Protocol Title	Physiological-based Pharmacokinetics Approach to Determine the Extent of Drug Exposure of Antiseizure Medications During Pregnancy and Breastfeeding
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This project focuses on anti-seizure medication (ASM) clearance and physiological factors in pregnant women with epilepsy. Recruitment will occur in the greater Pittsburgh, Pennsylvania area; we will recruit minorities in accordance with their representation in the region.

1. Risks to Human Participants.

Involvement of participants: The protocol for this grant will be developed with full consideration of the ethical standards of the PITT IRB. The PITT IRB oversees research protocols at UPMC, Magee Womens Hospital and other affiliated hospitals. Participants will be presented with the informed consent by the UPMC study staff (site principal investigator, co-investigator, research advanced practice provider (APP) or research coordinator), allowed to read over it, and then any questions they have concerning the project will be addressed. Each participant will receive a copy of their signed informed consent, and an additional copy will be filed in their medical records. Participants will include women with epilepsy planning pregnancy within the next 6 months and treated with lamotrigine (LTG) or levetiracetam(LEV) by their clinical neurologist. **This is a prospective, observational study and the ASM regimens will not be chosen or changed for the purpose of this study**.

Sources of research data will be obtained from the participants' medical records and interview, physical examination, seizure and medication diaries, questionnaires, blood, and urine assays. Details of the data collection are given below.

Participant population: A total of 60 participants (in order to enroll 30 per ASM group) between the ages of 14-45 years old will be recruited for this study. Only women will be recruited given the specific aims of the study.

Participants will be primarily recruited from UPMC neurology and obstetrics clinics by use of flyers in the waiting areas and exam rooms and weekly review of upcoming appointments by the study staff. The participant can receive and continue their care at another medical institution and participate in this observational study at UPMC.

Participants will be excluded if they have history of psychogenic non-epileptic spells, other major medicalillness including renal or hepatic disease, progressive cerebral disease, inability to maintain a seizure and medication daily diary, present or recent history of drug or alcohol abuse, polytherapy with other interacting ASMs, or the use of any concomitant medications that interact with the ASM they are

taking (lamotrigine or levetiracetam).

Study Procedures: **Schedule of Events for Cohort Participants**

Study Visit	01	02	03	04	05	06
Study Visit Timing	**Precon-ception**	**1st TM**	**2nd TM**	**3rd TM**	**Birth**	**6-12 wks postpartum**
Clinical Evaluations						
Eligibility Checklist, Contact information	X					
Informed Consent	X					
Demographics	X					
Socioeconomic Status	X					
Family History	X					
Preconception OB/Gyn History	X					
Initial Physical & Neurological Exam, Vital Signs	X					
Brief neurologic exam, Vital Signs		X	X	X	X	X
Medical History with updates	X	X	X	X	X	X
Seizure Factors (Classification of Seizures, Etiology, and Syndromes by Age of Onset, and Seizure Update)	X	X	X	X	X	X
ASM Dosing regimen with dates of changes	X	X	X	X	X	X
Non-ASM Medications and Vitamins	X	X	X	X	X	X
Paper Questionnaires						
ASM Side Effect Questionnaire	X	X	X	X	X	X
Paper Diary						
Seizure and Medication Calendar Reviews	X	X	X	X	X	X
Medical Record Review						
Ultrasound results		X				
OB & Neonatal Outcomes					X	
Medical Record Labs for OB care			X			
Local ASM Levels	X	X	X	X	X	X
Ancillary Studies (EEG/MRI/CT)	X					
Laboratory Evaluations *						
ASM concentrations	X	X	X	X	X	X
Hormones	X	X	X	X	X	X
Genetic sampling	X					
Serum Creatine for LEV participants	X	X	X	X	X	X
24-hour Urine collection for LEV participants		X	X	X	X	
LTG 2-N-GLU for LTG participants	X	X	X	X	X	X
Cord Blood, placental sample at Birth					X	
Volume	39 ml	30ml	30ml	30ml	30ml	30ml

TM = trimester

*Microsamples will be obtained in the participants' homes every two weeks after a positive pregnancy test x 3, and every week after delivery x 3. The participants will be instructed to fill out the Side Effects Questionnaire on the same day as the postpartum microsamples samples, with adjustment in the survey to query about symptoms over the past week (instead of the past four weeks).

Data and/or Specimen Collection and Analysis:

Samples will be collected at the Kaufmann Medical Building and Magee Women's Hospital.

i. Data collected:
   a. ASM Side Effects Questionnaire
   b. Seizure and medication daily diary
   c. Biological samples: blood, urine, breast milk, umbilical cord blood
   d. Demographic data
   e. Pharmacy-related data
   f. Seizure and outcome data
   g. Biological samples will be analyzed in the Birnbaum Lab, Fairview Research Laboratory (Minnesota), or Presbyterian Lab (Pennsylvania).
   h. Blood samples from mother
      i. ASM concentrations
      ii. LTG 2-N-GLU for LTG participants
      iii. Hormones (including estradiol and progesterone concentrations)
      iv. Serum and urine creatinine
      v. DNA
   i. Blood samples from infants (umbilical cord and heel stick/micro sampling):
      i. ASM concentrations
      ii. LTG 2-N-GLU for LTG participants
      iii. DNA

Potential Risks:

i. Potential risks include pain and rare instances of localized bleeding, bruising, infection and/or fainting from the needle sticks required to obtain blood samples from the participant. The umbilical cord sample will be obtained after the cord is severed and will not pose any discomfort or danger to the participants or the newborn.

ii. Data and records collected on participants in connection with this research project will be held confidential unless specifically required to be disclosed by state or federal law. Their records will become part of their hospital charts and study file books. They will not be personally identified in any publication that may come from this project.

2. Adequacy of Protection Against Risks.

Informed Consent and Assent: Eligibility for volunteer participants will be reviewed by the research study Advanced Practice Provider (APP) and research coordinator. All persons interested in the study will be contacted by the study APP who will describe the details of the study, ensure that the prospective participant meets all inclusion/exclusion criteria and, if so, will ask them to participate. Persons verbally agreeing to participate will be mailed consent forms containing the details of the study. This will provide the individual with the time and privacy to make a decision on whether or not to participate in the study. Follow-up telephone calls will be made within two weeks to ensure that the potential participant has received the consent forms andto address any questions about the study. No study related procedures will take place until a consent form is signed. Participants will be informed that they can withdraw at any time during the study without any consequences. The original signed consent forms will be kept on file by the research coordinator/APP.

Vulnerable Participants: While the project is specific to pregnant women and includes minors, the project does not result in deviation from the participants' standard of care throughout the study. The study will be carefully described to the participants prior to their consent. Any benefits as a result of the research data will be used to manage/improve health care in this exact population (pregnant 14-

45 year old females with epilepsy).

Confidentiality: To ensure confidentiality, all participants enrolled in the study will be assigned a study identification code. This code will be used on all study related data collection forms except for those on which the use of personal identifiers is mandatory (e.g., informed consent form). Forms that link the name of the participant and the participant identification code will be kept in a locked cabinet insidea locked office under the supervision of Dr. Pennell and in an electronic file stored on a password protected, strongly encrypted computer server that meets HIPAA guidelines. Access to participants' identifiable information will be limited to those that require this information such as the principal and co- investigators or others who have direct contact with study participants, such as the study nurses andcoordinators. Any personnel with data access will be identified and listed on the HIPAA form.

3. Potential Benefits of the Proposed Research to Research Participants and Others

i. The potential risks to the participant are balanced by the potential benefit of gaining understanding of how to optimize dosing of LTG and LEV during pregnancy and postpartum. Knowledge gained may be applicable to any future pregnancies of these participants.
ii. Compensation is not considered a benefit for this study as it is based on the amount of time spent rather than risk. Participants will be paid a total of $625 for participation in the entire study protocol for their travel costs, time and inconvenience ($75 for enrollment and birth visits, $50 for each trimester visit and the 6-12 weeks postpartum visit, $25 per microsample obtained x6), $75 for breast milk collection, and $50 for infant heel stick. If the participant completes only some of the study visits and/or microsamples, then she will be reimbursed accordingly. Parking will be covered by tokens provided by the study staff.
iii. Participants are informed that they can discontinue participation in the study at any time andstill be paid for the time they put in.

4. Importance of Knowledge to be Gained

Our long-term goal is to prospectively determine individualized dosing adjustments during pregnancy to maintain therapeutic concentrations for LTG and LEV, as well as drugs that undergo the same mechanisms of elimination. In addition, this research will provide a framework that can be extended to investigations of other ASMs and additional drug classes.