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SAFETY AND EFFECTIVENESS OF SSRIS AND SNRIS TREATMENT FOR PERINATAL DEPRESSION: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction and Purpose: Perinatal depression is a common and serious condition affecting maternal and child health. Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), are widely used despite ongoing safety concerns. This review aims to evaluate current evidence on the safety and effectiveness of antidepressant treatment during pregnancy and the postpartum period to support individualized clinical decision-making in the management of perinatal depression.
Methods: A narrative systematic review of population-based cohort studies, systematic reviews, and meta-analyses published between 2014 and 2025 was conducted using PubMed. Results: The evidence indicates that SSRIs and SNRIs exposure during pregnancy is associated with small increases in the risk of preterm birth, neonatal adaptation syndrome, postpartum hemorrhage, and rare outcomes such as persistent pulmonary hypertension of the newborn, particularly with late-pregnancy exposure. Absolute risks remain low, and associations with neurodevelopmental disorders largely attenuate after adjustment for familial and maternal psychiatric factors. Postpartum antidepressant treatment is consistently associated with sustained improvements in maternal mental health and functional outcomes.
Conclusions: Current evidence supports individualized risk–benefit assessment when considering antidepressant use during the perinatal period. Maintaining maternal mental health is essential, and treatment decisions should consider illness severity, timing of exposure, and patient preferences.

KEYWORDS

Perinatal Depression, Safety, Selective Serotonin Reuptake Inhibitors, Serotonin–Norepinephrine Reuptake Inhibitors, Pregnancy, Postpartum

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Introduction

Perinatal depression, which includes depressive disorders occurring during pregnancy (antepartum) as well as after childbirth (postpartum), represents a major public health concern due to its impact on maternal functioning, pregnancy outcomes, and child development. Available data indicate that perinatal depression affects approximately 26.3% of the female population worldwide. The burden is disproportionately greater in certain high-risk populations, including women experiencing substance use disorders during pregnancy or those delivering infants with low birth weight.[1]

The COVID-19 pandemic has been associated with a notable increase in the risk of depressive symptoms and a rising demand for effective treatments, particularly among women. In 2020, women had 1.5 times higher odds of experiencing frequent depressive symptoms compared with men, a disparity that persisted in 2022 with an odds ratio of 1.4.[2] Selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) are the most commonly prescribed pharmacological treatments during pregnancy when the expected clinical benefits outweigh potential risks. Although these agents primarily act by modulating neurotransmitter levels, growing evidence suggests they may influence fetal development. Maternal exposure to SSRIs and SNRIs has been associated in some studies with an increased risk of congenital anomalies, particularly cardiovascular, renal, and gastrointestinal defects. In addition, prenatal exposure to these medications has been linked to adverse perinatal outcomes, including preterm birth, low birth weight, and neonatal adaptation syndrome (NADA).[3]

Despite their widespread use, data evaluating the effectiveness of SSRIs and SNRIs in reducing depressive symptoms specifically within the perinatal population remain limited. In particular, there is a lack of robust controlled comparisons with non-pharmacological interventions or placebo.[4]

Given the clinical uncertainty and evolving evidence base, this review aims to examine the safety and efficacy of treatments for perinatal depression. Given the rising global prevalence of perinatal depression and the increasing use of SSRIs and SNRIs, the aim of this article is to review and summarize current research to improve clinical decision-making.

Methodology

A comprehensive literature search was conducted using the PubMed database to identify peer-reviewed systematic reviews and cohort studies published between January 2014 and October 2025 that examined the safety and effectiveness of selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors for the treatment of depression during pregnancy and the postpartum period. The search strategy included combinations of the following terms: "SSRIs," "SNRIs," "pregnancy," "postpartum," "perinatal," "depression," "safety," and "efficacy." Reference lists of relevant articles were also screened to identify additional eligible studies. Only articles published in English were included. Studies focusing on non-pharmacological interventions and animal-only studies were excluded. Publications meeting the criteria were analyzed, with particular emphasis on the effects of antidepressants on the mother, fetus, newborn and its long-term effects.

Results and Discussion

Our search identified multiple systematic reviews and cohort analyses examining SSRI and SNRI use during pregnancy and outcomes related to postpartum depression. A population-based cohort study using Swedish national registers included 27,773 women diagnosed with depression or anxiety disorders without comorbid severe psychiatric disorders. Among these women, 47.5% discontinued SSRI or SNRI treatment during pregnancy. Comparisons between women who continued antidepressant treatment and those who discontinued treatment showed no increased risk of adverse postpartum psychiatric outcomes, including psychiatric hospitalizations, outpatient visits, suicidal behavior, or sickness absence, assessed both within 90 days and up to 1.5 years after delivery. Adjusted hazard ratios for psychiatric hospitalizations were not statistically significant, while the risk of outpatient visits was lower among women who discontinued treatment. Although women who continued antidepressant therapy had higher overall rates of sick leave, there was no difference between groups in the proportion of women requiring sick leave for psychiatric reasons. [5]

The findings indicate that among women with mild to moderate depression or anxiety and without severe psychiatric illness, discontinuation of SSRI or SNRI treatment during pregnancy is not associated with an increased risk of serious postpartum psychiatric outcomes. This observation aligns with the study's objectives and supports existing evidence suggesting that a substantial proportion of women discontinue antidepressant therapy during pregnancy without experiencing a measurable increase in adverse mental health outcomes after delivery when appropriate confounders are taken into account. These results underscore the importance of individualized clinical assessment and shared decision-making when considering antidepressant continuation or discontinuation during pregnancy. [5]

At the population level, first-trimester SSRI exposure was associated with higher risks of several outcomes compared with unexposed pregnancies, including preterm birth (7.0% vs. 4.8%; odds ratio [OR] = 1.5, 95% confidence interval [CI] 1.4–1.6), small for gestational age (2.5% vs. 2.2%; OR = 1.2, 95% CI 1.1–1.3), autism spectrum disorder (ASD) (5.3% vs. 2.1%; hazard ratio [HR] = 2.0, 95% CI 1.8–2.3), and attention-deficit/hyperactivity disorder (ADHD) (12.6% vs. 5.5%; HR = 2.2, 95% CI 2.0–2.4). When shared familial and genetic factors were accounted for using sibling-comparison analyses, the associations with small for gestational age, ASD, and ADHD were no longer observed. In these within-family models, exposed siblings had comparable risks of ASD (HR = 0.8, 95% CI 0.6–1.1) and ADHD (HR = 1.0, 95% CI 0.8–1.3) relative to their unexposed siblings. Preterm birth remained significantly associated with antidepressant exposure (OR = 1.3, 95% CI 1.2–1.5). This cohort comprised 1,580,629 singleton offspring born in Sweden between 1996 and 2012, with follow-up through 2013. Of these, 1.4% (n = 22,544) were exposed to antidepressants during the first trimester, and 82% of exposed pregnancies involved SSRIs. [6]

Further analyses incorporating timing-of-exposure comparisons and the use of paternal antidepressant exposure as a negative control yielded consistent results, strengthening causal inference. These methodological approaches suggest that previously reported associations between prenatal antidepressant exposure and neurodevelopmental outcomes are largely attributable to shared familial, genetic, and environmental factors rather than direct intrauterine drug effects. In this context, the observed small increase in the risk of preterm birth associated with first-trimester antidepressant exposure appears robust, whereas associations with autism

spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) were attenuated after rigorous control for confounding. [6]

The most commonly prescribed SSRIs during pregnancy were sertraline, citalopram, escitalopram, and fluoxetine, while venlafaxine was the most frequently used SNRI. Studies examining the effects of antidepressant use during pregnancy on fetal development and neonatal outcomes reported that in utero exposure to SSRIs, including fluoxetine, sertraline, citalopram, escitalopram, and paroxetine, was associated in some analyses with congenital malformations, persistent pulmonary hypertension of the newborn (PPHN), and poor neonatal adaptation syndrome. Congenital anomalies were observed in 7.2% of infants born to mothers who used antidepressants during pregnancy; among these women, 39% used paroxetine. Cardiac defects occurred in 1.8% of exposed infants. Congenital anomalies were reported in 8% of infants exposed to paroxetine compared with 6% of infants exposed to other SSRIs or other antidepressants, while congenital heart defects occurred in 2% and 1% of infants, respectively. [7]

Potential biological mechanisms underlying teratogenic effects of SSRIs include the role of serotonin in fetal development, particularly in myocardial cell differentiation and cardiac septation. Elevated serotonin levels resulting from reuptake inhibition may plausibly contribute to cardiovascular anomalies. However, accumulating evidence indicates that teratogenic potential may differ across individual SSRIs, despite shared mechanisms of action. Fluoxetine and paroxetine have been most frequently implicated in associations with congenital anomalies, although these findings remain inconsistent across studies and may be influenced by underlying maternal psychopathology rather than pharmacotherapy alone. Importantly, many reported associations are likely confounded by the severity and chronicity of maternal depressive illness. [7]

A large prospective cohort study from the Norwegian Study included 61,081 participating people. Among these, 8,671 women (14.2%; mean [SD] age, 29.93 [4.76] years) met criteria for postnatal depression, and 177 of these women (2.0%; mean [SD] age, 30.20 [5.01] years) received SSRI treatment in the postnatal period. Analyses were adjusted using a propensity score model incorporating maternal age, parity, prenatal depressive symptoms, depression history, and maternal education and income levels. More severe postnatal depressive symptoms were associated with adverse maternal and child outcomes. In analyses limited to dyads with postnatal depression, postnatal antidepressant treatment was associated with reduced negative associations between postnatal depressive symptoms and maternal relationship satisfaction at 6 months and at 1.5 and 3 years postpartum. Additionally, treatment attenuated the association between depressive symptoms and child attention-deficit/hyperactivity disorder symptoms at age 5 years. Postnatal treatment also moderated associations with maternal depression, partner relationship satisfaction, and child externalizing problems up to 5 years after childbirth.[8]

The results are demonstrating that postnatal SSRI treatment is associated with sustained improvements in maternal mental health and functional outcomes, with benefits observable up to five years postpartum. In line with prior cohort studies, SSRI use after childbirth was associated with reduced depressive symptom severity and improved relational and psychosocial functioning. These findings suggest that pharmacological treatment may mitigate the long-term consequences of postnatal depression for both mothers and their children. Moreover, antenatal depression, anxiety, and a lifetime history of depressive disorders emerged as the strongest predictors of postnatal depression, exceeding the influence of obstetric or socioeconomic factors.The association between lifetime depression and subsequent SSRI use suggests that treatment decisions are shaped not only by current symptom burden but also by prior illness trajectories. Consistent with previous research, lower parity and lower maternal education were associated with SSRI use, indicating the influence of social determinants, mental health literacy, and access to nonpharmacological interventions on treatment uptake. The observed links between postnatal depression, reduced relationship satisfaction, and persistent maternal impairment further emphasize the bidirectional relationship between depressive symptoms and partnership functioning. Additionally, reported adverse cognitive, emotional, and behavioral outcomes in children of mothers with untreated or inadequately treated depression reinforce the importance of early and effective treatment. [8]

Studies assessing congenital anomalies have primarily focused on structural defects, particularly cardiac malformations. Early observational analyses reported an increased frequency of cardiac defects among infants exposed to paroxetine. In contrast, more recent studies applying advanced methods to control for confounding, including propensity score matching and the use of comparator groups of women with untreated depression, did not demonstrate a statistically significant association between SSRI exposure as a class and major congenital malformations. Meta-analyses evaluating first-trimester SSRI exposure identified associations with congenital heart defects, although effect estimates were attenuated after adjustment for maternal psychiatric illness.[9]

Maternal outcomes were evaluated in several cohort studies. Postpartum hemorrhage (PPH) was reported more frequently among women using SSRIs during pregnancy. In a large retrospective cohort, SSRI exposure was associated with increased odds of PPH (odds ratio [OR] approximately 1.34; 95% CI 1.24–1.44). Dose–response analyses demonstrated higher risks with increasing SSRI doses, with high-dose exposure associated with a relative risk of 2.51 (95% CI 1.69–3.71). Pre-eclampsia was also reported more frequently among SSRI-exposed pregnancies, with risk estimates increasing across low-, moderate-, and high-dose exposure categories. For gestational diabetes mellitus, earlier studies using healthy control groups reported elevated risk, whereas analyses adjusting for maternal depression did not show an increased risk associated with SSRI exposure (RR 0.69; 95% CI 0.31–1.51). [9]

Reported fetal and neonatal outcomes included preterm birth, reduced birth weight, neonatal adaptation syndrome, and persistent pulmonary hypertension of the newborn (PPHN). Several studies published before 2019 observed higher rates of preterm birth, lower birth weight, and reduced Apgar scores among infants exposed to SSRIs. A systematic review of 16 studies reported an increased risk of preterm birth in SSRI-exposed pregnancies compared with untreated depression. Meta-analyses demonstrated modest effect sizes that were reduced after restriction to women with diagnosed depression. For PPHN, pooled analyses reported an absolute risk of approximately 2.9 cases per 1,000 live births associated with SSRI exposure and an elevated odds ratio of approximately 1.82 (95% CI 1.31–2.54), with lower relative risk estimates reported for sertraline compared with other SSRIs. [9]

Long-term neurodevelopmental outcomes were variably reported. Associations between prenatal SSRI exposure and autism spectrum disorder or attention-deficit/hyperactivity disorder were reduced or not observed after adjustment for maternal psychiatric illness. Some studies reported small associations with cognitive or academic outcomes, including increased odds of scoring in the lowest developmental percentiles (aOR approximately 1.43; 95% CI 1.08–1.90) and minor reductions in academic performance. Evidence directly assessing the effectiveness of SSRIs and SNRIs in reducing perinatal depressive symptoms remains limited, particularly during pregnancy, due to the scarcity of randomized controlled trials. Ethical constraints preclude experimental designs in pregnant populations, resulting in reliance on observational studies that are vulnerable to confounding by indication and residual bias. Nonetheless, postpartum data suggest that SSRIs reduce symptom severity and relapse risk, although high-quality comparative effectiveness data remain insufficient. [9]

Selective serotonin reuptake inhibitors are the most commonly prescribed antidepressants during pregnancy and represent first-line pharmacologic therapy for perinatal mood and anxiety disorders, which affect approximately 10–20% of women of reproductive age. Overall, current evidence suggests that SSRIs as a class do not substantially increase the risk of major congenital malformations or gestational diabetes when maternal illness is appropriately accounted for. Small increases in the risk of preterm birth, pre-eclampsia, postpartum hemorrhage, and neonatal adaptation syndrome have been observed, although absolute risks remain low. In the case of ASD and ADHD, the modest associations with cognitive or affective outcomes warrant further investigation. Despite the inherent limitations of observational studies, recent high-quality evidence suggests that the absolute risks of SSRI use during pregnancy are low compared with the well-documented harms of untreated perinatal depression. Therefore, individualized benefit-risk assessment, taking into account disease severity, maternal preferences, and the availability of nonpharmacological interventions, should be the priority in clinical decision-making. [9]

Across studies included in a systematic review and meta-analysis, a total of 156,978 women and their offspring were exposed to selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs) during pregnancy. Among exposed infants, 452 cases of persistent pulmonary hypertension of the newborn were identified, corresponding to an incidence of approximately 2.9 cases per 1,000 live births. Meta-analysis demonstrated a statistically significant association between maternal antidepressant exposure and PPHN risk, with a pooled odds ratio of approximately 1.82 (95% CI 1.31–2.54) for exposure during any trimester. When analyses were restricted to exposure after 20 weeks' gestation, the odds ratio increased to approximately 2.08 (95% CI 1.44–3.01). Network meta-analysis comparing individual SSRIs ranked sertraline as having the lowest relative risk for PPHN among the agents examined, although confidence intervals overlapped and heterogeneity across studies was substantial. The association between antidepressant exposure and increased PPHN risk remained statistically significant. [10]

The meta-analysis addressed a central clinical question: whether prenatal exposure to selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) is associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN) independently of maternal psychiatric illness. The findings demonstrated a statistically significant association, particularly for exposure

occurring after 20 weeks' gestation, supporting earlier observations that late-pregnancy serotonergic modulation may interfere with neonatal pulmonary vascular adaptation. By incorporating network meta-analysis, this study extended previous literature through direct and indirect comparisons across individual antidepressants, suggesting a potentially lower relative risk associated with sertraline compared with other SSRIs. Key strengths of this meta-analysis include the large pooled sample size, increased statistical power, and application of contemporary analytical techniques that allow more refined estimation of rare outcomes such as PPHN. These methodological advances improve upon earlier single-cohort studies that were often underpowered to detect uncommon neonatal conditions. However, the reliance on observational data remains a central limitation. Residual confounding by indication, heterogeneity in exposure definitions and outcome ascertainment, and limited evaluation of dose–response relationships constrain causal inference. [10]

In a register-based cohort study 18,487 pregnant women diagnosed with depression or anxiety were included to evaluate the association between first-trimester antidepressant exposure and major congenital malformations. Of these women, 3,640 (19.7%) were exposed to antidepressants during the first trimester, while 14,847 (80.3%) were unexposed. Exposure was categorized by antidepressant class: SSRI users (n = 2,327; 63.9%), SNRI users (n = 738; 20.3%), tricyclic antidepressant users (n = 382; 10.5%), and users of other antidepressants (n = 193; 5.3%). SSRIs included paroxetine (n = 1,132), sertraline (n = 365), citalopram (n = 584), fluoxetine (n = 191), and fluvoxamine (n = 55). The mean duration of antidepressant exposure during the first trimester was 47.0 days (SD 17.0), with SSRI users exposed for a mean of 51.0 days (SD 27.3). Baseline characteristics indicated that antidepressant users were slightly older, more likely to live alone, and more frequently welfare recipients than non-users. They also had higher prevalences of comorbid conditions, including diabetes, hypertension, and asthma, as well as greater healthcare utilization in the year preceding pregnancy. Mean birth weight was lower among newborns exposed to antidepressants compared with unexposed infants. [11]

In analyses restricted to women with depression or anxiety, first-trimester citalopram exposure was associated with an increased risk of overall major congenital malformations (aOR 1.36; 95% CI 1.08–1.73; 88 exposed cases). Organ-specific analyses identified associations between paroxetine exposure and cardiac defects (aOR 1.45; 95% CI 1.12–1.88), including ventricular and atrial septal defects (aOR 1.39; 95% CI 1.00 – 1.93). Citalopram exposure was associated with musculoskeletal defects (aOR 1.92; 95% CI 1.40 – 2.62) and craniosynostosis (aOR 3.95; 95% CI 2.08–7.52). Among users of tricyclic antidepressants, increased risks were observed for eye, ear, face, and neck defects (aOR 2.45; 95% CI 1.05–5.72) and digestive system defects (aOR 2.55; 95% CI 1.40–4.66). Venlafaxine exposure was associated with respiratory defects (aOR 2.17; 95% CI 1.07–4.38). These associations remained statistically significant after adjustment for sociodemographic characteristics and medical comorbidities within the depressed or anxious cohort. [11]

The study met its objectives, demonstrating that among women with depression or anxiety, exposure to specific antidepressants during the first trimester of pregnancy was associated with an increased risk of selected major congenital malformations compared with depressed women who did not use them. The observed associations are consistent with previous reports identifying drug-specific teratogenic signals, particularly for paroxetine. These findings reinforce the notion that antidepressants cannot be assessed solely as a homogeneous group and emphasize the importance of distinguishing between individual drugs when assessing fetal risk. Major strengths of this study include its large, population-based design, prospective data collection, and detailed assessment of medication prescription and treatment outcomes, which enhance internal validity. However, limitations include the possibility of residual confounding related to the severity and chronicity of maternal mental illness, as well as the possibility of chance findings resulting from multiple comparisons in organ analyses. From a clinical perspective, these results highlight the need for careful consideration of antidepressant medication selection early in pregnancy. [11]

A total of 143,281 pregnancies were analyzed to assess the association between antidepressant use and persistent pulmonary hypertension of the newborn (PPHN). Overall, PPHN was identified in 267 newborns (0.2%). Antidepressant exposure between gestational week 21 and delivery (second half of pregnancy) occurred in 2,184 pregnancies (1.5%). Among these, 1,537 exposures (70.4%) involved selective serotonin reuptake inhibitors (SSRIs), 419 (19.2%) involved serotonin–norepinephrine reuptake inhibitors (SNRIs), and 346 (15.8%) involved other antidepressants. Mothers exposed to antidepressants during pregnancy were older, more frequently recipients of social assistance, more likely to live alone, and had higher prevalences of comorbid conditions, including depression or anxiety, hypertension, and asthma, as well as greater healthcare utilization, compared with unexposed mothers. Mean gestational age was similar across exposure groups (approximately 38.0–38.8 weeks), whereas mean birth weight was lower among exposed infants. In

multivariable analyses adjusted for maternal depression or anxiety and other confounders, SSRI use during the second half of pregnancy was associated with an increased risk of PPHN compared with non-use of antidepressants (adjusted odds ratio [aOR] 4.29; 95% confidence interval [CI] 1.34–13.77). Antidepressant exposure during the first 20 weeks of pregnancy was not associated with PPHN. Independent maternal factors associated with increased PPHN risk included higher maternal age (aOR 1.04 per year; 95% CI 1.02–1.07) and maternal diabetes (aOR 2.41; 95% CI 1.27–4.55). Other sociodemographic variables, including urban residence, social assistance status, and living alone, as well as medical comorbidities such as hypertension and asthma, were not significantly associated with PPHN after adjustment. Sensitivity analyses using alternative exposure definitions, including exposure limited to the second half of pregnancy or exposure throughout pregnancy, produced consistent results, identifying the second half of pregnancy as the relevant exposure window for SSRI-associated PPHN risk. [12]

The primary objective to assess the temporal association between antidepressant exposure and PPHN was achieved using robust adjustment for maternal depression and anxiety, which allowed for limiting confounding by indication. Results demonstrated a significant association between SSRI exposure in the second half of pregnancy and an increased risk of PPHN, whereas no statistically significant association was observed for exposure in the first half of pregnancy. In contrast, SNRI use was not significantly associated with PPHN, although wide confidence intervals reflected limited power for this subgroup. These findings are consistent with previous registry-based studies that indicate an increased risk of PPHN with SSRI exposure in late pregnancy and are biologically plausible given the role of serotonin in pulmonary vascular tone and remodeling. An important finding of this study is the identification of a critical window of exposure, suggesting that the timing of antidepressant use is a key determinant of neonatal risk. The large sample size and comprehensive adjustment for confounders strengthen the confidence in the observed association, and the identification of maternal age and diabetes as independent risk factors for PPHN contributes to a more detailed understanding of neonatal susceptibility to PPHN. However, the rarity of PPHN limits statistical precision, particularly for non-SSRI antidepressants, and residual confounding cannot be completely ruled out. Exposure misclassification based on prescription data may also bias the estimates, although sensitivity analyses confirmed the robustness of the results. This study strengthens existing evidence linking SSRI exposure in late pregnancy with PPHN, while emphasizing the need for cautious clinical decision-making and further research to clarify the risks associated with SNRIs and other classes of antidepressants. [12]

This review summarized evidence from epidemiological and experimental studies examining the effects of antidepressant use during pregnancy and lactation. The prevalence of depression during pregnancy ranged from approximately 9% to 16%, with some reports up to 20%. Antidepressant use was reported in 2–3% of pregnant women, increasing to 5–7% by the time of delivery. Selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors were the most commonly used pharmacological treatments. Reported outcomes associated with treated depression during pregnancy included preterm birth, reduced neonatal birth weight, intrauterine growth restriction, neonatal adaptation syndrome, and persistent pulmonary hypertension of the newborn. Clinical signs observed in newborns exposed to SSRIs or SNRIs late in pregnancy included excessive crying, restlessness, tremor, feeding difficulties, reflux, sleep disturbances, respiratory distress, and irritability, with some infants requiring prolonged hospitalization, tube feeding, or respiratory support. [13]

The review highlights that many adverse outcomes—such as preterm birth, neonatal adaptation syndrome, intrauterine growth restriction, and PPHN—have been reported in association with antidepressant use, particularly in later stages of pregnancy. At the same time, similar adverse outcomes are consistently observed in the context of untreated depression, underscoring the significant impact of maternal illness.However, these findings also illustrate the complexity of translating experimental data into clinical risk, as animal models do not always demonstrate structural abnormalities at clinically relevant doses. A major strength of this review is the comprehensive synthesis of human and experimental data, offering a multifaceted perspective on antidepressant safety. Limitations include the lack of randomized controlled trials, heterogeneity across observational studies, and variability in exposure time, dose, and outcome definitions.All evidence emphasizes that treating depression during pregnancy requires a detailed, individualized benefit-risk assessment. Although exposure to antidepressants is associated with some risk to the newborn, untreated maternal depression has well-documented and potentially serious consequences for both mother and child. These findings underscore the need for long-term, well-controlled studies with detailed characterization of psychiatric symptom severity and medication exposure to better inform clinical practice. [13]

A retrospective study of medication use conducted in the Netherlands included 2,482 singleton pregnancies in which at least one antidepressant was prescribed in the six months preceding pregnancy. The overall prevalence of antidepressant exposure increased over time, from 3.1% of singleton pregnancies in 2001–2005 to 4.8% in 2016–2020. The most frequently prescribed antidepressants before and during pregnancy were paroxetine (573 exposures), citalopram (516), amitriptyline (326), sertraline (251), and venlafaxine (224). Women prescribed antidepressants were slightly older than the general pregnant population across all study periods (mean age approximately 30.1 vs. 29.4 years), with statistically significant differences in most periods. Between 2001 and 2020, continuation of antidepressant therapy from before to during pregnancy increased from 25.1% to 57.9%, while discontinuation decreased from 72.9% to 39.9%. Switching between antidepressants during pregnancy remained uncommon, increasing slightly from 2.0% to 2.3%. Continuation rates increased substantially for SSRIs and SNRIs, with SSRI continuation rising from 27% to 65% and SNRI continuation from 19% to 65%, whereas tricyclic antidepressants and other antidepressant classes maintained discontinuation rates exceeding 60% throughout the study period. Continuation of sertraline increased from 5% to 62%, and continuation of citalopram increased from 26% to 71% across successive study intervals. Fluoxetine, escitalopram, and fluvoxamine also showed increasing continuation trends, while tricyclic antidepressants such as amitriptyline exhibited consistently high discontinuation rates exceeding 70%. Among switchers, SSRIs accounted for the majority of switch-to medications, representing 85% of switches during pregnancy. For most women who continued antidepressant therapy, changes in defined daily doses (DDDs) before versus during pregnancy were minimal (<10%). Among sertraline users in the low-dose group, mean DDDs increased by 15.4% during pregnancy ($P = 0.025$). Fluoxetine users exhibited the largest mean DDD increase (+16.7%), although this change was not statistically significant due to small sample size. Overall, average daily antidepressant doses remained largely unchanged among women who continued treatment during pregnancy. [14]

This large retrospective analysis characterizes patterns of antidepressant use before and during pregnancy in a well-defined Dutch population, providing insight into temporal trends in clinical practice. The main finding—that continued antidepressant therapy during pregnancy, particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), increased significantly between 2001 and 2020—reflects the evolving clinical approaches to treating perinatal depression and anxiety. This trend is consistent with the increasing emphasis in clinical guidelines on maintaining effective antidepressant treatment during pregnancy to reduce the risk of relapse and related maternal and fetal complications. The nearly doubling of treatment continuation rates during the study period suggests increasing confidence among researchers and patients in the balance between maternal mental health benefits and potential fetal risk. Avoiding medication changes may reduce the risk of destabilizing and withdrawal symptoms, which are particularly concerning during pregnancy. Dose adjustment patterns provide additional context for clinical decision-making. The minimal changes in defined daily doses observed in the majority of women continuing treatment indicate that antidepressant treatment regimens were generally maintained without significant modifications. Isolated increases in sertraline doses among women on low doses appear to reflect individual clinical response rather than a systematic increase in exposure-related risk. These findings suggest that continued antidepressant use during pregnancy was viewed as clinically necessary and therapeutically stable, rather than as temporary or experimental.From a clinical perspective, the observed prescription patterns reinforce the view that pregnant women with depressive or anxiety disorders are increasingly treated with continued pharmacotherapy, particularly SSRIs and SNRIs. This approach is consistent with evidence indicating that abrupt discontinuation of antidepressants during pregnancy is associated with a high risk of relapse, which in itself carries well-documented negative consequences for both mother and child. The extended 20-year follow-up period allows for a thorough assessment of temporal trends, and comprehensive prescribing data and stratification by antidepressant class and individual medications provide detailed insight into actual prescribing behavior. The use of a population-representative database and clearly defined operational categories for continuation, discontinuation, and switching further enhanced internal validity.However, significant limitations must be considered. Prescription data do not confirm actual medication use, which can lead to misclassification of exposure. The lack of detailed clinical information on depression severity, symptom course, indications for dose adjustment, and obstetric or neonatal outcomes prevents direct assessment of the clinical consequences associated with the observed prescribing patterns. Furthermore, the reasons underlying treatment decisions—such as patient preferences, adverse events, or physician concerns—could not be assessed.Despite these limitations, this study fills a significant gap in our understanding of the actual use of antidepressants during pregnancy. The results indicate that most women

who initiate antidepressant therapy before pregnancy maintain a stable medication regimen throughout pregnancy, with limited dose adjustments or changes. These findings provide valuable context for interpreting trends in perinatal antidepressant exposure and inform ongoing discussions about optimal management of maternal mental health during pregnancy.[14]

Conclusions

Perinatal depression, encompassing depressive disorders occurring during pregnancy and the postpartum period, constitutes a major public health challenge due to its substantial impact on maternal functioning, obstetric outcomes, and child development.Current data indicate that many women worldwide are affected by this problem, with a disproportionate burden observed among high-risk groups, including women with substance use disorders during pregnancy and women delivering low-birth-weight infants.The COVID-19 pandemic has further exacerbated this burden, with women consistently experiencing a higher risk of depressive symptoms compared to men. In this context, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) remain the most commonly prescribed medications when the expected benefits outweigh the potential risks.

The evidence collected in this review suggests that prenatal exposure to SSRIs and SNRIs is associated with a small increase in the risk of several adverse perinatal outcomes, including preterm birth, low birth weight, neonatal adaptation syndrome, and rare neonatal complications. However, the absolute risk is low, and many of these associations appear to be strongly related to maternal mental illness rather than solely to drug exposure.

Despite widespread clinical use, high-quality evidence regarding the effectiveness of antidepressants during pregnancy remains limited, particularly due to the lack of randomized controlled trials. In light of these findings, individualized risk–benefit assessment remains essential. Treatment decisions should integrate illness severity, timing of exposure, maternal preferences, and access to non-pharmacological interventions to optimize outcomes for both mother and child.

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