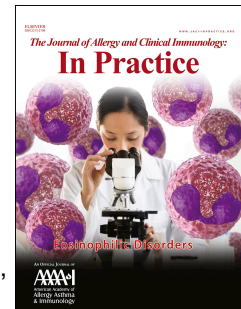


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Clinicians' Perspective of The New Pregnancy and Lactation Labeling Final Rule (PLLR): Results from an AAAAI/FDA Survey

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1 Title

2 Clinicians' Perspective of The New Pregnancy and Lactation Labeling

3 Final Rule (PLLR): Results from an AAAAI/FDA Survey

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32 **The authors report no conflicts of interest**

Abstract

Background: On June 30, 2015, the U.S. Food and Drug Administration (FDA) began implementation of the PLLR, which replaced the pregnancy letter category system (A, B, C, D or X) with integrated narrative summaries of the risks of using a drug or biological product during pregnancy and lactation. The letter category system, first established in 1979, was regarded as overly simplistic and misinterpreted as a grading system. The PLLR labeling format was created to improve the presentation of available data on use of the drug during pregnancy and/or lactation,

Objective: Survey clinician awareness, assessment, and use of this new labeling format

Methods: In January 2018, an online survey, developed in collaboration between the American Academy of Allergy, Asthma & Immunology (AAAAI) and the U.S. FDA, was sent to a random sample of the U.S. membership of the AAAAI. The survey content consisted of questions addressing the following: demographics, awareness and use of the PLLR, and value and understanding of the PLLR format based on an example of the pregnancy subsection of labeling.

Results: Of 1500 members who received an email survey, 184 (12%) completed the survey. Respondents were a mean age of 56 years and treated on average two pregnant women per month. Less than half (46%) of respondents were aware that the pregnancy letter category system was replaced with a narrative summary. After reading the example, most (68%) of the respondents did not feel that the narrative summary was concise, however, 71% of respondents found the background risk and disease-associated risk information helpful. The majority (95%) of respondents continued to use the pregnancy letter category system to make prescribing decisions.

Conclusions: These survey results suggest that the PLLR format was not known by a majority of prescribers and that the pregnancy letter category format is continuing to be used despite significant flaws in the

old system. However, the survey did not address why prescribers were continuing to rely on the pregnancy letter category system. Whether this is due to the PLLR format itself or the lack of quality data to inform the safe use of medications in pregnancy cannot be determined from these survey results. FDA will use these survey results to refine the communication of pregnancy safety information in labeling and will expand outreach efforts to educate healthcare providers in the new labeling system.

Key words: pregnancy, lactation, labeling, safety

Highlights Box

1. What is already known about this topic

On June 30, 2015, the U.S. Food and Drug Administration (FDA) began implementation of the PLLR, which replaced the pregnancy letter category system (A, B, C, D or X) with integrated narrative summaries of the risks of using a drug or biological product during pregnancy and lactation.

2. What does this article add to our knowledge?

A survey sent to U.S. Allergists showed that the PLLR format was not known by a majority of prescribers and that the pregnancy letter category format is continuing to be used despite significant flaws in the old system.

3. How does this study impact current management guidelines?

FDA will use these survey results to refine the communication of pregnancy safety information in labeling and will expand outreach efforts to educate healthcare providers in the new labeling system.

Abbreviations

PLLR- Pregnancy and Lactation Labeling Rule

FDA - U.S. Food and Drug Administration

EHR - electronic health record

Introduction

In 2017 there were about 4 million births in the United States, and many women had medical conditions during pregnancy that required treatment. (1) The majority of women use at least one medication during pregnancy despite limited safety data for many medications. (2) Drug labeling that is developed by the manufacturer and approved by the U.S. Food and Drug Administration (FDA) includes important information on the safe and effective use of a drug, including in pregnant women.

This article presents the results of a collaboration between the American Academy of Allergy Asthma and Immunology (AAAAI) and the FDA to assess the awareness, understanding, and value of the Pregnancy and Lactation Labeling Rule (PLLR) in clinicians' practice.

Between 1979 and 2015, FDA used a letter category system (A, B, C, D or X) in an effort to standardize the presentation of potential effects of prescription medications during pregnancy. (3, 4) This labeling system did not affect over-the-counter medications. What was initially created to help clinicians navigate through animal and human data was progressively seen as "over simplistic and misleading." Clinicians were

using the letter category system as a grading system with Category A viewed as safest and Category X viewed as least safe and did not understand the nuances of the letter categories. (5, 6)

In response to these concerns, the FDA sought stakeholder input through advisory committee meetings and focus group interviews. The Agency put forward the proposed rule in 2008 to reformat drug labeling for the pregnancy and lactation subsections. On December 4, 2014, the final rule, known as the Pregnancy and Lactation Labeling Rule (PLLR), was published, and its implementation began on June 30, 2015. (7) The PLLR requires that manufacturers of all prescription drug and biological products, including generic drugs, remove pregnancy letter categories from their product labeling. For drugs approved on or after June 30, 2001, the letter category is replaced with narrative summaries of the risks of using a prescription drug or biological product during pregnancy and lactation. Manufacturers of new medications or previously approved medications with new indications approved after June 30, 2015 must comply with the new labeling format. All manufacturers of medications have a specified timetable to have labeling comply with PLLR.

Under the “Pregnancy” subsection there are four headings:

1) The “Pregnancy Exposure Registry” heading is included only if a pregnancy exposure registry is available and includes contact information on how to enroll.

2) The “Risk Summary” heading includes a narrative summary of the human, animal and pharmacologic data and conveys what is known about the potential risk of exposure for the drug during pregnancy. There will also be a statement if there is an absence of data.

3) The “Clinical Considerations” heading provides information to inform prescribing and benefit-risk counseling and is further subdivided into five subheadings: Disease-associated Maternal and/or Embryo/Fetal Risk, Dose Adjustments During Pregnancy and the Postpartum Period, Maternal Adverse Reactions, Fetal/Neonatal Adverse Reactions, and Labor or Delivery.

4) The “Data” heading includes concise descriptions of the studies used to support the Risk Summary. (8)

Figure 1

The FDA determined that there was no consistent placement of information about pregnancy testing, contraception, and infertility, It was difficult for health care providers to find this

important information which could affect decision making.

Therefore, the new final rule required that the subsection titled “Females and Males of Reproductive Potential” (8.3) contain information about the need for pregnancy testing, contraception recommendations and information about infertility as it relates to the drug.

The “Nursing Mothers” subsection was renamed, the “Lactation” subsection (8). This section provides information about using the drug while breastfeeding, such as the amount of drug in breast milk and potential effects on the breastfed infant.

The goal of the PLLR is to help clinicians weigh the benefits and risks of treatments during pregnancy so they can present this information to the patient in a clear and meaningful manner (8).

In this article, we summarize the key findings of a survey that asked clinicians about their awareness of PLLR and their thoughts on how it compares to the pregnancy letter category system that preceded it.

Methods

In January 2018, AAAAI emailed an invitation to participate in an online survey to a random sample of its U.S. membership. This membership includes allergist/immunologists, other medical specialists, allied health and related healthcare professionals. The survey content and design were finalized in collaboration with members of FDA's Division of Pediatric and Maternal Health and Risk Communication Staff.

The survey assessed the following information:

1. Demographics: age, sex, type of practice and years in practice.

2) Awareness and use of the PLLR:

- Are you aware that the pregnancy letter categories (A, B, C, D and X) on prescription medication labeling are being replaced with narrative summaries of the risks of using a medication during pregnancy?
- How often do you use the medication labeling to obtain prescribing and safety information for your pregnant patients? If, Never, where do you obtain this information?
- On average, how many pregnant women do you prescribe medications to per month?

207 ◦ How often do you use the medication labeling to obtain
208 prescribing and safety information for your pregnant
209 patients?

210 ◦ On average, how many pregnant women do you prescribe
211 medications to per month?

212 3) Understanding of the new PLLR format and content. A sample
213 “pregnancy” subsection was supplied for DRUG ABC (Table 1). This
214 fictitious drug had animal data available, but no human data. This
215 subsection included a Risk Summary, Clinical Considerations, and Data
216 headings. Understanding of the new PLLR format for DRUG ABC was
217 assessed by the following questions:

218 ◦ How clear do you find the information in the label?

219 ◦ How relevant do you find the information in the label?

220 ◦ Did you find the background risk information in the label
221 useful?

222 ◦ Did you find the disease-associated risk information useful?

223 ◦ Would you be likely to prescribe the medication to your
224 pregnant patient?

225 ◦ How much would reassuring human data in the PLLR
226 increase your comfort with prescribing this medication?

4) Value of the new PLLR format:

- o Overall, how helpful or unhelpful is the narrative summary labeling for DRUG ABC compared to the pregnancy letter category (A, B, C, D, and X) that used to appear on the drug labels?
- o How often do you use the pregnancy risk letter categories (A, B, C, D, and X) instead of the narrative summary to make prescribing decisions for pregnant women?
- o Overall, do you think the new labeling has brought more meaningful information to you and your patients compared to prior labeling?

Results

1500 AAAAI members (33% of its U.S. membership) received an email invitation to participate in the survey. 184 (12%) of invited members participated in the survey, 66% were male, average age was 56 years old, and 56% were in single specialty or multi-specialty group practices. This was in line with non-responders who were 54% male with an average age of 60 years old. Responders on average treated 2 pregnant women per month in their clinical practice. Only 46% of responders were aware that the pregnancy

letter categories were replaced with a narrative summary, and almost 95% of responders continued to use the pregnancy letter categories (A, B, C, D and X) to make prescribing decisions (TABLE 1). 88% of responders use the medication labeling to obtain prescribing and safety information, while others cited UpToDate, Lexicomp, and Micromedex as other sources of safety information. After reviewing the sample narrative summary for DRUG ABC (Table 2), 51% of responders felt the summary was not clear, and 68% of responders felt it was not concise. 71% of responders had no experience referring pregnant women to a pregnancy exposure registry, but after reading the narrative summary, 51% would refer their pregnant patients to the pregnancy exposure registry. 71% of responders found the background risk and disease- associated risk information to be helpful. 62% of responders found the animal data to be helpful. Overall, 56% of responders found the narrative summary to be unhelpful when compared to the previous letter category system (Figure 2). 51% of responders felt that the new labeling did not bring more meaningful information to them and their patients. After reading the narrative summary of DRUG ABC, 53% were unsure if they would prescribe the medication.

Discussion

Determining the safety of medication use during pregnancy is a challenge, particularly because the clinical trials that support drug approval usually do not enroll pregnant women. Potential sources of safety data include pregnancy registries, prospective and retrospective cohort studies, case-control studies, case reports and animal studies. Prior to the letter category system implemented in 1979, physicians were presented with increasing amounts of animal and human data of variable quality, and classification systems were subsequently developed to organize and summarize these data. (3)

The PLLR was created to address concerns regarding the old labeling system, particularly the reliance on the letter categories, and the need for better, more comprehensive information regarding the safety of medications during pregnancy and lactation. Results from this survey provide a first look at how clinicians view these new changes. Most of the responders found the risk information included in the new labeling to be helpful. In addition, most responders found the inclusion of animal data to be useful. Since most drugs have limited human data, it is reassuring that most respondents would

refer their patients to a pregnancy registry. However, most found the narrative summary to be too detailed and unclear. Comments included that the previous letter system was much easier to understand. Most concerning was that the majority of responders were not aware of PLLR changes, and many continued to refer to letter categories when counseling patients.

If clinicians are finding the PLLR format to be unclear or too detailed, could this influence prescribing? Robinson et al, sought to answer this question through a randomized survey-based study (9). 162 surveys were randomly distributed: the first survey contained a clinical vignette with an indication for a drug in question, detailed information about the drug, and pregnancy category (either A, B, C, or D). The second survey contained the same information without the pregnancy letter category. Participants were significantly less likely to prescribe category B and C drugs, the most common medications prescribed in pregnancy, when the letters were not available for review. The authors suggest that, in the absence of a letter category system, pregnant women's access to medications may be more restricted. In the setting of asthma, physician under-treatment is already a documented occurrence (10). One study found

that over a quarter of family physicians would instruct their patients to decrease or discontinue asthma medications during pregnancy when asthma was well controlled by current therapy.(11)

The U.S. healthcare delivery system has undergone substantial changes over the last decade and, as a result, physicians are under a great deal of stress from the introduction of the electronic health record (EHR), increased workload and regulatory requirements. A recent study involving direct observation of 57 physicians for 430 hours indicated physicians spend about 27% of their work hours on direct clinical face time and almost 50% of their time on electronic health record and desk work. (12) It is understandable that physicians need a quick point of care reference for pregnancy and lactation medication safety information and will need time to adapt to the new labeling format where safety data are provided in a narrative form. While the new format is less misleading, there may be more opportunity for under-treatment if a clinician has not taken the time to review and understand the potential risks and benefits of treatment.

This study has several limitations. The labeling example used in the survey did not include human data, and therefore may have been

difficult to interpret. Survey responders may have had less awareness of the recent labeling changes as they were older and treated few pregnant patients (only 2 per month). The potential limited generalizability outside the specialty of Allergy and Immunology needs consideration. It would be valuable to distribute surveys, such as this one, among other specialties, particularly obstetricians. In addition, recirculating similar surveys when more drugs have updated labelings will provide additional information as clinicians become more accustomed to the new format. The response rate of 12% may appear to be a potential limitation. However, a typical response rate for this audience is about 10-15%.

For chronic medical conditions during pregnancy, such as asthma, inadequate management can have significant effects on maternal and fetal health. The PLLR removed the pregnancy risk categories with the intention to eliminate confusion regarding fetal health risk. However, this survey shows that, while most survey participants approved of this additional information to better evaluate risks versus benefits, they did not find that the new labeling met their needs overall for obtaining the critical information that the labeling is designed to provide.

The results suggest that outreach to asthma specialists is needed so that they are aware of the labeling changes and can adapt to prescribing without a letter category. Training and continuing education should be developed to ensure that asthma specialists who manage pregnant women are well informed of the new prescribing information system as well as the availability of pregnancy registries where they can refer patients to participate and contribute to data collection on the safety of asthma drugs during pregnancy. To address some of the data gaps on the safety of asthma drugs in pregnancy, stakeholders including academic groups and industry should develop a multiproduct asthma pregnancy registry. Such a collaboration would provide an efficient way to collect data through increased awareness among healthcare providers and pregnant women. This type of centralized process would enable data collection on existing asthma products as well as new products that enter the market. Submission of these data to FDA would help improve the content of labeling and inform prescribing of asthma medications in pregnant women.

The survey did not address why prescribers were continuing to rely on the pregnancy letter category system. Whether reverting to the old letter category is due to the PLLR format itself, the lack of quality data to inform the safe use of medications in pregnancy, or other factors such as the need to adapt to the new labeling system, cannot be determined from these survey results. There is a clear public health need to collect more data on the safety of medication use in pregnancy. These survey results will help inform FDA's efforts to continue to refine the communication of pregnancy safety information in labeling and expand its outreach efforts to educate clinicians on the new labeling system. Additionally, based on these survey results and other input on PLLR, FDA will perform end user testing with focus groups to obtain more detailed input on how busy clinicians prefer to receive pregnancy safety information in labeling. Clinicians are still learning and adapting to the new pregnancy labeling system. A future survey to assess how healthcare providers, in both primary care and other specialty areas, have adapted to the PLLR format, may be helpful.

The study was coordinated by the AAAAI and the Vaccines and Medications in Pregnancy Surveillance Systems (VAMPSS). VAMPSS is a nationwide surveillance system established to comprehensively monitor the use and safety of vaccines and medications during pregnancy. The VAMPSS team was responsible data collection and analysis. We would like to thank Lauri Sweetman for her efforts on this project.

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443 Figure 1 - Prescription Drug Labeling Changes as of 2015

444 Figure 2: Response to value of the narrative summary

Table 1: Sample of survey questions and responses

	% (N)				
	Always	Most of the Time	Sometimes	Rarely	Never
How often do you use the pregnancy risk letter categories (A,B,C,D,X) instead of the narrative summary to make prescribing decisions for pregnant women?	30.8(53)	43.0 (74)	15.7 (27)	5.2(9)	5.2 (9)
How often do you use the medication labeling to obtain prescribing and safety information for your pregnant patients?	39.7 (73)	32.6 (60)	17.9 (33)	8.2 (15)	1.6 (3)
	Strongly Agree	Agree	Disagree	Strongly Disagree	
How much do you agree or disagree that the narrative summary labeling of DRUGABC is:					
clear	5.1 (9)	43.4 (76)	37.1 (65)	14.3 (25)	
concise	4.0 (7)	28.0(49)	44.6 (78)	23.4 (41)	
	Very helpful	Somewhat helpful	Somewhat unhelpful	Not at all helpful	

Under the Risk summary heading: How helpful or unhelpful is the Background risk information?	18.1 (31)	54.4 (93)	18.7 (32)	8.0(15)	
Under the Clinical Considerations heading: How helpful or unhelpful is the disease-associated risk information	19.1(34)	52.1(89)	19.3(33)	8.8 (15)	

Table 2 – Assessing understanding with
SAMPLE NARRATIVE SUMMARY FOR DRUG
ABC

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DRUG ABC during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting www.mohtertobaby.org/asthma.

Risk Summary

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as drugabc, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of drug ABC throughout pregnancy at doses that produced exposures up to approximately 30 times the exposure at the maximum recommended human dose (MRHD) of 100 mg SC [see Data].

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.

Clinical Considerations

Disease-Associated Maternal and/or Embryofetal 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 in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data

In a prenatal and postnatal development study, pregnant cynomolgus monkeys received drugabc from gestation days 20 to 140 at doses that produced exposures up to approximately 30 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 100 mg/kg once every 4 weeks). DrugABC did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. DrugABC crossed the placenta in cynomolgus monkeys. Concentrations of drugABC were approximately 2.4 times higher in infants than in mothers up

to day 178 postpartum. Levels of drug ABC in milk were less than or equal to 0.5% of maternal serum concentration.

In a fertility, early embryonic, and embryofetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine IL-5, at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryofetal development of IL-5-deficient mice has been reported to be generally unaffected relative to wild-type mice.

Figure 1

Prescription Drug Labeling Changes as of 2015

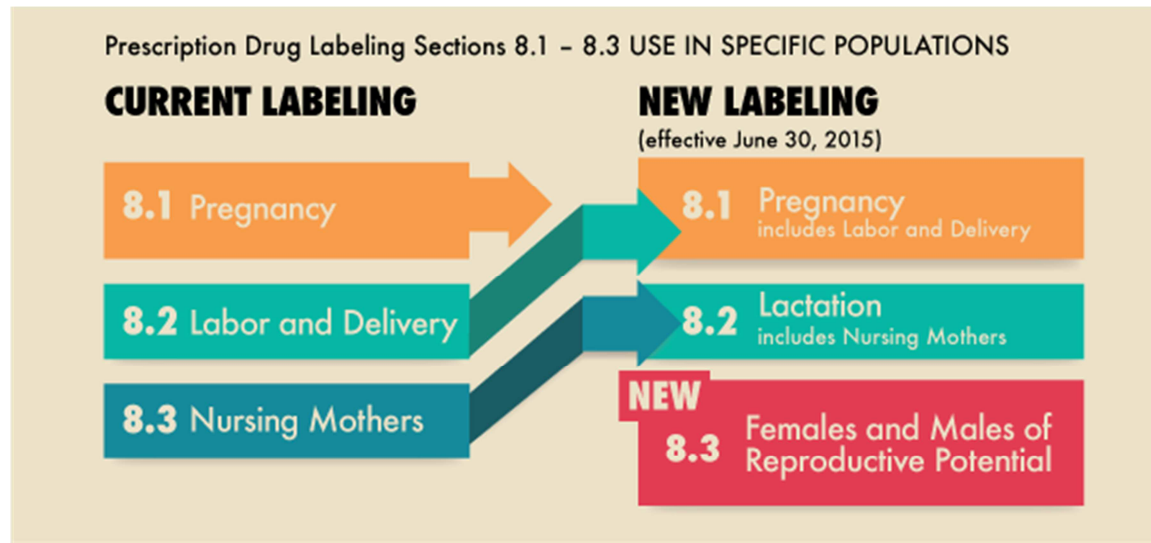


Figure 2: Response to value of the narrative summary

Q10 Overall, how helpful or unhelpful is the narrative summary labeling for DRUGABC compared to the pregnancy letter category (A,B,C,D and X) that used to appear on drug labels?

