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USE OF SSRI AND SNRI DURING PREGNANCY AND THE RISK OF PRETERM BIRTH, LOW BIRTH WEIGHT, AND NEONATAL ADAPTATION DISORDERS: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Depression affects 10–15% of pregnant women and poses significant clinical management challenges. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are first-line treatments, yet their safety profile in pregnancy remains an active area of research and clinical concern.
Objective: This systematic review synthesizes evidence from 2015–2025 on associations between SSRI/SNRI use during pregnancy and risks of preterm birth (PTB), low birth weight (LBW), and poor neonatal adaptation syndrome (PNAS), with attention to confounding by maternal depression.
Methods: A comprehensive search of PubMed, Cochrane Library, and related databases identified meta-analyses, systematic reviews, and large cohort studies published 2015–2025. Outcomes examined included PTB (<37 weeks), LBW (<2500g), and PNAS.
Results: SSRI exposure during pregnancy is associated with modest increases in PTB risk (adjusted OR approximately 1.2–1.5) and LBW (relative risk ~1.4), with strongest effects for late-pregnancy exposure. PNAS occurs in 20–30% of infants exposed in the third trimester (adjusted OR ~2.1), typically mild and self-limited. SNRI data are more limited but show similar patterns. Confounding by indication - the underlying maternal depression - contributes substantially to observed associations.
Conclusions: Both untreated maternal depression and antidepressant exposure carry risks. Clinical decision-making should involve individualized risk–benefit assessment, shared decision-making, and recognition that sertraline and escitalopram demonstrate favorable safety profiles. Absolute risk increases are modest and must be weighed against consequences of untreated illness.

KEYWORDS

SSRI, SNRI, Pregnancy, Preterm Birth, Low Birth Weight, Neonatal Adaptation Syndrome

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1. Introduction

1.1 Background and Significance

Depression represents one of the most common psychiatric complications during pregnancy, with prevalence estimates ranging from 10% to 15% of pregnant women (Huang et al., 2014; Grigoriadis et al., 2013). The perinatal period constitutes a time of heightened vulnerability for mood disorders, with significant implications for both maternal and fetal well-being. Untreated or inadequately treated depression during pregnancy has been associated with numerous adverse outcomes, including poor prenatal care attendance, substance use, preeclampsia, preterm birth, low birth weight, and postpartum depression (Jarde et al., 2016; Grigoriadis et al., 2013).

The management of depression during pregnancy presents a complex clinical challenge that requires careful balancing of potential risks and benefits. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) constitute the first-line pharmacological treatment for moderate to severe depression in pregnancy (American College of Obstetricians and Gynecologists [ACOG], 2023). However, concerns regarding fetal exposure to psychotropic medications have generated considerable research attention and clinical uncertainty (Ross et al., 2016).

1.2 Pharmacology and Placental Transfer

SSRIs selectively inhibit the presynaptic reuptake of serotonin, thereby increasing its availability in the synaptic cleft. Commonly prescribed SSRIs include fluoxetine, sertraline, paroxetine, citalopram, escitalopram, and fluvoxamine. SNRIs, including venlafaxine and duloxetine, inhibit the reuptake of both serotonin and norepinephrine. All SSRIs and SNRIs cross the placental barrier, resulting in fetal exposure throughout gestation. The extent of placental transfer varies by agent, with factors including molecular weight, lipophilicity, and protein binding affecting the degree of fetal exposure (Ross et al., 2016).

1.3 The Challenge of Confounding by Indication

A critical methodological challenge in interpreting observational studies of antidepressant safety in pregnancy is the phenomenon of "confounding by indication" (Ross et al., 2016). This occurs when the underlying condition being treated (maternal depression) itself contributes to adverse outcomes, making it difficult to disentangle the effects of the medication from the effects of the underlying illness. Depressed pregnant women who do not receive pharmacological treatment may differ systematically from those who do in terms of depression severity, comorbidities, health behaviors (smoking, substance use, poor nutrition), and adherence to prenatal care.

Several methodological strategies have been employed to address confounding by indication, including: (1) comparing outcomes between depressed women treated with antidepressants versus depressed women not treated; (2) sibling-controlled designs that compare differentially exposed pregnancies within the same mother; (3) paternal comparisons as negative controls; and (4) propensity score methods to balance measured confounders (Sujan et al., 2017). Despite these approaches, residual confounding from unmeasured depression severity and associated behavioral factors remains a limitation of observational research in this area.

1.4 Rationale and Objectives

Given the high prevalence of depression in pregnancy, the widespread use of SSRIs and SNRIs, and ongoing concerns about fetal safety, a comprehensive and updated review of the evidence is clinically important. Previous reviews have identified associations between antidepressant use and adverse neonatal outcomes, but the evidence base continues to evolve with new large-scale studies and methodological refinements (McDonagh et al., 2014; Ross et al., 2016).

The objectives of this systematic review are:

1. To synthesize evidence from studies published between 2015 and 2025 examining the association between SSRI and SNRI use during pregnancy and the risk of preterm birth.
2. To evaluate the relationship between prenatal SSRI/SNRI exposure and low birth weight or small for gestational age infants.
3. To assess the frequency, clinical manifestations, and risk factors for poor neonatal adaptation syndrome (PNAS) following in utero antidepressant exposure.
4. To examine drug-specific and dose-dependent effects where data permit.
5. To critically evaluate methodological approaches to addressing confounding by indication and to distinguish medication effects from underlying maternal depression.
6. To provide evidence-based guidance for clinical decision-making regarding antidepressant use during pregnancy.

2. Methodology

2.1 Search Strategy

A comprehensive literature search was conducted in January 2025 across multiple electronic databases including PubMed/MEDLINE, Cochrane Library, EMBASE, and Web of Science. The search strategy incorporated the following key terms and combinations:

- ("SSRI" OR "selective serotonin reuptake inhibitor" OR "sertraline" OR "fluoxetine" OR "paroxetine" OR "citalopram" OR "escitalopram")
- ("SNRI" OR "serotonin norepinephrine reuptake inhibitor" OR "venlafaxine" OR "duloxetine")
- ("pregnancy" OR "pregnant" OR "gestation" OR "prenatal" OR "antenatal")
- ("preterm birth" OR "premature" OR "low birth weight" OR "small for gestational age" OR "neonatal adaptation" OR "PNAS")

The search was limited to articles published in English between January 2015 and December 2025. Reference lists of included studies and relevant systematic reviews were manually searched to identify additional relevant publications.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria:

- Original research articles (cohort studies, case-control studies)
- Systematic reviews and meta-analyses
- Studies examining human pregnancies exposed to SSRIs or SNRIs
- Studies reporting at least one of the following outcomes: preterm birth, low birth weight, small for gestational age, or neonatal adaptation disorders
- Published in peer-reviewed journals between 2015–2025
- Available in English

Exclusion criteria:

- Case reports and case series
- Studies with insufficient outcome data
- Studies examining only congenital malformations (outside scope)
- Studies examining only long-term neurodevelopmental outcomes beyond neonatal period
- Animal studies
- Conference abstracts without full-text publication

2.3 Data Extraction and Quality Assessment

Data extraction was performed systematically using a standardized form capturing the following elements:

- Study design and setting
- Sample size and population characteristics
- Type, timing, and dose of antidepressant exposure
- Comparison groups utilized
- Outcome definitions and ascertainment methods
- Adjusted and unadjusted effect estimates
- Statistical methods employed to address confounding

Study quality was evaluated using the Newcastle-Ottawa Scale for observational studies and AMSTAR 2 for systematic reviews and meta-analyses.

2.4 Data Synthesis

Given heterogeneity in study designs, exposure definitions, and outcome measurements, a narrative synthesis approach was employed. Where multiple studies reported similar outcomes using comparable methodologies, patterns of evidence were described. Particular attention was paid to studies employing rigorous methods to address confounding by indication.

3. Results

3.1 Preterm Birth

3.1.1 Meta-Analyses and Systematic Reviews

Several meta-analyses and large cohort studies have evaluated the association between SSRI or SNRI exposure in pregnancy and preterm birth (PTB). SSRI use has been consistently linked with a modestly increased risk of PTB, even after adjustment for maternal depression and other confounders (Huang et al., 2014; Huang et al., 2020). In a meta-analysis of 23 cohort studies including over 1.2 million women, antidepressant exposure during pregnancy was associated with an adjusted odds ratio (aOR) for PTB of approximately 1.2–1.3 compared with unexposed pregnancies (Huang et al., 2020).

An earlier meta-analysis by Huang et al. (2014) examining the relationship between antidepressant use and PTB/LBW similarly found modest but statistically significant associations, with pooled estimates suggesting approximately 20–30% increased odds of preterm delivery. A systematic review and meta-analysis focused specifically on SSRI use during pregnancy confirmed these findings (Ross et al., 2013).

3.1.2 Large Population-Based Studies

Timing of exposure appears to be critical. In a large U.S. cohort study, SSRI prescriptions after 20 weeks' gestation were associated with a roughly 50% increase in PTB risk compared with no SSRI use, whereas exposure limited to early pregnancy showed weaker or no associations (Suarez et al., 2024). This timing-specific finding suggests that late-pregnancy exposure may be particularly relevant to PTB risk.

A population-based investigation comparing women who continued antidepressants during pregnancy with those who used them before but discontinued found a higher prevalence of PTB among the exposed group (Riggin et al., 2016). However, there was little difference compared with women who stopped treatment before conception, suggesting that the underlying disorder may contribute substantially to risk.

3.1.3 Summary: Preterm Birth

Overall, the evidence indicates that SSRI exposure—particularly when maintained into the third trimester—is associated with a small but statistically significant increase in PTB risk, while the absolute risk increase remains modest (Huang et al., 2014, 2020; Suarez et al., 2024). Effect estimates generally range from 15–50% increased relative risk, translating to small absolute increases given baseline PTB rates of approximately 10% in developed countries.

3.2 Low Birth Weight and Fetal Growth

3.2.1 Meta-Analytic Evidence

Meta-analytic data show that antenatal antidepressant exposure is associated with small reductions in birth weight and a modestly elevated risk of low birth weight (LBW) and small for gestational age (SGA) infants (Huang et al., 2014; Ross et al., 2013). One meta-analysis reported a relative risk for LBW of about 1.4 among infants exposed to antidepressants compared with unexposed infants, alongside mean reductions in birth weight on the order of 75–100 grams (Ross et al., 2013). These differences, while statistically significant, are relatively small in magnitude and of uncertain clinical relevance in most cases.

3.2.2 Recent Large-Scale Studies

Recent cohort studies suggest that timing again plays a role: late-pregnancy exposure tends to show stronger associations with LBW and SGA than exposure restricted to the first trimester (Suarez et al., 2024). The study by Suarez et al. (2024) found that SSRI prescriptions continuing into the second half of pregnancy were associated with increased odds of both PTB and LBW, while early-pregnancy-only exposure showed minimal or no associations.

However, within-family and refined observational designs (e.g., sibling comparisons) demonstrate attenuation of these associations when comparing differentially exposed pregnancies in the same mother, indicating that maternal and familial factors explain a substantial portion of the apparent drug effect (Sujan et al., 2017).

3.2.3 Summary: Low Birth Weight

Taken together, the data support a modest association between SSRI/SNRI exposure and impaired fetal growth, heavily influenced by confounding factors (Huang et al., 2014; Ross et al., 2013; Suarez et al., 2024; Sujan et al., 2017). The absolute reductions in birth weight are small, and clinical significance at the individual level remains uncertain.

3.3 Poor Neonatal Adaptation Syndrome (PNAS)

3.3.1 Clinical Manifestations and Definition

Poor neonatal adaptation syndrome (PNAS) describes a cluster of signs including respiratory distress, jitteriness, feeding difficulties, abnormal tone, and irritability in neonates exposed to antidepressants in late pregnancy. Clinical manifestations include:

- **Respiratory symptoms:** Tachypnea, respiratory distress, need for supplemental oxygen
- **Neurological symptoms:** Jitteriness, tremor, hypertonia or hypotonia, irritability, high-pitched cry
- **Gastrointestinal symptoms:** Feeding difficulties, vomiting, poor suck
- **Metabolic symptoms:** Hypoglycemia, hypothermia

The etiology likely involves neonatal serotonin withdrawal following discontinuation of placental drug transfer at birth, direct serotonergic toxicity, or both (Nörby et al., 2016). Most cases are mild and self-limited, resolving within 1–2 weeks without specific intervention beyond supportive care.

3.3.2 Prevalence and Risk Magnitude

Large observational studies and recent meta-analyses estimate that approximately 20–30% of infants exposed to SSRIs or SNRIs in the third trimester show some degree of PNAS (Nörby et al., 2016; Grzeskowiak et al., 2023). A systematic analysis using the Neonatal Abstinence Score found that in a cohort of 220 infants exposed in the third trimester, 13% were admitted to the neonatal ward, with 3% showing severe adaptation syndrome and 22% showing mild adaptation symptoms (*Neonatal adaptation*, 2014).

In a population-based Dutch cohort study, late-pregnancy SSRI exposure was associated with roughly a twofold increase in delayed neonatal adaptation (adjusted OR 2.14, 95% CI: 1.96–2.32), with dose-dependent effects and variation across individual SSRIs (Krikke-Workel et al., 2024). The association was strongest for escitalopram and fluoxetine.

A systematic review and meta-analysis focusing on third-trimester exposure found that higher SSRI doses were associated with significantly increased PNAS risk compared with standard doses (Grzeskowiak et al., 2023). Among individual agents, high-dose paroxetine and sertraline demonstrated elevated risks. Most cases were mild and self-limited, resolving with supportive care only (Nörby et al., 2016; Grzeskowiak et al., 2023).

3.3.3 Summary: Poor Neonatal Adaptation Syndrome

PNAS represents the most consistently documented short-term neonatal complication of late-pregnancy SSRI/SNRI exposure, affecting approximately 20–30% of exposed infants (Nörby et al., 2016; Grzeskowiak et al., 2023; *Neonatal adaptation*, 2014). The syndrome is typically mild and self-limited, though dose-dependent and drug-specific variations exist. Importantly, PNAS risk must be weighed against the consequences of inadequately treated maternal depression.

3.4 Respiratory Complications and Persistent Pulmonary Hypertension of the Newborn (PPHN)

3.4.1 Respiratory Distress

Respiratory symptoms are among the most frequent manifestations of PNAS. Studies of SSRI-exposed neonates report increased rates of transient tachypnea and respiratory distress, particularly among late-preterm infants, although most cases are mild (Krikke-Workel et al., 2024). A prospective cohort highlighted an approximately 1.8- to 2.7-fold increase in early respiratory problems among SSRI-exposed children compared with unexposed peers (Lupattelli et al., 2023).

3.4.2 Persistent Pulmonary Hypertension (PPHN)

PPHN is a rare but serious condition occurring in approximately 1–2 per 1,000 live births in the general population. An early study first raised concerns about a potential link between late-pregnancy SSRI exposure and PPHN (Chambers et al., 2006). A subsequent meta-analysis found that SSRI exposure in late pregnancy was associated with roughly doubled relative risk of PPHN, whereas early-pregnancy exposure did not appear to increase risk (Grigoriadis et al., 2014). However, the absolute risk remained low, with an estimated number needed to harm of 286–351.

Large cohort data by Huybrechts et al. (2015) examining SSRI use in late pregnancy found that after adjusting for maternal depression and other confounders, SSRI use during the second half of pregnancy was associated with increased PPHN risk (aOR 4.29, 95% CI: 1.34–13.77). A more recent Danish population-based study found variations in PPHN risk by timing of exposure and type of antidepressant (Kieler et al., 2021).

Importantly, at least one large population-based cohort did not find increased odds of PPHN after multivariable adjustment, suggesting that severe pulmonary complications remain rare even with exposure (Krikke-Workel et al., 2024).

3.4.3 Summary: Respiratory Complications

SSRI exposure, particularly in late pregnancy, is associated with increased risk of mild to moderate respiratory adaptation difficulties as part of PNAS (Lupattelli et al., 2023; Krikke-Workel et al., 2024). The evidence regarding PPHN remains mixed, with some but not all studies showing associations (Chambers et al., 2006; Grigoriadis et al., 2014; Huybrechts et al., 2015; Kieler et al., 2021). Where associations are observed, absolute risks remain low (approximately 3–5 per 1,000 exposed infants).

3.5 SNRI-Specific Data

Data on SNRI safety in pregnancy are more limited than for SSRIs but generally show similar patterns. A large cohort study examining duloxetine exposure found fully adjusted relative risk of 1.19 (95% CI: 1.04–1.37) for preterm birth with late pregnancy exposure, though the risk was not significantly elevated compared with SSRI-exposed comparison groups (Palmsten et al., 2020). For small for gestational age infants, duloxetine showed no major difference compared with SSRIs (fully adjusted RR 1.14, 95% CI: 0.92–1.41 vs unexposed; RR 1.26, 95% CI: 0.97–1.64 vs SSRI-exposed).

Limited data suggest venlafaxine exposure is associated with PNAS rates numerically similar to or slightly higher than SSRI exposure, in the range of 9–30% (Nörby et al., 2016). Overall, while the evidence base for SNRIs is smaller, available data do not suggest dramatically different risk profiles compared with SSRIs for the outcomes examined in this review.

3.6 Comparison with Untreated Depression

3.6.1 Adverse Outcomes of Untreated Maternal Depression

A critical consideration in assessing the risk–benefit balance of antidepressant use during pregnancy is recognizing that untreated maternal depression itself carries substantial risks for both mother and offspring. Systematic reviews of untreated antenatal depression demonstrate that the disorder itself is associated with increased risks of PTB, LBW, SGA, and other adverse obstetric outcomes (Jarde et al., 2016, 2021; Grigoriadis et al., 2013).

One meta-analysis reported that women with untreated depression had roughly 1.5-fold higher risks of PTB and LBW compared with women without depression, with stronger associations for more severe symptoms (Yin et al., 2016). A more recent systematic review confirmed these findings and highlighted increased risks of stillbirth, operative delivery, and postpartum complications among women with untreated or inadequately treated depression (Jarde et al., 2021).

Mechanisms linking untreated depression to adverse outcomes include:

- Activation of stress-responsive neurobiological systems (HPA axis dysregulation)
- Health risk behaviors (smoking, alcohol use, poor nutrition, inadequate sleep)
- Poor adherence to prenatal care
- Increased inflammation and oxidative stress
- Altered placental function

3.6.2 Summary: Risk–Benefit Context

The evidence clearly demonstrates that both untreated maternal depression and antidepressant medication use carry potential risks (Jarde et al., 2016, 2021; Yin et al., 2016). Thus, when comparing outcomes in women with depression who are treated versus untreated, both the illness and its pharmacological management are linked to adverse outcomes, making confounding by indication a central interpretive challenge (Ross et al., 2016; Sujan et al., 2017).

Table 1. Summary of key findings on SSRI/SNRI use in pregnancy

Outcome	Main Finding	Effect Size	Key Sources
Preterm birth	Modest increase, strongest with late-pregnancy exposure	aOR ~1.2–1.5	Huang et al., 2014, 2020; Suarez et al., 2024
Low birth weight	Small reduction in birth weight (~75–100g); modest increase in LBW risk	RR ~1.4	Huang et al., 2014; Ross et al., 2013
Poor neonatal adaptation (PNAS)	Occurs in 20–30% of infants exposed in third trimester; typically mild and self-limited	aOR ~2.1	Nörby et al., 2016; Grzeskowiak et al., 2023
PPHN	Mixed evidence; small absolute risk increase where observed	OR 2.0–4.3 (varies by study)	Chambers et al., 2006; Grigoriadis et al., 2014; Huybrechts et al., 2015
SNRI vs SSRI	Limited data; similar risk patterns	Comparable to SSRI	Palmsten et al., 2020
Untreated depression	Itself associated with PTB, LBW, and maternal morbidity	RR ~1.5 for PTB/LBW	Jarde et al., 2016, 2021; Yin et al., 2016

Note: aOR = adjusted odds ratio; RR = relative risk; PPHN = persistent pulmonary hypertension of the newborn

4. Discussion

4.1 Summary of Main Findings

This systematic review indicates that SSRI and SNRI use during pregnancy is associated with modest increases in the risk of preterm birth and low birth weight, as well as a clearly elevated risk of poor neonatal adaptation when exposure continues into late gestation (Huang et al., 2014, 2020; Suarez et al., 2024; Nörby et al., 2016; Grzeskowiak et al., 2023). The absolute risk increases for PTB and LBW are small, and observed reductions in birth weight are generally in the range of tens of grams (Ross et al., 2013; Huang et al., 2014). PNAS, by contrast, is relatively common among exposed infants, though it is typically mild and self-limited (Nörby et al., 2016; Grzeskowiak et al., 2023; *Neonatal adaptation*, 2014).

Evidence regarding severe respiratory complications such as PPHN is mixed, and where increased risks are observed, they remain low in absolute terms (Chambers et al., 2006; Grigoriadis et al., 2014; Huybrechts et al., 2015; Kieler et al., 2021; Krikke-Workel et al., 2024).

At the same time, untreated antenatal depression is consistently associated with similar or greater elevations in PTB and LBW risk, and with substantial maternal morbidity, underlining that the alternative to pharmacotherapy is not risk-free (Jarde et al., 2016, 2021; Yin et al., 2016; Grigoriadis et al., 2013). Methodologically sophisticated studies, including sibling and negative-control designs, show that maternal and familial factors explain a significant portion of the association between antidepressant exposure and adverse outcomes, highlighting the pervasive influence of confounding by indication (Sujan et al., 2017; Ross et al., 2016).

4.2 Clinical Implications and Recommendations

4.2.1 Individualized Treatment Decisions

From a clinical perspective, these findings support an individualized, risk–benefit approach to antidepressant use in pregnancy, in line with contemporary guideline recommendations (ACOG, 2023; ACOG, 2025). For women with mild, first-episode depression and strong preference to avoid medication, non-pharmacological strategies such as psychotherapy may be reasonable alternatives, particularly if adequate support and monitoring are available (McDonagh et al., 2014; Ross et al., 2016).

In contrast, for women with moderate-to-severe depression, recurrent illness, or prior severe relapse upon discontinuation, continuation of effective pharmacotherapy will often provide a more favorable overall risk profile than abrupt withdrawal (ACOG, 2023; Jarde et al., 2016, 2021).

The decision to continue, initiate, or discontinue antidepressant medication during pregnancy should consider:

- Severity and chronicity of maternal depression
- Prior response to treatment and relapse history
- Availability and acceptability of non-pharmacological treatments
- Patient preferences and values
- Specific medication safety profile
- Gestational timing

4.2.2 Medication Selection

Medication selection should favor agents with the most reassuring safety data. Among SSRIs, sertraline and escitalopram are frequently recommended as first-line options due to relatively favorable reproductive safety profiles (*SSRIs in pregnancy*, 2022; Ross et al., 2016). Paroxetine is generally avoided because of its stronger association with cardiac malformations. When SNRIs are needed, venlafaxine and duloxetine can be considered, recognizing that the evidence base is smaller but broadly similar in direction to that for SSRIs (Palmsten et al., 2020).

Preferred SSRIs:

- Sertraline: Most extensive safety data, favorable profile across outcomes
- Escitalopram: Growing evidence base, neutral cardiac outcomes

SNRIs:

- Venlafaxine: More safety data than duloxetine
- Duloxetine: Limited data, appears comparable to SSRIs (Palmsten et al., 2020)

4.2.3 Dosing and Timing Considerations

Dose and timing also matter. Using the minimum effective dose and avoiding unnecessary dose escalation may help reduce PNAS risk, which appears dose-related (Grzeskowiak et al., 2023). Late pregnancy (third trimester) exposure shows strongest associations with PNAS. For women who remain on medication

into the third trimester, clinicians should anticipate a higher likelihood of transient neonatal adaptation problems and ensure coordination with neonatal care providers (Krikke-Workel et al., 2024; Nörby et al., 2016).

4.2.4 Neonatal Management

For infants exposed to SSRIs or SNRIs in late pregnancy:

- Inform pediatric team of exposure
- Observe for signs of PNAS (respiratory, neurological, feeding, metabolic symptoms)
- Extended observation (48–72 hours) may be appropriate
- Most cases are mild and require only supportive care
- NICU admission should be based on clinical need, not exposure alone

4.3 Methodological Considerations and Confounding by Indication

A key lesson from the recent literature is that unmeasured or incompletely measured confounding substantially limits causal inference in this field (Ross et al., 2016; Sujan et al., 2017). Studies that compare exposed pregnancies to unexposed pregnancies in the general population tend to show stronger associations than those that restrict comparisons to women with depression or use within-family designs (Huang et al., 2014, 2020; Sujan et al., 2017).

Sibling-comparison designs demonstrate attenuation of risk estimates when differentially exposed pregnancies in the same woman are contrasted, implying that stable maternal and familial characteristics exert a major influence (Sujan et al., 2017). Meta-analyses that combine heterogeneous observational studies often cannot fully correct for this, and reported pooled risks should be interpreted as upper-bound estimates rather than definitive causal effects of the medications (Huang et al., 2014, 2020; Ross et al., 2013).

Clinically, this means that while a small medication-related risk cannot be excluded, a substantial fraction of the observed associations likely reflects the underlying illness and related behaviors (e.g., smoking, substance use, poor nutrition, inconsistent antenatal care) (Ross et al., 2016; Jarde et al., 2016, 2021).

4.4 Balancing Maternal and Fetal Interests

The comparative risks of untreated depression versus pharmacological treatment highlight that maternal and fetal interests are tightly interwoven rather than opposed (Jarde et al., 2016, 2021). Untreated depression is associated with poor self-care, increased substance use, impaired bonding, and elevated risk of postpartum depression, all of which can adversely affect child development (Grigoriadis et al., 2013; Yin et al., 2016). Pharmacological treatment introduces a small but measurable risk of certain obstetric and neonatal outcomes, particularly PNAS and, to a lesser extent, PTB and LBW (Huang et al., 2014, 2020; Grzeskowiak et al., 2023; Nörby et al., 2016).

Guidelines therefore emphasize shared decision-making, in which clinicians provide balanced, evidence-based information about both sets of risks and support women in choosing the option that best aligns with their values, illness history, and life circumstances (ACOG, 2023, 2025). For many women with significant depressive illness, continuation of an SSRI—preferably one with a relatively favorable safety profile—while planning for neonatal monitoring will represent an ethically and clinically sound strategy (*SSRIs in pregnancy*, 2022; ACOG, 2023).

4.5 Limitations

This review has several limitations that warrant acknowledgment:

1. **Observational study limitations:** The vast majority of evidence comes from observational studies subject to confounding, selection bias, and measurement error (Ross et al., 2016; Sujan et al., 2017).
2. **Publication bias:** Studies finding positive associations may be more likely to be published than null findings.
3. **Heterogeneity:** Substantial variations in study populations, exposure definitions, outcome ascertainment, and analytical approaches limit direct comparability (McDonagh et al., 2014).
4. **Limited SNRI data:** Evidence for SNRIs, particularly duloxetine, remains more limited than for SSRIs (Palmsten et al., 2020).
5. **Long-term outcomes:** This review focused on pregnancy and immediate neonatal outcomes; long-term neurodevelopmental effects were not comprehensively addressed.

4.6 Future Research Directions

Priority areas for future research include:

1. **Prospective cohort studies** with detailed, validated assessment of depression severity and symptom burden throughout pregnancy (Ross et al., 2016; Sujan et al., 2017).
2. **Biomarker-based studies** incorporating measures of stress physiology, inflammation, and placental function.
3. **Pharmacogenomic studies** examining how maternal and fetal genetic variations affect medication metabolism and effects.
4. **Long-term follow-up studies** with adequate control for confounding examining child neurodevelopmental and behavioral outcomes.
5. **Implementation research** examining how to effectively communicate risks and benefits to pregnant women and their providers (ACOG, 2023).

5. Conclusions

This systematic review of literature published between 2015 and 2025 demonstrates that SSRI and SNRI use during pregnancy is associated with modest increases in risks of preterm birth, low birth weight, and poor neonatal adaptation syndrome, with the strongest and most consistent evidence pertaining to PNAS following late-pregnancy exposure (Huang et al., 2014, 2020; Suarez et al., 2024; Nörby et al., 2016; Grzeskowiak et al., 2023). However, critical evaluation of study methodologies reveals substantial challenges related to confounding by indication, with evidence suggesting that the underlying maternal depression and associated factors contribute significantly to observed associations (Ross et al., 2016; Sujan et al., 2017).

Untreated maternal depression carries well-established risks for both mother and offspring, including poor maternal self-care, substance use, preterm birth, low birth weight, and postpartum complications (Jarde et al., 2016, 2021; Yin et al., 2016; Grigoriadis et al., 2013). For many women with moderate-to-severe depression, the benefits of continued antidepressant treatment during pregnancy outweigh the potential risks.

Clinical decision-making should be individualized, incorporating evidence-based counseling about risks and benefits, consideration of medication-specific safety profiles (favoring sertraline and escitalopram among SSRIs), use of minimum effective doses, and shared decision-making that respects patient autonomy and values (ACOG, 2023; *SSRIs in pregnancy*, 2022). Healthcare providers should be prepared to monitor exposed infants for signs of poor neonatal adaptation, recognizing that most cases are mild and self-limited (Nörby et al., 2016; Grzeskowiak et al., 2023; *Neonatal adaptation*, 2014).

The American College of Obstetricians and Gynecologists has reaffirmed that robust evidence shows SSRIs are safe in pregnancy, that most do not increase risk of birth defects, and that untreated depression poses significant risks (ACOG, 2023, 2025). Access to evidence-based, compassionate treatment options is essential for pregnant individuals struggling with depression.

Future research employing rigorous causal inference methods, detailed depression severity assessment, and integration of genetic and environmental factors will further refine our understanding of the complex relationship between maternal depression, antidepressant treatment, and pregnancy outcomes (Ross et al., 2016; Sujan et al., 2017).

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