Endeavor to Stop Nausea/Vomiting Associated with Pregnancy (E-SNAP)
NCT05452174
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STATISTICAL DESIGN AND POWER ANALYSIS

Our data management team includes a highly experienced clinical trials statistician and database programmer. The REDCap management system was developed and functioning at Northwestern and is being transferred via a DUA. We are mindful of subjects' time and we send links to allow women to enter self-report measure data from home (for example, for recording of daily PUQE scores).

Analytic Approach. Descriptive statistics such as demographic and baseline clinical information will be summarized for all eligible women. These results will inform the feasibility, design and statistical approach for construction of the subsequent randomized controlled trial if the findings from the proposed study demonstrate the acceptability and feasibility of the protocol. This R21 study is not expected nor intended to have the power to address the outcomes described below, but to provide data to guide the design of a phase 3 RCT.

Aim 1. Define acceptability of mirtazapine for refractory NVP. Acceptability is defined by the number of women who accept participation compared to the total who undergo the consent procedure. All women will be asked for the reason behind their decision. A standard consort chart[1] will be created to record subject flow through the protocol. The acceptability of mirtazapine for NVP/HEG is a factor in the feasibility of the eventual RCT and is an important factor in the ability to recruit subjects and define the number of sites required.

Aim 2. Determine the tolerability and safety of the dosing regimen. Measures of tolerability include the proportions of: 1) emergent side effects on the ASE, which will be isolated by comparison to symptom ratings at intake; 2) withdrawals attributable to side effects; and 3) women who elect to continue mirtazapine after the initial 3-week trial. The daily PUQE scores will be used to evaluate the time (in days) to remission during the 3 week trial. We will use Kaplan-Meier curves to visualize time to remission (defined by a PUQE score of 3 or 4. Additionally, we will fit Cox regression models to identify factors that may be associated with time to remission.

We will evaluate the potential need for change in the dosing for the subsequent RCT by balancing the time to response against the emergence of any side effects. For example, if the 15 mg/day dose is well tolerated but the major symptom reduction occurs at 30 mg/day, we will consider the advisability of a more assertive dosing regimen with our DSMB and FDA consultants.

Aim 3. The drug tapering strategy will be assessed by evaluating the emergence of somatic symptoms on the Asberg side effects profile during the taper. Obtaining weekly plasma concentrations in the initial 21-day trial allows an exploration of whether a relationship between mirtazapine concentration and antinauseant/ antiemetic efficacy is likely in this group of women. The patient's genotypes and corresponding phenotypes (ultrarapid, rapid, intermediate, poor metabolizers--by specific enzyme) will be evaluated for their relationship to plasma mirtazapine concentrations. Biotransformation is mediated by CYP2D6, CYP3A4, and 1A2.[2]

Aim 4. Evaluate the maternal and fetal safety of mirtazapine. The maternal and neonatal outcomes from the PES will be reviewed for consistently reported events across subjects. We will compare the mirtazapine exposure data to that of women who have taken SSRI through pregnancy in our Obstetric-Fetal Pharmacology U54 study (N=88), Optimizing Medication Management for Mothers with Depression. Neonatologist Malika Shah, MD (see letter of support) will collaborate with our team to interpret the OPTI-MOM neonatal outcome data from the PES in the proposed trial (fetal exposure to mirtazapine) and compare it with the PES from our current OPTI-MOM subjects (fetal exposure to SSRI antidepressants). We have used these measures in our studies of SSRI exposure on neonates.[3] The PES includes medical and obstetric risk factors, time in the delivery/ operating room, fetal monitoring, surgical complications, infant anthropometrics, special care/NICU admission, and post-birth complications. We will compare data using t-tests, chi-square test, and nonparametric tests as appropriate according to the type of data and their distributions.

Sample Size Considerations. The proposed study is not powered nor expected to evaluate the efficacy of mirtazapine for sNVP. To estimate a preliminary sample size for the efficacy of mirtazapine for NVP/HEG for the initial 3 week trial, we will assume 80% power, two-sided significance=.05, and a standard deviation of 2.1 (derived from Koren et al[4]), and a moderately severe PUQE score (≈10) at study entry. The standard deviation of the change in PUQE scores from baseline to week 3 is conservatively estimated to be 2.97 by assuming that the correlation is zero. With 20 subjects, we can detect a 23% reduction in mean symptom scores (a 2.3 point decrease in PUQE scores). Based on the case studies, we anticipate a more favorable symptom reduction than 2.3 points. To allow a 20%

dropout rate, we will enroll 25 subjects. We enrolled 2 participants, who completed the 3- week study at Northwestern, before the study was closed.

References.

1. Trials CTRo. The CONSORT Flow Diagram. Accessed.
2. Timmer CJ, Sitsen JM, Delbressine LP. Clinical pharmacokinetics of mirtazapine. *Clinical pharmacokinetics.* 2000;38(6):461-474.
3. Ulbrich KA, Zumpf K, Ciolino JD, Shah M, Miller ES, Wisner KL. Acute Delivery Room Resuscitation of Neonates Exposed to Selective Serotonin Reuptake Inhibitors. *The Journal of pediatrics.* 2021.
4. Koren G, Clark S, Hankins GD, et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. *American journal of obstetrics and gynecology.* 2010;203(6):571.e571-577.