The Safety of Asthma and Allergy Medications During Pregnancy: The Pregnancy and Lactation Labeling Rule and the Role of VAMPSS

Michael Schatz, MD, MS
Department of Allergy
Kaiser Permanente, San Diego
Pregnancy and Lactation Labeling Rule (PLLR)

Slides graciously provided by
Tamara Johnson, MD, MS
Division of Pediatric and Maternal Health
FDA/CDER/OND/ODEIV
Outline

• Introduction
• History of Pregnancy Labeling
• Overview of PLLR Labeling Changes
• Summary/Conclusion
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%)

Pregnancy and Medication Use

• 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?
Timeline of the PLLR

1979
Pregnancy Categories established by regulation

1994
Pregnancy Labeling initiative begins

1997-2003
Proposed Rule written with new labeling format

2008-2013
Draft PLLR issued; revised after public comment

2014
PLLR published December 4

1979
1994
1997-2003
2008-2013
2014

1979
1994
1997-2003
2008-2013
2014

Expert input; Advisory Committees, focus groups

Physician Labeling Rule (PLR); revises content and format of entire labeling

2006
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
Intent of PLLR

- Provide the prescriber with relevant information for critical decision-making when treating pregnant or lactating women
- More complete statement 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
PLLR

- **Effective date** June 30, 2015.
- **ALL** prescription drugs to remove pregnancy letter categories by June, 2020
- Prescription drugs approved on or after June 30, 2001 have additional content and formatting requirements
- Reorganizes information in prescription drug labeling to more clearly describe available data to aid decisions and counseling of patients using prescription drugs.
Prescription Drug Labeling Sections 8.1 - 8.3 USE IN SPECIFIC POPULATIONS

**CURRENT LABELING**

- **8.1** Pregnancy
- **8.2** Labor and Delivery
- **8.3** Nursing Mothers

**NEW LABELING** (effective June 30, 2015)

- **8.1** Pregnancy includes Labor and Delivery
- **8.2** Lactation includes Nursing Mothers
- **NEW** **8.3** Females and Males of Reproductive Potential
8.1 Pregnancy

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

*Required heading
8.1 Pregnancy- Pregnancy Exposure Registry

• Pregnancy Exposure Registry
  “There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to TRADENAME during pregnancy.”

• Includes specific contact information
  – Phone
  – Website
8.1 Pregnancy- Risk Summary*

• No drug systemic absorption

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

*Required heading(s)
8.1 Pregnancy- Risk Summary*

- Drugs with systemic absorption
  - When use of a drug is contraindicated during pregnancy, that information must be stated first in the 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
8.1 Pregnancy - Clinical Considerations

- Clinical Considerations (five optional 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
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.
8.1 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
  • Animal Data
8.2 Lactation

• Three headings:
  – Risk Summary*
  – Clinical Considerations
  – Data

*Required heading
PLL Summary

- PLLR implementation is a gradual process that will take another 2 to 4 years.
- **ALL** prescription drug labeling will be required to remove pregnancy letter categories.
- PLLR provides clearer communication of available data to assist the prescriber with critical decision-making when treating pregnant or lactating women.
- PLLR notes when there is no available data.
PLLRR Conclusion

• The PLLR provides a more structured approach to labeling to help more clearly describe available data that can be used to aid in complex risk/benefit discussions between prescribers and their patients.

• PLLR includes required statements when data are not available. Hopefully, all stakeholders will work together to proactively seek information to fill the gaps.
The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS)
Context For VAMPSS

• No systematic surveillance system exists in North America to provide information regarding risks or safety of drugs used during pregnancy

• Lack of adequate safety information
  – Prevention opportunities are missed
  – Under-treatment or under-prevention of medical problems which themselves cause maternal morbidity and possible perinatal complications
  – Other consequences
Structure of VAMPSS

American Academy of Allergy Asthma and Immunology
Michael Schatz, MD, MS

Prospective Cohort
Organization of Teratology Information Specialists Research Center at the University of California San Diego
Tina Chambers, PhD, MPH
Kenneth Lyons Jones, MD

Case-Control Study
Slone Epidemiology Center at Boston University
Allen A. Mitchell, MD
Carla Van Bennekom, BSN MPH

Database Study
Harvard Pregnancy Research Group
Sonia Hernandez-Diaz, MD DrPH
Krista F. Huybrechts, MS PhD
Brian T. Bateman, MD MSc

Independent Advisory Committee
Centers for Disease Control and Prevention
National Institute of Child Health and Human Development
National Institute of Allergy and Infectious Diseases
American College of Obstetricians and Gynecologists
American Academy of Pediatrics
Biostatistician
Consumer Representative
Overall Approach

- **Prospective Cohort**
  - Registry study (spontaneous abortion, stillbirth, preterm delivery, pre and postnatal growth deficiency, birth defects overall, and other outcomes)
  - Limited power to assess risk for specific birth defects

- **Case-Control Surveillance**
  - Birth defects surveillance (specific congenital malformations) and exposure prevalence for drugs available before 11-30-15
  - Does not address pregnancy loss or postnatal growth

- **Database**
  - Public and commercial databases (preterm delivery, prenatal growth deficiency, specific congenital malformation groups, and other outcomes)
  - Does not address pregnancy loss; some confounders not available
MAX Database

- **Data Source**
  - 2000-2010 Medicaid Analytic eXtract (MAX)
    - Medicaid enrollment & health care utilization data
    - Woman-infant linkage
    - Extensive data cleaning

- **Cohort**
  - >1.6 million pregnancies ending in live birth in which women were enrolled in Medicaid from 3 months before the LMP through 1 month post delivery, and infants were enrolled for ≥3 months
Advantages of VAMPSS for the New Label

– Will contribute data that are needed to address gaps in knowledge
– Simultaneous and coordinated research design to evaluate medication safety using three complimentary approaches
– All three approaches include ability to compare pregnancies with a specific medication exposure to internal comparison pregnancies in mothers who have the same underlying diseases
– All three approaches include measures of disease severity/control
VAMPSS and Measures of Asthma Severity/Symptom Control

• Cohort and Case-Control arms
  – From maternal interviews (and medical records)
    • Exacerbations including using of steroids, hospitalizations, ER visits, and unscheduled asthma visits
    • Classification of medication use according to GINA guidelines
VAMPSS and Measures of Asthma Severity/Symptom Control

• Cohort and Case-Control arms
  – From maternal interviews (and medical records)
  • Measures of symptom control using the Asthma Control Test
    – In cohort arm in 4 interviews throughout pregnancy reflecting previous 4 weeks
    – In case-control arm, retrospectively reflecting each of the trimesters of pregnancy
Original Article

Validation of the Pregnancy Asthma Control Test

Kristin Palmsten, ScD<sup>a</sup>, Michael Schatz, MD, MS<sup>b</sup>, Priscilla H. Chan, MS<sup>a</sup>, Diana L. Johnson, MS<sup>a</sup>, and Christina D. Chambers, PhD, MPH<sup>b,c</sup>  La Jolla and San Diego, Calif

**What is already known about this topic?** The Asthma Control Test (ACT) is a patient-based validated tool for the assessment of asthma control.

**What does this article add to our knowledge?** Telephone interview administration of the Pregnancy ACT is a valid tool for assessing asthma control throughout pregnancy.

**How does this study impact current management guidelines?** This study suggests that telephone interview administration of the Pregnancy ACT may be clinically useful for tracking asthma control during pregnancy.

BACKGROUND: Suboptimal asthma control during pregnancy may affect perinatal outcomes. US guidelines recommend questionnaires to assess asthma control including the Asthma Control Test (ACT).

OBJECTIVE: To validate telephone administration of a modified version of ACT during pregnancy.

METHODS: MotherToBaby Pregnancy Studies (2011-2013) enrolled 159 pregnant women with asthma. Participants were interviewed by telephone at intake, at approximately gestational weeks 20 and 32, and postpartum. The ACT was modified to exacerbatons. Possible p-ACT scores ranged from 5 to 25; higher score indicated better control. Reliability, criterion validity, construct validity, prospective validity, and responsiveness were assessed.

RESULTS: Cronbach’s alpha for internal consistency was similar across time points (0.84-0.90). The p-ACT score varied by impairment; for example, at intake, the mean score was 23.2 for well-controlled versus 13.7 for very poorly controlled asthma. The p-ACT score change between interviews differed by asthma course; for example, women reporting that their asthma was
VAMPSS and Measures of Asthma Severity/Symptom Control

• Database arm
  – From claims data
    • Measures of exacerbation
    • Treatment according to GINA Guidelines
    • Other markers of disease severity including comorbidities
VAMPSS and New Sections of the Label

• Will be able to provide data requested for Section 8.1 Pregnancy Risk Summary

  – Will provide new and relevant concurrent background risk for birth defects and spontaneous abortion for the indicated population
VAMPSS and New Sections of the Label

- Will be able to provide data requested for Section 8.1 Clinical Considerations
  - Will provide new and relevant concurrent data on the risks associated with the underlying condition
Summary: VAMPSS and Goals of the PLLR

- PLLR: To provide a more complete statement of the risks of a medication based on available data with consideration of medical and disease factors that will enable decisions for treatment.
- VAMPSS: Will contribute to filling gaps in available data for the label, with concurrent data considering the contribution of the disease being treated, supporting more informed treatment decisions.
Pregnancy Studies

Although medications are frequently used during pregnancy, pregnant women are generally not allowed to be in studies designed to test drug safety because of the potential risks to the fetus. As a
Test Question 1

Controlled trials addressing safety of medications used for asthma during pregnancy are:

A. Unethical
B. Limited in number
C. Less ideal than database studies
D. The most common types of studies available in this population of patients
Controlled trials addressing safety of medications used for asthma during pregnancy are:

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D. The most common types of studies available in this population of patients
Which of the following has been shown to be related to adverse pregnancy outcomes in asthma during pregnancy:

A. Increased uteroplacental blood flow
B. Asthma medication use the year prior to conception
C. Maternal allergy
D. Poor asthma control
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D. Poor asthma control
Test Question 3

Which of the following is true regarding the current Pregnancy and Lactation Labeling Rule

A. The letter designations have been retained for quick reference
B. It applies only to drugs taken for pregnancy indications
C. It includes information about Pregnancy Exposure Registries if they exist
D. It only contains information about the pregnancy effects of drugs, not the diseases for which they are being used
Question 3 Answer

Which of the following is true regarding the current Pregnancy and Lactation Labeling Rule

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Test Question 4

Which of the following is NOT true regarding the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS)?

A. It does not provide information about asthma control or severity
B. The prospective cohort arm includes maternal interviews
C. The case-control arm has adequate power to address specific birth defects
D. The database arm is population-based
Which of the following is NOT true regarding the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS)?

A. It does not provide information about asthma control or severity
B. The prospective cohort arm includes maternal interviews
C. The case-control arm has adequate power to address specific birth defects
D. The database arm is population-based
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