Pregnancy and Lactation Labeling Changes: Beyond the A, B, C's

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Pregnancy and Lactation Labeling Changes: Beyond the A, B, C's

ACTIVITY DESCRIPTION

The Pregnancy and Lactation Labeling Changes CE will help pharmacists, pharmacy technicians, and nurses to interpret new prescribing information labeling. This information can improve counseling interactions between healthcare providers and their patients

TARGET AUDIENCE

The target audience for this activity is **pharmacists** and **pharmacy technicians** in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES

After completing this activity, the **pharmacist and pharmacy technician** will be able to:

- Review the background and history behind pregnancy and lactation label classifications.
- Explain the new pregnancy, lactation, and females/males of reproductive potential labeling changes.
- Discuss the effects of pregnancy, lactation, and females/males of reproductive potential label changes to health care practice.

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Overview

On December 4, 2014, the U.S. Food and Drug Administration (FDA) passed the Pregnancy and Lactation Labeling Rule (PLLR), which revamped the pregnancy and lactation sections of prescribing information (PI).[1,2] The pressure to update these sections stemmed from complaints that the pregnancy letter categories –A, B, C, D, and X --were vague and inaccurately describe differences in degrees of fetal risk.[2,3,4] As of June 30, 2015, the pregnancy letter categories found in prescribing information will gradually be replaced with a narrative divided into three parts: risk summary, clinical considerations, and data.[1,2,3,5] The PLLR will also standardize the format for providing information about the risks and benefits of prescription drug and biological agents under the following sections: Pregnancy, Lactation, and Females and Males of Reproductive Potential.

Who Does the PLLR Affect?

The PLLR, also known as the final rule, was designed to improve clinician prescribing decisions in the United States for pregnant and nursing women as well as for fertile females and males.[2] In the United States, there are an estimated 6.5 million pregnancies annually.[6] It is reported that the number of pregnant women taking medication has more than doubled over the past 30 years.[7] It is estimated that about two-thirds of women use at least one prescription during pregnancy.[7] Specifically, nearly 5% of pregnant women require a prescription medication to treat a chronic condition such as hypertension.[8] The approved PLLR changes are intended to improve communication between clinicians and pregnant, breastfeeding, and those of childbearing potential who require pharmacological treatment.

PLLR Timeline

The biggest PLLR impact for many clinicians is that all new medications approved after June 30, 2015 will no longer be assigned a pregnancy letter category, but instead will have an integrated risk assessment that will be continually updated by the manufacturer.[1,2] Medications that were approved between June 30, 2001 and June 29, 2015 will have a staggered timeline of 3 to 5 years to submit updated labeling information.[1,2,5] Of note,

medications approved prior to June 29, 2001 are not required to implement updated content requirements, but they must remove the pregnancy risk category.[5] Over-the-counter (OTC) medications are not affected by PLLR and will continue to carry the same warning that pregnant and/or breastfeeding women should consult their health care providers before taking or using the medication.[5]

Timeline Summary

- **Drug approval June 30, 2015 and beyond:** Medications will have an integrated risk summary instead of a pregnancy letter category in the pregnancy section.
- **Drug approval June 30, 2001 to June 29, 2015**: Medication labeling must be updated over a period of 3 to 5 years from June 30, 2015.
- **Drug approval prior to June 29, 2001**: Pregnancy letter categories must be removed from the labeling, but an updated labeling format is not required.
- OTC medications are not affected by the PLLR.

History of Pregnancy Safety Warnings

The pregnancy and lactation sections found in section 8 of prescribing information under special populations have evolved over the years due to safety issues. One of the incidents that prompted U.S. regulations to change drug safety labeling was the thalidomide tragedy.[9,10] Thalidomide was initially manufactured as a hypnotic agent and for nausea and vomiting during pregnancy, but it was never approved for use in the United States.[9] It was first submitted to the FDA for approval in 1960, but due to insufficient safety data—evidence submitted was more anecdotal than clinical—thalidomide was rejected.[9,10] Even without FDA approval, the manufacturer –William S. Merrell Co.—distributed thalidomide to over a thousand U.S. physicians for investigational use, which caused 17 confirmed cases of phocomelia, the congenital absence or underdevelopment of extremities, in the United States.[9,10] In Western Europe, thalidomide was marketed as a sleeping agent, and was associated with birth defects in thousands of babies.[9,10]

In response to the thalidomide tragedy, Congress passed the Kefauver-Harris amendments in 1962, which required that medications be proven both safe and effective.[9,10] With this amendment, the FDA has 180 days to approve a new drug application before it can be marketed.[10] The Kefauver-Harris Drug Amendment also included requirements for informed consent among study participants and the need for manufacturers to report adverse events.[10]

In 1979, the FDA created *Labeling for Prescription Drugs Used in Man*, which introduced the five letter pregnancy letter risk designations A, B, C, D, and X and included pregnancy labeling regulations.[4] The pregnancy classification system assessed the risk of medications to the fetus during pregnancy.[4] These regulations were the first to provide guidance to clinicians counseling women about the safety of medication during pregnancy and breastfeeding.

Former Pregnancy Category Letter System

"Category 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.[1,4,12]

- **Category 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 that demonstrate an adverse effect, but AWC studies in pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk in later trimesters).[1,4,12]
- **Category 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.[1,4,12]
- **Category 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.[1,4,12]

- **Category 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."[1,4,12]

In 1993, the FDA passed the Guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, also known as the Gender Guidelines, which called for the assessment of medication responses in both genders.[9,11] The guidelines lifted a restriction on most women of childbearing potential with regards to participation in Phase 1 and early Phase 2 clinical trials.[11] In the Federal Register notice that announced this guideline, the FDA revoked the 1977 guideline that excluded women of childbearing potential from early clinical studies.[9,11] These changes opened the door to study drug effects in women and provide prescribing guidance.

In 1994, the Pregnancy and Lactation Labeling Rule revision was initiated due to a position paper published by the Public Affairs Committee of the Teratology Society.[4,9] Between 2008 to 2013, the FDA held public hearings to amend the Physicians Labeling Rule. The proposed rules from these hearings were written with new PLLR guidelines that were finally published in 2014.[1,2] As of June 30, 2015, due to the PLLR, the pregnancy letter categories will be gradually phased out of prescribing information in the United States.[2,3]

Pregnancy letter category systems are not exclusive to the United States. In Sweden, the Swedish Catalog of Approved Drugs (known as the FACC) uses four separate categories (A, B, C, D) in which A is the safest and D carries the most fetal risk.[12] Their system also has subgroups of risk –B1, B2, B3—in which B3 would be similar to the category C previously used in the United States.[12] The Australian Drug Evaluation Committee (ADEC) also uses a pregnancy letter category system with subgroups; however, similar to the former U.S. system, there is a category X for teratogenic medications.[12]

The inconsistencies within the U.S. pregnancy classification system compared to medications in the Swedish and Australian systems demonstrate the flaws in the letter designation system.[12] A study comparing medications in the U.S. to those in Sweden and Australia found that certain medications classified X by the FDA received a category B designation by the Australian and Swedish systems (See Table 1).[12] Conversely, a few medications classified as category C by the FDA, such as gentamicin, amikacin, tobramycin, were considered potentially teratogenic by the Australian and Swedish systems.[12] The authors concluded that only 61 (26%) of the 236 drugs common to the FDA, Australian, and Swedish systems were even placed in the same risk factor category.[12]

Table 1. Inconsistently Classified Medications within the U.S., Australian, and Swedish Pregnancy Systems[12]

	Category for each classification system		
Medication	**FDA**	**Australia (ADEC)**	**Sweden (FACC)**
Estradiol	X	B1	B2
Oral contraceptives	X	B3	B3
Clomiphene	X	B3	B3
Triazolam	X	C	C

The differences between the U.S., Australian, and Swedish systems stemmed from how the original data was interpreted and due to a lack of updated information.[12] The Australian and Swedish systems based their classifications on recent studies compared to the FDA approach where medication pregnancy categories were rarely updated.[12] For example, oral contraceptives are considered a B3 medication based on the Australian and Swedish systems because of two meta-analyses studies that found no association between first-trimester exposure to oral contraceptives and genital malformations.[12] However, despite recent human data, oral contraceptives in the U.S. maintained a category X classification.[12]

Criticism of the Pregnancy Letter System

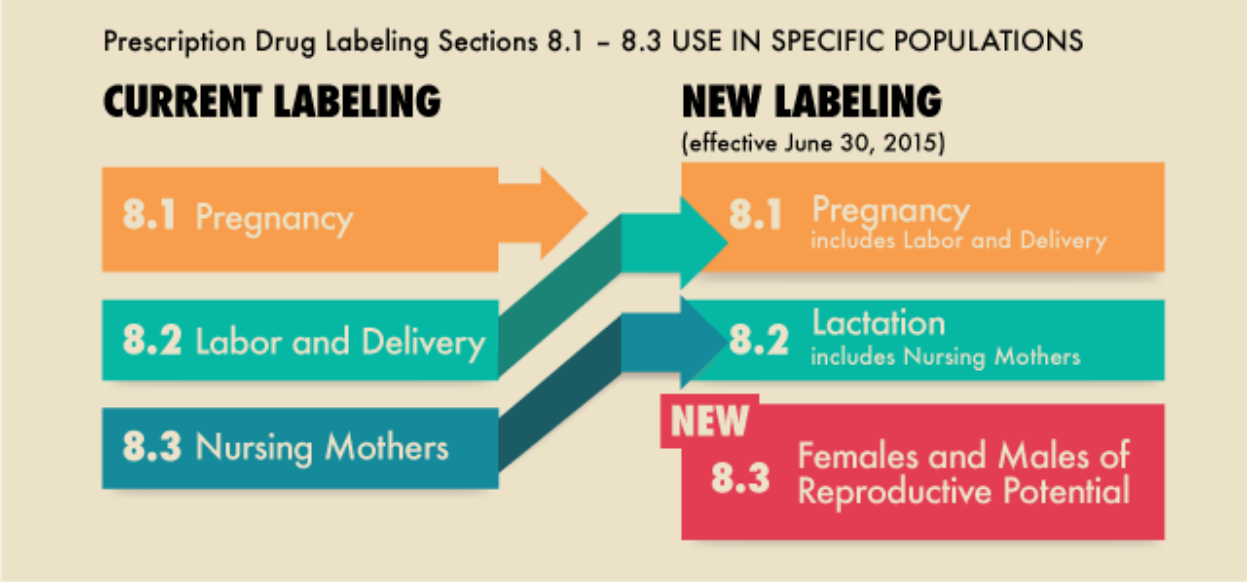
The FDA passed the PLLR to address years of criticism regarding the pregnancy category system.[1,2,3,4,5] Specifically, the Teratology Society Public Affairs Committee complained that the pregnancy letter categories implied an incorrect degree of risk with each letter.[4] The FDA states, "we have decided to eliminate the pregnancy categories because they are often viewed as confusing and overly simplistic and do not effectively communicate the risk a drug may have during pregnancy and lactation and in females and males of reproductive potential."[5]

When a medication was assigned to a letter category many variables –animal versus human data, benefits versus risk for the mother and fetus—were considered that may not be studied during the initial drug approval process. Due to a lack of pregnancy data during the drug approval stage, some medications received their pregnancy category based on similar medications in their class.[12,13] For example, triazolam, was classified as a category X medication based on studies from older benzodiazepines that noted an increased risk of birth defects after fetal exposure to diazepam and chlordiazepoxide.[12,13,14] Of note, diazepam was labeled as a pregnancy category D and the decades old medication chlordiazepoxide does not have a reported pregnancy category.[13,15,16] Since the pregnancy category for a drug is usually decided during the medication pre-marketing approval process by the manufacturer, some medications were assigned a pregnancy category based on similar medications and the labeling was never revised.[12,13]

Among the pregnancy letter categories, categories A and B were considered relatively safe in pregnant and lactating women, and categories D and X were deemed risky for the fetus; however, category C medications have caused uncertainty among health care providers. Category C medications, which represent over 66% of the medications taken in the United States, are those in which an animal reproduction study shows an adverse effect on the fetus, but there is a lack of evidence based on human studies.[4] A medication could also receive a category C classification; however, if animal and human studies were never even conducted. For example, albuterol, commonly used for asthma relief, was labeled as a category C

medication due to adverse effects in animals, but it is recommended for use during pregnancy in asthma guidelines.[17,18] Despite animal studies, the National Asthma Education and Prevention Program states that, "albuterol is the preferred short-acting inhaled beta2-agonist because it has an excellent safety profile and the greatest amount of data related to safety during pregnancy of any currently available inhaled beta2-agonist."[18]

Another major criticism of the FDA's pregnancy classification system was that medications in the same category posed an unequal risk of fetal toxicity. For example, isotretinoin—used for severe acne—and oral contraceptives are both category X medications, but do not share the same degree of fetal risk.[13] Even though oral contraceptives exposure late in pregnancy has been associated with masculinization of the female infant, they were classified as category X only because there was no benefit in taking a hormonal contraceptive while pregnant.[12,13] Whereas isotretinoin received a category X rating due its proven teratogenic effects.[13]



New Sections

Previously, the prescribing information section was divided into: pregnancy, labor and delivery, and nursing mothers.[1] The new format will include three sections: (8.1) pregnancy- which now includes labor and delivery, (8.2) lactation- which includes nursing mothers, and a new section (8.3) for females and males of reproductive potential.[1] Each section will include a detailed risk summary, clinical considerations, and relevant data.[1,2]

Pregnancy

The new pregnancy section (8.1) is divided into the following subsections: risk summary, clinical considerations, and pregnancy exposure registry.[1,5] If a medication is contraindicated for a pregnant woman, the first sentence of the risk summary will have a teratogenic statement, along with a brief description of the observed or anticipated consequences instead of a category X designation.[1,2] The risk summary also describes the risk of adverse developmental outcomes based on all relevant human data, animal data, and the drug's pharmacology.

The clinical considerations section will describe any risks to pregnant women and/or the fetus associated with a specific disease or condition for which the drug is indicated.[1,2] For example, diabetes is a disease in which there can be serious risks -- diabetic ketoacidosis, pre-eclampsia-- to the pregnant woman and fetus if untreated.[2] Therefore, due to the PLLR, diabetes medications may have a statement in the clinical considerations section about the importance of taking the medications to control the disease during pregnancy. Another example to describe this new pregnancy/clinical considerations labeling is the recently approved medication reslizumab injection for asthma.[19] The 2016 PI warns women of the risks associated with non-adherence with this medication and states the following:[19]

"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 in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control."[16]

The new pregnancy section will also include an overview of fetal development abnormalities from drug exposure. The likelihood of these abnormalities will be discussed in a fetal risk subheading with explanations from human or animal studies.[1] If outcomes are based on human data, this section will provide information on the incidence, severity, and reversibility of the developmental abnormalities.[2] Previously, fetal development toxicities were not clearly distinguished by severity, incidence or type, but now, adverse developmental outcomes will include the following groups of developmental toxicities:[2]

- 'Structural abnormalities: Describes dysmorphology, which includes malformations, variations, deformations, and disruptions.
- Embryo-fetal and/or infant mortality: Describes developmental mortality, which includes miscarriage, stillbirth, and infant death (including neonatal death).
- Functional impairment: Describes functional toxicity, which includes such outcomes as deafness, endocrinopathy, neurodevelopmental effects, and impairment of reproduction.
- Alterations to growth: Describes such outcomes as growth restriction, excessive growth, and delayed and early maturations."

A PLLR updated 2016 medication labeling as an example of the new pregnancy section with the risk summary and data.[17]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on TALTZ use in pregnant women to inform any drug associated risks. Human IgG is known to cross the placental barrier; therefore, TALTZ may be transmitted from the mother to the developing fetus. An embryofetal development study conducted in pregnant monkeys at doses up to 19 times the maximum recommended human dose (MRHD) revealed no evidence of harm to the developing fetus. When dosing was continued until parturition, neonatal deaths were observed at 1.9 times the MRHD *[see Data]*. The clinical significance of these nonclinical findings is unknown.

The 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 to 4% and 15 to 20%, respectively.

Data

Animal Data

An embryofetal development study was conducted in cynomolgus monkeys administered ixekizumab. No malformations or embryofetal toxicity were observed in fetuses from pregnant monkeys administered ixekizumab weekly by subcutaneous injection during organogenesis to near parturition at doses up to 19 times the MRHD (on a mg/kg basis of 50 mg/kg/week). Ixekizumab crossed the placenta in monkeys.

In a pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of ixekizumab up to 19 times the MRHD from the beginning of organogenesis to parturition. Neonatal deaths occurred in the offspring of two monkeys administered ixekizumab at 1.9 times the MRHD (on a mg/kg basis of 5 mg/kg/week) and two monkeys administered ixekizumab at 19 times the MRHD (on a mg/kg basis of 50 mg/kg/week). These neonatal deaths were attributed to early delivery, trauma, or congenital defect. The clinical significance of these findings is unknown. No ixekizumab-related effects on functional or immunological development were observed in the infants from birth through 6 months of age.

Pregnancy Registries

The new pregnancy section requires that manufacturers provide pregnancy registry information, which was previously not a labeling requirement.[2,5,22] A pregnancy registry is an ongoing, observational study that collects and assesses data on medications, biologicals, or vaccines given to a mother when pregnant.[2,5,22,23] The registries are overseen by a pharmaceutical company or a special interest group.[2,22] The FDA does not conduct pregnancy exposure registries, but may recommend or require that a drug company implement a pregnancy registry based on certain criteria.[22] The FDA's Office of Women's Health maintains a list of registries, posted on the FDA's website, including those for cancer, epilepsy, arthritis, diabetes, and psychiatric conditions.[22]

The FDA requires that the pregnancy registry report annually specific information including: demographics, gravidity and parity status, time of onset of exposure, and pregnancy outcomes.[13] Previously, prescribers and patients had to find a pregnancy registry on the FDA's

website and search by medication, medical condition, vaccine, or external medical device. Of note, medication data will be collected for not only new medications, but for existing and generic products.[13,22]

FDA pregnancy registry home page website:[22]

http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm

Lactation

The new lactation section (8.2) will replace the former breastfeeding or nursing section. Through the PLLR, all medications will be required to have a lactation section to provide health care providers with information about whether the medication is safe in breastfeeding women.[1] Of note, the PLLR uses the term lactation to refer to the biological state during which a woman's body produces and excretes milk.[2] The term breastfeeding refers to all human milk feeding situations when an infant or child is fed with human milk, whether the milk is received directly from the breast or as expressed milk.[2] The PLLR addresses not only medications found in breast milk, but also how a drug affects the milk supply.[3,12] Drug levels in human breast milk will be collected on the drug, prodrug, and the active metabolite(s) for this section. It will also include information on how much of a drug is secreted in breast milk, and how this amount compares to blood concentrations at steady state.[1,3]

The new lactation section will take into consideration pediatric age-related differences -- absorption, distribution, metabolism, and elimination of the drug.[2] Manufacturers must include data about how medication exposure in breast milk affects infants of different ages.[2] For example, a medication for a newborn may have a different effect compared to a child who is nine months old.[12] Medication exposure also depends on whether the child is exclusively breastfed or if it is also receiving formula feeding.[2] The labeling may also include interventions to minimize exposure of the breastfed child to a drug and/or its active metabolite(s), such as

timing the administration of the drug relative to feedings at the breast, pumping sessions, or expressing milk, if needed, to discard it for a specified time period.[2]

Lactation data may come from a clinical lactation study(s) or from other sources (e.g., published literature, lactation databases). Using this information, the consumption of the drug consumed by the infant will be estimated.[2] If a medication is found in breast milk, there will be a description of the concentration and sensitivity used to measure the quantity of drug found in breast milk along with the estimated daily infant dose during breastfeeding.[2] A drug that is undetected in breast milk that does not adversely affect the quantity or quality of breast milk, or affect the breastfed child, will contain the following label: "The use of (medication name) is compatible with breastfeeding."[2]

Females and males of reproductive potential

A new subsection, *Females and Males of Reproductive Potential* (8.3), was added to provide a consistent location for information about pregnancy testing, contraception, and infertility.[2,5] This section will allow providers to directly find information regarding contraception recommendations, pregnancy testing, and information about infertility before, during, and after drug therapy.[2] Previously, recommendations for pregnancy testing and contraception were inconsistently distributed throughout the labeling throughout the pregnancy and the nonclinical toxicology sections.[2]

The recommendations and requirements for pregnancy testing and contraception may be based on concerns for potential or demonstrated adverse developmental outcomes associated with drug exposure during pregnancy. The *Females and Males of Reproductive Potential* section will appear under the following subheadings:[2,5]

- Pregnancy Testing
- Contraception
- Infertility

The *Females and Males of Reproductive Potential* section was designed to give an overview of any precautions that should be made when patients are using this medication, and

provide clinical trial or post-marketing data.[1,2] If a medication requires a safety registry, then information on it will be in this section. According to the FDA: "The new subsection created under the final rule, Females and Males of Reproductive Potential, provides a dedicated subsection for pregnancy testing, contraception, and infertility information when pregnancy testing or contraception is required or recommended before, during, or after drug therapy or when there are human or animal data that suggest drug-associated fertility effects."[2]

Data

The PLLR encourages the inclusion of human pregnancy data in the labeling. Usually, when medications are first-approved, it is rare –due to obvious ethical reasons—to have human pregnancy data; therefore, the risk determination is typically made based on animal data from studies. Unless, a medication is specifically approved for use in pregnancy, pregnant women are not included in pre-marketing clinical trials. Through the PLLR changes, when adequate human data—observational studies or post-marketing studies—becomes available it should be added to the labeling. According to the FDA, "Data –for the pregnancy and lactation sections—could come from a variety of sources, including well-conducted studies published in the medical literature about the use of prescription drugs and biological products during pregnancy and breast-feeding. In addition, sources of human data will include pregnancy exposure registries, clinical trials, and other large-scale epidemiologic studies. Companies will be required to include clinically relevant information from such published studies in the labeling."[2]

If the fetal risk is based on human data, there will be a brief description of data supporting the risk statement. Human data in this section will be described before animal data. If the potential risk is implied from animal data, then a standard statement will describe the risk with a specific scale: none, low, moderate, high, or unknown.[2] Animal data must include species information and compare to human dose equivalent.[2] The PLLR will apply to all medications, including those without systemic absorption and with limited risk data. If a medication is a locally absorbed medication, not systemically absorbed into the bloodstream, then it must contain the following statement within the risk summary: "(Medication name) is not absorbed systemically from (part of body) and cannot be detected in the blood. Maternal use is not expected to result in fetal exposure to the drug."[7,9]

Many new pregnancy safety decisions stem from surveillance systems because medications are rarely studied in pregnant patients. Two major U.S. multicenter, case-control studies –the National Birth Defects Prevention Study (NBDPS) and the Birth Defects Study (BDS)—have contributed to recent antenatal pregnancy information.[20,24] The Centers for Disease Control and Prevention's (CDC) NBDPS, conducted from 1997 to 2003, collected data from 10 birth defects surveillance systems.[24,25] Case subjects had at least one of over 30 eligible birth defects. The Boston University Slone Epidemiology Center's BDS, from 1976 to 2008, followed 25,313 mothers of infants with and without birth defects in regional study centers.[6,24,25] In addition, the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) is a U.S. post-marketing surveillance system used to monitor the safety of vaccines and medications during pregnancy.[25] These studies and other surveillance systems help to identify the most commonly used medications during pregnancy and highlight the need to research the safety of certain medications in this population.

Table 2. Most Commonly Prescribed Prescription Medications in First Trimester (BDS)[7]

BDS (Data from 2004-2008)
1. Influenza vaccine- not specified
2. Antibiotic- not specified
3. Albuterol
4. Progesterone
5. Levothyroxine
6. Ondansetron
7. Amoxicillin
8. Sertraline
9. Azithromycin
10. Fluticasone

Table 3. Most Commonly Prescribed Prescription Medications in First Trimester (NSDPS)[7]

NBDPS (Data from 1997-2003)
1. Amoxicillin
2. Antibiotic- not specified
3. Progesterone
4. Albuterol
5. Clomiphene
6. Loratadine
7. Levothyroxine
8. Gonadotropin chorionic
9. Azithromycin
10. Leuprolide

Kinetic Data

Another PLLR highlight is the inclusion of pharmacokinetic data to support dose adjustment(s) during pregnancy and the postpartum period. For example, it is reported that during pregnancy cytochrome (CYP)1A2 activity decreases and CYP2D6 activity increases.[26] If a drug is primarily metabolized via a specific cytochrome P450 enzyme with reported activity changes in pregnancy, this subsection should include this information and inform the prescriber about how this change may affect serum drug levels in the pregnant woman.[26]

New Pregnancy and Lactation Labeling Overview[1]

"General information: Contact information if pregnancy registry available and a general statement about background risk.

Fetal risk summary:

- Based on all available data, this section explains the likelihood that the drug increases the risk of developmental abnormalities in humans and other relevant risks; more than one risk conclusion may be needed.
- Drugs that are not systemically absorbed, there is a standard statement that states that maternal use is not expected to result in fetal exposure.
- Medications systemically absorbed:
  - When there are human data, include a statement about the likelihood of increased risk based on these data. This statement is followed by a description of findings.
  - Include a standard statement about likelihood of increased risk based on animal data.

Clinical considerations

- Inadvertent exposure: Known or predicted risk to the fetus from inadvertent exposure to drug early in pregnancy

Prescribing decisions for pregnant women:

- Describes any known risk to the pregnant woman and fetus from the disease or condition that the drug is intended to treat.
- Information about dosage adjustments during pregnancy.
- Maternal adverse reactions unique to pregnancy or increased in pregnancy.
- Effects of dose, timing, and duration of exposure to drug during pregnancy.
- Potential neonatal complications and needed interventions

Data:

- Human and animal data are presented separately, with human data presented first.
- Describe study type, exposure information (dose, duration, timing), any identified fetal developmental abnormality, or other adverse effects.
- Human data: Include positive and negative experiences, number of subjects, and duration of study.
- Animal data: Include species studied, and describe doses in terms of human dose equivalents."

Conclusion

The replacement of familiar pregnancy letter categories that have been used for over 35 years with an individualized narrative is a dramatic shift. The changes place more responsibility and time on clinicians to determine medication safety; however, the PLLR update also provides more current human data in a consistent format to counsel those planning a pregnancy, pregnant, or lactating. The PLLR can also help clinicians to consider other medication variables such as maternal disease and the impact of an untreated disease on the fetus. Overall, the PLLR medication labeling changes are designed to improve the risk versus benefit medication assessment for the pregnant, lactating, or reproductive population.

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ACTIVITY TEST

1. **Which regulation introduced pregnancy letter risk categories – A, B, C, D, and X – to prescription labeling?**
    a. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products in 2006
    b. Gender guidelines in 1993
    c. Kefauver-Harris amendments in 1962
    d. Labeling for Prescription Drugs Used in man in 1979

2. **Which of the following regulations were issued after the thalidomide tragedy?**
    a. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products in 2006
    b. Gender guidelines in 1993
    c. Kefauver-Harris amendments in 1962
    d. Labeling for Prescription Drugs Used in man in 1979

3. **What group challenged the FDA to remove pregnancy letter category systems?**
    a. The Teratology Society Public Affairs Committee
    b. General Motors
    c. General Electric
    d. Drug manufacturers

4. **Which of the following will not be a designated section based on the new PLLR format?**
    a. Pregnancy section
    b. Labor and delivery section
    c. Lactation section
    d. Females and males of reproductive potential section

5. **How many pregnancies are estimated annually in the United States?**
    a. 6.5 million
    b. 4 million
    c. 2.5 million
    d. 7 million

6. **Which answer includes a study and/or surveillance system that has contributed to pregnancy medication data?**
    a. National Birth Defects Prevention Study (NBDPS)
    b. Birth Defects Study (BDS)
    c. Vaccines and Medications in Pregnancy Surveillance System (VAMPSS)
    d. All of the above

7. **The Females and Males of Reproductive Potential section was added to provide a consistent location for information about which of the following:**
    a. Pregnancy testing, contraception, infertility
    b. Breastfeeding, contraception, infertility
    c. Pregnancy testing, drug levels in milk, infertility
    d. Contraception, developmental toxicities, infertility

8. **Which of the following defines a pregnancy registry?**
    a. A case-control study in pregnant women
    b. An ongoing, observational study that collects and assesses data on medications, biologicals, or vaccines given to a mother when pregnant
    c. A list of medications to avoid
    d. A hotline to help pregnant women

9. **Which kinetic changes have been reported during pregnancy?**
    a. CYP1A2 activity increases and CYP2D6 activity decreases
    b. CYP1A2 activity decreases and CYP2D6 activity increases
    c. CYP3A4 activity increases and CYP2D6 activity decreases
    d. CYP3A4 activity increases and CYP1A2 activity decreases

10. **Which of the following was included in the BDS and NSDPS as a medication frequently used in the first trimester?**
    a. Hydroxyzine
    b. Albuterol
    c. Labetalol
    d. Ibandronate

11. Where can you find information on disease-associated maternal and/or embryo-fetal risks within the product labeling?

a. Pregnancy section – Data
b. Lactation section – Data
c. Females and males of reproductive potential – Data
d. Pregnancy section – Clinical considerations

12. What percentage of people in the U.S. reportedly take category C medications?

a. 80%
b. 66%
c. 25%
d. 85%

13. Which of the following medications will not require label changes due to the PLLR?

a. Medication approved after June 30, 2015
b. Medications approved between June 30, 2001, and June 29, 2015
c. OTC Medications
d. Medications approved prior to June 29, 2001

14. Which description describes possible events included in the pregnancy developmental toxicities section?

a. Structural abnormalities
b. Functional impairment
c. Alterations to growth
d. All of the above

15. When did the PLLR go into effect?

a. June 30, 2015
b. January 1, 2015
c. December 20, 2006
d. June 1, 2010

16. What percentage of pregnant women in the United States require a prescription medication for chronic conditions such as hypertension?
    a. 8%
    b. 10%
    c. 5%
    d. 15%

17. The 1993 Gender Guideline did the following:
    a. Permitted women of childbearing potential to participate in Phase 3 trials
    b. Allowed most women of childbearing potential to participate in Phase 1 and early Phase 2 trials
    c. Blocked women of childbearing potential from participating in clinical trials
    d. Permitted women of childbearing potential to submit post-marketing adverse effects

18. Which pregnancy category (A, B, C, D, or X) was considered the most unspecific?
    a. Category A
    b. Category B
    c. Category C
    d. Category D

19. Which of the following category X medications in the United States is considered a category C medication in Australia and Sweden?
    a. Estradiol
    b. Oral contraceptives
    c. Clomiphene
    d. Triazolam

20. Due to the PLLR, the pregnancy section will no longer have a letter category, but a narrative divided into the following three subsections:
    a. Risk summary, clinical considerations, and data
    b. Risk summary, special information, and kinetics
    c. Data, special information, and product labeling
    d. Clinical considerations, data, and product stability

Please submit your final responses on freeCE.com. Thank you.