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Review

Treatment Strategies for Perinatal Depression Beyond Conventional Antidepressants: A Narrative Review

Seoyoung Yoon[1,*]

[1]Department of Psychiatry, Daegu Catholic University School of Medicine, 42472 Daegu, Republic of Korea
*Correspondence: syyoon@cu.ac.kr (Seoyoung Yoon)

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Abstract

Objectives: Perinatal depression is prevalent and affects the physical and psychological well-being of both mothers and their offspring. Conventional antidepressants represent the most commonly used pharmacological treatments. However, concerns about safety during pregnancy and breastfeeding persist, alongside limitations such as delayed onset of action and suboptimal response rates. This review comprehensively examines biological treatment strategies for perinatal depression, with a focus on evidence for conventional antidepressants, novel neurosteroid-based therapies, emerging experimental treatments including oxytocin and perioperative esketamine, and neuromodulation methods. **Mechanism**: Conventional antidepressants modulate monoamine neurotransmission. Novel agents such as brexanolone, zuranolone, and esketamine act through neurosteroid modulation and N-methyl-D-aspartate (NMDA) receptor antagonism, producing rapid antidepressant effects. Oxytocin, a neuropeptide involved in social bonding and stress regulation, contributes to maternal mood regulation. Neuromodulation techniques, including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), target relevant brain circuits. **Findings in Brief**: Evidence indicates a slight increase in the risk of congenital malformations, particularly cardiovascular (CV) defects, and birth complications such as preterm birth or low birth weight associated with antidepressant use. However, absolute risks remain small and warrant cautious interpretation, as maternal depression itself is linked to adverse birth outcomes. Late pregnancy exposure to antidepressants may increase the risk of neonatal withdrawal symptoms or persistent pulmonary hypertension, but clinical guidelines do not recommend tapering treatment solely to prevent these outcomes. Brexanolone, zuranolone, and esketamine have emerged as rapid postpartum treatments, often used alongside standard antidepressants. Intranasal oxytocin and perioperative esketamine administered during cesarean section show promise, warranting further study. Neuromodulation techniques like rTMS and tDCS offer potential as adjuncts or alternatives. **Conclusions**: Biological treatments for perinatal depression are evolving rapidly. While conventional antidepressants remain the foundation of therapy, neurosteroids, esketamine, and oxytocin offer promising complementary options. Neuromodulation methods provide emerging alternatives. Ongoing research is essential to establish their safety and efficacy in perinatal populations and tailor personalized treatments that balance maternal and fetal-neonatal health.

Keywords: pregnancy; depression; selective serotonin reuptake inhibitors; zuranolone; brexanolone; esketamine; intranasal oxytocin; repetitive transcranial magnetic stimulation; transcranial direct current stimulation

1. Introduction

Pregnancy and the postpartum period are vulnerable times for the onset of depression. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR), includes a "with peripartum onset" specifier for depressive disorders, defined as the emergence of mood symptoms during pregnancy or within 4 weeks following delivery [1]. Perinatal depression refers to a broader period, encompassing depressive episodes occurring within the first year after childbirth [2]. Both the antenatal and postpartum periods are vulnerable to depression, with prevalence rates of 15% and 14%, respectively [3,4]. "Maternity blues" or "baby blues", a milder form of mood disturbance, are far more common than perinatal depression [1].

Childbearing and childbirth can fundamentally alter a person's life. Fear of change, concerns about economic and social burdens, worries about bodily changes, and anxiety regarding the health of the offspring can all represent significant sources of stress. Lack of support from social networks or an intimate partner, unplanned or unwanted pregnancy, maternal financial difficulties, and a history of adverse birth outcomes or complications during current or previous pregnancies may increase the risk of antenatal depression [5]. Various physiological and biological changes during the perinatal period also contribute to the development of depression. Levels of neurosteroids, such as estrogen, progesterone, and their derivatives, fluctuate dramatically during this time. Estrogen exerts various regulatory and neuroprotective functions in the central nervous system, influencing brain-derived neurotrophic factor (BDNF), serotonergic neurotransmission, and inflammatory processes [6]. Allopregnanolone, a progesterone metabolite, modulates gamma-aminobutyric acid (GABA)-mediated neurotransmission and is now recognized as a major factor in the pathophysiology and a treatment target of

postpartum depression (PPD) [7]. Characteristic changes in the immune system during pregnancy are also considered potential mechanistic pathways for perinatal depression, such as pro-inflammatory changes in late pregnancy, postpartum drops in regulatory T cells, and a shift toward pro-inflammatory responses by T helper 1 cells or type 1 macrophages [8]. Bodily changes during pregnancy and the demands of childcare in the postpartum period can disrupt sleep quality, further increasing the risk of depression [9].

Maternal depression has been associated with adverse birth outcomes, such as low birth weight and preterm birth, as well as with long-term effects on the development and well-being of offspring [5,10–12]. Severe, untreated perinatal depression can constitute a psychiatric emergency, with risks of suicide and thoughts of infanticide [13,14]. Maternal depression can negatively affect mother-infant attachment, potentially affecting their interactions [15]. Proper recognition and timely management of perinatal depression are crucial for the well-being of women during the perinatal period, their children, and the entire family.

Clinical practice guidelines recommend psychological interventions as the first-line treatment for perinatal depression [16–18]. Cognitive–behavioral therapy (CBT), interpersonal therapy (IPT), mindfulness-based interventions, and behavioral activation all have level 1 evidence supporting their efficacy [16]. A recent meta-analysis also confirmed that IPT, CBT, and mindfulness-based interventions significantly reduce depressive symptom severity compared with treatment as usual [19]. Psychological treatment is particularly emphasized in the perinatal period because, unlike pharmacotherapy, it poses no risk of placental transfer or exposure through breast milk.

Nevertheless, biological treatment may be necessary in certain clinical scenarios: when symptoms are severe and require rapid or combined interventions, when patients do not respond adequately to psychological treatment alone, when access to psychotherapy is limited, or when women have a history of recurrent or persistent depression requiring pharmacotherapy.

While conventional antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), remain the most widely used biological treatments, their use is limited by concerns regarding safety during pregnancy and lactation, variable efficacy with partial or nonresponse in some patients, and a delayed onset of therapeutic effects. These limitations have prompted the exploration of alternative approaches, including neurosteroid-based therapies, esketamine, and experimental agents such as intranasal oxytocin, which target distinct biological mechanisms and, in some cases, may provide a more rapid antidepressant response. Moreover, the unique biological characteristics of perinatal depression, driven by profound hormonal and neurobiological changes, further highlight the need for novel therapeutic strategies.

Accordingly, this review focuses on biological treatment strategies for perinatal depression. It summarizes current evidence on the safety and efficacy of conventional antidepressants, explores recently approved neurosteroid-based treatments, and discusses both neuromodulation techniques and emerging experimental approaches, including oxytocin.

2. Methods

A narrative review was conducted to summarize the current evidence on biological treatment strategies for perinatal depression. Literature searches were performed in PubMed up to July 2025 using keywords including “perinatal”, “pregnancy”, “postpartum”, and “depression” or “depressive”, combined with treatment-related terms such as “antidepressants”, “SSRI”, “SNRI”, “brexanolone”, “zuranolone”, “esketamine”, “oxytocin”, “noninvasive brain stimulation”, “rTMS”, and “tDCS”. Reference lists of key studies and reviews were also manually screened to identify additional relevant papers. Priority was given to recent, high-quality evidence, including meta-analyses and randomized controlled trials (RCTs). Studies were included when focusing on adult women during pregnancy or the first postpartum year, reporting clinical efficacy or safety outcomes.

3. Conventional Antidepressants

Although perinatal depression exhibits some distinct features in its pathogenesis and clinical manifestations, the mainstay of pharmacotherapy is conventional antidepressants, as in other forms of depression [20]. In this review, conventional antidepressants refer to widely used medications, including monoamine reuptake inhibitors—SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and norepinephrine-dopamine reuptake inhibitors (NDRIs)—based on the monoamine hypothesis, as well as multimodal agents that act on specific receptor subtypes of monoamine neurotransmitters, such as mirtazapine, vortioxetine, and agomelatine. The efficacy of antidepressants during the perinatal period is likely comparable to that observed in the general population [17]. A recent meta-analysis on antidepressant treatment for postnatal depression found that most of the included studies used SSRIs and showed improved outcomes in response rate, remission rate, and reduction of depressive symptoms, with acceptability similar to placebo [21]. In women with a past history of major depressive disorder (MDD), the overall relapse rate during pregnancy was 43%. Those in the group that discontinued medication experienced a significantly higher relapse rate compared with the group that maintained treatment (hazard ratio [HR] = 5.0; 95% confidence interval [CI]: 2.8–9.1; $p < 0.001$) [22].

However, concerns remain regarding fetal and neonatal health when mothers use antidepressants during pregnancy. Prenatal exposure to SSRIs and SNRIs, particularly in late pregnancy, appears to increase the risk of persis-

tent pulmonary hypertension of the newborn (PPHN) (odds ratio [OR] = 1.82; 95% CI: 1.31–2.54), although the absolute increase in risk is small [23]. In a network meta-analysis, sertraline was associated with the lowest probability of PPHN among the SSRIs and SNRIs studied [23]. Withdrawal signs and symptoms, exhibited as poor neonatal adaptation syndrome (PNAS) in neonates exposed to antidepressants during the third trimester, have been reported after birth. These include hypoglycemia, tremors, hypotonia, tachycardia, rapid breathing, respiratory distress, and hypertonia [24]. A meta-analysis reported increased estimated pooled ORs for hypoglycemia (OR = 1.30; 95% CI: 1.08–1.57) in included studies restricted to SSRIs, and for rapid breathing (OR = 3.10; 95% CI: 1.38–6.98), tremors (OR = 5.25; 95% CI: 2.58–10.67), hypotonia (OR = 3.31; 95% CI: 1.36–8.04), and tachycardia (OR = 3.47; 95% CI: 1.56–7.74) in studies examining exposure to SSRI or venlafaxine [24]. A recent disproportionality analysis using VigiBase found a high reporting odds ratio (ROR) for neonatal withdrawal syndrome in the antidepressant group (ROR = 6.18; 95% CI: 5.45–7.01; Bayesian information component [IC]: 2.07; 95% CI: 1.92–2.21) compared with all other drugs [25]. Fluoxetine, duloxetine, citalopram, and bupropion were assigned low clinical priority scores (green light), and none of the antidepressants were scored as high clinical priority (red light) [25].

A higher risk of adverse perinatal outcomes, such as preterm birth (risk ratio [RR] = 1.62; 95% CI: 1.37–1.90), low birth weight (RR = 1.37; 95% CI: 1.04–1.80), and admission to the neonatal intensive care unit (NICU) (RR = 1.60; 95% CI: 1.38–1.85) has been reported with maternal antidepressant exposure during pregnancy, compared with untreated depressed pregnant women [26]. Associations between prenatal antidepressant exposure and autism spectrum disorders (ASD) have also been reported; however, the potential for a causal relationship remains debatable due to confounding factors [27]. A more recent study suggests that maternal depression, genetic factors, and environmental influences are more likely to contribute to ASD than intrauterine exposure to antidepressants [28].

Regarding teratogenicity, older drug labels classified pregnancy risk according to the US Food and Drug Administration (FDA) classification system (A, B, C, D, and X). However, this system has gradually been replaced by the Pregnancy and Lactation Labeling Rule (PLLR). According to the older classification, most antidepressants were rated as category C, except for paroxetine, which was rated as category D due to its potential increased risk of congenital cardiovascular (CV) malformations (Table 1).

A meta-analysis has reported an increased risk of CV defects in neonates born to women who used paroxetine during pregnancy [29]. One study also reported an increased risk of ventricular septal defects with fluoxetine; however, subsequent studies have produced conflicting findings [30,31]. A meta-analysis of cohort studies involving more than 9 million births found a small but significant increase in the risk of overall major congenital anomalies (RR = 1.11; 95% CI: 1.03–1.19) and congenital heart defects (RR = 1.24; 95% CI: 1.11–1.37) associated with SSRI exposure during early pregnancy [32]. A more recent meta-analysis, not limited to SSRIs, also reported an increased risk for any antidepressant use (OR = 1.23; 95% CI: 1.09–1.38), as well as for SSRIs (OR = 1.21; 95% CI: 1.05–1.39), SNRIs (OR = 1.71; 95% CI: 1.36–2.14), and tricyclic antidepressants (TCAs) (OR = 1.37; 95% CI: 0.81–2.32) in subgroup analyses [33]. A large population-based case-control study from the National Birth Defects Prevention Study reported increased adjusted odds ratios (aORs) for congenital heart defects as well as for other malformations. In this study, venlafaxine was associated with multiple defects, including anencephaly and craniorachischisis, while citalopram was associated with diaphragmatic hernia [34]. However, many of these associations were based on a small number of cases, resulting in a wide CI [34].

All risk summaries in drug labels under the PLLR for SSRIs, SNRIs, and vortioxetine mention an increased risk of postpartum hemorrhage (PPH), particularly when exposure occurs within the month preceding delivery. A recent meta-analysis found that antidepressant use increases the risk of PPH (aOR = 1.47; 95% CI: 1.28–1.70) [35]. Serotonergic antidepressants may cause serotonin depletion in platelets, interfering with blood clotting [35]. Although the absolute risk of PPH associated with SSRI or SNRI exposure is lower than other known risk factors, careful monitoring is warranted, especially in women undergoing cesarean section or those with additional risk factors for PPH [35,36].

However, the reported risks of antidepressants should be interpreted cautiously, considering the effects of confounding factors such as the mother's underlying mental illness. A maternal history of anxiety or mood disorders may independently increase the risk of congenital heart disease, even in the absence of exposure to antidepressants [37]. The studies mentioned above also found that the risk of congenital anomalies associated with antidepressant use was attenuated or became statistically non-significant after adjusting for maternal mental illness [32,34]. Maternal depression itself also increases the risk of low birth weight and preterm birth, even in studies that controlled for confounders, including antidepressant use [12]. A recent large cohort study found that depression unexposed to antidepressants increased the risk of preterm birth (HR = 1.10; 95% CI: 1.04–1.15) [38]. However, patients exposed to SSRIs during the first 22 weeks of gestation, or those who continued treatment after using antidepressants before pregnancy, did not show an increased risk [38]. Both depression and antidepressant use may affect birth outcomes through different mechanistic pathways. Decreased health-promoting behaviors, such as poor nutrition, self-treatment with inappropriate substances, nonadherence to medical advice, and reduced antenatal care, as well as alterations in the

Table 1. FDA pregnancy risk categories, PLLR safety summaries, and major guidelines recommendations for antidepressant use in pregnancy and lactation.

Drug class	Drug name	FDA category (year)[1]/ PLLR (year)[2]	PLLR: pregnancy summary	PLLR: lactation summary	Guideline recommendation
	Fluoxetine	C (2017)/2023	No established risk of major birth defects or miscarriage. Some studies report increased CV malformations; causality not confirmed. Risks of PPHN and poor neonatal adaptation possible.	Present in milk; reports of infant agitation, irritability, poor feeding, poor weight gain; no data on milk production effects.	1st-line (ACOG), 2nd-line (CANMAT)
	Paroxetine	D (2021)/2024	<2-fold increased risk of CV malformations, especially in 1st trimester; inconsistent findings but meta-analyses indicate increased risk. Risks of PPHN and poor neonatal adaptation possible.	Present in milk; reports of infant agitation, irritability, poor feeding, poor weight gain; no data on milk production effects.	2nd-line (ACOG), 3rd-line (CANMAT)
SSRIs	Sertraline	C (2014)/2023	No overall increased risk of major birth defects; some inconclusive findings for specific defects.	Low levels in milk; no data on milk production effects.	1st-line (ACOG), 1st-line (CANMAT)
	Citalopram	C (2019)/2024	No clear increased risk of major birth defects or miscarriage; risks of PPHN and poor neonatal adaptation possible.	Present in milk; RIDs 0.7%–9.4%; reports of infant irritability, somnolence, decreased feeding, weight loss; no data on milk production.	1st-line (ACOG), 1st-line (CANMAT)
	Escitalopram	C (2017)/2024	No clear increased risk of major birth defects or miscarriage; risks of PPHN and poor neonatal adaptation.	Present in milk; reports of infant sedation, restlessness, poor feeding, poor weight gain; no data on milk production.	1st-line (ACOG), 1st-line (CANMAT)
	Fluvoxamine	C (2017)/–	NA	NA	2nd-line (ACOG), 2nd-line (CANMAT)
	Venlafaxine	C (2021)/2023	No established risk of major birth defects or miscarriage; possible increased risk of preeclampsia and PPH with late pregnancy exposure.	Present in milk; no adverse reactions reported.	2nd-line (ACOG), 2nd-line (CANMAT)
	Desvenlafaxine	C (2017)/2023	No human pregnancy data; parent drug venlafaxine shows no clear risk.	Low levels in milk; no reported adverse effects.	2nd-line (CANMAT)
SNRIs	Duloxetine	C (2017)/2023	No clear risk of major birth defects; data limited; neonatal adaptation issues possible.	Present in milk; reports of sedation, poor feeding, poor weight gain.	2nd-line (ACOG), 2nd-line (CANMAT)
	Milnacipran	C (2021)/2024	Insufficient data for risk evaluation; no specific risks identified.	Present in milk; infant effects unknown; limited data.	Insufficient data (CANMAT)
	Levomilnacipran	C (2017)/2024	Insufficient data for risk evaluation.	No human milk data; parent drug present in milk; infant effects unknown.	Insufficient data (CANMAT)

Table 1. Continued.

Drug class	Drug name	FDA category (year)[1]/ PLLR (year)[2]	PLLR: pregnancy summary	PLLR: lactation summary	Guideline recommendation
NDRIs	Bupropion	C (2017)/2024	No increased risk of major malformations identified in epidemiological studies.	Present in milk; no clear adverse infant effects reported.	2nd-line (ACOG), 2nd-line (CANMAT)
Melatonergic	Agomelatine	Not FDA approved; Australian TGA classifies as Pregnancy Category B1.			Insufficient data (CANMAT)
NaSSA	Mirtazapine	C (2016)/2021	No drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes identified in published observational and postmarketing data.	Present in milk at low levels; most reports show no infant adverse effects.	2nd-line (ACOG), 2nd-line (CANMAT)
Multimodal	Vortioxetine	C (2016)/2023	Limited human data; no established risk but very sparse evidence.	No human milk data; present in animal milk; safety unknown.	Insufficient data (CANMAT)

[1] Most recent year of US FDA pregnancy category assignment or update.

[2] Latest year of FDA PLLR update. "–" means no update or not FDA-approved.

All FDA PLLR labels for SSRIs, SNRIs, and vortioxetine note <2-fold increased PPH risk with use near delivery. This is omitted from the table for clarity.

FDA, Food and Drug Administration; PLLR, Pregnancy and Lactation Labeling Rule; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; NDRIs, norepinephrine-dopamine reuptake inhibitors; NaSSA, Noradrenergic and Specific Serotonergic Antidepressant; CANMAT, Canadian Network for Mood and Anxiety Treatments; RID, relative infant dose; ACOG, American College of Obstetricians and Gynecologists; PPHN, persistent pulmonary hypertension of the newborn; PPH, postpartum hemorrhage; CV, cardiovascular; TGA, Therapeutic Goods Administration; NA, not available.

hypothalamic–pituitary–adrenal axis and proinflammatory changes due to stress and depression, may mediate the relationship between maternal depression and adverse outcomes [38–40]. Conversely, alterations in fetal serotonin and norepinephrine signaling due to prenatal antidepressant exposure may impair fetal development and growth [40]. Although some studies that attempted to exclude the effects of maternal depression still reported a higher risk of adverse outcomes with antidepressant use compared with untreated depression [34], selection bias may exaggerate the apparent risks, as these studies are not controlled and antidepressants are more likely to be prescribed in more severe cases. Moreover, due to ethical concerns, most clinical trials during pregnancy are observational or retrospective rather than prospective, well-controlled randomized trials, and are therefore subject to inherent limitations in study design, including recall bias and inadequately controlled variables.

Studies on antidepressant use during pregnancy are mostly restricted to SSRIs and, to a lesser extent, SNRIs, as these medications are the most commonly prescribed for depressive disorders and, consequently, the most extensively studied in pregnant women. Clinicians tend to be cautious when treating pregnant patients and prefer medications supported by existing study data. In clinical practice, SSRIs are the most commonly prescribed antidepressants during pregnancy, with an estimated international prevalence of 3.0%. Among SSRIs, sertraline has the highest prevalence, followed by citalopram, and fluoxetine [41]. In a large case-control study involving 30,630 mothers of infants with birth defects and 11,478 control mothers, approximately 3% of mothers used SSRIs, while less than 0.5% used SNRIs. Exposure to other antidepressants was rare [34]. Research on antidepressants beyond SSRIs and SNRIs during pregnancy is limited. Among them, mirtazapine and bupropion have been relatively well studied, with some systematic reviews and meta-analyses suggesting no substantial evidence of adverse outcomes in pregnancy or offspring, except for reports of PNAS associated with mirtazapine. However, these findings are based on a limited number of studies with generally low-quality evidence, making it difficult to draw firm conclusions regarding their safety [42,43].

Clinical practice guidelines from the Canadian Network for Mood and Anxiety Treatments (CANMAT), the American College of Obstetricians and Gynecologists (ACOG), and the National Institute for Health and Care Excellence (NICE) are consistent with the findings from the aforementioned studies. All three guidelines recommend psychological treatment as the first-line treatment for perinatal depression [16–18]. However, the guidelines also suggest individualized recommendations for pharmacotherapy, based on weighing the potential benefits and risks. Pharmacotherapy can be considered when initial symptoms are moderate-to-severe or severe [16,17], or in milder cases depending on patient preference [16,18], access to psychological interventions [16–18], lack of response to non-pharmacological therapies [16–18], a prior history of severe depression [18], or previous positive response to treatment [17].

The guidelines generally agree that SSRIs and SNRIs are the most well-studied medications, while evidence for other antidepressants is limited. Accordingly, SSRIs are regarded as first-line pharmacotherapy for perinatal depression, and SNRIs are considered reasonable alternatives [17]. The CANMAT guideline summarizes safety evidence as follows: paroxetine may be associated with a higher risk of CV malformations, while paroxetine, venlafaxine, and fluoxetine may pose higher risks of PNAS; sertraline and escitalopram may be associated with a lower risk of PPHN compared with fluoxetine [16]. CANMAT recommends citalopram, escitalopram, and sertraline as first-line medications during pregnancy. The NICE guideline recommends considering TCAs, SSRIs, or SNRIs when appropriate but does not specify specific agents as first-line options [18]. ACOG recommends continuing previously effective medications when applicable; for treatment-naïve cases, sertraline or escitalopram are considered reasonable choices [17]. Additionally, sertraline, fluoxetine, citalopram, and escitalopram are included as first-line treatment options, while duloxetine, venlafaxine, fluvoxamine, paroxetine, mirtazapine, and bupropion are categorized as second-line options [17].

In addition to the general recommendations from the clinical guidelines mentioned above, the selection of antidepressant therapy should consider maternal comorbidities and specific symptom characteristics. Pregnancy is associated with medical conditions requiring pharmacotherapy, such as gestational diabetes, hypertensive disorders of pregnancy (including preeclampsia/eclampsia), and thyroid disease, and the prevalence of chronic medication use increases with maternal age. These factors may affect both drug choice and monitoring needs. Drug–drug interactions should also be considered when patients are taking concomitant medications. Among SSRIs, fluvoxamine strongly inhibits cytochrome P450 (CYP) 1A2 and CYP2C19, while fluoxetine and paroxetine are potent inhibitors of CYP2D6 [44]. Although direct pharmacokinetic interactions between SSRIs and commonly used obstetric medications, such as insulin or labetalol, have not been reported, caution is warranted when these drugs are co-prescribed with agents metabolized by these enzymes.

Individual drug characteristics may also guide selection in specific clinical scenarios. SNRIs can increase blood pressure through their noradrenergic activity. A recent meta-analysis found that SNRI use during pregnancy was associated with an increased risk of gestational hypertension/preeclampsia after adjustment for depression itself, whereas SSRIs were not [45]. Therefore, blood pressure should be monitored when prescribing SNRIs during pregnancy, and they should be used cautiously in women

with hypertensive disorders or in high-risk populations, particularly at higher doses. Mirtazapine, through antagonism of 5-hydroxytryptamine 2 receptor (5-HT2) and 5-HT3 receptors, produces sedative, antiemetic, and appetite-stimulating effects. It has been considered an alternative therapy for refractory hyperemesis gravidarum and may be used in pregnant patients with severe nausea, poor appetite, or insomnia [46]. However, its appetite- and weight-promoting effects may be unsuitable for women experiencing excessive weight gain or gestational diabetes [47]. Bupropion may help manage depressive symptoms and support smoking cessation; however, RCTs in pregnancy have shown limited efficacy for smoking cessation, so its use should be individualized [48,49].

For women already taking antidepressants prior to conception, guidelines provide nuanced recommendations. The NICE guideline recommends that, for mild to moderate depression, clinicians may consider gradually tapering antidepressant medication [18]. However, discontinuation has been associated with a higher risk of relapse compared with continuation in women with a history of major depression [22]. More recent guidelines recommend against withholding or discontinuing medications solely due to pregnancy or lactation status. Shared decision-making is essential, but the ACOG guideline emphasizes that, in general, the balance favors continuation of pharmacotherapy, particularly in patients at higher risk of recurrence, such as those with incomplete remission or multiple lifetime depressive episodes [17]. In addition, ACOG recommends that any previously effective antidepressant should be considered first. An Italian expert consensus also advises continuing medications that have been effective or switching only to agents with more favorable safety profiles and epidemiologic data, such as SSRIs at the lowest effective dose [50]. Shared decision-making regarding discontinuation, switching, or continuation should be individualized. The risk of recurrence should be carefully weighed, and in most cases, continuation of a previously effective antidepressant is preferred, as most antidepressants are considered relatively acceptable during pregnancy, whereas discontinuation or switching may destabilize depressive disorder.

Although previous studies have consistently reported an increased risk of PNAS, some researchers have suggested reducing the dosage or gradually discontinuing antidepressants before delivery. However, neither the CANMAT guideline nor the Italian consensus panel recommends reducing or discontinuing antidepressants near delivery, as PNAS is typically mild and self-limiting [16,50]. The ACOG guideline also states that current evidence does not support tapering antidepressants during the third trimester [17]. Nonetheless, close monitoring of neonatal complications, including PPHN and PNAS is recommended [50].

Antidepressant use may influence both patients' and clinicians' decisions regarding breastfeeding, due to concerns about the potential exposure of the infant to medication through breast milk. As a result, some women may be reluctant to take antidepressants or may even discontinue ongoing medication to continue breastfeeding. In a large retrospective cohort study, women treated with antidepressants in late pregnancy were less likely to initiate breastfeeding. Initiation of antidepressants in the postpartum period was also associated with earlier discontinuation of breastfeeding [51].

Relative infant dose (RID) is defined as the percentage of the infant's daily dose per kilogram received via breast milk divided by the maternal daily dose per kilogram. An RID of 5%–10% is generally considered a threshold for safety risk assessment [52]. Clinical studies have reported that most antidepressants have an RID of less than 5%, except for desvenlafaxine, venlafaxine, citalopram, escitalopram, fluoxetine, and mirtazapine. However, these values are mostly still below 10% [53,54]. According to RID values, all TCAs, fluvoxamine, paroxetine, sertraline, duloxetine, vortioxetine, and bupropion appear to be compatible with breastfeeding [54]. Most medications pass into breast milk through passive diffusion, and drugs with high plasma protein binding are considered safer options. In this regard, SSRIs are generally considered safe during lactation [53]. Most infants exposed to antidepressants through breast milk have not experienced adverse effects. However, isolated cases of irritability, restlessness, serotonin syndrome, or gastrointestinal symptoms have been reported with maternal SSRI or SNRI use. Additionally, seizures or abnormal movements have been reported with maternal bupropion use, though causality remains undetermined [54].

The CANMAT guideline recommends citalopram, escitalopram, and sertraline as first-line antidepressants during lactation. Paroxetine is downgraded to a third-line option due to its potential risk of CV malformation in a future pregnancy [16]. Doxepin is the only antidepressant not recommended during lactation according to CANMAT, due to its potential to cause excessive somnolence in infants. According to the ACOG guideline, among first-line antidepressants for perinatal mood disorders, sertraline is considered to have the lowest transfer into breast milk [17].

4. Novel or Alternative Pharmacological Approaches

Conventional antidepressants have been widely used for perinatal depression and remain the mainstay of pharmacotherapy during the period. However, newer therapeutics targeting mechanisms beyond traditional monoamine pathways are now approved or under investigation. Some of these medications address the relationship between hormonal fluctuations during the perinatal period and the development of PPD, such as progesterone, its analog allopregnanolone, and oxytocin [55–58]. Esketamine is a novel antidepressant that acts as an N-methyl-D-aspartate (NMDA) receptor antagonist and has a rapid onset of action. It is indicated for treatment-resistant depression and

for patients with suicidal ideation or behavior [59–61]. This medication is currently under investigation for the prevention and treatment of PPD [62–66].

4.1 Brexanolone and Zuranolone

Recently, the FDA approved the novel antidepressants brexanolone and zuranolone for the treatment of PPD [58]. Both drugs are synthetic analogs of allopregnanolone, a metabolite of progesterone. Allopregnanolone is a neurosteroid that functions as a positive allosteric modulator of the GABA A receptor. A study has reported that a dramatic decrease in progesterone and allopregnanolone levels after delivery may contribute to the development of PPD [55]. Preclinical studies indicate that synthetic neurosteroids, such as zuranolone, modulate both synaptic (γ-containing) and extrasynaptic (δ-containing) GABA-A receptor subtypes, acting at sites distinct from those targeted by benzodiazepines, another well-known class of GABA-A positive allosteric modulators. This unique mechanism is believed to contribute not only to their potential antidepressant effects but also to a reduced risk of tolerance and dependence, as suggested by preclinical data [67–70].

Brexanolone is the first medication approved specifically for PPD [71]. It is administered intravenously over 60 hours, starting at 30 µg/kg/h, gradually increasing to 90 µg/kg/h if tolerated, then tapering gradually [71]. The optimal timing for initiating brexanolone after delivery is not specified, but clinical trials included women up to 6 months postpartum [71]. During administration, patients should be monitored for excessive sedation, loss of consciousness, and oxygen saturation via pulse oximetry. One phase 2 and two phase 3 clinical trials evaluated the efficacy and safety of brexanolone, showing significant efficacy over placebo in Hamilton Depression Rating Scale (HAM-D) scores. The onset of efficacy was rapid, showing differences from placebo at 24 hours after administration [72]. A post-hoc analysis reported that the favorable effect of a single 60-hour brexanolone infusion was both rapid and sustained through day 30, reaching statistical significance [73]. Although response and remission rates showed little or no difference between treatment and placebo at 30 days, according to a recent meta-analysis [74]. Symptoms of anxiety and insomnia also improved rapidly, and the effect persisted for up to one month in the brexanolone treatment group [73]. Common adverse effects included dizziness, headache, and somnolence. Approximately 4% of participants discontinued treatment due to excessive sedation or loss of consciousness [72].

However, existing studies were placebo-controlled, and direct comparisons with conventional SSRIs are still lacking. One study has attempted indirect comparisons between brexanolone and SSRIs. The study using matching-adjusted indirect comparisons (MAIC) reported that brexanolone showed greater reductions in depression scores at both day 3 and week 4 compared to SSRIs [75]. It should be noted that the indirect comparison study was funded by the drug manufacturer, and further studies with direct head-to-head comparisons are warranted. However, brexanolone can be used concurrently with other antidepressants. Clinical trials did not exclude participants taking antidepressants, and approximately 28% of subjects received concomitant medications. Beneficial effects of brexanolone were observed in both participants who used other antidepressants and those who did not [76].

Although brexanolone was developed with a unique mechanism of action and demonstrated early onset and sustained efficacy, its limitations include intravenous administration, the need for hospitalization and continuous monitoring, and a relatively high cost. Four years later, the FDA approved zuranolone, an oral synthetic allopregnanolone analog, for the treatment of PPD [55]. A 2-week course of oral zuranolone demonstrated rapid treatment efficacy, beginning as early as day 3 and persisting through day 45, in phase 3 double-blind, placebo-controlled RCTs using 30 mg and 50 mg doses [77,78]. A recent meta-analysis performed a dose-response analysis and found that increasing the dose up to 30 mg daily effectively improved both depression and anxiety. However, doses over 30 mg appeared to increase the risk of side effects [79]. Zuranolone was generally well tolerated, with common adverse events being somnolence, dizziness, and sedation [78].

Because zuranolone is administered orally and has a distinct mechanism of action, its efficacy has also been investigated in MDD, beyond perinatal onset. A recent meta-analysis found that zuranolone showed greater improvement in depressive symptoms than placebo in both PPD and MDD patients. However, the effect size was larger in the PPD subgroup, and the reduction in anxiety symptoms was significant only in this group. These findings suggest that zuranolone may be particularly effective for PPD compared with other depressive disorders, possibly due to differences in pathophysiology [80].

Clinical trials for zuranolone did not exclude participants taking concomitant antidepressants, and efficacy was observed regardless of baseline antidepressant use [78]. An indirect comparison study using a matching-adjusted indirect comparison reported that zuranolone treatment resulted in greater symptom improvement than SSRIs in patients with PPD, beginning on day 15, with the largest mean difference observed on day 45 [81].

The most recent ACOG guideline recommends considering postpartum brexanolone for moderate-to-severe perinatal depression when symptoms begin between the third trimester and four weeks postpartum [17]. The guideline recommends weighing the benefits of its rapid onset of action against the challenges, such as high cost, limited accessibility, lack of long-term efficacy data, and insufficient safety data regarding breastfeeding [17]. Zuranolone is not mentioned in the ACOG guideline as its approval is more recent. In contrast, the CANMAT guideline addresses both

zuranolone and brexanolone [16]. The guideline notes their rapid onset of action and common side effects, including headache, dizziness, and drowsiness or sedation. It also emphasizes the need for continuous monitoring during brexanolone administration. Furthermore, the CANMAT guideline recommends that these medications be considered outside of the lactation period, as there is currently insufficient safety data to support their use during breastfeeding [16].

4.2 Esketamine

Esketamine nasal spray is an NMDA receptor antagonist approved for treatment-resistant depression and for depression with acute suicidal ideation or behavior, in combination with an oral antidepressant [82]. Recently, esketamine monotherapy also demonstrated efficacy in treatment-resistant depression, leading to FDA approval as monotherapy in 2025 [83,84]. As an adjunctive agent in treatment-resistant depression, esketamine has shown superior efficacy compared to quetiapine—another commonly used adjunctive agent—in remission rate, response rate, and reduction in depressive symptom severity from week 8 to 32 [85].

Although sufficient clinical data are lacking for its use during pregnancy, preclinical studies raise potential concerns regarding perinatal exposure to ketamine. These concerns include increased neuronal cell death, altered neurogenesis and synaptogenesis, elevated oxidative stress, and disruption of the development of GABAergic and glutamatergic neurotransmission [86]. The CANMAT guideline recommends ketamine only as a second-line adjunctive treatment for depression and specifically advises against its use during pregnancy until sufficient safety data are available [16,87].

Regarding breastfeeding, a small study reports that the RID of both ketamine and its metabolite, norketamine, is less than 1%, suggesting minimal transfer through breast milk. However, close monitoring is advised for potential neonatal sedation, poor feeding, and inadequate weight gain [87]. The CANMAT guideline categorizes ketamine as a drug with insufficient data for use during lactation [16]. In postpartum patients who are not breastfeeding, esketamine may be used in accordance with general guidelines.

The effectiveness of intraoperative esketamine for the prevention of PPD has been investigated in women receiving epidural anesthesia for cesarean section. Esketamine is considered a relatively safe adjunct during spinal anesthesia for cesarean delivery. Meta-analyses on the prevention of PPD after cesarean section found that perioperative esketamine use was associated with a lower incidence of PPD and reduced Edinburgh Postnatal Depression Scale (EPDS) scores within 1 week postpartum compared with the control group [88], with a decreased incidence of PPD also observed at 6 weeks postpartum [89]. Subgroup analysis showed that high-dose esketamine (>0.25 mg/kg) was significantly more effective than control in reducing PPD incidence within the first week, whereas the lower-dose group was not. Regarding the route of administration, studies were divided into three subgroups: (a) intravenous administration during surgery, (b) use of an analgesic pump post-surgery, and (c) a combination of both. Among these, only subgroup (c) showed significantly reduced incidence of PPD within 1 week of treatment. Subgroup (b) was associated with improved EPDS scores within the first week postpartum. Further research is needed to determine the optimal administration strategy [88]. A recent RCT found that intraoperative infusion of esketamine at 0.25 mg/kg in 20 mL of saline over 20 minutes was effective in reducing the incidence of PPD at 6 weeks compared to placebo [90].

However, most previous studies focused on prevention in the general population rather than specifically on women with pre-existing perinatal depressive symptoms. A pilot RCT evaluated a single intravenous administration of ketamine (0.5 mg/kg) during cesarean delivery after umbilical cord clamping in women with perinatal depressive symptoms. This study did not find a significant difference in EPDS scores between groups on day 2 postpartum [91]. However, a subsequent large, double-blind, placebo-controlled RCT assessed the efficacy of esketamine at 0.2 mg/kg, administered intravenously over 40 minutes after childbirth once the umbilical cord was clamped. The esketamine group demonstrated significantly lower depression severity on days 7 and 42, with approximately a 75% reduction in the incidence of major depressive episodes at day 42 postpartum [65].

4.3 Intranasal Oxytocin

Synthetic oxytocin is commonly used during labor and delivery for the induction and augmentation of labor, as well as for the prevention of PPH [92]. Oxytocin is a hormone involved in lactation, parturition, and the regulation of physiological homeostasis, and it also plays a role in human psychological behavior. It appears to exert anxiolytic and antidepressant-like effects by modulating social and affiliative behaviors, emotional regulation, and stress response [57].

Oxytocin levels fluctuate dynamically during pregnancy, labor, delivery, and lactation. However, one study reported a specific decrease in oxytocin levels during the early postpartum period in mothers with PPD, a pattern not observed in healthy controls [93]. Although findings remain inconsistent, a systematic review reported that 8 of 12 studies suggested an inverse relationship between endogenous oxytocin levels and the severity of depressive symptoms [94]. Genome-wide association studies have identified that single-nucleotide polymorphisms associated with PPD are overrepresented in genes involved in oxytocin signaling pathways [95]. A recent study suggested that salivary oxytocin levels, combined with EPDS scores and lack of social support, may help predict perinatal depression [96].

However, the effects of exogenous oxytocin administration on depressive symptoms have been heterogeneous [94]. A population-based data analysis even found that perinatal exposure to synthetic oxytocin was associated with an increased risk of postpartum depressive or anxiety disorders [97].

These unexpected results may reflect the route of administration and its impact on central nervous system oxytocin levels. Unlike endogenous secretion, which elevates both peripheral and cerebrospinal fluid (CSF) oxytocin levels, administration of synthetic oxytocin may not increase, or may even decrease, CSF oxytocin concentrations [92].

Intranasal administration of oxytocin appears to allow central nervous system penetration, thereby enhancing functionally relevant brain oxytocin activity [98]. Recent RCTs assessing intranasal oxytocin reported modest positive effects on postnatal mood symptoms [99–101]. However, these studies typically examined the effects of a single 24 international unit (IU) dose of oxytocin on surrogate depression-related outcomes, such as negative affect, positive affect, and negative thought patterns, within one hour of administration and included a small number of participants [99–101]. Thus, although intranasal oxytocin may have therapeutic potential in PPD, more rigorous studies are needed to support its clinical use.

5. Noninvasive Brain Stimulation (NIBS)

During pregnancy, many patients prefer to avoid pharmacotherapy. In such cases, NIBS may serve as an alternative option [102]. rTMS and transcranial direct current stimulation (tDCS) have been studied for the treatment of MDD and shown efficacy [103]. NIBS can be used as monotherapy or in combination with antidepressants in clinical practice. A meta-analysis suggests that combining rTMS or tDCS with antidepressants provides superior efficacy compared with antidepressant monotherapy [104]. NIBS has also been studied in perinatal depression.

5.1 Repetitive Transcranial Magnetic Stimulation (rTMS)

rTMS is a form of NIBS that uses electromagnetic pulses to stimulate cortical neurons and modulate neuronal excitability [105]. It received FDA clearance in 2008 for treatment-resistant depression and has since been widely used, including in perinatal populations. The classic rTMS protocol uses an 8-coil at 10 Hz, targeting the left dorsolateral prefrontal cortex (DLPFC), typically administered 5 days per week over 4–6 weeks [105]. More recently, advanced protocols, such as theta burst stimulation and neuroscience-informed accelerated protocols, have also received FDA clearance to reduce treatment time or the number of sessions required [105–107].

A systematic review and meta-analysis suggested that rTMS is effective for treating depression during pregnancy, with no serious adverse effects observed in mothers or fetuses [108]. However, sham-controlled RCTs remain scarce, and sample sizes are small, partly due to ethical concerns regarding clinical trials in pregnant populations [108,109]. The stimulation protocols of rTMS in perinatal depression have been heterogeneous. A systematic review identified 2 RCTs, 3 open-label trials, and 5 case reports or case series examining the efficacy of rTMS in perinatal depression [108]. The systematic review reported that most included studies demonstrated clinical improvement, although treatment parameters varied, with stimulation intensity most frequently set at 100% of the resting motor threshold, ranging from 90% to 120%. High-frequency stimulation was most commonly employed on the left DLPFC, including one study at 5 Hz, one at 10 Hz, and one at 25 Hz. Case reports also described the use of 25 Hz, 10 Hz, and 20 Hz stimulation of the left DLPFC. In contrast, a smaller number of studies applied 1 Hz low-frequency stimulation to the right DLPFC. The number of sessions in prospective studies typically ranged from 18 to 25, whereas case reports varied widely from a single session to 77 sessions. To date, more advanced stimulation protocols, such as theta burst stimulation, have not yet been investigated in perinatal populations [108].

Reported side effects of rTMS include headache and pain at the stimulation site, which are generally mild and did not affect participants' health [108]. Although some small studies suggest that rTMS is relatively safe for fetal health and outcomes, comprehensive investigations into potential fetal effects remain insufficient. One small sham-controlled RCT reported three late preterm births in the active treatment group, although no differences were found between groups in NICU admissions, gestational age at delivery, or major congenital anomalies [110]. Due to the limited sample size, the authors could not conclude whether active rTMS poses a risk for preterm birth [110].

Although high frequencies above 40 Hz may affect fetal lungs and immune system, the electromagnetic field generated by standard rTMS remains below the 800 mV/m threshold considered safe for fetal exposure [108]. There are some concerns that changes in peripheral endocannabinoid levels associated with rTMS may affect fetal neurodevelopment [111]. While preliminary studies suggest short-term safety, further research is needed to examine long-term outcomes and subtle developmental effects [111].

Unlike pharmacotherapy, rTMS appears to have no effect on breastfeeding. The CANMAT guideline recommends rTMS as an adjunctive treatment for PPD [16]. However, due to limited safety data, rTMS is not recommended as a routine treatment during pregnancy [16].

5.2 Transcranial Direct Current Stimulation (tDCS)

tDCS modulates cortical excitability using low-amplitude direct current (typically $\leq$2 mA) applied via electrodes placed on the scalp. A recent meta-analysis demonstrated that tDCS is clinically effective for treating depression, including in patients with medical or psychi-

atric comorbidities [112]. When combined with antidepressants, tDCS produced a greater effect size than when used alone [112]. tDCS is generally well tolerated, with dropout rates due to adverse events not significantly different from placebo. Reported adverse events include rare cases of hypomania or mania, as well as mild to moderate effects such as electrode site discomfort, skin redness, headache, dizziness, nausea, and sleep disturbances [112].

Unlike rTMS, tDCS is portable and can be administered at home. However, a meta-analysis found no significant benefit of home-based tDCS compared with sham treatment, possibly due to small sample sizes and short intervention durations, typically 6 weeks [112]. tDCS is permitted for clinical or limited clinical or research use in several countries, including Australia, South Korea, and parts of Europe [113]. However, no tDCS device has received FDA approval for the treatment of depression, and evidence regarding its use during pregnancy remains limited [114,115].

Only one small pilot RCT assessed the efficacy of tDCS (2 mA, 30 minutes, anode over F3, cathode over F4, 5 days per week for 3 weeks) compared with sham treatment in pregnant women with MDD who declined pharmacotherapy. Although the post-treatment difference did not reach statistical significance, possibly due to the small sample size, the remission rate at 4 weeks postpartum was significantly higher in the tDCS group [116]. The treatment was well tolerated, with no abnormalities observed in maternal vital signs or fetal monitoring, and no serious pregnancy complications were reported [116]. Another open-label pilot involving six drug-free pregnant patients, with twice-daily sessions over 10 days (2 mA, 30 minutes, anode over F3, cathode over F4) and an optional additional once-daily course for 10 days, also found a statistically significant reduction in depression severity with tDCS [117].

Although studies on tDCS safety during pregnancy are limited, current modeling data suggest that the electrical current reaching the fetus stays below the threshold for activation [115]. In the postpartum period, no systematic trials have evaluated the efficacy of tDCS for depression to date [118]. A case report documented the successful use of tDCS in a breastfeeding mother with depression, with no adverse effects on breastfeeding or the infant [114]. Similar to rTMS, tDCS is expected to have minimal impact on breast milk and may represent a suitable alternative for patients reluctant to use pharmacotherapy due to breastfeeding-related concerns [114,115].

Given the insufficient evidence on safety and efficacy in perinatal populations, the CANMAT guideline recommends adjunctive tDCS as a third-line option for mild to moderate PPD and does not support its routine use during pregnancy [16].

6. Summary and Conclusions

The perinatal period carries an increased risk of depression due to dramatic psychological and physiological changes. Perinatal depression is linked to poor obstetric outcomes, adverse effects on maternal and offspring health and development, and impaired maternal-infant bonding. In this manuscript, we provide a comprehensive review of biological treatment strategies, ranging from conventional antidepressants, novel pharmacological agents, NIBS and experimental approaches. Key findings from recent meta-analyses or RCTs regarding each treatment are summarized in Table 2 (Ref. [21,23,24,26,33,35,74,81,88,89,99–101,108,116]).

Pharmacotherapy based on the monoamine hypothesis remains the cornerstone of treatment during pregnancy and postpartum. SSRIs are the most widely studied and prescribed antidepressants during this period, with sertraline and escitalopram considered first-line treatments by both ACOG and CANMAT guidelines. However, conventional antidepressants present several limitations, such as delayed onset of action and a substantial proportion of treatment-resistant cases. Moreover, even when risks are small or influenced by confounding factors, some perinatal risks remain, including congenital heart defects, neonatal withdrawal symptoms, PPHN, and increased PPH.

Novel therapeutics may address some of these limitations. Allopregnanolone analogs and intranasal esketamine demonstrate rapid efficacy and may be used adjunctively to enhance treatment response. However, these strategies are currently studied and recommended only after parturition, not during pregnancy. Their effects on breast milk and infant exposure warrant further investigation before widespread clinical use. Esketamine can be administered intranasally, as approved by the FDA for depression treatment. Its perioperative use during cesarean section has also been studied as a unique approach to the management and prevention of peripartum depression. Meta-analyses of several RCTs suggest that perioperative esketamine may reduce the risk of PPD; however, these studies were not conducted in high-risk or clinically depressed populations and do not support its use solely for preventive purposes. Several studies suggest its effectiveness in managing existing depressive symptoms; however, small sample sizes limit clinical recommendations. NIBS is also a promising option, both as an adjunctive treatment and as a non-pharmacological alternative for patients concerned about fetal or neonatal exposure. Although modeling studies suggest minimal fetal impact under standard conditions, clinical safety data are still warranted. Other pathophysiology-based approaches, such as intranasal oxytocin, show potential in small studies; however, current evidence only assesses immediate positive effects and does not provide information on long-term treatment outcomes or safety. Trials on long-term intranasal oxytocin use have been conducted in other psychiatric disorders, such as autism, for du-

Table 2. Summary of efficacy and safety outcomes from recent meta-analyses and RCTs in peripartum depression treatments.

Treatment	Efficacy	Safety
Results from recent meta-analyses		
Conventional antidepressants	Response (SSRIs): RR = 1.27 (95% CI: 0.97–1.66); Remission (SSRIs): RR = 1.54 (95% CI: 0.99–2.41); Depression severity (SSRIs): SMD = –0.30 (95% CI: –0.55 to –0.05) [21]	Acceptability/dropout (SSRIs): RR = 1.10 (95% CI: 0.74–1.64) [21]; PPHN (SSRIs and SNRIs): OR = 1.82 (95% CI: 1.31–2.54), NNH 1000 [23]; Neonatal adaptation syndrome (SSRIs or SNRIs, varying by symptom type): OR = 3.10–6.86 [24]; Preterm birth: RR = 1.62 (95% CI: 1.37–1.90) [26]; Congenital heart defects: OR = 1.23 (95% CI: 1.09–1.38) [33]; PPH: OR = 1.47 (95% CI: 1.28–1.70) [35]
Brexanolone	Response: RR = 1.24 (95% CI: 0.74–2.06); Remission: RR = 1.18 (95% CI: 0.59–2.38); Depression severity: MD = –4.22 (95% CI: –8.46 to 0.02) [74]	Maternal adverse events: RR = 1.02 (95% CI: 0.71–1.48); Dropout: RR = 2.77 (95% CI: 1.22–6.26) [74]
Zuranolone	Response: RR = 1.26 (95% CI: 1.03–1.55); Remission: RR = 1.65 (95% CI: 1.22–2.22); Depression severity: MD = –3.79 (95% CI: –5.60 to –1.97) [74]	Maternal adverse events: RR = 1.24 (95% CI: 1.03–1.48); Acceptability: RR = 0.95 (95% CI: 0.50–1.81) [74]
Esketamine (perioperative, cesarean section)	PPD incidence: RR = 0.49 (95% CI: 0.30–0.79); EPDS severity: SMD = –1.10 (95% CI: –1.67 to –0.52) [88]; Week 6 PPD incidence: RR = 0.51 (95% CI: 0.37–0.69) [89]	Vomiting: RR = 0.79 (95% CI: 0.52–1.20) [81]; Headache/dizziness: RR = 1.37 (95% CI: 1.02–1.85) [88]; Hallucinations: RR = 12.68 (95% CI: 4.01–40.09); Dizziness: RR = 4.21 (95% CI: 1.70–10.41); Diplopia: RR = 10.70 (95% CI: 2.45–46.69); Blurred vision: RR = 27.93 (95% CI: 2.89–269.79) [89]
rTMS	Depression severity: SMD = 1.39 (95% CI: 0.94–1.84), $p < 0.01$ [108]	Side effects: SMD = 0.35 (95% CI: 0.21–0.51); No severe maternal or fetal adverse events. Infant events included preterm birth (n = 5) and one brachial plexus injury unrelated to treatment [108]
Results from individual RCTs (modalities not yet covered by meta-analyses)		
Intranasal oxytocin (24 IU single dose)	↓ Negative mood only in moderate EPDS scorers: $\eta^2 = 0.12$, $p < 0.01$ [99]; ↓ BRM-NT: MD = 2.77 (95% CI: 0.51–5.03), $p = 0.02$ [100]; ↑ Positive affect vs. placebo: Cohen's d = 0.23, $p < 0.01$ [101]	Not reported
tDCS	MADRS post-treatment: mean 11.8 vs. 15.4 ($p = 0.34$); Remission at 4 weeks postpartum: 75% vs. 12.5%, $p = 0.04$ [116]	Minor transient maternal adverse events: 17.7% vs. 4.7%, $p = 0.001$ [116]

OR, odds ratio; CI, confidence interval; RCTs, randomized controlled trials; SMD, standardized mean difference; NNH, Number Needed to Harm; EPDS, Edinburgh Postnatal Depression Scale; PPD, postpartum depression; BRM-NT, baby-related and motherhood negative thoughts; PPHN, pulmonary hypertension of the newborn; MADRS, Montgomery-Åsberg Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; RR, risk ratio; IU, international unit; ↑, an increase; ↓, a decrease.

rations of up to 12 weeks [119]. The efficacy of intranasal oxytocin in perinatal depression still requires confirmation through large, multicenter RCTs assessing long-term outcomes, including response rate, remission rate, and reductions in standardized depression scale scores.

Appropriate treatment of perinatal depression is essential. However, clinicians often face challenges when weighing treatment benefits against risks, especially during pregnancy. Most clinical trials exclude pregnant women for ethical reasons, leading to a lack of robust safety and effi-

cacy data. Evidence remains particularly limited regarding the efficacy of antidepressants during pregnancy, intranasal esketamine use in treatment-resistant perinatal depression, and perinatal use of NIBS modalities, especially tDCS, which have supportive evidence in other populations. This paucity of evidence fosters a defensive and often suboptimal treatment approach in clinical practice. Encouragingly, novel therapeutics and alternative strategies are under investigation. Well-designed, ethically conducted studies are urgently needed to expand treatment guidelines and provide effective, individualized options for women experiencing perinatal depression. Future research should systematically address key questions, including: (1) long-term safety of these interventions for both mothers and infants, including neurodevelopmental outcomes; (2) optimal timing, dosage, and administration routes for interventions such as intranasal oxytocin and perioperative esketamine; (3) robust measures of treatment efficacy using standardized scales, remission, and response rates; and (4) long-term effectiveness and safety of NIBS and other non-pharmacological approaches. Addressing these questions is essential for translating experimental findings into safe and effective clinical applications.

Abbreviations

SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; NDRIs, norepinephrine-dopamine reuptake inhibitors; TCAs, tricyclic antidepressants; PPH, postpartum hemorrhage; PNAS, poor neonatal adaptation syndrome; PPHN, persistent pulmonary hypertension of the newborn; RID, relative infant dose; FDA, Food and Drug Administration; PLLR, Pregnancy and Lactation Labeling Rule; NaSSA, Noradrenergic and Specific Serotonergic Antidepressant; CANMAT, Canadian Network for Mood and Anxiety Treatments; ACOG, American College of Obstetricians and Gynecologists; NICE, National Institute for Health and Care Excellence; HAM-D, Hamilton Depression Rating Scale; EPDS, Edinburgh Postnatal Depression Scale; GABA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate; ROR, Reporting odds ratio; MAIC, matching-adjusted indirect comparison; CSF, cerebrospinal fluid; BDNF, brain-derived neurotrophic factor; RCTs, randomized controlled trials; MDD, major depressive disorder; PPD, postpartum depression; DLPFC, Dorsolateral Prefrontal Cortex; SMD, standardized mean difference; NNH, Number Needed to Harm; BRM-NT, baby-related and motherhood negative thoughts; MADRS, Montgomery-Åsberg Depression Rating Scale; CBT, cognitive–behavioral therapy; IPT, interpersonal therapy; OR, odds ratio; HR, hazard ratio; CI, confidence interval; RR, risk ratio; NICU, neonatal intensive care unit; ASD, autism spectrum disorders; IC, Bayesian information component; CYP, cytochrome; HT, hydroxytryptamine; CV, cardiovascular; TGA, Therapeutic Goods Administration; NA, not available; IU, international unit.

Author Contributions

SY was solely responsible for the conception, literature review, manuscript writing, data interpretation, editorial changes, and final approval of the submitted version. SY has participated sufficiently in the work and agrees to be accountable for all aspects of the work.

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During the preparation of this work, the authors used ChatGPT-4o in order to check spelling and grammar. After using this tool, the author reviewed and edited the content as needed and took full responsibility for the content of the publication.

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