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The Relationship Between Maternal Antidepressants and Neonatal Hypoglycemia: A Systematic Review

ABSTRACT

The aim of the article is to review systematically current researches investigating the relationship between intrauterine exposure to antidepressants and neonatal hypoglycemia. This paper included studies published in electronic databases from January 2005 to July 2020. The searched keywords were as follows: antidepressants, pregnancy, selective serotonin reuptake inhibitors (SSRIs), citalopram, fluoxetine, paroxetine, escitalopram, sertraline, fluvoxamine, selective serotonin-norepinephrine reuptake inhibitors (SNRIs), venlafaxine, tricyclic antidepressants (TCAs), neonatal outcomes, neonatal hypoglycemia, imipramine, clomipramine, amitriptyline, bupropion, trazodone, and mirtazapine. This review examined 10 relevant studies. The odds ratio/risk ratio reported in the studies were 1.33-1.73 for any antidepressant, 1.30-1.35 for SSRI, 1.42-2.11 for SNRI, and 2.07 for TCAs. The risk of neonatal hypoglycemia in infants exposed to maternal TCAs appears to be slightly higher compared to infants exposed to maternal SSRIs. Data from current studies consistently show that exposure to maternal antidepressants during pregnancy may be related to increased risk of neonatal hypoglycemia in infants.

Keywords: Antidepressive agents, hypoglycemia, pregnancy, therapeutics

Introduction

Hypoglycemia, a prime metabolic issue in newborns, is defined as a blood glucose level less than 47 mg/dL. It can be observed in up to 10% of healthy term newborns. Although neonatal hypoglycemia is mostly transient and asymptomatic and represents an adaptation to postnatal life, it may progress to coma and death if it becomes severe or prolonged.[1,2] Studies have demonstrated that neonatal hypoglycemia can lead to neurodevelopmental impairment and motor developmental delay at childhood.[3,4] Maternal, fetal and neonatal factors can contribute to neonatal hypoglycemia. Maternal diabetes mellitus, prematurity, intrauterine growth issues, perinatal hypoxia, congenital heart disease and maternal medications are some of the risk factors for neonatal hypoglycemia.[1,5]

Molenaar et al[6] have showed that the use of antidepressants during pregnancy is frequent and varies significantly between communities. Consequently, a growing body of researches has evaluated the safety of maternal use of antidepressants during pregnancy in the last 2 decades. Evidence suggesting an elevated risk of neonatal issues such as prematurity, low birth weight, persistent pulmonary hypertension, neonatal seizures, and poor neonatal adaptation syndrome[7-12] have led to increased concerns on treatment with antidepressants of pregnant patients. Hypoglycemia is considered to be among neonatal morbidities, neonatal complications, or symptoms of neonatal adaptation syndrome.[13-15] However, compared to other perinatal conditions, such as respiratory distress, the requirement of neonatal care, and Apgar score, the risk of neonatal hypoglycemia in newborns of a mother receiving antidepressant medication has been less frequently investigated. Therefore, the goal of the current review was to systematically assess whether there is any connection between intrauterine exposure to antidepressants and neonatal hypoglycemia in newborns based on data from recently published studies.

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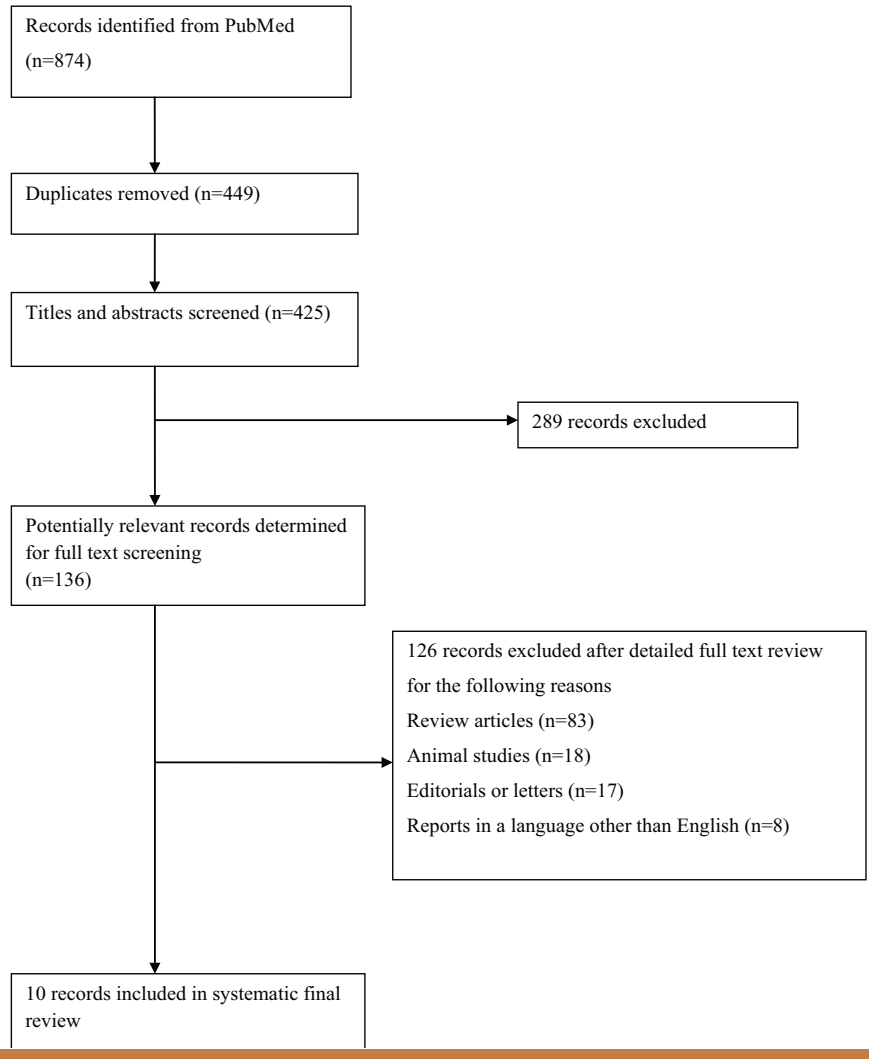

Figure 1. PRISMA flow diagram showing identification of studies included in this review.

Methods

This systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[16] guidelines and checklist. The review included English language papers published in electronic databases including PubMed, Web of Science, PsycInfo from January 2005 to July 2020. The following keywords for literature search were used: pregnancy, antidepressants, selective serotonin reuptake inhibitors (SSRIs), citalopram, fluoxetine, paroxetine, escitalopram, sertraline, fluvoxamine, selective serotonin-norepinephrine reuptake inhibitors (SNRIs), venlafaxine, tricyclic antidepressants (TCAs), neonatal outcomes, neonatal hypoglycemia, imipramine, clomipramine, amitriptyline, bupropion, trazodone, and mirtazapine. Additionally, the citations in the papers were examined to refer to other relevant studies.

The studies included in this article had the following criteria: (1) publication in a peer-reviewed journal, (2) clearly reported results including odds ratio (OR), hazard ratio, risk ratio (RR), or prevalence rate of neonatal hypoglycemia, and (3) inclusion of infants exposed and unexposed to antidepressants. This review excluded comments on published studies, editorials, letters to the editor, reviews, meta-analyses, animal studies, and case reports. After screening the literature with the search words indicated above, non-duplicated titles were identified. Abstracts of these titles were examined for the exclusion criteria and relevance to the topic of this review. The relevant full texts were provided and reviewed to determine whether they met their criteria for inclusion. Figure 1 presents the flow diagram of studies included in this review.

MAIN POINTS

- *Antidepressants are frequently used to treatment of depression and anxiety disorders in pregnant women.*
- *Antidepressants seem to be associated with higher risk of neonatal hypoglycemia.*
- *The results of the current studies should be evaluated with caution owing to the reported methodological limitations and small sample sizes in prospective comparative studies.*

Results

Table 1 shows the general characteristics and results of the current 10 studies. Four of the 10 studies were based on Swedish Medical

Table 1. Characteristics of Studies Included in this Review

Study	Design/Sample characteristics	Main results	Adjusted confounders	Major limitations
Lennestål and Källén, 2007[17]	Swedish Medical Birth Registry Database Sample Total population: 860 215 SNRI/NRI (mianserin, mirtazapine, reboxetine, or venlafaxine): 732 SSRI: 6481	Prevalence of hypoglycemia: SNRI/NRI: 4.64% SSRI: 3.65% Adjusted RR (95% CI) SNRI/NRI, early exposure: 1.42 (1.00-1.99) (S) SNRI/NRI, late exposure: 2.11 (1.01-3.89) (S) SSRI, early exposure: 1.17 (1.02-1.33) (S) SSRI, late exposure: 1.32 (1.05-1.68) (S)	Maternal age, parity, smoking, previous miscarriages, and body mass index	Did not exclude potential effects of other psychotropics used concurrently Unclear data on duration of actual use of antidepressants No data on psychiatric diagnoses No data on daily dose of antidepressants used by the patients Did not exclude potential effects of preterm birth
Källén, 2004[18]	Prospectively recorded data from Swedish Medical Birth Registry Database Sample Total population: 581 787 Antidepressant: 997 TCA:395 SSRI:558 Others:63	Prevalence of hypoglycemia Antidepressant: 4.91% TCA:5.83% SSRI: 4.30% Total population: 3.04% Adjusted OR (95% CI), overall Antidepressant: 1.62 (1.22-2.16) (S) TCA: 2.07 (1.36-3.13) (S) SSRI: 1.35 (0.90-2.03) (S) Adjusted OR (95% CI), late exposure Antidepressant: 1.49 (1.00-2.23) (S)	Maternal age, parity, and smoking	Did not exclude potential effects of other psychotropics used concurrently Unclear data on duration of actual use of antidepressants No data on psychiatric diagnoses No data on daily dose of antidepressants used by the patients Did not exclude potential effects of preterm birth and low birth weight
Jordan et al, 2008[19]	Retrospective cohort study Sample SSRI and venlafaxine: 49 Control: 59	Prevalence of hypoglycemia SSRI and venlafaxine: 0% Control: 5.08%	Both groups have similar demographic features and psychiatric diagnoses	Small sample size Unclear effects of severity of psychiatric diagnoses
Reis and Källén, 2010[13]	Data from Swedish Medical Birth Register Database Sample Antidepressant: 15 017	Adjusted OR (95% CI) Early exposure: 1.33 (1.22-1.45) (S) Late exposure: 1.43 (1.31-1.65) (S)	Maternal age, parity, smoking, and body mass index	Unclear data on duration of actual use of antidepressants No data on psychiatric diagnoses No data on daily dose of antidepressants used by the patients Did not exclude potential effects of preterm birth and low birth weight
Engelstad et al, 2014[20]	Retrospective study Sample Depression: 254 SSRI: 126 No SSRI: 128 Control: 222	Prevalence of hypoglycemia Depression: 2.75% SSRI: 3.96% No SSRI: 1.56% Control: 1.80% Statistical comparisons Depression vs control NS SSRI vs no SSRI: NS	-	Small sample size Unclear effects of preterm birth and low birth weight Unclear effexts of severity of depression Not clear whether data on diagnosis of depression were entered by psychiatrist

(*Continued*)

Table 1. Characteristics of Studies Included in this Review (*Continued*)

Study	Design/Sample characteristics	Main results	Adjusted confounders	Major limitations
Shah et al, 2020[21]	Prospective comparative cohort study Sample Antidepressant: 59 SSRI: 47 SNRI: 6 TCA: 1 Unexposed: 61	Prevalence of hypoglycemia Antidepressant: 6.78% Unexposed: 3.27% Adjusted RR (95% CI) 1.73 (0.37-8.92) (NS)	Maternal age, gestational age, smoking, and alcohol and substance use	Small sample size No data on psychiatric diagnoses
Nörby et al, 2016[15]	Swedish Medical Birth Register and Prescribed Drug Register Database Sample SSRI: 17736 No antidepressants: 718 533	Prevalence of hypoglycemia SSRI: 3.95% No antidepressant: 2.42% Adjusted OR (95% CI) SSRI: 1.3 (1.2-1.4) (S)	Maternal age, primiparity, smoking, other neurotropic drugs, body mass index, cesarean delivery, gestational age, and birth weight	Unclear data on duration of actual use of antidepressants No data on psychiatric diagnoses No data on a daily dose of antidepressants used by the patients
Costei et al, 2002[22]	Prospective, controlled cohort study Sample Paroxetine (late exposure): 55 Paroxetine (early exposure): 27 Control: 27	Prevalence of hypoglycemia Paroxetine Late exposure: 1.81 Early exposure: 0 Control: 0	-	Small sample size Unclear effects of preterm birth and birth weight No data on psychiatric diagnoses Unclear effects of daily dose
Forsberg et al, 2014[14]	Retrospective cohort study Sample Antidepressant: 220 SSRI: 208 Citalopram: 77 Sertraline: 76 Fluoxetine: 34 Escitalopram: 13 Paroxetine: 8 Venlafaxine: 11 Duloxetine: 1	Prevalence of hypoglycemia Antidepressant: 19.09% Citalopram: 10.39% Sertraline: 19.73% Fluoxetine: 35.29% Others: 21.21% Statistical significance Fluoxetine vs. citalopram (S) Citalopram vs sertraline (NS) Citalopram vs. other antidepressants (NS)	Maternal age, gestational age, gender of the baby	Small sample size No data on psychiatric disorders Lack of control group with unexposed infants
Levinson-Castiel et al, 2006[23]	Cohort study Sample SSRI: 60 Control: 60	Prevalence of hypoglycemia SSRI: 5.00% Control: 0	Other medications, alcohol or substance use, congenital anomalies	Small sample size No data on psychiatric disorders Unclear effects of daily dose

NS, non-significant; SRI, serotonin reuptake inhibitor; SSRI, selective erotonin reuptake inhibitor; SNRI, serotonin-noradrenaline reuptake inhibitor; NRI, noradrenaline reuptake inhibitor; TCA, tricyclic antidepressants; OR, odds ratio; RR, risk ratio.

Birth Databases.[13,15,17,18] The remaining 6 studies had a retrospective or prospective cohort design.[14,19-23] Shah et al[21] specifically examined the risk of neonatal hypoglycemia. The other authors reported the risk of several neonatal outcomes. Most studies evaluated the effects of SSRIs[15,17,18,20,23] or any antidepressant.[13,14,18,21] Single studies were available for patients who received TCAs,[18] SNRI,[17] SSRI and venlafaxine,[19] no SSRIs,[20] and individual SSRIs.[14,22]

It was reported that neonatal hypoglycemia was observed in 0-5.08% of non-exposed controls.[15,18-23] In contrast, this rate was 4.91-19.0% in infants exposed to any antidepressant,[14,18,21] 3.50-5.0% in infants exposed to SSRIs,[15,17-19,23] 4.65% in infants exposed to SNRIs,[17] and 5.85% in infants exposed to TCAs.[18] Forsberg et al[14] reported the highest prevalence of neonatal hypoglycemia ranging from 10.39% for citalopram to 35.29% for fluoxetine. The prevalence rate for any antidepressant in their study was about 3-fold higher than reported in other studies. Forsberg et al[14] also reported that while the prevalence rate of neonatal hypoglycemia in newborns exposed to fluoxetine was significantly higher compared to newborns exposed to citalopram, the prevalences with citalopram, sertraline, or other antidepressants were similar. In addition, Engelstad et al[20] reported that the difference in the prevalence rate of neonatal hypoglycemia in infants exposed to SSRIs and non-SSRIs did not reach statistical significance.

When compared to controls, the reported OR/RR was 1.33-1.73 for any antidepressant,[13,14,18,21] 1.30-1.35 for SSRI,[15,17,18] 1.42-2.11 for SNRI,[17] and 2.07 for TCAs.[18] The OR/RR reached statistical significance in all of the studies except Shah et al[21] The latter authors reported a RR of 1.73 for any antidepressant versus the control group

in a prospective comparative study, but statistical analysis suggested a non-significant difference, which could have resulted from a small sample size (n = 59 for the antidepressant group, n = 61 for the control group). Källén[18] noted that the elevated OR for neonatal hypoglycemia was stronger after maternal use of TCAs compared to SSRIs. In another study based on the Swedish Medical Birth Register Database, Reis and Källén[13] reported that the OR for hypoglycemia was significantly increased in infants of women using primarily TCAs but also SNRIs and SSRIs.

Three studies[13,17,22] analyzed the relationship between the risk of hypoglycemia in newborns and the timing of antidepressant exposure during pregnancy. Two Swedish Medical Birth Database studies[13,17] suggested that antidepressant exposure at both early and late gestational periods was significantly related to elevated neonatal hypoglycemia. Although a statistical comparison was not reported, the ORs were higher with late exposure compared to early exposure. In addition, a prospective controlled cohort study reported that the prevalence rates of neonatal hypoglycemia in infants exposed to paroxetine in early and late periods of pregnancy were 0 and 1.81%, respectively.

None of the available studies included any adjusted analyses for maternal psychiatric disorders such as depression and anxiety disorders. In a retrospective cohort study,[19] antidepressant and control groups had similar characteristics for maternal psychiatric diagnoses, and the reported prevalence rates for neonatal hypoglycemia were 0% in the SSRI/venlafaxine group and 5.08% in the control group. Additionally, Engelstad et al[20] reported that the difference in the prevalence rate of neonatal hypoglycemia in the depression (2.75%) and the control (1.80%) groups were not statistically significant.

Discussion

The prevalence rates of neonatal hypoglycemia in infants of antidepressant users in the studies included in this systematic review were mostly between 3 and 6%. The available data on the risk of neonatal hypoglycemia with maternal use of antidepressants is consistent, with an up to 73% elevated risk compared to the controls. When the reported prevalence rates in the unexposed infants are also considered, the absolute risk appears to be 1-3%.

The most commonly prescribed antidepressants in pregnant women are SSRIs.[6] Therefore, more data on antenatal exposure to SSRIs are available and consistently suggest an increased risk of neonatal hypoglycemia with these antidepressant groups. Similarly, limited available data demonstrate this significantly increased risk with TCAs and SNRIs. It is unclear which antidepressant group or individual antidepressant is associated with higher risk compared to others. According to a study by Källén,[18] the risk of neonatal hypoglycemia was slightly greater in infants of TCA users compared to SSRI users. Engelstad et al[20] reported that infants exposed to SSRIs and other antidepressants had similar risk profiles. Although fluoxetine specifically appeared to have the highest risk among SSRIs for neonatal hypoglycemia,[21] this data derived from a single study and should be confirmed with further studies.

Two important factors evaluating risks on neonatal outcomes are the role of timing of antidepressant exposure and underlying maternal psychopathology. The Swedish Medical Birth Register Database studies[13,17] suggested that exposure during both early pregnancy (representing the first and second trimester) and late pregnancy (representing the third trimester) were risky for neonatal hypoglycemia. Further studies should compare differences in the risk profiles of these 2 periods. It has been indicated that maternal depression and anxiety disorders, which are the most common diagnoses in patients who are prescribed antidepressants, may negatively affect intrauterine growth and gestational age.[24-27] Both of these neonatal outcomes may lead to neonatal hypoglycemia due to the presence of inadequate glycogen stores and immaturity of glucose regulatory hormones.[5] Nonetheless, the current scientific evidence is insufficient to understand the possible role of such maternal mental issues in elevated risk of hypoglycemia in newborns exposed to antidepressants in utero.

As shown in Table 1, the current studies have several major methodological limitations. The available data were derived from either electronic birth registry databases or retrospective or prospective studies with small sample sizes. Indeed, prospective observational comparative studies with large sample sizes would provide stronger data; however, the execution of such a study design in pregnant patients is challenging. Although birth register database studies present enough data for powerful statistical analyses, they have considerable limitations such as lack of information on the duration of actual use of antidepressants, the daily dose of antidepressants prescribed, and clinical indication for the use of antidepressants (psychiatric and non-psychiatric). In addition, 4 birth registry database studies included in this review used data from only one country; therefore, the results may be specific to the population of that country. Most studies did not examine possible effects of confounders such as concurrent use of psychotropic medications other than antidepressants, preterm birth, and birth weight. Many patients with severe depression and anxiety disorders require combinations of psychotropic drugs. In addition, the use of antidepressants in the gestational period may negatively affect gestational age and birth weight in newborns.[7,8] Lack of data on the possible effects of maternal psychiatric conditions and their severity is another important limitation. Finally, most studies did not examine the etiology underlying neonatal hypoglycemia, clinical features (clinically symptomatic or asymptomatic), and severity or prognosis in infants with hypoglycemia. It is expected that similar to other poor neonatal adaptation signs, neonatal hypoglycemia due to antidepressant exposure in utero may be generally mild and transient; however, this topic should be investigated by future studies.

In conclusion, the current systematic review suggests that pregnant women who receive antidepressant treatment have a greater likelihood of their infants developing neonatal hypoglycemia compared to pregnant women who do not use these medications. However, the study results should be evaluated with caution owing to the reported methodological limitations and small sample sizes in prospective comparative studies. Future studies should be designed by considering the limitations noted in this review. Large-scale multicenter prospective observational studies including comparative groups with similar characteristics for gestational age, birth weight, concurrently used medications, and maternal psychiatric diagnoses are required to reach definitive conclusions.

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