DrugWAS X PheWAS: A pharmacoepidemiologic framework to investigate the effect of drug exposure during pregnancy on pediatric outcomes

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Introduction

The lack of post-market safety surveillance of drugs used for pregnant women, fetuses, newborns, and children represents a significant void in medicine. Little is currently known about the safety, risks, drug-interactions, and teratogenic effects of many drugs used during pregnancy due to the regulations that limit the participation of pregnant women in drug development trials. Further, the scarcity of clinical trials involving children has resulted in limited knowledge about the safety and effectiveness of numerous drugs intended for pediatric use. For this reason, pediatric practice often involves "off-label" use of drugs. This can lead to uncertainty about side effects on children, including severe adverse drug reactions and toxicity that can affect their development and future reproductive capacity. The availability of real-world healthcare data from sources such as electronic health records (EHRs) provides an opportunity to improve precision therapeutics for pregnant women and children. Here, we describe a framework to enable conducting high-throughput pharmacoepidemiologic studies to investigate the effect of maternal drug exposures on pediatric populations.

Methods

We developed a drug-wide X phenome-wide association study (DrugWAS X PheWAS) framework to investigate associations between every maternal drug exposure and pediatric outcome in EHR. For this, we selected all mother-child dyads from the Vanderbilt University Medical Center (VUMC) Research Derivative (RD), a repository of identified EHRs containing data for over 5 million distinct patients. For each mother-child dyad, we extracted the drug exposures of the mother during pregnancy from the medication table and health outcomes of the child (including death, premature birth, and disease diagnosis) observed from birth until the age of two. We also extracted drug exposure information before pregnancy and during each trimester of pregnancy as well as outcomes during child developmental milestones to enable various sensitivity analyses (**Figure 1**). Leveraging this framework and our previous experience, we will estimate the effect of each drug exposure on pediatric outcomes by applying multivariable logistic regression with overlap weighting using propensity score.[1]

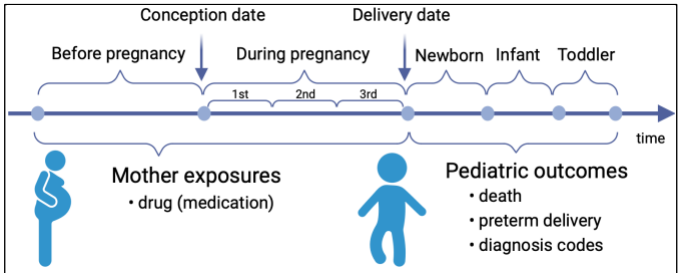

Figure 1 The Mother-DrugWAS X Child-PheWAS study design.

Results

We identified 73,358 mother-child dyads of 55,624 women (66% White, 17% Black, 4.5% Asian, and 12.5% Other/Unknown) with EHR data at VUMC. Based on our preliminary analysis, which estimated a gestational length of 40 weeks, we found that 47,719 (86%) mothers had at least one drug (in the medication table) prescribed during their pregnancy, while 43,485 (78%) had two or more drugs prescribed. Frequent drugs used during pregnancy include ondansetron (22%), promethazine (17%), folic acid (15%), docusate (14%), famotidine (11%), and nitrofurantoin (10%). High ranked outcomes by International Classification of Diseases, 9th/10th Revision, Clinical Modification (ICD-9/10-CM) codes in children up to 1-year old include P59.9: Neonatal jaundice (N=10,911, 15%), Q21.1: Atrial septal defect (N=4,228, 6%), Q25.0: Patent ductus arteriosus (N=2,893, 4%), R01.1: Cardiac murmur (N=2,681, 4%), and 771.81: Septicemia of newborn (N=1765, 2%). Out of the 73,358 children in this cohort, 1,316 (1.8%) died during their first year.

Conclusions

We presented a framework that uses large-scale EHR data to systematically search for adverse drug reactions in children due to maternal drug exposures. Future work includes improving drug exposure and outcome identification using natural language processing methods and extraction of substance use exposure during pregnancy.

References

1. Bejan CA, Cahill KN, Staso PJ, Choi L, Peterson JF, Phillips EJ. DrugWAS: Drug-wide Association Studies for COVID-19 Drug Repurposing. *Clin Pharmacol Ther*. Jul 27 2021;doi:10.1002/cpt.2376