Prescription Medication Exposures and Multi-Fetal Pregnancies: Medication-Wide Association Study (MWAS) Using Electronic Health Record Data

Lena Davidson¹, MS, Silvia P. Canelón², PhD, Mary Regina Boland³, MA, MPhil, PhD
¹Department of Biostatistics, Epidemiology & Informatics, ²Center for Excellence in Environmental Toxicology, ³Institute for Biomedical Informatics, University of Pennsylvania, ⁴Department of Biomedical and Health Informatics, Children's Hospital of Philadelphia

Our approach highlights the importance of exploring medication histories in addition to diagnosis codes, as many patients receiving treatments did not have corresponding diagnosis codes. These patients would be mistakenly labeled as having not received treatment. This underscores the importance of exploring multi-data modalities in retrospective electronic health record studies.

Objective
To illustrate a proof-of-concept MWAS approach for hypothesis-driven pharmacovigilance research Electronic Health Record (EHR) data, with a particular focus on multiple birth.

Background
Multi-fetal pregnancies are associated with risk for adverse fetal and infant outcomes, and increased risk of maternal morbidity and mortality. The following increase risk of multi-fetal pregnancy:
- Higher maternal age
- Genetics, history of twin pregnancy, and family history of twin pregnancy
- Advanced parity
- Use of assisted reproductive technology (ART)

Fertility treatment indicates medical treatment or procedure to increase the likelihood of pregnancy success. ART refers to treatments that include the handling of eggs, sperm and/or embryos (i.e. in-vitro fertilization) and non-ART indicates no handling of eggs, sperm and embryos (i.e. medically stimulated ovulation).

Ryan et al. proposed a medication-wide association study (MWAS) approach, in which an outcome of interest is compared with all drugs available for comparison. Prior approaches address risk of: cancer, spontaneous preterm birth, acute myocardial infarction, acute liver failure, acute renal failure, and upper gastrointestinal cancer. No prior MWAS work utilizes electronic health record data.

Methods
We used electronic health record (EHR) data between 2010-2017 on patients who delivered babies at Penn Medicine, a healthcare system in the Greater Philadelphia area. We explored three logistic regression models: a) Model 1 (no adjustment), b) Model 2 (adjustment for maternal age), and c) our final logistic regression called Model 3 with adjustment for maternal age, ART usage, and infertility diagnosis. In all models: Multiple Birth as our outcome of interest (binary outcome) and each medication exposure to treatments that include the handling of eggs, sperm and/or embryos (i.e. medically stimulated ovulation).

Results
Of the 63,334 total distinct deliveries in our cohort (Figure 1) only 1,877 pregnancies (3.0%) were prescribed any medication during the pre-conception/first-trimester period (Table 1). Of the 123 medications prescribed, we found 26 medications associated with MB (using nominal P-values) and 10 medications associated MB (using Bonferroni adjustment) in the fully adjusted Model 3 (Figure 2). We found that our Model 3 algorithm had an accuracy of 85% (using nominal P-values) and 89% (using Bonferroni adjusted P-values) (Table 3).

Discussion
Our work demonstrates the opportunities in applying the MWAS approach with EHR data to explore associations between pre- and peri-conception medication exposure and risk of MB while identifying novel candidate medications for further study. Appendix 7 demonstrates that many patients with fertility/ART medications were not assigned the corresponding diagnostic code, indicating that fertility studies using EHR data should include medication history to fully capture affected patients. This concept and relationship is further illustrated in Figure 3. Overall, we found 3 novel medications linked with MB that could be explored in further work this demonstrates the potential for our method to be used for hypothesis generation.