Executive Summary for STTI National Small Grant Final Report

"Vasopressin, Depression Symptoms, Pain and Preeclampsia"

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Aims Summary

The purpose of this study is to understand the early pregnancy action of arginine vasopressin (AVP), as measured by its stable byproduct of copeptin, to develop preventative, and therapeutic modalities against preeclampsia (PreE). The first aim was to determine the association of copeptin with depression symptoms and pain throughout pregnancy. The second aim was to determine how depression symptoms and pain affect early pregnancy copeptin levels in order to predict late pregnancy preeclampsia. Based on our data and others, our ***central hypothesis*** is that early depression and pain coupled with early pregnancy copeptin as a marker AVP secretion will robustly predict the development of late pregnancy PreE.

Theoretical Framework

The Integrated Perinatal Health Framework (IPHF) was utilized as the conceptual framework to guide the study (Misra, Guyer, & Allston, 2003). The IPHF integrates a "life span" approach to perinatal care using multiple determinants (Halfon & Hochstein, 2002). Determinants are powerful forces that shape pregnancy outcomes. Pain and depression are proximal determinants as they are biomedical and behavioral responses shaping short term and long-term pregnancy outcomes like PreE.

Methods, Procedures, and Sampling

The proposed exploratory pilot study will utilize a nested case-control design to identify if *the separate and combined effects of pain and depression* significantly contribute to maternal plasma copeptin level throughout gestation; and thereby modulating *PreE incidence*. The Maternal Fetal Tissue Bank (MFTB) (IRB#200910784) at the University of Iowa (UI) is a cross sectional, prospectively collected biorepository by which samples and clinical data were obtained, coded, and uniformly processed as previously published (Santillan et al., 2014). The MFTB corresponds with the MFTB data warehouse in which demographic and clinical data from the patients' electronic health record may be obtained.

This study has IRB approval to use de-identified patient data and corresponding coded biosamples from the secure Iowa MFTB data warehouse for all cases and controls. Their samples are coded, processed, and frozen for use by future investigators. Women enrolled in the MFTB give an additional 5-10ml blood sample to the repository every time blood is drawn as part of their routine medical care which include the following time points: 1) first trimester (first obstetrical visit), 2) second trimester (at the Glucose Tolerance Test and Quad Screen), 3) third trimester (admission to Labor and Delivery), and 4) at delivery (fetal cord blood). Standardized data collection forms assist data extraction with additional information being obtained with the assistance of bioinformatic specialists at the University of Iowa Institute for Clinical and

Translational Science. Specific clinical data extraction, security, and veracity procedures in addition to biosample processing has previously been published (Santillan et al, 2014.) Patients in the MFTB were first identified with preeclampsia and depression through the MFTB data warehouse. Patients were identified through the Patient Health Questionnaire-9 (PHQ-9) (during pregnancy). Then MFTB plasma samples were identified through Labmatrix software. Copeptin was measured using a commercial enzyme-linked immunosorbent assay. To account for the affects of creatinine, copeptin values were normalized to total plasma protein.

Summary of Findings

Initially, an entire sample of 433 women was obtained from the data warehouse review. However, as identified by the PHQ-9 during pregnancy, 85 women were identified as having depression symptoms while 148 women screened as having no depression symptoms. Therefore, a subsample of 233 women were utilized for further analysis. For both the depression and no depression symptom groups, the average maternal age was 30 years (±5.2-5.7 respectively). Both groups also had averages of three pregnancies (gravida), an overweight BMI average ranging from 28.9±8.6 to 29.9±7.1, and delivered at 38 weeks gestational age. However, the group with depression symptoms had 18.1% less private/commercial insurance, 13.2% less partners (as a potential measure of social support), and were more diverse with 14.1% more Hispanics and 5.1% more Blacks.

Interestingly, a review of the MFTB data warehouse found only 36 women who documented with pain during pregnancy by the Numerical Pain Rating Scale. However, using ICD-9 codes, 33.8% (n=50) of the no depression symptom group and 31% (n=26) of the depression symptom group identified as having a chronic pain condition such as back pain or fibromyalgia. Copeptin levels will require further investigation with additional pain patients.

Contrary to our hypothesis, our findings reveal that the levels of CopeptinLog10 were lower in the depression symptoms than the no depression symptom group (1.77 ± 0.60 vs. 1.94 ± 0.47, $p < 0.001$). In addition, rates of preeclampsia (2.4%) were lower in the depression symptom group than in the general population (5-8%).

Recommendations

With approximately two-thirds of pregnant women experiencing back pain worldwide, our lack of pain findings yet are similar results to a recent Cochrane review (Pennick & Liddle, 2013). The paucity of pain screening and treatment requires additional investigation into nurse and provider awareness of pain during pregnancy in order to promote proper pain screening and diagnosis. Additional research is also needed into individualized effective pain treatments during pregnancy.

Depression symptoms and Copeptin. Our findings suggest there are other factors that may lower levels of copeptin and potentially decrease the incidence of PreE. Further exploration of subtypes of PreE, medications, and other potentially influencing factors influencing copeptin levels with pain, depression symptoms, and preeclampsia is needed.

Select References

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