Effects of adverse perinatal outcomes (apo)

Specific Aims

Adverse perinatal outcomes (APO) include infant's birth defects, maternal pregnant and obstetric complications. Birth defects, including major congenital malformation (MCM) and minor anomaly (MA), become the leading causes of infant morbidity, mortality, and years of potential life lost in the United States. [1] Low birth weight (LBW), abnormal condition of new born (ACNB), preterm birth, and Developmental Delay or Disability (DDD) are also birth anomalies that impacts the infant's health. [2-5]

The association of in utero exposure to teratogenic medications with infant birth defects and other anomalies has been widely investigated. [6, 7] The literature has shown that taking antiepileptic drugs (AEDs) poses an increased risk of having child with congenital malformations in women with epilepsy. [79] The most common MCMs caused by in utero exposure to AEDs are orofacial clefts, cardiac abnormalities, neural tube defects, urologic defects, and skeletal abnormalities. [80] In utero exposure to valproate, the most teratogenic AED, was associated with elevated risk of impaired cognitive function for children at 3 years of age, and reduced cognitive abilities for children at 6 years old. [98, 101] However, study results for many medications, such as antidepressants, opioids, antipsychotics, and antibiotics, are inconsistent for fetal safety.[1*-8*] The limited data source and rare incidence of birth defects, ACNBs, and other anomalies restrain the study power, and makes some studies inconclusive. [8-10]

Our long term goal is to determine the association between teratogenic effects of medications that mothers exposed during pregnancy and infants' birth defects. The major objective of this study is to build a linked database in Rhode Island (RI) to facilitate the subsequent research on teratogenic effects of medication in RI population.

The birth defects and birth certificates data from the Department of Health (DoH) and pharmacy claims from the Medicaid program offer an essential resource to investigate these aims. The availability of hospital diagnoses and birth records offers a significant advantage for investigating birth defects with corresponding clinical conditions in large population with a longitudinal approach.

Our team is well suited to conduct this research given extensive expertise in contemporary pharmacoepidemiology, many years of experience on drug safety research, prior drug utilization and birth defects study with the linked data from another state, and clinical expertise from obstetric and gynecologic physicians.

Our specific aims are to generate a linked data and investigate the medication utilization and assess the corresponding birth defects with the following efforts:

Aim 1: To build a linked database that includes mother's medications prescribed during pregnancy and subsequent adverse perinatal outcomes.

We hypothesize that the data from two state departments can be internally linked using identifiers. Mother's medication prescriptions will be extracted

from Medicaid claims provided by the RI Executive Office of Health & Human Services (EOHHS). The adverse perinatal outcomes include: MCMs, MAs, abnormal conditions of new born, fetal death, and low birth weight, and maternal adverse pregnancy and obstetrical complications. All of these outcomes will be obtained from birth certificates, institutional and professional claims that are collected and managed by RI Department of Health (DoH). These two parts of data will be linked by the deterministic or probabilistic linking strategy using mother's medical record number, name, and date of born. We will apply for IRB approval with a waiver of informed consent by RI DoH, EOHHS, Brown, and URI.

Aim 2: To characterize the patterns of medication use in women during pregnancy.

We hypothesize that medication use in women during pregnancy changes in recent years. Many medications, such as AEDs, statin, or angiotensin converting enzyme (ACE), have been classified as teratogens and categorized as " D" or " X" by the Food and Drug Administration (FDA). However, studies have found that these teratogenic drugs still have been prescribed to pregnant women. [5-7] Some medications with contradictive results reported from the literature may have increased use in pregnant women. We will examine the prescribing patterns of these medications in pregnant women with varied age, race, comorbidities, co-medications, as well as medication types and doses. The utilization pattern will be delineated in secular trends and mapped geographically, as will facility, provider, and state-level variations.

Aim 3: To assess infant's birth defects and birth anomalies using advanced statistical model.

We will identify all corresponding birth defects, including MCM, MA, LBW, ACNB, DDD, preterm birth, and fetal death and compare the birth defect rates in mothers with varied demographic characteristics and medication exposure. Previous studies have suggested that the LVM can be used to combine four specific birth defects together to create a severity index. [16-18] We hypothesize that this LVM can be improved and optimized to combine any number of components with a proper weight on severity and frequency to evaluate the overall health status of infants.

B. Significance and Innovation

Birth defects occur in 3 – 5% of children born in the United States and account for 20% of all infant deaths. [1, 2] During 2010-2012, RI DoH identified 1, 390 newborns with at least one birth defect. [3] The rate of birth defects in RI increased by 14. 2% from 2008 to 2012. [3] It was reported that 2-3% of birth defects are due to teratogen-induced malformations, which refer to malformations resulting from environmental or in utero exposure to teratogens. [4] In the United States, about 3 million people currently live with teratogen-induced malformations. [4]

The FDA defined the pregnancy category to enforce the labeling of drugs with respect to their effects on pregnant women. Some medications, such as AEDs, statin, or ACEs, have been classified in FDA pregnant category ' D' or ' X' due to their teratogenic effects. Previous studies reported a two- to three-

fold increase in the malformation rate among infants with in utero exposure to AEDs. [21, 22, 81, 82] The incidence rates in infants with in utero exposure to AEDs were 3. 1% to 9. 0% for MCMs, 37% for one MA, and 11% for two MAs. [21, 80-83] The risk of malformations for infants with in utero exposure to valproate is 7. 3-fold higher than that of non-exposed, and 4-fold higher than those exposed to all other AEDs. [7]

Some widely used medications, such as antidepressants, opioids, antipsychotics, and antibiotics, tend to have increased utilization in pregnant women while the results from teratogenic studies are controversial and inclusive.[1*-8*] It is difficult to distinguish between the real non-inferior results and power deficiency owing to rare outcomes.

It has led to an urgent need to determine the fetal safety of these medications and prevent teratogenic medications prescribing to pregnant women. However, the limited data source and rare incidence of birth defect outcomes impact the study power, and makes studies inconclusive. [8-10] Traditional claims data (data from Medicaid or private health plans) is not suitable for birth defect research as it only contains medical information for either mother or infant, not both. Birth certificates or birth defects data doesn't include mother's medication information. As such, to investigate utilization patterns and teratogenic effects of medications, we need to link mother's pharmacy claims with infant's birth defects assessments. The linkage should be conducted in a secure data server with patient's identifiers.

The main goal of this proposed one-year pilot study is to collaborate with the RI EOHHS and RI DOH and generate a linked statewide dataset that includes mother's pharmacy claims and infant's birth defect outcomes. This linked dataset will facilitate the researchers in Brown and URI to conduct studies regarding drug-induced birth defects in RI and provide a potential for combining RI linked data with the linked data from other states to conducting drug teratogenic studies in large population.

Innovation

This proposed study will generate a linked data with combining Medicaid pharmacy claims from the RI EOHHS and birth certificates and birth defects from the RI DOH. This would make RI become the fourth state that possesses the linked mother-infant data in the United States, besides California, Texas, and Florida. Our approach will provide a large linked dataset to facilitate the researchers from URI and Brown to conduct drug-induced birth defects studies. This linked dataset will provide a potential for future drug teratogenic research in large population with combining the RI linked data with the linked data from other states.

Our approach will employ state of the art, innovative pharmacoepidemiologic study designs and statistical models, to improve the study power and efficiency. A latent variable model will be employed in this study to combine all birth defects outcomes into a continuous severity score to assess the overall infant's morbidity and mortality.

C. Approach

Data Sources

This study is based on a statewide, retrospective 11-year data sources: RI birth certificates and birth defects from January 1, 2006 to December 31, 2016. In Rhode Island, birth certificates are collected in the hospital within 24 to 48 hours after the baby birth. The RI DoH collects and manages birth certificate data for all infants born in RI. Birth dates and places for infants, and demographic characteristics for infants, mothers, and fathers are all recorded in birth certificates. The RI Birth Defects dataset consists of birth defects registry data prepared and maintained by RI DoH. Infant birth defects, including MCMs and MAs, were identified 0-365 days after live birth from hospital inpatient and outpatient claims. This study includes infants who were born in RI between January 01, 2006 and December 31, 2016.

Medication information will be provided by the RI EOHHS. The data is comprised of eligibility, medical, and pharmacy claims for services from inpatient hospitals, outpatient clinics, emergency rooms, and pharmacies from January 01 2005 to December 31 2016. Brief demographics for enrolled members are included in Medicaid claims data, such as age, gender, race, residency, etc.

Medicaid claims data do not include claims for managed care or Medicare enrollees. We excluded patients with dual eligibility, and thus restricted the drug exposure cohort to pregnant women who were only in the fee-for-service or primary care case management program.

Each data source will be cleaned first, and then linked with other corresponding datasets using a multi-step linkage approach in which three

methods of linkage are applied in sequence Deterministic, Fuzzy Matching, and Probabilistic. [156]

Records will be first matched deterministically, based on exact matches of unique combinations of personal identifiers including Social Security Numbers, Date of Birth, and Mothers' Names (used for the linkage of BVS to Medicaid only). Records that cannot be exactly matched due to missing or poor data quality will be linked using Fuzzy Matching. [156, 157] Fuzzy Matching allows at least one occurrence of Social Security Number digit transpositions, name misspelling, or day or month errors in birth date fields. [157]

Remaining unmatched records will be linked using probabilistic techniques, based on statistical weighting of combinations of personal identifiers. Probabilistic linkage involved a two-step process. 1) Deterministic matching from the first merging step empirically derived weights to the non-missing fields based on successful linkages. 2) After the unlinked data matched with several records by weights, the matches with the highest statistical probability (indicating by high weights) will be chosen. The record remained unmatched when no high weights could be obtained.

Study Cohort

This study includes female Rhode Island Medicaid enrollees who were older than 15 years of age, delivered a live singleton infant between January 01, 2006 and December 31, 2016, and are enrolled in the Medicaid program as identified by pregnancy status. The study cohort of mother-infant pairs will

be generated by linking the Rhode Island Medicaid claims data and Rhode Island Birth defects data using strategies described above.

Many women joined the Medicaid program after becoming pregnant. We excluded the women who were enrolled in Medicaid program after a positive pregnant test. More exclusion criteria for maternal-infant pair include: mothers with less than 6 months of Medicaid eligibility before pregnancy; mothers who lost Medicaid eligibility during pregnancy; mothers with dual enrollment with Medicare, HMO, or other private health plans; mothers giving multiple births; mothers with diabetes mellitus (ICD-9-CM: 249. x, 250. x, 790. 29, or used of any antidiabetics during baseline), hypertension (ICD-9-CM: 401. x, 416. x, 796. 2, , 997. 91, 459. 3, or used of any antihypertensive drugs during baseline), or HIV pre-pregnancy (ICD-9-CM: 042, 079. 53, V08, V01. 79, 795. 71, or used of any antiretroviral drugs); Infants who were twins, triplets, quadruplets or more; outliers involving infants with birth weight less than 350 g or above 6000 g; mothers or infants missing critical information, such as infant's birth weight, mother's demographic information, or perinatal medical information. Only less than 1% of infants are missing birth weight records in the birth certificate, these will be excluded from the study. [20]

Overall Study Design

This is a retrospective cohort study based on linked mother's Medicaid claims and state birth registry data. The infant's birth date will be the study index date. The drug exposure window will be defined as the subsequent 9-month pregnancy period after the first day of mother's last menstrual date.

We will use a 6-month baseline period prior to the first date of mother's last menstrual date to obtain the baseline demographic and clinical information. Birth defect outcomes will be detected 0-365 days after the live birth. The entire study period lasts from January 01 2005 to December 31 2016.

Drug Exposure

Pharmacy claims in Medicaid have been approved as an accurate source for the assessment of drug exposure in observational studies. [158] Mother's medication exposure during pregnancy will be obtained from Medicaid pharmacy claims using NDC codes for filled prescription medications, and the number of days for which the medication is supplied. [160] The birth anomalies are associated with exposure during entire pregnancy, MCM relates to the teratogen exposure during the first trimester, and MA and LBW associates with the maternal medication exposure at the third trimester. [161] Maternal medication exposure during entire pregnancy period can affect the occurrence of varied birth defects. The exposure window, thus, will be established as a period of 14 days prior to the first day of the mother's last menstrual period (LMP) to the date when infant is born. The drug exposure will be defined as any one dose of study medications dispensed during the exposure window, including which the medication is dispensed before the exposure window but its supply days cover at least 1 day of the exposure window. Adding 14 days prior to the pregnancy is to include the conception period and the residual effects of medications. Sensitivity study will be conducted to examine the different definitions of medication exposure windows.

The mother's LMP will be obtained from birth certificates. If the dates are not available in birth certificates (about 13% of LMP in birth certificates are missing), then this information will be imputed from clinical estimates. [163-165] The literature suggests that LMP from birth certificates and clinical estimates agrees within 2 weeks. [166]

Outcome Assessment

In this study, we will identify all individual adverse infant outcomes: birth defects (involving MCM and MA), ACNB, LBW, DDD, and preterm birth from the DoH birth defects data.

MCM is defined as " an abnormality of an essential anatomic structure that is present at birth and interferes significantly with function and/or requires major intervention". [38, 39] MCM includes heart malformations, urological defects, oro-facial defects, neural tube defects, and skeletal abnormalities, etc.. [38, 40, 41] Drug-induced MCMs mostly occur between the third and eighth week of gestation. [44] Any impairment before three weeks is more likely to result in fatality. The fetus becomes less sensitive to teratogenic effects after the eighth week, when the organs have developed. 2-1 delineates the time window of exposure to teratogens and associated MCMs and MAs. [44] MA, also called minor congenital malformations, is the abnormal morphologic feature that does not cause serious medical or cosmetic consequences [45]. Identification of MA can be difficult due to the definition and the easy-variable occurrence area. [46] Approximately 70% of MAs occur on the face or hands. [46] The prevalence of MA is less than 4% in the general population,

and varies by race, ethnicity, and gender. [45, 46] In healthy newborns, about 15% to 20% have one MA, 0. 8% have two MAs, and 0. 5% have three or more MAs. [46] MA mostly occurs after the eighth week of gestation, which is so-called fetal period. [44] The use of teratogens during this period may induce MAs by disturbing the growth of tissues or organs. [44] ACNB includes seven medical conditions for new born infants. Infants' birth weight less than 2500g, 1500g, and 1000g are categorized respectively as low birth weight (LBW), very low birth weight (VLBW), and extremely low birth weight (ELBW). Infants with low birth weight are likely to be born before 37 weeks of pregnancy. In 2009, 8. 16% of live born infants showed low birth weight. [50] The high risk of infant mortality and morbidity associated with low birth weight has been documented. [51] Although this positive association has been ameliorated over time with improved perinatal technology and intensive care, low birth weight and prematurity still have been identified as risk factors predisposing to cardiovascular dysfunction, lung disorder, hypertension, type 2 diabetes, renal diseases, autism, and developmental delay. [52-56]

MCM, MA, DDD, and fetal death will be collected from birth to the first 365 days of life using the ICD-9 CM code (740-759. 9, 315, 768. 0, 768. 1) from inpatient and outpatient claims. ACNB and preterm birth will be identified from Rhode Island birth certificatedata, and one year follow ups in infant hospital discharge data. Infant birth weight is accurately recorded in the birth certificate. [19]

It was noted in previous studies that these birth defects outcomes are highly related to each other. [59, 70-75] MCM, MA, VLBW, and ELBW relate to significant morbidity, mortality, and childhood disability or serious pregnancy or obstetric complications. [58, 70-75] About 6-42% of evolving cognitive dysfunction, 9-26% of neurosensory disabilities, 1-15% of blindness, and 0-9% of deafness occurred in infants born with VLBW and ELBW. [71] A significantly higher risk of DDD was found in infants born with MCM (prevalence rate: 8. 3, 95%CI: 7. 6-9. 0). [72] A 44% – 86% of mortality rate occurs in infants with ELBW (500-750g). [73] Moreover, infants with 1, 2, or 3 MAs had a risk rate of corresponding MCMs at 3%, 10%, or 20%, respectively. [46]

Some risk factors, such as infant gender, maternal age, race, social-economic status, BMI, smoking, alcohol use, nulliparity, comorbidity, and comedication during pregnancy are risk factors for all of these outcomes. [75-78]

Latent Variable Model

Liu and Roth developed an LVM to incorporate four important BD outcomes into a single measurement, the infant morbidity index, to describe an infant's overall tendency to BD. [13] We will apply this model to combine all birth defects outcomes defined in this study into a continuous index of overall adverse perinatal outcome (APO) in this study. The combined outcome will be evaluated in terms of validity and reliability to ensure the appropriate use of this new methodology.

MCM, MA, ACNB, Fetal Death, and DDD will be categorized as a binary variable, and assumed Bernoulli distributed. [21] Four levels of LBW will be modeled as a multinomial variable since the four birth weight categories are mutually exclusive and each has its own probability. The summation of the individual probabilities of birth defects outcomes equals one. The unobserved index score will be assumed log-normally distributed. Based upon the assumption of " local independence", responses of individual component outcomes are independent given the latent variable. [22, 23] Thus, the overall probabilities of component outcomes conditional on the latent variable are equal to the products of conditional probability for each individual component outcome. [21]

Based on the " local independence" and Baye's rule, the joint distribution for component outcomes can be expressed as an integral of product of multinomial variable for conditional distribution of each component outcome and marginal distribution of latent variable. [22-24] Marginal distribution of the latent variable is described as log normal. Given the observed outcomes, we can obtain the posterior distribution of the latent severity score.

Furthermore, we assume that the conditional distribution of each categorical observed outcome is nonlinear function of the latent variable. [13] The conditional distribution of observed outcome and the latent variable will be linked by two parameters in the non-linear function. The probability of any specific observed outcome equals to 0 when the value of the latent variable equals to 0 because the latent variable accounts for all variation of the observed component outcomes and the relationship among these

component outcomes. [13] In the non-linear function, the probability of an infant having an individual birth defect outcome is assumed zero if the latent variable is zero, and every normal level (no birth defect or normal weight) will be treated as a reference. The latent variable positively associates with observed outcomes. The larger the latent variable, the higher the probability of the observed outcome. [13]

Latent Trait Model will be conducted using SAS Proc IML. The proportion of each outcome combination will be calculated. Then each parameter will be estimated using the iteration function for EGNLS starting from iteration 0 with initialized value until the stepping coefficient is less than 10^{-9}. The final results are the estimates of all parameters. The estimate of latent variable will be obtained by entering the computed parameters into posterior function. [13]

Sensitivity Studies

In order to examine the proper definition of exposure window, sensitive studies will be conducted with the exposure window defined as the period of 3, 7, 21, or 30 days prior to the first day of the mother's LMP to the infant's birth date.

D. Timeline

Table. Study Timeline of the Study.

Time	Study Progress
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Before 07/01/2017	Obtain IRB approval from URI, Brown, RI DoH, and RI EOHHS. Complete DUA with RI DoH and RI EOHHS.
07/01/2017 – 08/01/2017	Complete data linkage for specific aim 1
08/01/2017 – 10/01/2017	Complete data cleaning, manipulating, variable editing, and analyses for demographic and clinical characteristics
10/01	Complete specific

/2017

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aim 2
01/31

/2018

Submit an abstract

02/01 to the annual

/2018 meeting of

–   International

02/28 Society of

/2018 Pharmacoepidemio

logy (ISPE)

03/01

/2018 Complete specific

–   aim 3 and submit a

06/30 journal article

/2018