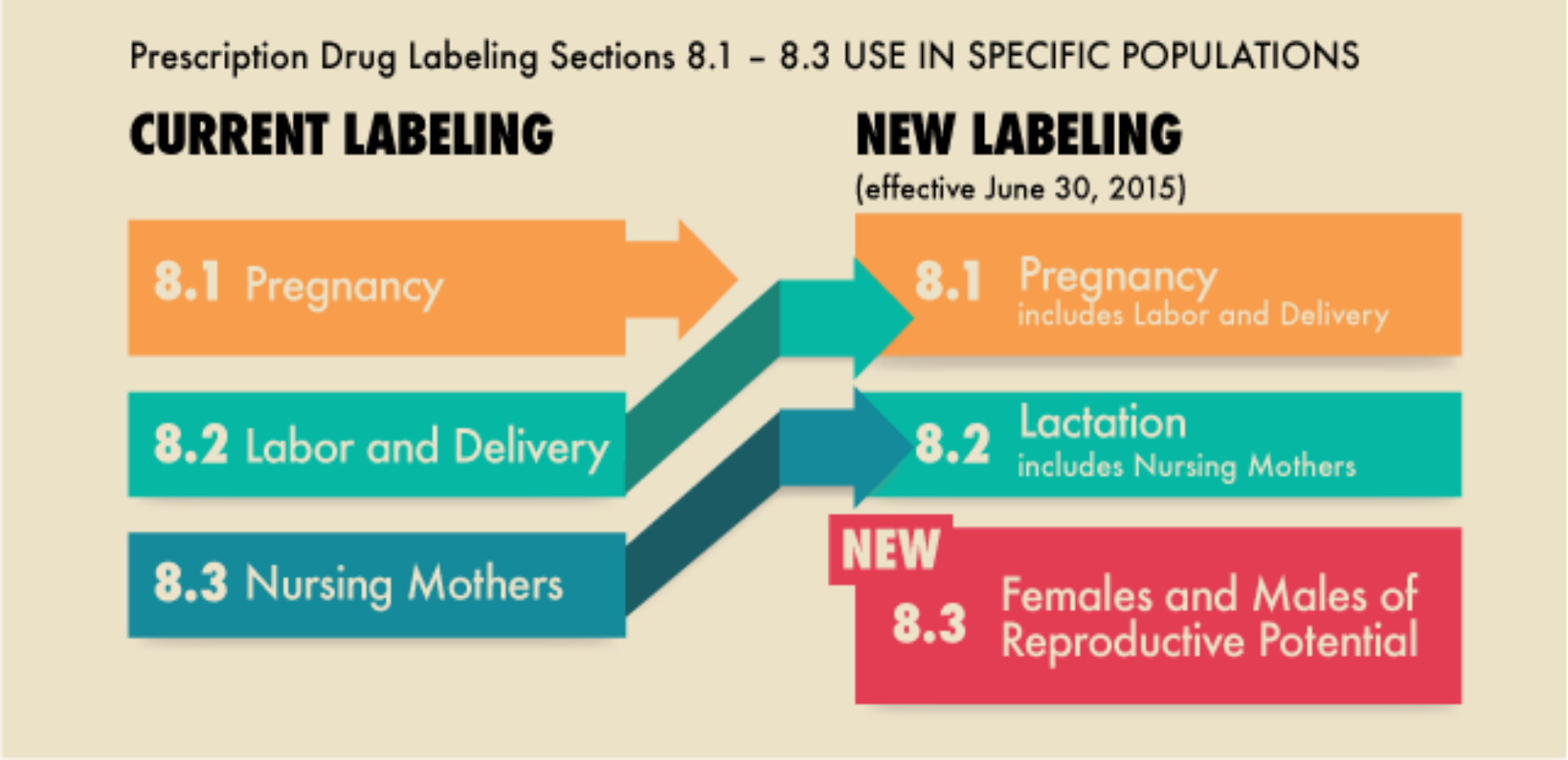
Pregnancy and Lactation Labeling Rule

- Took effect on June 30, 2015
- **ALL** prescription drugs are required to remove pregnancy letter categories over the next 3-5 years
- Prescription drugs approved on or after June 30, 2001 must revise content and format of the Pregnancy and Lactation sections of labeling
  - Pregnancy letter categories are replaced with an integrated Risk Summary

Intent of PLLR

- Provide the prescriber with relevant information for critical decision-making when treating pregnant or lactating women
- More complete assessment of the known risks based on the available data
- Considerations of medical/disease factors
- Animal data put in context of human exposure
- Human data added when available
- Explicitly states when no data are available

What is Changing



8.1 Pregnancy

- Four headings
  - Pregnancy Exposure Registry*
  - Risk Summary
  - Clinical Considerations*
  - Data*

*Optional headings will be included if applicable

8.1 Pregnancy- Risk Summary

- Drugs with systemic absorption
  - When use of a drug is contraindicated during pregnancy, that information must be stated first
  - 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**

**is not included if there is no risk information

EXAMPLE: Pregnancy - Risk Summary:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes…

Risk Summary

There are no data with TRADENAME use in pregnant women to inform a drug-associated risk. No adverse developmental effects were observed in animal reproduction studies with oral administration of [drug name] to pregnant rats and rabbits during organogenesis at exposures less than the exposure at the maximum recommended human dose (MRHD) of 10 mg twice daily [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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8.1 Pregnancy - Clinical Considerations

- Provides information to further inform prescribing and benefit-risk counseling*
  - *Disease-Associated Maternal and/or Embryo/Fetal Risk*
  - *Dose Adjustments During Pregnancy and the Postpartum Period*
  - *Maternal Adverse Reactions*
  - *Fetal/Neonatal Adverse Reactions*
  - *Labor or Delivery*

*Heading and subheadings are optional; use if applicable

Examples of Clinical Considerations

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

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

Maternal Adverse Reactions

TRADENAME may increase hyperglycemia in pregnant women with diabetes. Monitor maternal blood glucose levels regularly and adjust insulin dosages as needed *[see Warnings and Precautions (5.x)]*.

Pregnancy - Data

Data: Detailed 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.

8.2 Lactation

- 3 headings:
  - Risk summary
  - Clinical considerations*
  - Data*

*Optional headings that are used if applicable

8.2 Lactation – Risk Summary

- Systemic drug absorption
  - Presence of drug in milk*
  - Effects of drug on the breastfed infant*
  - Effects of the drug on milk production*
  - Risk/Benefit Statement
    - The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed child from TRADENAME or from the underlying maternal condition.
- When use of a drug is contraindicated during lactation, this information must be stated first in the risk summary

*if unknown, must state so.

8.2 Lactation - Clinical Considerations and Data

- Clinical Considerations
  - Minimizing exposure to the breastfed infant
  - Monitoring the breastfed infant for Adverse Reactions

- Data - Include only when information are available
  - Description of clinical lactation study/data
  - Description of animal lactation study (only if there are no human data)

8.3 Females and Males of Reproductive Potential

- When there are requirements or recommendations for pregnancy testing and/or contraception and/or when human and/or animal data suggest drug effects on fertility
  - Pregnancy Testing
  - Contraception
  - Infertility

*Optional subsection/headings - include if applicable

Example
8.3 Females and Males of Reproductive Potential

Based on its mechanism of action, TRADENAME can cause fetal harm when administered to a pregnant woman. [see Use in Specific Populations (8.1)]

Pregnancy Testing

Female patients of reproductive potential should have a negative pregnancy test …

Contraception

Females: Advise female patients of reproductive potential to use effective contraception during treatment and for at least 2 weeks after the last dose of TRADENAME. Advise patients that TRADENAME can reduce the effectiveness of oral contraceptives and to use alternative effective contraception during treatment with TRADENAME *[see Warnings and Precautions (5.x), Drug Interactions (7.x), Clinical Pharmacology (12.x)].*

Infertility

Females: Decreased fertility and ovarian toxicity were observed in female rats treated with DRUGNAME. Advise female patients of reproductive potential …

Males: Effects on spermatogenesis have been observed in animals treated with DRUGNAME. Advise male patients of the potential risk…

Conclusion

- The PLLR changes are aimed at improving communication of the key information [based on available data] to enable the complex risk/benefit discussions that are important for health care providers and their patients.

Thank You

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PLLR Resources

- Draft Guidance for Industry: *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format*
  http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425398.pdf
- Pregnancy and Lactation Labeling Final Rule
  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
- PLR Requirements for Prescribing Information
  http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

Where to find product labeling and other resources

- Drugs @FDA
  http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
- Daily Med (National Library of Medicine)
  http://dailymed.nlm.nih.gov/dailymed/about.cfm

- LactMed (National Library of Medicine)
  http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
- CDC (Centers for Disease Control)
  http://www.cdc.gov/pregnancy/meds/index.html

EXAMPLE:
8.2 Lactation-Risk Summary

Risk Summary

There are no data on the presence of DRUGNAME in human milk, the effects of DRUG NAME on the breastfed infant, or the effects of the drug on milk production. However, DRUGNAME is present in rat milk *[see Data].* The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed child from TRADENAME or from the underlying maternal condition.