Abstract

Background: In the United States, congenital malformation is the leading cause of infant mortality and potential life-year lost. Congenital malformations include major malformation and minor anomalies. Teratogen-induced congenital malformation is preventable. Anticonvulsant drugs, prescribed for epilepsy, bipolar depression, migraine, or chronic pain, have been demonstrated to be significant teratogens. Recent studies suggest that taking anticonvulsant drugs poses an increased risk of having a child with congenital malformations in women with epilepsy (WWE). Previous studies reported that the rate of major congenital malformations in WWE was 4.5% for anticonvulsant monotherapy, and 8.6% for anticonvulsant polytherapy. Neural tube defects, orofacial clefts, cardiac abnormalities, urologic defects, and skeletal abnormalities are the most common major congenital malformations caused by in utero exposure to anticonvulsants. Current guidelines for anticonvulsant use in WWE recommends monotherapy with lowest effective dosage and avoiding valproate. Neurologists like to switch to second generation anticonvulsants after patients are or plan to be pregnant. However, the teratogenic effects of second generation anticonvulsants have not been investigated. The specific pattern of second generation anticonvulsants exposure and major congenital malformations has not been established.

Purpose: The study purpose is to determine the teratogenic effects of second generation anticonvulsants. We will investigate the association of specific major congenital malformations with in utero exposure to second generation anticonvulsants, mainly focusing on lamotrigine, topiramate, and levetiracetam. Corresponding dose response characteristics will be examined.
Methods: Our study cohort includes Florida Medicaid female enrollees who delivered an infant between January 01, 2001 and December 31, 2008 and were continuous eligible for Medicaid fee-for-service program at least during the first trimester of pregnancy. Mothers with dual eligibility and infants with less than 365 days post-delivery follow up will be excluded. Data sources include: Florida Medicaid fee-for-service program, Florida Birth Vital Statistics, AHCA hospital discharge data, and Florida CMS early intervention program. Deterministic and probabilistic data link strategies will be used to create final study dataset from multiple data sources. Exposure of the study is defined as anticonvulsants prescribed to the mothers to be taken on at least one day during the first trimester of pregnancy. Drug exposure will be ascertained using NDC code from Medicaid pharmacy claims. Primary outcome is identified as diagnosed major congenital malformations using combined information from multiple sources: hospital discharge code (inpatient, outpatient), CMS early intervention, birth certificate, and Medicaid claims (inpatient, outpatient). Cases of major congenital malformations will be identified using the definition from CDC Metropolitan Atlanta Congenital Defects program.

Our study will be conducted in four subsequent steps with different study designs and analyses: utilization of anticonvulsants in pregnant women during the study period, outcome ascertainment, risk of major congenital malformations and in utero exposure to second generation anticonvulsants, and pattern of specific major congenital malformations associated with in utero exposure to lamotrigine, topiramate, and levetiracetam.

Utilization of anticonvulsants in pregnant women will be investigated by describing the utilization rate of second and first generation of anticonvulsants and identifying the pattern of switching between the two during the pregnancy or 6 months prior to pregnancy. Baseline sociodemographic characteristics, comorbidities (i.e., epilepsy, seizure, hypertension, diabetes,
etc.), and co-medications (i.e., antidepressants, antidiabetic and antihypertensive agents, etc.) will be evaluated and analyzed in the statistical models to identify the significant predictors of specific anticonvulsants use.

Incidence of major congenital malformations will be identified from different sources. An algorithm will be developed to ascertain and validate the cases based upon the diagnosis codes, pharmaceutical therapy, and hospital procedures from Medicaid claims, hospital discharge data, and CMS early intervention records.

Incidence of major congenital malformations in infants with in utero exposure to second generation anticonvulsants during first trimester of pregnancy will be compared with no in utero exposure to any anticonvulsants during whole pregnant period. Baseline sociodemographic characteristics, comorbidities, co-medications that may induce major congenital malformations in infants and relate to anticonvulsants use in mothers will be adjusted in the analysis model. Adjusted risk ratio will be estimated from multivariate Poisson regression with the use of generalized estimating equations.

Risk of specific major congenital malformations in infants with in utero exposure to lamotrigine, topiramate, and levetiracetam during first trimester of pregnancy will be assessed by using multivariate logistic regression analysis with the reference group of no in utero exposure to any anticonvulsants during whole pregnant period.

Our study will have important clinical applications to the future care of WWE in childbearing age. The results will help to prevent the major congenital malformations for WWE or women taking anticonvulsants for other indications.