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Review Article

Drug Safety Ten Years After Implementation of the Pregnancy and Lactation Labeling Rule and Abolition of Letter-Based Pregnancy Risk Categories

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Abstract

Most pregnant patients use prescription or over-the-counter medicines, yet high-quality human safety data remain limited and often inconsistently communicated. This narrative review synthesizes contemporary evidence on medication use in pregnancy and appraises the impact, implementation, and gaps of U.S. Food and Drug Administration (FDA) labeling reforms-especially the 2015 Pregnancy and Lactation Labeling Rule (PLLR). Epidemiologic studies show medication exposure is common and increasing, while robust human data lag; uncertainty, cultural factors, and clinician communication styles amplify perceived teratogenic risk and can undermine adherence. The PLLR replaced letter categories (A, B, C, D, X) with structured narrative sections (Pregnancy, Lactation, and Females/Males of Reproductive Potential) intended to reduce oversimplification and improve risk-benefit decisions. However, clinician awareness and use of PLLR content remain inconsistent, with persistent reliance on legacy categories and secondary databases. Post-approval evidence streams-pregnancy exposure registries and health-care utilization databases-now supply most human data, yet studies are frequently delayed, underpowered, or methodologically constrained, and labeling changes may take years. Internationally, FDA and European Medicines Agency labeling often diverge in language and directionality despite drawing on similar sources, further complicating counseling. Label modernization is necessary but insufficient. Priority actions include ethically including pregnant and lactating persons in clinical trials, accelerating harmonized post-approval evidence generation, standardizing clear communication that quantifies background versus drug-attributable risks, and educating clinicians to navigate PLLR narratives. Aligning evidence generation with effective risk communication is essential to support evidence-based prescribing and improve maternal-fetal safety.

Keywords: *Pregnancy and Lactation Labeling Rule; Letter Categories*

Abbreviations

PLLR: Pregnancy and Lactation Labeling Rule; FDA: Food and Drug Administration; AAAAI: American Academy of Allergy, Asthma and Immunology; FAERS: FDA Adverse Event Reporting System; EMA: European Medicines Agency; US: United States of America; EU: European Union; PRGLAC: Health and Human Services Task Force on Research Specific to Pregnant Women and Lactating Women; NIH: National Institute of Health; NDA: New Drug Application; BLA: Biological Licensing Application; PMCs: Post-Marketing Commitments; PMRs: Post-Marketing Requirements

Introduction

Medication use in pregnant women

Over 200 million pregnancies occur annually, worldwide, with about 6 million of these in the United States [1]. Antenatal exposure to prescription or over-the-counter medications poses a therapeutic dilemma whenever physicians care for pregnant women. For most medications, the safety profiles for the mother and fetus are inadequate, and the risks are uncertain [2-5]. Cultural and social influences, scientific uncertainty, and regulatory ambiguity regarding medication use during pregnancy tend to increase physicians' and patients' perception of risk [6]. Likewise, physicians' communication styles strongly affect pregnant women's risk perception [7]. Thus, on one hand, faced with a scarcity of reliable information, physicians and pregnant patients may struggle to make evidence-based decisions about medication use. On the other hand, worry about potential birth defects may discourage some pregnant women from starting or adhering to beneficial treatments [7-10]. Nevertheless, use of medications for health care of the mother during pregnancy is vital to lessen complications arising from underlying chronic conditions typified by diabetes, epilepsy, hypertension and kidney disease, asthma, thyroid disorders, and sexually transmitted infectious diseases [11-14]. Women may also require treatment for common acute conditions caused, or worsened by pregnancy, including nausea and gastritis, headache, low back pain, rashes and cystitis [15,16].

Estimates vary, but one highly cited study reported that women used prescription or over the counter medications in 88% of all pregnancies in the United States between 1976-2008 [9]. Another study confirmed extensive medication use in a geographically and ethnically diverse cohort of pregnant women in the United States, with 97% of women taking at least one medication during pregnancy, 95% taking a medication in the first trimester, and 30% taking at least five medications [17]. Two recent investigations [18,19] reported that therapeutic drug use during pregnancy continues to rise in the United States despite the shortage of safety data for pregnant and lactating women [2,3,5,20]. In the United Kingdom, a systematic review and retrospective cohort study of 577 medication categories reported an increased prevalence of polypharmacy (2-11 medications) during pregnancy from 2000 and 2019 [21,22]. Overall, medication use during pregnancy vastly exceeds the amount of reliable human safety data available to guide evidence-based treatment decisions [3,23-26].

US food and drug administration initiatives to improve safety of medications used in pregnant women: Focus on drug label content and format 1979-2014

When the FDA approves a drug for therapeutic use in adults, it becomes approved for use in pregnant women, unless otherwise specified. A decision to prescribe medication during pregnancy and lactation is highly individualized and influenced by intricate maternal, fetal, and neonatal risk-benefit considerations. While risk is often framed in terms of drug exposure versus no exposure, clinical decisions regarding medication use in pregnancy balance the risk of drug exposure versus the risk of untreated disease - both have consequences [25]. Resources for patient counselling include online databases and professional society recommendations [27]. However, the primary risk management tool is the United States Food and Drug Administration (FDA) approved drug label [28]. Since 1979 the FDA has worked diligently to improve the availability of safety data for prescription medication use in pregnant women [29,30]. FDA initiatives spanning the years 1997 - 2014 centered on enhancing the format and content of the prescription drug label, which physicians use to assess risk versus benefit of a medication in patients, including women who are pregnant. Figure 1 adapted from FDA publications, depicts milestones that culminated with the issuance of the Pregnancy and Lactation Labeling Rule (PLLR) in 2014 [31].

The drug label (package insert) is a legal document owned by the pharmaceutical company sponsor who seeks, or has obtained, FDA approval for a medication [28]. During the New Drug Application (NDA) or Biological Licensing Application (BLA) approval process FDA

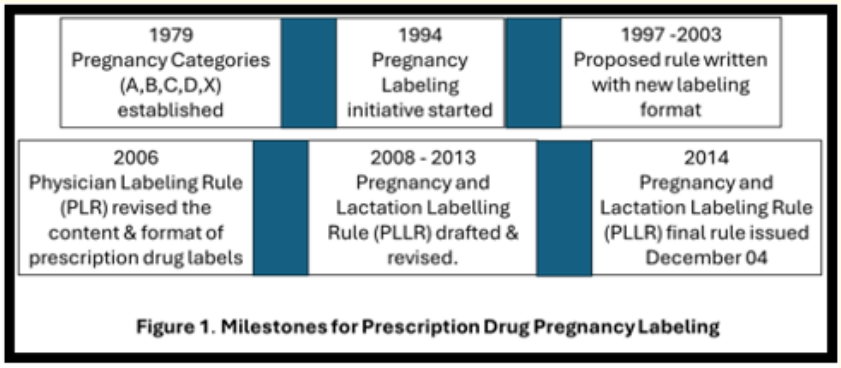

Figure 1: *Timeframe for milestones in American prescription drug pregnancy labeling.*

staff review the label to ensure that all claims are accurate and supported by evidence. FDA approval of the label permits pharmaceutical company sponsors to promote and market their drugs in the United States. For countries in the European Union, the European Medicines Agency (EMA) reviews and approves the drug label (Summary of Product Characteristics), which is not identical to the FDA approved label [32]. A drug label informs health care providers, who may then prescribe the corresponding medication for individual patients in a shared decision-making process. The drug label typically contains the FDA approved clinical indications, dosage and administration instructions, contraindications (situations where risks are never outweighed by potential benefits), warnings and precautions, adverse reactions, drug interactions, use in specific populations, including pregnant and lactating women, and efficacy findings in clinical trials. The drug label is not a clinical practice guideline, nor should it contain promotional material. The drug label is a 'living document' that must be revised to comply with changing regulations, such as the Pregnancy Risk Categories updating to PLLR.

Prior to 2015, physicians and their patients used the FDA approved Pregnancy Risk Categories on drug labels to assess the safety of drugs during pregnancy. These alphabetical, letter categories of A, B, C, D, and X, established in 1979, are:

- Category A: No risk in human studies (studies in pregnant women have not demonstrated a risk to the fetus during the first trimester).
- Category B: No risk in animal studies (there are no adequate studies in humans, but animal studies did not demonstrate a risk to the fetus).
- Category C: Risk cannot be ruled out. There are no satisfactory studies in pregnant women, but animal studies demonstrated a risk to the fetus; potential benefits of the drug may outweigh the risks.
- Category D: Evidence of risk (studies in pregnant women have demonstrated a risk to the fetus; potential benefits of the drug may outweigh the risks).
- Category X: Contraindicated (studies in pregnant women have demonstrated a risk to the fetus, and/or human or animal studies have shown fetal abnormalities; risks of the drug outweigh the potential benefits).

According to these definitions the pregnancy risk alphabetical letter category for a drug corresponds to the research findings for that drug. Namely, did the research involve human studies or animal studies? What were the outcomes of the studies? What are benefits vs. risk for the mother and fetus exposed to the drug? This system has received criticism over the years, due to concern that some physicians misinterpret the alphabetical categories and conclude that the degree of risk increases with each letter. Likewise, all drugs within a letter

category do not pose equal risk of fetal toxicity, and fetal malformations are not clearly distinguished by severity, incidence or type. Thus, the FDA concluded that more detailed information is needed for prescribers to fully understand the efficacy and safety of any medication used during pregnancy and lactation. While such concerns are valid, especially for medications in categories B and C, those in letter category A have human safety data indicating no evident risk from exposure during trimester 1. Likewise, category D and category X drugs have concrete evidence of risk in pregnant women. Thus, for certain drugs, the designation of pregnancy letter category A, D or X on their labels succinctly highlighted their safety or danger in pregnant women, and there is no evidence to suggest that removal of these categorical labels has advanced health care of pregnant women. Wesley., *et al*. who at the time of publication were scientists and physicians from the Division of Urology, and Gynecology of the US Food and Drug Administration, caution that changes in the medication label format, with or without letter-based pregnancy risk categories, will not necessarily improve safe and effective use of medications during pregnancy. To quote Wesley., *et al*.: "Importantly, although the PLLR provides a cohesive and standard structure according to which drug safety during pregnancy and lactation is labeled, it does not address or resolve the considerable dearth of data to inform drug safety in pregnant and lactating women" [28].

Abolition of the pregnancy risk letter categories on drug labels and implementation of the pregnancy and lactation labelling rule

In 2009, FDA researchers concluded that physicians relied more on the FDA pregnancy risk alphabetical letter categories than they did on any other resource when making therapeutic decisions [33]. This led the FDA to devise a replacement system intended to thwart misinterpretation of labeling data and facilitate evidence-based clinical decisions. From 1979 through 2020 almost one half of all pregnant women received prescription drugs from categories C, D, or X of the letter-based, risk classification system, emphasizing the need for health care providers to understand the effects of these medications on the developing fetus and on the pregnant woman [29,34,35]. To address the agency's concerns about oversimplification and misinterpretation of pregnancy risk alphabetical letter category labelling, the FDA created and implemented the Pregnancy and Lactation Labeling Rule (PLLR) which went into full effect on June 30, 2015. According to the FDA, the PLLR offers prescribers essential information required to make the correct decision regarding the safe and effective use of a medication by pregnant and lactating women. Drug companies must provide a thorough disclosure of the medication risks by considering animal data put into the human context, examining factors such as medical diagnoses and background risks, stating previous human data and clearly specifying when there is no human data. To permit drug companies time to accurately label their medication, all drugs were required to have the pregnancy risk letter categories removed by June 2020 [26]. To the extent that information is available, PLLR compliant labels are organized as shown in figure 2 [31].

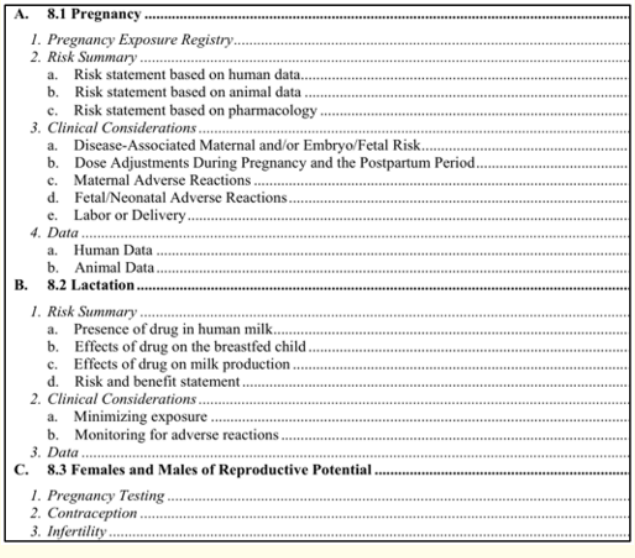
A. 8.1 Pregnancy
1. Pregnancy Exposure Registry
2. Risk Summary
a. Risk statement based on human data
b. Risk statement based on animal data
c. Risk statement based on pharmacology
3. Clinical Considerations
a. Disease-Associated Maternal and/or Embryo/Fetal Risk
b. Dose Adjustments During Pregnancy and the Postpartum Period
c. Maternal Adverse Reactions
d. Fetal/Neonatal Adverse Reactions
e. Labor or Delivery
4. Data
a. Human Data
b. Animal Data
B. 8.2 Lactation
1. Risk Summary
a. Presence of drug in human milk
b. Effects of drug on the breastfed child
c. Effects of drug on milk production
d. Risk and benefit statement
2. Clinical Considerations
a. Minimizing exposure
b. Monitoring for adverse reactions
3. Data
C. 8.3 Females and Males of Reproductive Potential
1. Pregnancy Testing
2. Contraception
3. Infertility

Figure 2: *Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling.*

Instead of alphabetical risk categories, PLLR compliant drug labels convey information about drugs in a narrative form. The pregnancy section explains the use of the drug in pregnant women (e.g. dosing, fetal risks) and specifies whether there is a registry that collects and monitors data on how pregnant women are affected by the drug. The lactation section describes the amount of drug in breast milk and its potential effects on the breastfed child. The females and males of reproductive potential section describe pregnancy testing, contraception, and infertility effects of the drug. The Pregnancy and the Lactation sections each include 3 subsections (risk summary, clinical considerations, and data) that provide details. The section on clinical considerations is the most relevant for evidence-based decisions because it discloses information available on disease-associated maternal and/or embryo/fetal risk; dose adjustments during pregnancy and postpartum period; maternal adverse reactions; fetal/neonatal adverse reactions; and labor or delivery. Importantly, the PLLR does not apply to non-prescription, over-the-counter drugs, which are also used extensively by pregnant women [36]. Many over-the-counter medications are considered safe at the recommended doses; however, dosage and treatment schedule depend on the mother and vary with her knowledge, her adherence to label instructions, and the frequency or severity of her symptoms [37]. Circa 2014-2017, around the time of the official implementation of the PLLR, numerous publications described the history of drug labeling during pregnancy and the rationale and expected clinical consequences of the PLLR [2,38-46]. While each publication is well-written and informative we recommend Moseley., *et al*. [41], to learn more about the changes in labeling imposed by the PLLR, the discontinuation of pregnancy risk letter categories and the expected effects of the labeling changes on clinical practice contemporaneous with the implementation of the PLLR.

Many physicians and pharmacists are not fully informed about the pregnancy and lactation labelling rule and its intended clinical utility

Ten years have elapsed since the FDA issued the final Pregnancy and Lactation Labelling Rule, which abolished the pregnancy risk alphabetical letter category system (A, B, C, D, and X) and replaced it with integrated summaries of the risks of using a drug or biological product during pregnancy, lactation, and in women and men with reproductive potential [31]. Despite the deliberative process used by the FDA to develop and promulgate the PLLR, it appears that many practicing physicians and pharmacists are unfamiliar with the current rule and its clinical significance. This void may impede safer medication use in pregnancy because a crucial step toward that goal is the dissemination and utilization of the evidence and guidance to health care providers and women of reproductive age [47]. A survey of members of the American Academy of Allergy, Asthma and Immunology (AAAAI) addressed physician awareness and use of the PLLR, and the value and understanding of the PLLR format. Based on an example of the "Pregnancy" subsection of labelling, less than half (46%) of the 184 respondents were aware that the pregnancy risk letter category system had been abolished and replaced with a narrative summary [48]. Most respondents (68%) indicated that the narrative summary was not concise. However, 71% of the respondents found the background risk and disease-associated risk information helpful. Notably, nearly all respondents (95%) continued to use the pregnancy risk letter category system to make prescribing decisions. Thus, four years after its introduction, it appeared that the PLLR format was not yet widely known by most of the AAAAI survey respondents and the pregnancy risk letter classification format was still being used, despite its discontinuation from newly approved drug labels after June 2015. The survey by Namazy., *et al*. did not address why prescribers were continuing to rely on the pregnancy letter category system [48].

Two surveys by Alem., *et al*. also found gaps in knowledge and application of the PLLR among physicians and pharmacists [49,50]. While the survey respondents were knowledgeable about the older pregnancy risk category letter classification (A, B, C, D, X) and medication labelling, their understanding of the new PLLR labelling standard was lacking or flawed. The average number of questionnaire items answered correctly was only 3 out of 7, demonstrating a need for further professional education efforts to improve awareness of PLLR compliant labelling and its utility. Again, many respondents preferred the letter category pregnancy risk labelling over the PLLR narrative summaries.

An investigation of the consequences of the PLLR discovered that the absence of a letter category (A, B, C, D, X) on a drug label significantly affected the decision to prescribe various drugs [51]. Namely, if a pregnancy risk category letter was absent from a PLLR compliant medication label, physicians were less likely to use formerly called category B and C drugs, which were the most common medications prescribed according to a review of more than 150,000 pregnancies [35]. Many physicians still use the letter-based pregnancy risk categories despite the PLLR requirement for all prescription drugs to remove these categories from their labels by June 2020 [26,33]. Comparable to findings cited above for the Pregnancy section 8.1, few participants in online focus groups were aware of the PLLR updates to the Lactation section 8.2 of the label [52]. Most health care providers were unaware of the changes because they did not typically rely on or consult the Prescribing Information of the label to obtain drug safety information for lactation. Participants were more likely to review summaries and recommendations from websites and databases (e.g. LactMed, Lact Rx)

Outdated (archival) drug labels, which contain pregnancy risk letter categories, are still accessible via the internet, and even FDA websites. Thus, it is doubtful that the PLLR will successfully compel all currently practicing physicians to abandon their awareness of, and partial reliance on, the letter category pregnancy risk system. One useful resource is the DailyMed database which contains labelling for prescription drug and biological products. The DailyMed database summarizes the essential scientific information needed for the safe and effective use of the product, including boxed warnings, indications, dosage and administration, contraindications, warnings and precautions, adverse reactions, drug interactions, information about use in specific populations. The "in use" labeling on DailyMed may not be identical to the most recent labeling distributed with products or FDA-approved labeling.

The pregnancy and lactation labeling rule relies extensively on fulfillment of post-marketing requirements or post-marketing commitments to establish drug safety

Investigations to understand the effects of medication use on the developing fetus are complex from both ethical and mechanistic perspectives. Exclusion or poor enrollment of pregnant and lactating women in prospective, randomized, controlled clinical trials persists and contributes to voids in evidence-based medicine, despite the 2018 recommendations from the Health and Human Services Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) [23,53,54]. After PRGLAC recommendations were accepted, pregnant women were removed as a vulnerable population from the Common Rule. However, NIH-funded clinical research trials do not require justification for excluding pregnant or lactating women. Among 419 actively recruiting NIH-funded phase 3 and 4 clinical trials, 69% explicitly excluded pregnant women and 50% excluded lactating women [54]. All therapeutic products introduced since 2015 complied with the new PLLR labelling rules; however, human data on pregnancy and lactation risk were found on less than 20% of these new products [26]. The PLLR does not require sponsors to obtain human safety data from randomized, controlled clinical trials, which have the potential to improve evidence-based therapeutic decisions. Instead, observational studies involving case reports, primary cohort and case-control studies, pregnancy exposure registries, and electronic health claims data, acquired after drug approval, are the main sources of information about medication safety in pregnancy [29,55]. Of concern, adverse event reporting strategies based on epidemiological surveillance methods often take a decade, and in some cases 25 years, to recognize the teratogenic potential of a newly marketed medication [34].

Whether intended or not, PLLR compliant labels convey the impression that pregnancy exposure registries are the highest priority for acquiring safety data because they list this topic first - preceding the risk summary and clinical considerations [39]. The section entitled Pregnancy Exposure Registry discloses whether a registry exists and advises on how to prospectively enroll pregnant women with medication exposure. Participants in a registry are followed through delivery, and often post-partum, to assess adverse effects in infants exposed to the drug. Pregnancy exposure registries are valid tools for acquiring data to assess drug safety [56-58]. The North American Antiepileptic Drug Pregnancy Registry established in 1997, with about 15,000 women currently enrolled, exemplifies the challenges and limitations of a pregnancy registry to detect malformations from exposure to medications [59]. Foremost, is that the evaluation is

indirect, and the reliability of the data may be limited by lack of an appropriate control group, wherein the observed rates are compared to expected rates obtained from population-based surveillance systems [55]. Other limitations include participant bias, incomplete reporting, and especially non-adherence to drug therapy [60,61]. Comparisons across registries are complicated because the methodology for determining the risk of major malformations among registries varies, and they have different populations, ascertainment strategies, follow-up, and reporting criteria. Adequate recruitment and complete ascertainment of pregnancy and infant outcomes are critical for success; however, many registries lack the statistical power to draw reliable conclusions regarding risks of drug specific malformations [57].

A review of pregnancy and lactation related post-marketing commitments (PMCs) and post-marketing requirements (PMRs) for new drug applications (NDA) approved by the FDA between 2000-2022 shows favorable trends. Prior to 2007 all studies were PMCs, which sponsors were not obligated to complete. Since the enactment of the US Food and Drug Administration Amendments Act in 2007 and the PLLR in 2015, post-approval pregnancy and lactation studies have increased steadily. Between 2000 and 2022 approximately 12% of approved NDAs included PMRs/PMCs related to pregnancy and/or lactation [62]. Similarly, FDA required sponsors to conduct PMR/PMC studies for 16% of drugs approved between 2007-2020 for use in females of reproductive potential [63]. Maintenance of pregnancy registries was the most common type of required study (37%), followed by a descriptive pregnancy safety study (27%), and a retrospective cohort study (26%). Moneer., *et al*. examined drugs that were approved with at least one post-marketing requirement (PMR) or post-marketing commitment (PMC), found that neither was completed more than two-thirds of the time. Importantly, half of completed PMCs and PMRs did produce novel information for clinical practice or regulatory action, such as confirmation of benefit or a labeling change [64].

The TransCelerate survey, which examined sponsor-initiated or FDA-required post-approval activities performed by pharmaceutical companies, found that all 17 survey participants conducted at least one post-approval activity [65]. Consistent with the findings of Krastein., *et al*. pregnancy registries were the most often mentioned. Nearly half of the participants proposed sponsor-initiated pregnancy registries, which the authors speculated was a reaction to perceived regulatory expectations during the time span of the survey (2013-2023) [63]. Most survey participants (59%) reported that post-approval activities on pregnancy led to changes in prescribing information. However, these changes often took from 5 years to greater than 10 years after study completion. Most survey participants reported no impact of outcomes from post-approval activities on lactation.

Health claims database studies, which yield extensive, generalizable data compared with other types of post-approval pharmacovigilance activities have gained favor with the FDA [66-68]. Time- and cost-efficient identification of pregnancies in large, population-based cohorts is advantageous compared to voluntary pregnancy registries for specific drugs. However, since these databases originate from administrative and billing records their limitations include reliance on retrospective cohort design, exposure misclassification (e.g. prescription records do not necessarily confirm patient exposure to drug), and a lag period between the date of medical claim (e.g. diagnosis, prescription, clinic visit) and the date when information is available for analysis [68]. Overall, a comprehensive approach using pregnancy/lactation registries, plus electronic health care utilization databases may provide optimal post-approval surveillance for the detection of safety signals that may go undetected when these methods are used in isolation. One database, which should be used with great hesitation for evidence-based safety decisions is the FDA Adverse Event Reporting System (FAERS), a centralized database used for post-marketing drug safety surveillance. Adverse event reporting systems are primarily a safety signal detection and hypothesis generating system. FAERS data interpreted alone or out of context can lead to erroneous conclusions about cause and effect. In some cases, abrupt, transient increases in adverse events reported through FAERS may represent false signals temporally associated with extensive media coverage of FDA recall/warnings [69]. The FDA acknowledges the limitations of FAERS and explicitly cautions: “First, there is no certainty that the reported event (adverse event or medication error) was due to the product. FDA does not require that a

causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Furthermore, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. There are also duplicate reports where the same report was submitted by a consumer and by the sponsor. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population".

Discordance between FDA versus EMA labelling of drug risk during pregnancy and lactation

There are no internationally harmonized regulations governing post-approval activities to generate human safety data for medications. The US Food and Drug Administration and the European Medicines Agency review data independently and have distinctive standards for format and content of labeling, leading to differences in their recommendations for use. The FDA's prescription drug label is termed the Package Insert and the EMA's drug label is termed the Summary of Product Characteristics. For the pregnancy and lactation sections of their labels both the FDA and EMA rely on animal reproductive data, developmental toxicity data, and any available human data, which often originates from observational studies conducted in the post-approval setting, including pregnancy registries and health claims databases. In at least one way, the EMA label seems superior for pregnancy because its Appendix 3 defines "No or limited amount of data from the use of [generic drug name] in pregnant women," as data from <300 pregnancy outcomes; "moderate amount" of human data involves 300 to 1,000 exposure outcomes and a "large amount" of human data involves >1,000 exposure outcomes. While FDA labels emphasize access to and enrollment in pregnancy registries, the EMA's label emphasizes the numerical basis for the outcomes, while omitting instructions for enrolling patients in registries. Overall, an analysis of labels from 31 medications showed that the EMA and the FDA had high discordance between pregnancy and lactation labeling language, in 68% and 71% of labeling, respectively. Only 10% of pregnancy labeling and 16% of lactation labeling included human data. The discordance between US and EU health authorities is evident in the language from the pregnancy and lactation sections. EMA labeling was more direct, whereas the FDA language simply stated the data, thereby compelling the prescriber to assess the benefit-risk for individual patients, particularly when no human pregnancy exposure data are available. For example, the FDA pregnancy labeling language discourages use for only 3 of the 31 drugs (10%) examined. In contrast, the EMA pregnancy labeling language discourages use for 28 of the same 31 drugs (90%). In 27 of the 28 drugs, the EMA states its recommendations are based on "no to a limited amount of human data", i.e. < 300 pregnancy outcomes [32].

Discussion and Conclusion

Prescription drug labeling cannot substitute for lack of safety data in pregnant and breast-feeding women [28,32]. Multiple, longstanding barriers complicate randomized, controlled clinical trials in pregnant women, and underlying realities have negated attempts to modify them [4]. Officially, women or fetuses may participate in clinical research if all ten conditions specified in 45 CFR 46.204 are met. Doubtless, the most substantial barrier is the reluctance of pregnant and lactating women to give informed consent, either for fear of fetal risk or an inability to commit the time required for such studies. The FDA's Pregnancy and Lactation Labeling Rule of 2015 intended to provide patients, physicians and healthcare practitioners with detailed information regarding medication use during pregnancy, lactation, and reproduction. Collectively, the medical literature suggests some numerical increase in the amount of human data now available, since the benchmark study of 290 new molecular entities or therapeutic products approved by the FDA between 2010 and 2019 [26]. As more post-marketing surveillance activities proceed to completion, data will progressively accumulate, but it will still take years before it impacts the use of prescription drugs during pregnancy and lactation, and the corresponding health outcome.

The PLLR provides a standardized template for narrative disclosure and labelling of information that is available on drug safety during pregnancy and lactation. The PLLR also dictates the elimination of the alphabetical (A, B, C, D, X) pregnancy risk categories from prescription drug labels. This letter-based risk evaluation system has been widely recognized and used by physicians since its inception in 1979. Consequently, since 1979 most licensed physicians have used, still use, or are aware of the letter-based pregnancy risk categories.

Eliminating the letter-based risk information from prescription drug labels has not eliminated it from human memory or from the archives in libraries or the internet. For example, asking an artificial intelligence system the question: "What are the pregnancy risk categories for labetalol?" will yield the result shown in figure 3.

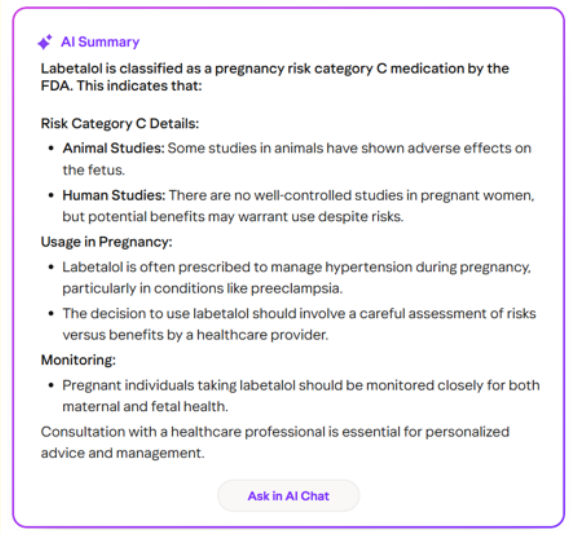

Figure 3: *Artificial intelligence summary of labetalol safety in pregnancy.*

We speculate that many busy physicians will often use resources such as AI, rather than read the narrative of a PLLR compliant label. That said, a recently published monograph that connects the "abolished" FDA letter classification for pregnancy risk and the PLLR label is commendable [70]. For each drug, three sections of data (FDA letter-based Risk Category, PLLR Risk Summary, and further reading) provide a basis for physicians to develop a balanced opinion about a drug safety profile during pregnancy.

The PLLR places responsibility, and any attendant culpability, on physicians to be knowledgeable about the risks associated with medications they prescribe. Implicitly, the FDA intended the PLLR to improve safety and reduce maternal-fetal risks in women who are of childbearing age, pregnant, and/or breastfeeding. Ten years have elapsed since its implementation, and there is a trend toward slow accumulation of human safety data derived from post-approval activities, such as pregnancy registries, health claims databases, case reports and cohort studies [55]. Acquisition of data from participation of pregnant or breast-feeding women in randomized, controlled clinical trials is not improving, despite recommendations from the Health and Human Services Task Force on Research Specific to Pregnant Women and Lactating Women. Since its implementation the PLLR has influenced prescribing practices [51,71]; however, we found no published evidence that directly established its reduction of birth defects of any type. Evaluation of the impact of FDA regulatory actions with outcomes measures relating directly to patient health and adverse events are rare [72]. For the PLLR, such an evaluation will be complicated because assessing the risks of a birth defect is inseparable from communicating the risks of a birth defect to the patient [55]. 'Framing' refers to the way in which information about the likelihood or significance of adverse effects is communicated (e.g. negative frame: 30% will experience an adverse effect vs. positive frame: 70% will not experience an adverse effect) [73]. For instance, a physician communicating the teratogenic risk of a drug may tell a pregnant woman that she has a 1-3% chance of having a malformed child (negative-framing), or that she has a 97-99% chance of having a normal child (positive framing). An investigation of this 'framing' phenomenon found that women in the negative group had a significantly higher perception of teratogenic risk than those in the positive group and were less likely to consent to taking the drug [74]. It is unclear how physicians and epidemiologists will address this challenge.

Conflict of Interest

There are no conflicts of interest or financial interests.

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