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Antidepressant use in pregnancy and the risk of neonatal outcomes: a scoping review

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Abstract

Background: Depression is a frequently encountered issue during pregnancy and postpartum. Both depression itself and the use of antidepressant medications can have implications for the infant's well-being. Studies have linked maternal depression to adverse outcomes like preterm birth, low birth weight, fetal growth restriction, and potential cognitive and emotional challenges for the child after birth. On the other hand, exposure to antidepressants during pregnancy has been associated with an increased risk of preterm birth, a decrease in birth weight, and congenital malformations.

Objectives: In light of these considerations, a scoping review was conducted to examine recent research findings concerning antidepressant use during pregnancy.

Methods: This study was a scoping review. Pubmed and Scopus databases were used to search for all relevant studies published from 2019 until 2023. Studies were excluded if they were case reports, narrative reviews, systematic reviews, or meta-analyses. Finally, all eligible articles were assessed for their outcomes.

Results: The use of SSRIs and duloxetine antidepressants in perinatal women was linked to preterm birth and smaller gestational sizes compared to controls, according to three cohort studies. Congenital malformation was also associated with duloxetine, mirtazapine, and atomoxetine use during pregnancy (3 cohort studies).

Conclusions: Recognizing the potential risks to the infant and the risk of leaving maternal depression untreated is crucial when making the decision to use antidepressants during pregnancy. This underscores the importance of a thoughtful and informed approach to managing depression in pregnant women.

Keywords: Antidepressant, drug safety, perinatal depression, pregnancy

1. Introduction

Antenatal depression is classified as a Major Depressive episode in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), which is largely impacted by a combination of environmental and genetic variables (Vahia, 2013). The period of childbearing for women represents the highest vulnerability to developing depression, with antenatal depression being a significantly understudied and undertreated condition (Vigod *et al.*, 2016). The illness is thought to be exacerbated by the fluctuating amounts of peptide and steroid hormones that occur during pregnancy (Goodman, 2007). The prevalence of antenatal depression varies between 7 and 20% in each trimester of pregnancy (Underwood *et al*., 2016; Woolhouse *et al*., 2014) and longitudinal studies indicate that symptoms of antenatal depression tend to persist or recur in subsequent pregnancies (Kingston *et al*., 2018).

Neglected mental health conditions during and following pregnancy can have negative consequences for both the mother and the infant. In the situation of prenatal depression, the probability of having concerns such as low birth weight, early birth, fetal growth restriction, and pregnancy complications is increased (Accortt *et al*., 2015; Byrn & Penckofer, 2013; Hoirisch-Clapauch *et al.*, 2015). Antidepressants have been shown to pass the placenta, be present in amniotic fluid, and enter breast milk in low quantities. Prenatal exposure from depression medication in pregnancy must thus address the teratogenic effects on the baby's growth and development, birth abnormalities, pregnancy problems, perinatal morbidity and mortality, and long-term sequelae. Medication exposure during nursing was shown to be lower than SSRI transplacental exposure during pregnancy. SSRI exposure may result in neonatal problems that mirror withdrawal (Zeszutek, 2021). Nevertheless, a significant number of women do not receive adequate treatment, often because healthcare providers are cautious about prescribing medications to pregnant individuals. Since these studies were published, further research has been undertaken on antidepressant exposure during pregnancy. Thus, the purpose of this study was to perform a scoping review that included the most recent studies on prenatal depression and the risk of neonatal outcomes.

2. Methods

This research constitutes a literature review employing a scoping review design. The process of searching for relevant literature involved utilizing electronic databases, specifically Pubmed and Scopus. The searches conducted on these databases incorporated Medical Subject Headings (MeSH) search terms, which encompassed "Antidepressant," "Antidepressive agent," "Pregnancy," and "Safety." To streamline the article selection process, a Boolean Logic approach was employed within PubMed, resulting in the following search query: ((("Antidepressant"[Mesh]) OR "Antidepressive agent"[Mesh]) AND "Pregnancy"[Mesh]) AND "Safety"))).

Articles meeting specific criteria were considered for inclusion. These criteria included the following: the article originated from either the Pubmed or Scopus electronic database within five years of publication, available in full-text format and accessible, the subject of the article pertains to a pregnant woman experiencing depression, and the article explores the use

of antidepressants during pregnancy. Exclusion criteria include articles in the form of case reports, narrative reviews, systematic reviews, or meta-analyses.

3. Results and discussion

The literature search conducted in both Pubmed and Scopus databases yielded a total of 22 articles that merited further examination. Out of these, 6 articles were ultimately chosen as they were pertinent to the discussion regarding the safety of employing antidepressants to manage depression in pregnant women. However, 16 other articles were excluded from consideration due to their nature as case reports, in vivo studies, incomplete articles, or the fact that they did not specifically address the use of antidepressants for depression. A visual representation of the literature search process can be found in Figure 1, while the detailed results of the article search are presented in Table 1.

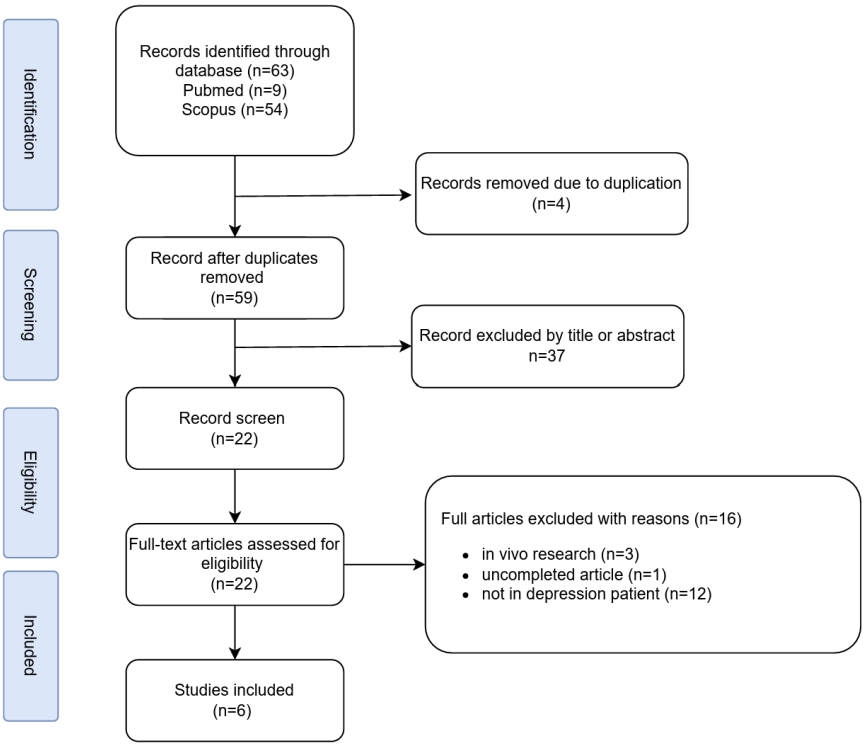

Figure 1. Flow chart for study selection

Table 1. Finding of the studies that fulfilled the inclusion criteria

Article	First author, year	Study design	Aims of study	Outcomes
1	Sujan *et al.* (2021)	Cohort study, (n=668.914)	To examine the impact of concurrent prescriptions for opioid analgesics and selective serotonin reuptake inhibitors (SSRIs) during pregnancy on two specific birth outcomes.	▪ The risk of preterm birth was higher among women who had a prescription for opioid analgesics only (5.9%; risk ratio [RR] 1.27, 95% confidence interval [CI] 1.22, 1.33), selective serotonin reuptake inhibitors (SSRIs) only (6.2%; RR 1.34, 95% CI 1.27, 1.42), both medications (7.8%; RR 1.70, 95% CI 1.47, 1.96), compared to women who were not exposed to these medications (4.6%). ▪ In the case of small for gestational age, the risk remained approximately 2% across all groups, and there was no significant interaction observed between the medications.
2	Ankarfeldt *et al.* (2021)	Cohort study, (n=2.132.163)	To explore the potential link between exposure to duloxetine during pregnancy and the likelihood of the offspring being born either small for gestational age or prematurely.	▪ In this study, a total of 2,083,467 pregnancies were analyzed. Among them, 1589 pregnancies had exposure to duloxetine during early pregnancy, and 450 pregnancies had exposure to duloxetine during late pregnancy. ▪ When considering the risk of small for gestational age, there was no significant increase in risk associated with duloxetine exposure when compared to various comparison groups, with odds ratios of 0.64 (95% CI 0.44–0.95) and 1.48 (95% CI 0.85–2.57). ▪ However, concerning preterm birth, duloxetine-exposed pregnancies exhibited an elevated risk when compared to pregnancies without duloxetine exposure, those exposed to selective serotonin reuptake inhibitors, and those who discontinued duloxetine in both early and late exposure groups. The odds ratios ranged from 1.17 to 2.04, with some not reaching statistical significance.

Table 1. Finding of the studies that fulfilled the inclusion criteria

Article	First author, year	Study design	Aims of study	Outcomes
				▪ Notably, there was no apparent association observed when comparing duloxetine-exposed pregnancies with venlafaxine-exposed pregnancies, with odds ratios of 0.91 (95% CI 0.73–1.14) for early exposure and 1.26 (95% CI 0.86–1.86) for late exposure. It's worth noting that the majority of preterm births (79.2%) occurred between weeks 33 and 36 of gestation.
3	Heinonen *et al*. (2021)	A double-blind randomized controlled (n=16)	To investigate the variation in plasma concentrations of sertraline in pregnant women and its transfer to their infants.	▪ The analysis included nine mothers and seven infants. The median dose-adjusted sertraline concentration during the second trimester was 0.15 (ng/mL) / (mg/day), while during the third trimester and at delivery, it was 0.19. One month postpartum, it reached 0.25, indicating a 67% relative difference between the second trimester and the postpartum period. Notably, there was a 10-fold interindividual variation among the participants. The infants' median concentrations were 33% and 25% of their mothers' levels, as measured in cord blood and infant plasma, respectively. Importantly, only mild and transient adverse effects were observed in the infants.
4	Ankarfeldt *et al.* (2023)	Cohort study, (n= 2.132.163)	To assess the relationship between exposure to duloxetine during pregnancy and the likelihood of major and minor congenital malformations as well as the risk of stillbirths.	▪ In both adjusted and propensity score-matched analyses, there was no observed increase in the risk of major malformations, minor malformations, or stillbirths across the comparison groups. Specifically, in the propensity score-matched analysis comparing duloxetine-exposed pregnancies with duloxetine-nonexposed pregnancies, the odds ratios (OR) were as follows: OR 0.98 (95% confidence interval [CI] 0.74 to 1.30, p = 0.909) for major

Table 1. Finding of the studies that fulfilled the inclusion criteria

Article	First author, year	Study design	Aims of study	Outcomes
				malformations; OR 1.09 (95% CI 0.82 to 1.45, p = 0.570) for minor malformations; and OR 1.18 (95% CI 0.43 to 3.19, p = 0.749) for stillbirths. These findings suggest that exposure to duloxetine during pregnancy did not appear to increase the risk of major or minor congenital malformations or the risk of stillbirths when compared to pregnancies without duloxetine exposure.
5	Bröms *et al*. (2023)	Cohort study, (n=990)	To determine the prevalence of major congenital malformations in general, with a particular focus on cardiac malformations and limb malformations, following exposure to atomoxetine during the first trimester of pregnancy.	▪ The pooled crude Prevalence Ratio (PR) for any major congenital malformation was 1.18 (95% CI, 0.88–1.60), and the adjusted PR was 0.99 (95% CI, 0.74–1.34). For cardiac malformations, the adjusted PR was 1.34 (95% CI, 0.86–2.09). Regarding limb malformations, the adjusted PR was 0.90 (95% CI, 0.38–2.16). ▪ In summary, there was no observed increase in the prevalence of major congenital malformations overall, and although there was some uncertainty due to sample size, there were no statistically significant elevated risk estimates for cardiac malformations or limb malformations following atomoxetine exposure in early pregnancy.
6	Ostenfeld *et al.* (2022)	**Cohort study, (n=1.650.649)**	To explore the potential connection between mirtazapine exposure during pregnancy and the likelihood of experiencing specific adverse pregnancy outcomes.	▪ Among pregnancies exposed to mirtazapine, 3.5% of children were diagnosed with major congenital malformations, while 4.3% of unexposed pregnancies had such malformations. The odds ratio (OR) was 0.81 (95% CI 0.55–1.20), indicating no significant difference in risk. ▪ Spontaneous abortion occurred in 12.5% of pregnancies exposed to mirtazapine and 12.3% of

Table 1. Finding of the studies that fulfilled the inclusion criteria

Article	First author, year	Study design	Aims of study	Outcomes
				unexposed pregnancies. The hazard ratio (HR) was 1.04 (95% CI 0.91–1.20), suggesting no substantial difference in the risk of spontaneous abortion. ▪ The analysis of stillbirth did not reveal an increased risk, with 0.3% of stillbirths among the exposed pregnancies and 0.4% among the unexposed pregnancies. The hazard ratio (HR) was 0.88 (95% CI 0.34–2.29), indicating no significant difference in stillbirth risk. ▪ Likewise, there was no observed increase in the risk of neonatal death, with 0.3% of cases among the exposed pregnancies and 0.6% among the unexposed pregnancies. The hazard ratio (HR) was 0.60 (95% CI 0.18–2.02), suggesting no significant difference in neonatal death risk. ▪ In summary, the study did not find a significant association between mirtazapine exposure during pregnancy and an elevated risk of major congenital malformations, spontaneous abortion, stillbirth, or neonatal death.

This scoping review has compiled and summarized the existing literature on the use of antidepressants during pregnancy, offering researchers and clinicians an overview of the current state of knowledge in this relatively emerging area of adherence research. Through this review, several clinical and practical shortcomings have been recognized, along with gaps in the existing research that warrant further investigation.

3.1 Perinatal depression

Perinatal depression can manifest during pregnancy (prenatally), in the year following childbirth (postpartum), or even in both periods. While it's common for new mothers to experience moments of weepiness and emotional fluctuations, often referred to as the "baby blues," which can affect up to 80% of them within a few days after giving birth, these symptoms typically resolve on their own and do not persist beyond about 10 days (Van Niel & Payne, 2020). Perinatal depression, on the other hand, is distinguished by its long duration (more than 14 days) and considerable influence on a woman's quality of life. Several factors increase the risk of experiencing peripartum depression, with the most influential risk factor for depression during pregnancy being a history of major depressive disorder (Räisänen *et al*., 2014). Women who choose to discontinue their antidepressant medications during pregnancy face an increased risk of experiencing a relapse of depression. Depression during pregnancy has been linked to various complications, affecting both the prenatal and postpartum periods. Depression during pregnancy has been correlated with adverse outcomes such as preterm birth (Grigoriadis *et al*., 2013; Szegda *et al*., 2014), low birth weight, and fetal growth restriction (Ciesielski *et al*., 2015).

3.2 General approach to the pregnant patient

The US Prevention Task Force Services (USPTF) and the American College of Obstetricians and Gynecologists advise healthcare providers to conduct depression screening in pregnant and postpartum patients at least once. This helps in ensuring a correct diagnosis and facilitates access to appropriate treatment and follow-up care (Siu *et al*., 2016). For cases of mild to moderate depression, psychotherapy is recommended as the primary treatment. However, when dealing with moderate to severe depression or a previous history of depression that responded well to medication, antidepressant medication should be considered as the initial treatment option (Byatt *et al.*, 2013).

3.3 Antidepressants and pregnancy

3.3.1 Preterm birth and birth weight

Preterm birth, categorized as delivery before 37 weeks of gestation, has been linked to the use of antidepressants during the second and third trimesters of pregnancy (Huybrechts *et*

al., 2014). When examining the risk of preterm birth, an elevated risk was observed with early exposure to duloxetine in comparison to women who were not exposed to duloxetine. However, when compared to those exposed to SSRIs, venlafaxine, and women who discontinued duloxetine, there was no statistically significant increase in risk associated with duloxetine use. Importantly, it is unlikely that exposure to duloxetine during pregnancy increases the risk of having a baby born small for gestational age (Ankarfeldt *et al*., 2023). More evidence from a systematic review and meta-analysis found is consistent with an increased risk of preterm birth in women taking antidepressants during the 2nd and 3rd trimesters (Huybrechts *et al*., 2014). Another study showed that women who used antidepressants during pregnancy had a 20% (95% CI: 10–40%) increased prevalence of both PTB and LBW compared to those who never used antidepressants (Cantarutti *et al.*, 2016).

In preliminary, unadjusted assessments, women who were not exposed to either SSRIs or opioids had a preterm labor rate of 4.6%. In comparison, women prescribed both SSRIs and opioids had the highest risk of preterm labor at 9.4%, followed by women solely prescribed opioids at 6.3%, and then women solely prescribed SSRIs at 6.5%. Additionally, the findings implied that the prevalence of small-for-gestational-age infants did not seem to be influenced by exposure to either medication alone or by combined exposure to both medications (Sujan *et al*., 2021).

3.3.2 Teratogenesis

Our findings indicate that the use of antidepressants during pregnancy can carry potential risks for infants. However, Regarding duloxetine, both adjusted and propensity score-matched analyses did not reveal any noticeable increase in the risk of major malformations, minor malformations, or stillbirths when comparing different groups (Ankarfeldt *et al*., 2021). As for mirtazapine exposure during pregnancy, no associations were found with major congenital malformations, spontaneous abortion, stillbirth, or neonatal death (Ostenfeld *et al.*, 2022). It is important to note that in some other studies investigating mirtazapine exposure during pregnancy, different outcomes have been explored, and some have reported an elevated risk of poor neonatal adaptation syndrome (PNAS) resulting from withdrawal after late-pregnancy mirtazapine exposure (Smit *et al*., 2016; Winterfeld *et al*., 2015). However, it's important to recognize that PNAS is a rare condition, and the study in question may not have had the statistical power to thoroughly investigate this particular outcome. In summary, while

antidepressant use during pregnancy warrants careful consideration due to potential risks, the specific risk profile can vary depending on the medication and the outcomes under study. Healthcare providers should weigh the potential benefits and risks when making clinical decisions regarding antidepressant use in pregnant patients.

A multinational study, encompassing more than 4 million births across Nordic countries and the United States, did not find a significant connection between maternal use of atomoxetine and major congenital malformations overall. Although there was a slightly elevated relative risk estimate for cardiac malformations, it's important to note that this association was not estimated with precision (Bröms *et al*., 2023). Indeed, Bérard *et al*. (2017) found that In a group of pregnant women with depression, antidepressants with effects on serotonin reuptake increased the incidence of various organ-specific abnormalities. Numerous thorough evaluations have found no identifiable pattern of significant abnormalities in women exposed to SSRIs during pregnancy, and SSRIs are not commonly categorized as teratogens (Furu *et al.*, 2015). However, it's important to approach these findings with caution, as these studies did not account for various factors such as antidepressant dosage, the severity of depression, duration of exposure, serum concentration levels of exposure, and the educational background of the mothers. These factors may all potentially influence the outcomes and need to be considered when interpreting the results.

The study involved a cohort of 16 pregnant women who were taking sertraline. The findings revealed that the median concentration of sertraline in the mothers' plasma at delivery (n=8) was 14.38 ng/mL, with a range of 3.64-24.17 ng/mL. In infants, the median concentration was 4.28 ng/mL in cord blood (n=5) and 4.59 ng/mL in infant plasma at 48 hours of age (n=5), with respective ranges of 1.22-6.12 ng/mL and 1.25-7.04 ng/mL. These results confirm that the concentration of sertraline is generally lower in infants compared to their mothers. The penetration ratio into cord blood (CB) and newborn plasma was used to calculate this (Heinonen *et al*., 2021). However, further information from long-term follow-up studies is required to offer a more thorough knowledge of the hazards and safety associated with the use of antidepressants during pregnancy.

This review comes with certain limitations that warrant acknowledgment. While a substantial amount of data was collected, it is important to note that no quantitative synthesis of this data was conducted in the course of this review. This outcome aligns with the design of

a scoping study, which doesn't aim to address this specific aspect. Scoping studies are intended to offer a narrative and descriptive overview of the existing literature related to a topic, covering a broader spectrum of study designs when compared to systematic reviews, which typically focus on a narrowly defined research question.

4. Conclusion

Neglected maternal depression during pregnancy can lead to unfavorable consequences for both the mother and the baby. While most antidepressant medications are not typically categorized as major teratogens, it is crucial to remain informed about and educate patients on the considerations associated with using these medications during pregnancy. A comprehensive psychiatric history should be collected, and a personalized discussion should take place to evaluate the pros and cons of prenatal medication exposure versus the risks posed to both the mother and the child by untreated maternal depression. The goal should be to use the lowest effective dose necessary to achieve a stable mood, with the aim of avoiding unnecessary exposure to both the medication and the effects of maternal illness.

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