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Review

Antidepressants during pregnancy and postpartum hemorrhage: a systematic review

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ABSTRACT

The use of antidepressants in pregnancy is increasing. Concerns have risen about the use of antidepressants during pregnancy and the risk of postpartum hemorrhage (PPH). The aim of this systematic review is to summarize evidence on the association between use of antidepressants during pregnancy and the risk of PPH. An Embase and Pubmed search was conducted. English and Dutch language studies reporting original data regarding bleeding after delivery associated with exposure to antidepressants during pregnancy were selected. Quality appraisal was conducted using the Newcastle Ottawa Scale (NOS). Out of 81 citations, 4 studies were included. Based on the NOS, 3 were considered of good quality and 1 was considered of satisfactory quality. Two studies reported an increased incidence of PPH in women who used antidepressants during pregnancy. The other two studies identified no overall increased risk of PPH among pregnant women exposed to antidepressants. The existing evidence remains inconclusive whether use of antidepressants during pregnancy is associated with an increased risk of postpartum hemorrhage. If there is such an association the absolute increased risk will be low and the clinical relevance needs to be further examined.

Contents

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Introduction

Recently, several studies have described the association between use of antidepressants (ADs) during pregnancy and postpartum hemorrhage (PPH) [1]. Use of ADs, especially ADs that inhibit serotonin reuptake (SSRIs) or have affinity with the serotonergic system, may increase the risk of bleeding events [2]. The suggested underlying mechanism is depletion of serotonin storage in platelets by inhibition of serotonin reuptake, since platelets themselves do not synthesize serotonin. Platelets play a fundamental role in coagulation and the repair of vascular injury. Depletion of serotonin may result in disrupted platelet aggregation and adhesion, and eventual prolongation of bleeding times [3].

Depression and other mood disorders are common during pregnancy. The prevalence of depression during pregnancy is estimated to be 10–16% [4]. There has been a steady increase in the use of ADs in pregnancy. Recent studies have shown that 2–9% of women in the Western world are prescribed ADs during pregnancy [5–7].

PPH is a common obstetric complication (13%) and a leading cause of maternal morbidity and mortality [8]. PPH is defined according to the International Classification of Diseases, Ninth revision (ICD-9) as blood loss at least 500 ml or blood loss in an amount that adversely affects the maternal physiology, such as blood pressure and hematocrit [9]. The maternal morbidity includes blood transfusions, admissions to the intensive care and later subfertility. The rate of deliveries complicated by severe PPH has shown an increase from 1.9 to 4.2 per 1000 deliveries in the period of 1999–2008 [10]. The rising incidence of PPH cannot be fully explained by increase in established risk factors for PPH, including maternal age, multiple pregnancy and preeclampsia. Therefore, other risk factors need to be examined.

Due to the increasing use of ADs in pregnancy and the increasing incidence of PPH, we studied the association between use of ADs during pregnancy and the risk of PPH in this review.

Methods

Search strategy and data sources

A PubMed and Embase search was conducted on May 28, 2014. Search strategies were developed for each database in collaboration with a medical information specialist. Studies were included if they were published in English or Dutch and reported original data regarding bleeding during or after delivery associated with exposure to any type of antidepressant medication during pregnancy. The following set of keywords was used: (SSRI or NSRI or SRI or TCA or second generation antidepressive agents or the individual names of any type of antidepressive agents) AND (postpartum or puerperium) AND (hemorrhage or bleeding or blood loss). The complete search strategy is shown in Appendix A.

Study selection

Two reviewers (AB and HH) independently assessed inclusion eligibility. Initial selection for inclusion was based on screening of title. Thereafter, included titles were screened on abstract. Following this, full-text versions of the selected studies were assessed for eligibility. Disagreement about inclusion was solved by discussion. The reference lists of identified articles were examined for additional pertinent publications.

Quality assessment

Quality assessment was conducted utilizing the Newcastle-Ottawa quality assessment scale (NOS, Appendix B), an assessment scale recommended by the Cochrane Collaboration [11]. For each study, two reviewers (AB and NK) assessed 8 criteria within the categories: selection, comparability, and exposure or outcome measure. Based on the NOS, each study was evaluated using the star system. Eight to 9 stars were defined as very good quality, 6–7 as good quality, 4–6 as satisfactory quality and 0–3 as unsatisfactory quality. The comparability category included evaluation whether studies had been controlled for confounders, i.e. risk factors for PPH. Risk factors for PPH are numerous. We used a list of risk factors for PPH provided by the Royal College of Obstetricians and Gynecologists (RCOG) to define the factors most strongly associated with increased odds of PPH (see Appendix C) [12]. The reviewers resolved differences in quality assessment through consensus.

Results

Description of inclusion and exclusion

Of the 81 unique citations reviewed, 65 citations were excluded on the basis of the title (see Fig. 1). During abstract review, another 2 abstracts were excluded. After the full-text review, 4 articles, all published in English, remained. Reasons for article exclusions were: (1) no reporting of original data ($n = 7$), (2) only available as conference abstract ($n = 3$), (3) no reporting of data regarding bleeding during or after delivery associated with exposure to any type of antidepressant medication during pregnancy ($n = 67$).

Overview of the studies

Table 1 contains the descriptions of the included studies. Salkeld et al. [13] conducted a population-based case-control study of Canadian women. Aim of the study was to determine if exposure to SSRIs in late pregnancy was associated with an increased risk of PPH. Case patients ($n = 2460$) were identified as patients with a diagnosis code of PPH according to the ICD-9. Exposure was defined as a prescription for either class of ADs (SSRIs or non-SSRIs) within 90 days before delivery. The final multivariate models included number of previous PPH episodes, multiple pregnancy, prolonged labor, abnormalities of the forces of labor, various obstetric traumas, placenta previa, placental abruption, and hypertensive disorders of pregnancy. Risk estimates for PPH were not significantly increased after exposure to either SSRIs (OR 1.30; 95% confidence interval (CI) 0.98–1.72) or non-SSRIs (OR 1.12; 95% CI 0.62–2.01) [13].

A retrospective register study in Sweden (Reis and Källén [14]) used data from 1 July 1995 up to 2007 obtained from the Swedish national health registers to present data on different aspects of delivery outcome after maternal use of ADs ($n = 14{,}821$). PPH was not the main outcome in this study and was solely mentioned in a table. The definition of PPH was not stated. There was a slightly increased risk of bleeding after delivery when ADs were used early (between week 10 and 12) in pregnancy (OR 1.11; 95% CI 1.03–1.19). No significantly increased risk of bleeding after delivery was present when ADs were used late (prescribed later during pregnancy by the attending doctor, OR 1.02; 95% CI 0.92–1.14) or both early and late in pregnancy (OR 1.08; 95% CI 0.95–1.22) [14].

Aim of the retrospective cohort study conducted by Palmsten et al. [15] was to determine whether use of SSRIs or non-SSRIs near to delivery was associated with PPH. Data from the joint state and federal health insurance program for low income individuals in the US (Medicaid) were used. 106,000 women with a diagnosis for mood or anxiety disorders were included from 2000 to 2007. A total of 33,678 women used ADs during pregnancy. PPH was defined as an ICD-9 code for 666.x (i.e. PPH). Potential confounders