Assessing the potential risk in drug prescriptions during pregnancy

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Introduction

Over eighty percent of pregnant women in the United States are prescribed at least one drug during pregnancy. The U.S. Food and Drug Administration (FDA) regulates the labeling of drug products and has established five risk categories for drug use during pregnancy. This classification was introduced in 1979. New FDA regulations (June 30, 2015) deeply revised the pregnancy and lactation labeling by eliminating these categories and replacing them with narrative summaries describing the risk of the drug and supporting evidence [1]. In a recent study on Medicaid data, 40% of pregnant women were dispensed at least one medication from categories D or X, for which there is positive evidence of human fetal risk [2]. In this work, our objective is to assess the potential risk in drug prescriptions during pregnancy, with respect to the new FDA standard. A secondary objective is to contrast risk assessment between the old FDA categories and the newly introduced narratives.

Materials and methods

Acquiring reference risk categories. As a proxy for the new FDA standard, we used the "pregnancy recommendations" from a reference textbook (Briggs, 10th ed. 2015) [3]. For each ingredient, it provides the level of risk (contraindicated, high risk, moderate risk, low risk, probably compatible and compatible with pregnancy), the source of evidence, if any (human or animal data), and other information as appropriate (trimester, dose and drug association restrictions). For the original FDA categories, we used an older version of the same textbook (Briggs, 8th ed. 2008), where each ingredient was associated with one of the 5 categories used at that time (A, B, C, D and X). When an ingredient was associated with more than one category (e.g., to account for risk variation based on dose, length of exposure, or associated comorbidities), we used the highest risk category. For vitamins, however, we took the lowest risk category, because prescriptions were generally within the Recommended Dietary Allowance (RDA).

Acquiring and processing prescription data. We analyzed patient-level, de-identified claims data of a privately insured population of 159.7M patients from 2003 to 2014 provided by the IMEDS Research Lab. We relied on procedure codes for delivery to identify pregnant women (13 CPT (Current Procedural Terminology v4) codes covering all vaginal deliveries and caesarean sections). We considered a period of 270 days prior to delivery or C-section for drugs dispensed during pregnancy. We used the RxNorm API to relate drugs from claims data to the reference. We derived the risk and supporting evidence associated with each drug, taking the highest risk in case of multi-ingredient drugs. We restricted our analysis to systemic drugs, because topical drugs generally pose a much lower risk. We counted prescriptions by category, using the new standard (level of risk and source of evidence) and the old FDA categories. We also contrasted the two standards. Two OB/GYNs (FD and LR) reviewed the top 50 of each category to ensure the reliability of the results.

Results

A total of 3,741,743 pregnant women were selected, to which 19,654,083 prescriptions were dispensed (15,815,624 for systemic drugs). The level of risk was defined using the classification extracted from Briggs (for the old and new risk categories) for 14,719,736 prescriptions (93%).

New risk categories and supporting evidence. Overall, 40.2% of the prescriptions were "compatible" with pregnancy and 1.2% were "probably compatible". The prescriptions were contraindicated in 2.8%. There was a potential risk in 8,191,485 prescriptions (55,6%). For prescriptions for which the risk was quantified, the risk was low (37.6%), moderate (1.5%), and high (0.03%). For 60.8% of prescriptions, however, the risk was not quantified.

Overall, evidence based on human data is available for 91.85% of all prescriptions. For "compatible" and "contraindicated" prescriptions (i.e., 43.0% of all prescriptions), the evidence was always based on human data, as defined in the Briggs recommendations. For prescriptions with a potential risk, the source of evidence was "human data" in 87.8%, "limited human data" in 10.7%, and "only animal data" in 1.49%. Only for a small fraction of the prescriptions with a potential risk (0.005%) was the evidence based on limited data, irrelevant animal data, or no data at all.

Comparison with the old FDA risk categories. (The definitions of the categories are adapted from Briggs 8th ed.)

- Almost all prescriptions originally categorized as **A** (i.e., controlled studies in women fail to demonstrate a risk to the fetus) are now listed as compatible with pregnancy.

- Similarly, all prescriptions originally categorized as **X** (i.e., with positive evidence of fetal risk that clearly outweighs any possible benefit) are now listed as contraindicated. Differences are generally due to trimester, dose and drug association restrictions.

- Prescriptions originally categorized as **D** (i.e., with positive evidence of fetal risk but benefits from use during pregnancy may be acceptable despite the risk) are now associated with a potential risk in 92.3% (low risk for 36.3%) and are contraindicated in 2.3%.

- Prescriptions originally categorized as **C** (i.e., either animal studies indicate a fetal risk, and there are no controlled studies in women, or no studies are available) are now listed as compatible with pregnancy in 46.6%, are associated with a potential risk in 51.2% (low risk for 29.1%) and are contraindicated in 0.5%.

- Finally, prescriptions originally categorized as **B** (i.e., either animal studies do not indicate fetal risk and there are no controlled studies in women, or animal studies have shown an adverse effect, but controlled studies in women failed to demonstrate a risk) are now listed as compatible or probably compatible with pregnancy in 41.2%, and are associated with a potential risk in 58.7% (low risk for 18.1%). None of these are contraindicated.

Discussion

Findings. This investigation demonstrates the feasibility of assessing the potential risk in drug prescriptions during pregnancy from a large claims dataset using RxNorm and the Briggs reference, with finer-grained recommendations compared to the old FDA categories, as well as stronger evidence. It had already been demonstrated that pregnant women are commonly prescribed drugs associated with fetal risk [2]. However supporting evidence was not reported. Our results show that the proportion of prescriptions without reliable human data evidence was small (8.15%). Interestingly, in the Briggs reference, human data evidence is available for only a third of the ingredients associated with a potential risk. In contrast, in our cohort, there is human data evidence for 87.8% of the prescriptions for drugs with potential risk.

Limitations and future work. This preliminary investigation did not take into account recommendations for specific trimesters of pregnancy, which we will address in future work. This is of particular importance since risk may significantly differ over time. For example, *misoprostol*, an abortive drug, is contraindicated during pregnancy, but it is also widely used near term for labor induction [4]. Dose can impact the level of risk as well. For example, vitamin A is compatible with pregnancy under the Recommended Dietary Allowance (RDA), but contraindicated above the RDA. Several common drugs have a dose-related risk (e.g., *aspirin*, *fluconazole* and most vitamins), but the drug products commonly prescribed during pregnancy generally correspond to lower doses (e.g., *baby aspirin*, *multi-vitamin supplements*). However, for complex risk assessment (comorbidities, co-prescriptions, precise dose, duration of exposure), claims data may be insufficient.

References

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