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Is third trimester serotonin reuptake inhibitor use associated with postpartum hemorrhage?

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ABSTRACT

As serotonin reuptake inhibitor (SRI) use may decrease platelet function, previous research has shown a relationship between SRI use and an increased risk for bruising and bleeding. The literature regarding the association between SRI use during pregnancy and increased bleeding at delivery, referred to as postpartum hemorrhage (PPH), is mixed. In secondary analyses from two prospective observational studies of pregnant women with mood disorders, 263 women were exposed to an SRI (n = 51) or not (n = 212) in the third trimester. To be precise, we used the terminology estimated blood loss (EBL) >600 cc rather than the term PPH because the current definition of PPH differs. The occurrence of EBL >600 cc was determined using the Peripartum Events Scale (PES) completed from obstetrical records by a blinded medically trained member of the study team. EBL >600 cc occurred in 8.7% of women in this cohort. There was no statistically significant difference in the rates of EBL >600 cc in the 24 h after delivery in women taking SRIs during the third trimester (9.8%) compared to non-exposed women (8.5%). Utilizing generalizing estimating equations, the odds of EBL >600 cc in each group were not significantly different (OR 1.17, CI-0.41-3.32, p = 0.77). When the SRI group was limited to women with exposure at the time of delivery, the difference in the odds of EBL >600 cc was unchanged (OR 1.16, CI = 0.37–3.64, p = 0.79). In population, both third trimester and use at delivery of SRIs during pregnancy was not associated with an increased risk of excessive blood loss.

1. Introduction

Major depressive disorder occurs in 8–13% of pregnant women (Bennett et al., 2004; Gavin et al., 2005; Vesga-Lopez et al., 2008), and approximately 4–8% of pregnant women are exposed to serotonin reuptake inhibitor antidepressants (SRIs) (Alwan et al., 2011; Andrade et al., 2008; Mitchell et al., 2011). Antidepressant use during pregnancy increased from less than 1% prior to 1990 to 7.5% in 2006-08 (Alwan et al., 2011). Some investigations (Grzeskowiak et al., 2015; Lindqvist et al., 2014; Palmsten et al., 2013) but not all (Lupattelli et al., 2014; Salkeld et al., 2008) have shown an association between third trimester SRI or antidepressant use and postpartum hemorrhage (PPH). In some non-pregnant populations SRI use is associated with an increased bleeding risk (Anglin et al., 2014; Hankey, 2014; Harirchian et al., 2012; Jiang et al., 2015; Tavakoli et al., 2012). The impact of SRIs on increased bleeding risk is inconsistent in non-pregnant populations as well. For example, these drugs have been associated with spontaneous gastrointestinal bleeding (Andrade et al., 2010; Lee et al., 2012) but not hemorrhage during surgical procedures (Tavakoli et al., 2012).

PPH is a primary cause of maternal morbidity and mortality (Rath, 2011; World Health Organization, 2007) and occurs in 4–6% of births (Combs et al., 1991; Salkeld et al., 2008). PPH is classified as primary (occurring within 24 h of delivery) or secondary (occurring from 24 h after delivery to 12 weeks postpartum), also referred to as acute or delayed PPH (American College of Obstetricians and Gynecologists, 2006). Almost 50% of all postpartum deaths are

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attributed to acute PPH (Rath, 2011). Risk factors for PPH include placental abruption or previa, multiple gestation, gestational hypertension, pre-eclampsia, prolonged or induced labor, infection, obesity, use of forces, vaginal trauma and multiple previous births; however, each individual risk factor is a poor predictor of PPH (Mathai et al., 2007). PPH is generally related to uterine atony but can be caused by defects in coagulation. Antidepressants that affect serotonergic pathways have the potential to decrease platelet aggregation and increase bleeding; thus the question of whether third trimester SRI use is associated with an increased risk of PPH is clinically relevant.

Six investigators have examined the association between SRI use during pregnancy and PPH with two reporting no significant association, three finding a significant positive relationship, and one reporting results that are difficult to interpret due to a non-specific definition of PPH (Reis and Kallen, 2010). Given these disparate findings in the literature we used our well characterized cohort to conduct a secondary analysis to evaluate whether women taking SRIs in the third trimester differed with respect to the incidence of acute postpartum blood loss from women not taking SRIs.

2. Methods

2.1. Subjects

The sample is comprised of women from two National Institute of Mental Health-supported observational studies (Antidepressant Use during Pregnancy, R01-MH60335; and Antimanic Use During Pregnancy, R01-MH07592; Principal investigator: K.L.W.) with similar designs that followed women throughout pregnancy and 12 months after birth. Details of the study procedures have been reported elsewhere (Wisner et al., 2009). Briefly, women with a lifetime history of major depressive disorder (MDD) (n = 173) or bipolar disorder (n = 151) and a comparison group of women with neither psychiatric disorder (n = 140) were enrolled in Cleveland, Ohio and Pittsburgh, Pennsylvania from 2000 to 2011. Pregnant women between 18 and 44 years old were recruited by self-referral, physician referral, advertising, and screening in obstetric ultrasound suites. Main exclusion criteria included active substance abuse disorders or gestational exposure to benzodiazepines or prescription drugs defined as category D or X by the U.S. Food and Drug Administration (FDA). In addition, for this analysis, women on medications that could affect bleeding (e.g. Omega-3 fatty acids, aspirin, etc.) were excluded (for a complete list see Appendix I (UW Health)). All procedures and consents were approved by the institutional review boards from Case Western Reserve University and University of Pittsburgh. All women provided written informed consent prior to study entry.

A total of 263 women with singleton gestations were divided into exposed (n = 51) and unexposed (n = 212) groups, based on whether they took an SRI in the third trimester. Women were classified as exposed if they were taking an SRI in the third trimester (defined as ≥27 weeks gestation). Unexposed women were not taking an SRI during pregnancy at any time. The exposure timeframe was determined by adding one week to the start date and two weeks to the stop date for the SRI to account for time needed to develop meaningful levels following SRI initiation and to achieve clearance following SRI cessation. For all women, baseline assessments (prior to or at week 20 of pregnancy) included a clinical interview, physical measurements, a urine drug screen, a blood draw for drug levels (if an antidepressant or anti-manic drug was being taken), and completion of questionnaires. Women were assessed again at 30 and 36 weeks gestation and at 2, 12, 26 and 52 weeks after birth. Follow-up assessments included the same measurements (excluding the urine drug screen) as those administered at baseline.

2.2. Measures

Demographic characteristics were assessed at baseline via standard instruments and included: age, race, employment status (categorized as employed/unemployed), and education (dichotomized by college completion). Psychiatric diagnosis was established at baseline via the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1994). Pre-pregnancy body mass index (BMI) was calculated using the woman's reported pre-pregnancy weight and measured height. The Peripartum Events Scale (PES) (O'Hara, 1986) is an 11-category scale which records obstetric history, medical history, indication for labor and delivery, method of delivery, duration of labor and infant outcome. It also assesses delivery complications which include estimated blood loss >600 cc, which we used as our primary outcome. Because this definition is differs from the current definition of PPH, which is >500 cc blood loss after vaginal delivery and >1000 cc blood loss after cesarean delivery (American College of Obstetricians and Gynecologists, 2006), our primary outcome is specifically named estimated blood loss (EBL) >600 cc. The PES was completed through abstraction from obstetrical records by a blinded medically trained member of the study team (an obstetrician, a nurse doctoral student, or a nurse family practitioner).

For interviews after the baseline assessment, the Longitudinal Interval Follow-up Evaluation (LIFE) was used in conjunction with the SCID to assess for diagnostic status change. Depressive symptoms were assessed with the 29-item Structured Interview Guide for the Hamilton Depression Rating Scale with the Atypical Depression Supplement (SIGH-ADS) (Williams and Terman, 2003). Psychotropic drug exposure was documented by recording the subject's drug doses at each visit and documenting any changes that occurred between visits (Wisner et al., 2009). Use of tobacco, alcohol, and illicit drugs was assessed at each visit.

2.3. Data analysis

Women with third-trimester SRI exposure were compared to women with no SRI exposure during pregnancy on sociodemographic, behavioral, clinical, and delivery measures. Descriptive statistics were calculated as means and standard deviations for continuous measures and as frequencies and percentage distributions for categorical measures. Tests of association included Student's t or Mann–Whitney U for continuous measures (depending on whether distributional assumptions were met) and Chi-Square and Fisher's exact for categorical measures (depending on expected cell frequencies). Due to some mothers having more than one pregnancy while participating in the study, hemorrhaging during delivery was modeled using generalized estimating equations to account for the possibility of correlation among siblings. Three models were estimated: Model I included SRI exposure alone; in Model II we added imbalanced baseline measures including age, race, education, parity, and comorbid anxiety to the SRI exposure variable; Because Lupattelli et al. (2014) reported that depression was independently associated with vaginal bleeding, Model III added the baseline$SIGH\text{-}ADS_{29}$ to the measures in Model II.

3. Results

Of the 581 women screened, 473 were eligible for study entry (Fig. 1). For the purpose of this analysis, women were initially excluded if: a) hemorrhage data were not available (usually due to delivery at an outside hospital, n = 156), b) they were exposed to an