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The Role of Estrogen and Progesterone Fluctuations in the Pathogenesis of Postpartum Psychosis: A Neurobiological Review

Wa Ode Sri Apriani Taufan[1], Ilma Khaerina[2], Agus Japari[2]

[1]*Medical Professional Education Program, Faculty of Medicine, Universitas Muslim Indonesia, Indonesia*
[2]*Department of Psychiatry, Faculty of Medicine, Universitas Muslim Indonesia, Indonesia*

**Corresponding Author: Wa Ode Sri Apriani Taufan*
Email: **:** *waodesriaprianiapriani@gmail.com*

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Abstract

Postpartum psychosis is an acute psychiatric disorder characterized by rapid onset following childbirth, posing significant risks to both maternal and neonatal safety. Its underlying mechanisms remain incompletely understood; however, fluctuations in reproductive hormones particularly estrogen and progesterone are strongly implicated in its pathogenesis. The abrupt decline of these hormones after delivery may disrupt neurotransmitter systems, especially dopaminergic and GABAergic pathways, thereby precipitating neurobiological imbalance in vulnerable individuals. This study employs a literature review method using a narrative review approach, drawing upon databases such as PubMed, ScienceDirect, and Google Scholar, complemented by manual searches. Following the PRISMA framework, a total of 20 articles met the inclusion criteria and were systematically analyzed. The findings indicate that estrogen demonstrates a more consistent association with psychotic symptomatology, whereas progesterone exerts its effects primarily through its metabolite, allopregnanolone, which modulates the GABAergic system. In addition, genetic predisposition, sleep disturbances, and alterations in neuroplasticity contribute to the condition. Postpartum psychosis therefore emerges as a multifactorial disorder resulting from the complex interplay between hormonal fluctuations and underlying neurobiological vulnerability.

Introduction

Postpartum psychosis is an acute and severe psychiatric disorder that typically emerges within a few days to two weeks after childbirth (Meltzer-Brody et al., 2024; Sit et al., 2006; Sanadi et al., 2026). Its clinical presentation is not limited to delusions or hallucinations but is often accompanied by prominent affective symptoms, such as mania, mixed episodes, depression with psychotic features, agitation, confusion, and rapidly evolving behavioral changes. Although its incidence is low approximately 1–2 cases per 1,000 births this condition is considered a perinatal psychiatric emergency due to its association with increased risks of suicide, infanticide, and safety concerns for both the mother and the infant. Therefore, postpartum psychosis must be understood as a serious clinical syndrome requiring immediate detection and management (Bergink et al., 2025; Toor et al., 2024).

The highly characteristic timing of postpartum psychosis following childbirth provides strong evidence that this disorder has a clear biological basis (Camoni et al., 2026; Özdilek et al., 2026). Immediately after the placenta is delivered, levels of estradiol and progesterone drop

sharply, while at the same time the mother's body undergoes major adjustments in the immune system, the stress axis, and maternal brain function. However, since nearly all women experience these hormonal changes while only a small fraction develop psychosis, the primary issue is likely not merely the drop in hormone levels, but rather an individual's biological sensitivity to hormonal fluctuations. In other words, the postpartum period can be viewed as a neuroendocrine transition phase capable of triggering severe symptoms in women who already possess a pre-existing vulnerability (Bergink et al., 2025; Dukic et al., 2024).

Estrogen plays a crucial role in maintaining brain function stability by influencing neurotransmitter systems involved in psychosis, particularly dopamine, as well as serotonergic and glutamatergic systems (Raji et al., 2025; Naoi et al., 2025; Mallick et al., 2026). Recent studies indicate that estrogen decline during specific phases such as the premenstrual period, menopause, and the postpartum period is associated with increased vulnerability to relapse or the emergence of psychotic symptoms in susceptible women. In the postpartum context, the sudden drop in estradiol is thought to reduce estrogen's protective effects on dopamine regulation and the stability of emotional processing. Although direct evidence regarding postpartum psychosis remains inconsistent, the estrogen hypothesis remains one of the strongest neurobiological frameworks for explaining why psychotic episodes often occur shortly after childbirth (Mu et al., 2024; Palacios-Hernández et al., 2024).

In addition to estrogen, progesterone is also highly relevant, particularly through its neuroactive metabolite, allopregnanolone. This compound acts as a positive modulator of GABA_A receptors, which constitute the brain's primary inhibitory system and help maintain calm neural activity, emotional stability, and the regulation of the stress response. After childbirth, a decrease in progesterone is followed by a decrease in its derivative neurosteroids, potentially disrupting the balance between neural inhibition and excitation. Neurobiologically, this state is thought to reduce emotional stability and increase vulnerability to psychiatric decompensation; nevertheless, it must be acknowledged that most of the mechanistic evidence for this pathway still largely stems from research on postpartum depression and general neurosteroid studies, rather than specifically postpartum psychosis (Grötsch & Ehlert, 2024; Patterson et al., 2024; Reddy, 2023).

The postpartum period is also a phase of highly active maternal neuroplasticity. Longitudinal neuroimaging studies indicate that the first six weeks postpartum are accompanied by restructuring in several brain regions, particularly the amygdala, hippocampus, prefrontal/subgenual cortex, and insula areas involved in emotional regulation, stress responses, and adaptation to the presence of the infant. These changes are fundamentally adaptive and essential for the transition into the role of motherhood. However, in women with affective or psychotic vulnerabilities, these rapid brain changes may become less stable, particularly when occurring alongside the postpartum decline in estrogen and progesterone (Nehls et al., 2024; Paternina-Die et al., 2024).

Recent evidence increasingly suggests that postpartum psychosis does not arise solely from hormonal fluctuations, but from the interaction between postpartum biological changes and pre-existing vulnerability factors. A recent systematic review indicates that genetic and epigenetic factors do play a role, and the risk architecture for postpartum psychosis overlaps partially with bipolar disorder. This aligns with the latest consensus that in approximately half of cases, the first postpartum psychotic episode also serves as an early manifestation of bipolar disorder. Additionally, circadian factors appear to play a role: in women with bipolar disorder, losing at least one full night's sleep during the birthing process is associated with a roughly fivefold increase in the odds of postpartum psychosis. These findings confirm that fluctuations in estrogen and progesterone operate within a broader network of factors, rather than in isolation (Bergink et al., 2025; Perry et al., 2024; Tsokkou et al., 2024).

Although research over the past five years has advanced rapidly, the exact mechanisms linking changes in estrogen and progesterone to the onset of postpartum psychosis remain not fully understood. One reason is that postpartum psychosis itself is heterogeneous, both in terms of symptoms, its association with bipolar disorder, and its clinical course. Furthermore, longitudinal studies that simultaneously assess hormone levels, brain changes, sleep, and psychotic symptoms remain relatively limited. Therefore, this literature review aims to critically examine how fluctuations in estrogen and progesterone may influence neurotransmission, neurosteroids, the stress axis, and maternal brain neuroplasticity in the pathogenesis of postpartum psychosis.

Methods

This study employs a literature review method, specifically a narrative review. To ensure the article search and selection process is systematic, transparent, and easily replicable, the stages of identification, screening, eligibility assessment, and article inclusion were structured in accordance with PRISMA 2020. Although this study was not designed as a full systematic review, the use of the PRISMA flowchart remains important to clearly demonstrate how articles were selected until the final studies to be analyzed were obtained.

The literature search was conducted across several scientific sources, namely PubMed, Google Scholar, and ScienceDirect, and was supplemented by manual searches through the reference lists of relevant articles as well as open-access publisher platforms that provide downloadable full-text manuscripts. The search focused on articles published within the last 10 years (2016–2025) to ensure relevance to the latest evidence. The keywords used were structured with Boolean operators, including: "postpartum psychosis" OR "perinatal psychosis" AND estrogen OR progesterone OR allopregnanolone OR "hormonal fluctuation" AND neurobiology OR neuroendocrine OR GABA OR dopamine OR "steroid sulfatase". This expansion of keywords was necessary because evidence regarding hormones in perinatal psychosis is still considered limited and heterogeneous, so the search needed to include both direct clinical studies and supporting mechanistic studies.

Inclusion criteria for this review include: peer-reviewed journal articles, available in full text and downloadable, published within the last 10 years, in English or Indonesian, and having a direct or mechanistic relevance to the study's title namely, the role of estrogen and progesterone fluctuations in the pathogenesis of postpartum psychosis. The included articles are not limited to clinical studies on patients with postpartum psychosis but also studies examining estradiol, progesterone, allopregnanolone, the GABAergic system, neuroendocrine systems, and steroid metabolism during the postpartum period, provided they scientifically support the explanation of the pathogenesis of postpartum psychosis. Articles such as editorials, letters to the editor, conference abstracts, articles without full text, and publications that only discuss postpartum depression without any connection to psychosis or hormonal mechanisms were excluded from the review.

The selection process was conducted in stages according to the PRISMA flowchart. First, all articles identified from various sources were collected, and duplicate articles were removed. Second, a screening based on titles and abstracts was performed to assess relevance to the topic. Third, articles that passed the initial stage were read in full text to ensure the relevance of the content, the quality of the sources, alignment with the hormonal-neurobiological focus, and the availability of data suitable for synthesis. At this stage, articles were excluded if they did not address postpartum/perinatal psychosis, did not evaluate estrogen, progesterone, or related neurobiological pathways, or provided only overly general information that did not support the study's focus. After all selection stages were completed, 20 articles deemed most relevant were identified and included in the narrative synthesis. This approach is also consistent with findings from recent reviews confirming that the literature on hormones in perinatal psychosis remains

limited, making the selection of articles that are truly focused and mechanistically meaningful critically important.

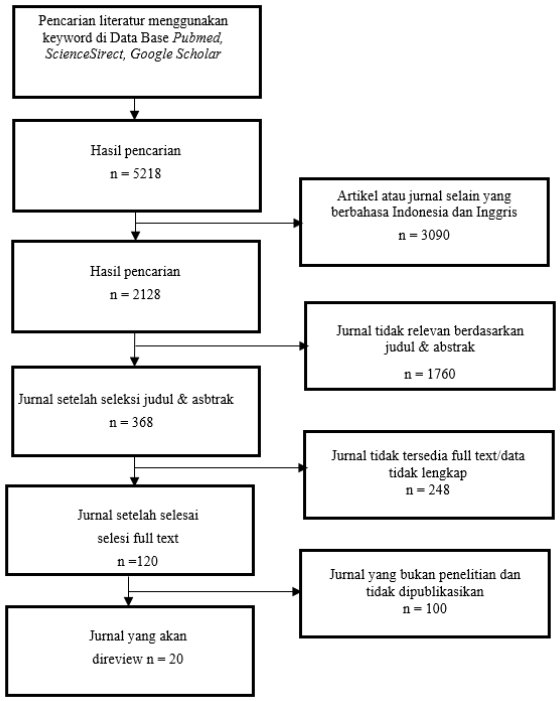

Figure 1. PRISMA Flowchart for Research Articles on the Role of Estrogen and Progesterone Fluctuations in the Pathogenesis of Postpartum Psychosis

The literature screening process in this study aims to comprehensively examine the role of estrogen and progesterone fluctuations in the pathogenesis of postpartum psychosis from a neurobiological perspective. The literature search was conducted through various scientific databases, namely PubMed, ScienceDirect, and Google Scholar, and supplemented with a manual search of relevant article references and open-access journals aligned with the research topic.

The initial search yielded 5,218 articles, comprising 1,640 from PubMed, 1,120 from ScienceDirect, 2,310 from Google Scholar, and an additional 148 from the manual search. In the initial selection phase, 3,090 articles were eliminated, comprising 1,980 duplicate articles and 1,110 articles not written in Indonesian or English, thus failing to meet the established inclusion criteria.

Following this process, 2,128 articles were obtained and subsequently screened based on their titles and abstracts. At this stage, 1,760 articles were eliminated because they were irrelevant to the research topic, such as not addressing postpartum psychosis, focusing solely on postpartum depression without psychotic components, or failing to assess the role of estrogen, progesterone, or related neurobiological mechanisms. Subsequently, the remaining 368 articles were evaluated in full text. At this stage, 248 articles were eliminated because they were not available in full text or contained incomplete information, making a comprehensive assessment impossible.

After this stage, 120 articles were obtained and subsequently reselected based on more specific quality criteria, such as publication within the last 10 years, study design, and source credibility. At this stage, 100 articles were eliminated because they were not original research, were non-systematic reviews lacking in-depth analysis, or were not officially published. Consequently, at the end of the selection process, 20 articles were identified as having the strongest relevance to the research topic and were used in the literature review.

Result and Discussion

Table 1. Analysis of the Role of Estrogen and Progesterone Fluctuations in the Pathogenesis of Postpartum Psychosis

No	Author	Title	Method	Main Findings	Conclusion
1	Palacios Hernández et al., 2024	Hormones, Psychotic Disorders, and Cognition in Perinatal Women: A Mini Review	Mini review; multi-database search up to 2023, 14 studies met inclusion criteria	This review summarizes 5 hormonal hypotheses regarding perinatal psychosis: dopamine, cortisol, estrogen, thyroid hormones, and oxytocin. Evidence regarding estrogen and progesterone is considered to exist, but it remains mixed, and is not yet consistent.	Hormones play a role in perinatal psychosis, but direct evidence specifically regarding estrogen and progesterone in postpartum psychosis remains limited.
2	Khedr et al., 2023	Risk Factors Related First Episode Postpartum Psychosis among Egyptian Women: The Role of Psychosocial and Biological Factors	Cross-sectional case-control study; 60 women with PP vs. 30 postpartum controls	Plasma estrogen levels were significantly lower in the PP group; estrogen levels correlated with BPRS scores. Progesterone levels did not differ significantly between groups, but low progesterone was associated with more severe symptom scores in regression analysis.	This is one of the most direct clinical evidences in humans that a decrease in estrogen is associated with postpartum psychosis; the role of progesterone appears weaker but may still be relevant.
3	Isik et al., 2022	Investigation of Hormone Levels in Postpartum Psychosis	Case-control study; 23 PP patients vs. 30 controls	fT3 was lower in the PP group, but most other hormones did not differ significantly. This study does not support the presence of widespread peripheral hormonal disturbances in all PP patients.	Postpartum psychosis is likely not merely the result of a general endocrine disorder; this supports a model of biological sensitivity to hormonal changes rather than absolute hormone deficiency alone.
4	González Rodríguez and Seeman, 2019	The Association between Hormones and Antipsychotic Use: A Focus on Postpartum and Menopausal Women	Narrative review	This review emphasizes that estradiol and progesterone levels drop sharply after childbirth, and these changes are	Fluctuations in estrogen and progesterone make perfect sense as triggers for postpartum psychosis,

				temporally associated with the onset of postpartum affective or psychotic disorders. The authors also suggest that what may be more important is not the level of a single hormone, but the balance between hormones.	although evidence for hormonal therapy remains controversial.
5	Perry et al., 2021	Phenomenology, Epidemiology and Aetiology of Postpartum Psychosis: A Review	Narrative review	This review states that the sudden withdrawal of progesterone and estrogen after childbirth coincides with the peak onset of PP. However, absolute steroid levels are not always different between affected and unaffected women.	The strongest model is not "hormone deficiency," but rather abnormal sensitivity to postpartum hormone withdrawal.
6	Bergink et al., 2025	Postpartum Psychosis and Bipolar Disorder: Review of Neurobiology and Expert Consensus Statement on Classification	Neurobiology review and expert consensus	The highly characteristic timing of PP onset is thought to point to a strong biological basis because the postpartum period is marked by massive endocrine, immune, neuroanatomical, and brain physiological changes.	Postpartum endocrine changes are an important trigger, but they act upon a broader biological vulnerability, particularly the bipolar spectrum.
7	Davies, 2017	Understanding the Pathophysiology of Postpartum Psychosis: Challenges and New Approaches	Critical review	Davies reviews hormonal, immune, and serotonergic hypotheses, then proposes a new pathway involving steroid sulfatase as a biological risk model for PP.	Postpartum steroid hormone fluctuations are likely linked to psychosis through molecular pathways that are more complex than simply a decrease in serum estrogen or progesterone.
8	Humby et al., 2016	A Pharmacological Mouse Model Suggests a Novel Risk Pathway for Postpartum Psychosis	Animal experimental study; STS inhibition in postpartum mice	STS inhibition induces postpartum behavioral abnormalities that partially improve with ziprasidone. This study also	The steroid sulfatase and steroid hormone metabolism pathway is a robust molecular model for explaining

				links these changes to genes such as CCN3, which are considered biologically plausible for PP.	susceptibility to postpartum psychosis.
9	Thippeswamy and Davies, 2021	A New Molecular Risk Pathway for Postpartum Mood Disorders: Clues from Steroid Sulfatase Deficient Individuals	Open-access review article	STS converts relatively inactive steroid sulfates into more active estrogen or androgen precursors. STS dysfunction is thought to alter neuronal calcium signaling, extracellular matrix proteins, and the response to postpartum steroid depletion.	Changes in steroid metabolism may serve as a link between estrogen or progesterone fluctuations and postpartum neurobiological disorganization.
10	Humby and Davies, 2019	Brain Gene Expression in a Novel Mouse Model of Postpartum Mood Disorder	Brain gene expression study in a postpartum mouse model with STS inhibition	Small but widespread changes in brain gene expression were found, particularly in genes related to the olfactory system and maternal behavior, in an STS based model of postpartum mood disorder.	Steroid fluctuations and STS disruption may alter postpartum brain circuits relevant to psychotic or affective symptoms.
11	Dukic et al., 2024	Estradiol and Progesterone from Pregnancy to Postpartum: A Longitudinal Latent Class Analysis	Longitudinal study; 130 women; saliva ELISA from pregnancy to postpartum	Estradiol and progesterone rise during pregnancy and then drop sharply after delivery, but their trajectories vary greatly between individuals.	Postpartum estradiol and progesterone withdrawal is a genuine physiological phenomenon, but its intensity and pattern differ among women.
12	Gilfarb and Leuner, 2022	GABA System Modifications During Periods of Hormonal Flux Across the Female Lifespan	Review	This review explains that estradiol, progesterone, and allopregnanolone influence the GABA system. In the postpartum period, failure of GABA_A adaptation to neurosteroid withdrawal can disrupt the inhibition excitation balance.	The progesterone allopregnanolone GABA_A pathway is one of the strongest neurobiological explanations for psychiatric decompensation following childbirth.

13	Grötsch and Ehlert, 2024a	Allopregnanolone in the Peripartum: Correlates, Concentrations, and Challenges: A Systematic Review	Systematic review	This review indicates that allopregnanolone, a progesterone metabolite, is biologically highly relevant during the peripartum period, but research results remain inconsistent due to variations in sampling time and analytical methods.	Evidence regarding progesterone in the postpartum period is stronger when assessed through allopregnanolone rather than serum progesterone levels alone.
14	Grötsch and Ehlert, 2024b	Allopregnanolone and Mood in the Peripartum: A Longitudinal Assessment in Healthy Women	Longitudinal study; 61 healthy women; weekly saliva samples over 12 weeks	Allopregnanolone levels rise during pregnancy and then decline as delivery approaches; allopregnanolone trajectories vary and are associated with a history of mental health disorders, sleep disturbances, premenstrual symptoms, and resilience. The relationship between allopregnanolone and depressive symptoms appears U-shaped.	Not only low allopregnanolone levels, but also unstable allopregnanolone fluctuation patterns may indicate sensitivity to hormonal changes.
15	Pinna et al., 2022	Allopregnanolone in Postpartum Depression	Pathophysiological review	This review confirms that allopregnanolone, as a progesterone metabolite, modulates GABA_A and decreases after childbirth. The neurosteroid withdrawal model is used to explain the rapid onset of postpartum psychiatric symptoms.	To understand the role of progesterone in postpartum psychosis, progesterone must be considered alongside its neuroactive metabolites, particularly allopregnanolone.
16	Patterson et al., 2025	Open Label Study of the Efficacy, Safety and Tolerability of Brexanolone in the Treatment of Adult Women with Postpartum Psychosis	An open-label study of 10 women with postpartum psychosis. Patients received a 60-hour infusion of brexanolone. They were assessed using the YMRS, PANSS, and HAM-D through day 7,	Symptoms of psychosis, mania, and depression improved following treatment. All participants completed the treatment.	These findings suggest that the neurosteroid pathway derived from progesterone, particularly that acting through GABA_A receptors, likely plays a role in the pathophysiology of postpartum

			then monitored through day 90.		psychosis. However, due to the small sample size and open-label study design, these results still need to be confirmed through larger controlled studies.
17	Li et al., 2020	Transdermal Estradiol for Postpartum Depression: Results from a Pilot Randomized, Double Blind, Placebo Controlled Study	A small, randomized, double-blind, placebo-controlled clinical trial. Comparing transdermal estradiol with placebo over 6 weeks in women with postpartum depression.	The estradiol group showed symptom improvement on several measures, particularly in secondary analyses. Interestingly, blood estradiol levels did not differ significantly between groups.	These results support the notion that changes in the biological response to estrogen, rather than estrogen levels alone, may contribute to postpartum psychiatric disorders. Thus, the nervous system's sensitivity to postpartum estrogen fluctuations may be one relevant mechanism in postpartum psychosis vulnerability.
18	Deligiannidis et al., 2016	Peripartum Neuroactive Steroid and γ Aminobutyric Acid Profiles in Women at Risk for Postpartum Depression	A longitudinal study of 56 peripartum women not taking psychotropic medications. Measured progesterone, pregnanolone, allopregnanolone, and GABA using LC-MS/MS, then associated these with symptoms of depression and anxiety.	Women at risk for postpartum depression had lower GABA levels, as well as higher progesterone and pregnanolone levels compared to healthy controls. Some neurosteroids were also associated with symptom severity.	Imbalances in neurosteroids and the GABAergic system may play a role in postpartum psychiatric disorders. Although this study focused on postpartum depression, the biological mechanisms identified are also relevant for elucidating potential neuroendocrine underpinnings of postpartum psychosis.
19	Pestana et al., 2023	The Impact of the Ovarian Cycle on Anxiety, Allopregnanolone, and Corticotropin Releasing Hormone Changes after Motherhood in Female Rats and Women	A translational study in female rats and women. Comparing changes in anxiety, allopregnanolone, and stress markers before and after the experience of motherhood.	After becoming a mother, the influence of the ovarian hormonal cycle on anxiety changes. In the animal model, changes in allopregnanolone, GABA_A receptor subunit expression,	This study suggests that pregnancy and childbirth can alter hormonal regulation and neurobiological brain responses, particularly within the progesterone neurosteroid pathway. These

				and CRH were also observed.	changes are thought to increase vulnerability to postpartum psychiatric disorders in individuals with specific biological sensitivities.
20	Sha et al., 2021	Associations between Estrogen and Progesterone, the Kynurenine Pathway, and Inflammation in the Post Partum	An observational study of 163 postpartum women. Measuring estrogen, progesterone, inflammatory cytokines, and kynurenine metabolites after childbirth.	Postpartum estrogen was associated with higher postpartum IL-6 levels and a more pro-inflammatory profile. Conversely, progesterone was associated with a more anti-inflammatory profile.	Estrogen and progesterone appear to function differently after childbirth. Estrogen tends to be associated with inflammation, whereas progesterone is more protective. This is important because inflammation is also thought to play a role in postpartum psychiatric disorders.

Source: Primary Data

Based on the 20 articles reviewed, it appears that the role of estrogen and progesterone fluctuations in the pathogenesis of postpartum psychosis is best understood as a biological trigger in susceptible women, rather than as a sole cause. Reviews that directly address postpartum psychosis consistently identify the period immediately following childbirth as a highly distinctive biological window, characterized by a rapid decline in reproductive steroid hormones, changes in the immune system, and major adaptations in the maternal brain. However, the same review also emphasizes that human studies that actually measure estrogen and progesterone in postpartum psychosis remain limited, and the results are not yet fully consistent (Bergink et al., 2025; Davies, 2017; Palacios-Hernández et al., 2024). Overall, existing findings suggest that postpartum hormonal changes do not act solely through alterations in hormone levels, but also through changes in the central nervous system's sensitivity to estrogen, progesterone, and their neuroactive metabolites (Perry et al., 2021).

Clinical findings indicate that women with a first episode of postpartum psychosis have lower plasma estrogen levels compared to postpartum controls, and lower estrogen levels correlate with symptom severity as measured by the BPRS (Brief Psychiatric Rating Scale). Interestingly, in the same study, progesterone did not show significant differences between groups; however, lower progesterone levels remained associated with more severe symptom scores in regression analysis. These results suggest that estrogen appears to be a stronger clinical marker, whereas progesterone's role seems more subtle and may not always be evident in single serum measurements. This pattern aligns with a mini-review, where the estrogen withdrawal hypothesis has more tangible clinical support compared to the progesterone hypothesis, although neither is yet conclusive. (González-Rodríguez & Seeman, 2019; Khedr et al., 2023; Palacios-Hernández et al., 2024).

Transdermal estradiol administration in postpartum psychiatric disorders may be followed by symptom improvement even if not always accompanied by a clear change in serum estradiol

levels. These findings support the hypothesis that the more critical factor is not merely low estrogen- e levels, but rather how the brain responds to the postpartum decline in estrogen. Thus, estrogen likely acts through the loss of its protective effects on dopamine regulation, affect, and postpartum psychological stability (Li et al., 2020).

Nevertheless, the role of progesterone cannot be assessed solely based on serum progesterone levels. Mechanistic studies suggest that progesterone likely acts primarily through allopregnanolone (ALLO), a neuroactive metabolite that modulates GABA_A receptors. Estradiol and progesterone rise throughout pregnancy and then drop sharply after childbirth, but the pattern of this decline varies significantly among individuals. Changes in progesterone and ALLO can alter the plasticity of the GABA system, the inhibition-excitation balance, and stress responses (Gilfarb & Leuner, 2022; Grötsch & Ehlert, 2024; Pinna et al., 2022). From this perspective, progesterone may appear "weak" when measured solely as a peripheral hormone, but becomes highly significant when understood as part of the progesterone–allopregnanolone–GABA_A axis (Dukic et al., 2024).

In peripartum women at risk for postpartum disorders, there are changes in neurosteroid profiles and GABA levels, indicating that the progesterone-neurosteroid system is indeed closely linked to emotional regulation and psychiatric vulnerability following childbirth. Furthermore, administration of brexanolone, an allopregnanolone analog, can improve symptoms of psychosis, mania, and depression in women with postpartum psychosis. These findings provide clinical support that the progesterone pathway is not only theoretically relevant but also has tangible therapeutic implications through the GABAergic system (Deligiannidis et al., 2016; Patterson et al., 2025).

These findings also help explain why not all studies identify clear hormonal abnormalities. Studies have not found widespread patterns of hormonal abnormalities in patients with postpartum psychosis beyond mild changes in thyroid function. Such results are particularly important because they support the idea that what is most relevant is not always the absolute level of hormones, but the brain's biological response to normal hormonal changes following childbirth. Criticism of overly simplistic models suggests that while nearly all mothers experience a decline in estrogen and progesterone after childbirth, only a small fraction develop postpartum psychosis. Thus, hormones appear to act on the basis of other vulnerabilities, such as bipolar vulnerability, circadian sleep disorders, or neurotransmitter sensitivity (Bergink et al., 2025; Isik, 2022).

Following the experience of pregnancy and childbirth, the brain's response to ovarian hormone cycles, allopregnanolone, and the stress system may change. These findings support the view that the postpartum period is not merely a phase of hormonal decline but also a phase of neurobiological reorganization; consequently, in vulnerable women, these changes may increase the risk of developing severe psychiatric symptoms (Pestana et al., 2023).

In addition to the estrogen and GABA pathways, a series of studies by Davies and Humby introduced a particularly intriguing molecular pathway: steroid sulfatase (STS). Dysregulation of STS may serve as a biological model for postpartum psychosis. In animal models, STS inhibition in postpartum rats resulted in behavioral abnormalities that partially improved with ziprasidone. There were small but widespread changes in brain gene expression, with STS acting as a link between steroid metabolism, neuronal calcium signaling, and susceptibility to mood disorders/psychosis following childbirth. This pathway is highly relevant to your topic because the STS plays a role in the metabolism of estrogen precursors and other steroids, thereby providing a biological bridge between hormonal fluctuations and postpartum changes in brain function (Davies, 2017; Humby et al., 2016; Humby & Davies, 2019; Thippeswamy & Davies, 2021).

Estrogen and progesterone interact differently with inflammatory pathways during the postpartum period. In these studies, estrogen was more associated with a profile tending toward pro-inflammatory effects, whereas progesterone was associated with a more anti-inflammatory profile. These findings expand the understanding that the effects of estrogen and progesterone on postpartum psychosis occur not only through neurotransmitters but also through interactions with the immune system, which has long been suspected to be involved in the pathogenesis of postpartum psychosis (Sha et al., 2021).

If all these findings are synthesized, estrogen appears to have stronger direct clinical support in postpartum psychosis, particularly through the hypothesis of the loss of estrogen's protective effect on the dopaminergic system following childbirth. Conversely, progesterone appears more significant when understood through its metabolite, allopregnanolone, and the failure of GABA_A receptor adaptation to neurosteroid changes after childbirth. In other words, the pathogenesis of postpartum psychosis is likely not due to a mere "hormonal deficiency," but rather the result of interactions between rapid estrogen-progesterone decline, individual biological sensitivity, and the vulnerability of dopaminergic, GABAergic, immunological, and circadian circuits (Khedr et al., 2023).

Overall, this synthesis of 20 journals suggests that estrogen appears to play a greater role through withdrawal mechanisms and receptor sensitivity, whereas progesterone is more relevant via neurosteroid pathways and GABA modulation. Furthermore, existing evidence also indicates that the effects of these two hormones must be understood in conjunction with stress and inflammatory systems; thus, the most appropriate model for the pathogenesis of postpartum psychosis is a multifactorial-neuroendocrine model, not a single-hormonal model. The main limitations of the available literature are the small number of human studies, the predominance of review or cross-sectional designs, and the fact that much of the evidence regarding progesterone comes from the literature on postpartum depression or animal models, rather than from postpartum psychosis directly.

Conclusion

Based on a literature review of 20 journals, it can be concluded that fluctuations in estrogen and progesterone levels, particularly the sharp decline following childbirth, play a significant role in the pathogenesis of postpartum psychosis, though not as a sole factor. Estrogen shows a more consistent association with the emergence of psychotic symptoms, particularly post , through its effects on the dopaminergic system, emotional regulation, and affective stability, whereas progesterone acts indirectly via its neuroactive metabolites, such as allopregnanolone, which modulate the GABAergic system and the brain's inhibition-excitation balance. Furthermore, these hormonal changes are not only related to hormone levels but also to an individual's biological sensitivity to these changes, and they interact with other factors such as genetic vulnerability, circadian rhythm and sleep disturbances, the stress system, inflammatory processes, and maternal brain neuroplasticity. Therefore, postpartum psychosis is more appropriately understood as a multifactorial neuroendocrine condition resulting from the complex interaction between postpartum reproductive hormonal changes and the mother's biological susceptibility and brain adaptive responses to these changes.

Based on these findings, it is recommended that future research employ a longitudinal design capable of simultaneously evaluating levels of estrogen, progesterone, allopregnanolone, and other neurobiological parameters from late pregnancy through the early postpartum period, thereby providing a clearer picture of the causal mechanisms underlying postpartum psychosis. Additionally, the development of a more comprehensive clinical approach is needed, including hormonal and neurobiological risk screening, as well as the exploration of therapies targeting neuroendocrine system stabilization, to improve early detection and the effectiveness of postpartum psychosis management in clinical practice.

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References

Bergink, V., Akbarian, S., Byatt, N., Chandra, P. S., Cirino, N., Dazzan, P., De Witte, L., Di Florio, A., Dolman, C., Jones, I., Kamperman, A., Mahjani, B., Meltzer-Brody, S., Munk-Olsen, T., Nagle-Yang, S., Osborne, L. M., Rasgon, N., Robakis, T., Thippeswamy, H., … Payne, J. L. (2025). Postpartum Psychosis and Bipolar Disorder: Review of Neurobiology and Expert Consensus Statement on Classification. Biological Psychiatry. https://doi.org/10.1016/j.biopsych.2025.10.016

Davies, W. (2017). Understanding the Pathophysiology of Postpartum Psychosis: Challenges and New Approaches. World Journal of Psychiatry, 7(2), 77. https://doi.org/10.5498/wjp.v7.i2.77

Deligiannidis, K. M., Kroll-Desrosiers, A. R., Mo, S., Nguyen, H. P., Svenson, A., Jaitly, N., Hall, J. E., Barton, B. A., Rothschild, A. J., & Shaffer, S. A. (2016). Peripartum Neuroactive Steroid and Y-Aminobutyric Acid Profiles in Women At-Risk for Postpartum Depression. Psychoneuroendocrinology, 70, 98–107. https://doi.org/10.1016/j.psyneuen.2016.05.010

Dukic, J., Johann, A., Henninger, M., & Ehlert, U. (2024). Estradiol and Progesterone from Pregnancy to Postpartum: a Longitudinal Latent Class Analysis. Frontiers in Global Women's Health, 5. https://doi.org/10.3389/fgwh.2024.1428494

Gilfarb, R. A., & Leuner, B. (2022). GABA System Modifications During Periods of Hormonal Flux Across the Female Lifespan. Frontiers in Behavioral Neuroscience, 16. https://doi.org/10.3389/fnbeh.2022.802530

González-Rodríguez, A., & Seeman, M. V. (2019). The Association between Hormones and Antipsychotic Use: A Focus on Postpartum and Menopausal Women. Therapeutic Advances in Psychopharmacology, 9. https://doi.org/10.1177/2045125319859973

Grötsch, M. K., & Ehlert, U. (2024). Allopregnanolone in the Peripartum: Correlates, Concentrations, and Challenges – A Systematic Review. Psychoneuroendocrinology, 166, 107081. https://doi.org/10.1016/j.psyneuen.2024.107081

Humby, T., Cross, E. S., Messer, L., Guerrero, S., & Davies, W. (2016). A Pharmacological Mouse Model Auggests a Novel Risk Pathway for Postpartum Psychosis. Psychoneuroendocrinology, 74, 363–370. https://doi.org/10.1016/j.psyneuen.2016.09.019

Humby, T., & Davies, W. (2019). Brain Gene Expression in a Novel Mouse Model of Postpartum Mood Disorder. Translational Neuroscience, 10(1), 168–174. https://doi.org/10.1515/tnsci-2019-0030

Isik, M. (2022). Investigation of Hormone Levels in Postpartum Psychosis. Dusunen Adam:The Journal of Psychiatry and Neurological Sciences. https://doi.org/10.14744/DAJPNS.2022.00171

Khedr, E. M., Ramadan, E. S., Osman, M. N., & Ahmed, G. K. (2023). Risk Factors-Related First Episode Postpartum Psychosis among Egyptian Women: the Role of Psychosocial and the Biological Factors. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery, 59(1), 51. https://doi.org/10.1186/s41983-023-00653-3

Li, H. J., Martinez, P. E., Li, X., Schenkel, L. A., Nieman, L. K., Rubinow, D. R., & Schmidt, P. J. (2020). Transdermal Estradiol for Postpartum Depression: Results from a Pilot Randomized, Double-Blind, Placebo-Controlled Study. Archives of Women's Mental Health, 23(3), 401–412. https://doi.org/10.1007/s00737-019-00991-3

Mu, E., Gurvich, C., & Kulkarni, J. (2024). Estrogen and Psychosis a Review and Future

Directions. Archives of Women's Mental Health, 27(6), 877–885. https://doi.org/10.1007/s00737-023-01409-x

Nehls, S., Losse, E., Enzensberger, C., Frodl, T., & Chechko, N. (2024). Time-Sensitive Changes in the Maternal Brain and Their Influence on Mother-Child Attachment. Translational Psychiatry, 14(1), 84. https://doi.org/10.1038/s41398-024-02805-2

Palacios-Hernández, B., Ramírez-Alvarado, G., Téllez-Alanís, B., Lino-González, A. L., Penagos-Rivera, M., & Hernández-Galván, A. (2024). Hormones, Psychotic Disorders, and Cognition in Perinatal Women: a Mini Review. Frontiers in Psychiatry, 14. https://doi.org/10.3389/fpsyt.2023.1296638

Paternina-Die, M., Martínez-García, M., Martín de Blas, D., Noguero, I., Servin-Barthet, C., Pretus, C., Soler, A., López-Montoya, G., Desco, M., & Carmona, S. (2024). Women's Neuroplasticity during Gestation, Childbirth and Postpartum. Nature Neuroscience, 27(2), 319–327. https://doi.org/10.1038/s41593-023-01513-2

Patterson, R., Balan, I., Morrow, A. L., & Meltzer-Brody, S. (2024). Novel Neurosteroid Therapeutics for Post-Partum Depression: Perspectives on Clinical Trials, Program Development, Active Research, and Future Directions. Neuropsychopharmacology, 49(1), 67–72. https://doi.org/10.1038/s41386-023-01721-1

Patterson, R., Krohn, H., Richardson, E., Pearson, C., Xia, K., Kimmel, M., & Meltzer-Brody, S. (2025). Open-Label Study of the Efficacy, Safety and Tolerability of Brexanolone in the Treatment of Adult Women with Postpartum Psychosis. General Hospital Psychiatry, 97, 237–240. https://doi.org/10.1016/j.genhosppsych.2025.10.017

Perry, A., Gordon-Smith, K., Jones, L., & Jones, I. (2021). Phenomenology, Epidemiology and Aetiology of Postpartum Psychosis: A Review. Brain Sciences, 11(1), 47. https://doi.org/10.3390/brainsci11010047

Perry, A., Gordon-Smith, K., Lewis, K. J. S., Di Florio, A., Craddock, N., Jones, L., & Jones, I. (2024). Perinatal Sleep Disruption and Postpartum Psychosis in Bipolar Disorder: Findings from the UK BDRN Pregnancy Study. Journal of Affective Disorders, 346, 21–27. https://doi.org/10.1016/j.jad.2023.11.005

Pestana, J. E., Kershaw, K. A., & Graham, B. M. (2023). The Impact of the Ovarian Cycle on Anxiety, Allopregnanolone, and Corticotropin Releasing Hormone Changes after Motherhood in Female Rats and Women. Translational Psychiatry, 13(1), 183. https://doi.org/10.1038/s41398-023-02480-9

Pinna, G., Almeida, F. B., & Davis, J. M. (2022). Allopregnanolone in Postpartum Depression. Frontiers in Global Women's Health, 3. https://doi.org/10.3389/fgwh.2022.823616

Reddy, D. S. (2023). Neuroendocrine Insights into Neurosteroid Therapy for Postpartum Depression. Trends in Molecular Medicine, 29(12), 979–982. https://doi.org/10.1016/j.molmed.2023.07.006

Sha, Q., Achtyes, E., Nagalla, M., Keaton, S., Smart, L., Leach, R., & Brundin, L. (2021). Associations between Estrogen and Progesterone, the Kynurenine Pathway, and Inflammation in the Post-Partum. Journal of Affective Disorders, 281, 9–12. https://doi.org/10.1016/j.jad.2020.10.052

Thippeswamy, H., & Davies, W. (2021). A New Molecular Risk Pathway for Postpartum Mood Disorders: Clues from Steroid Sulfatase–Deficient Individuals. Archives of Women's Mental Health, 24(3), 391–401. https://doi.org/10.1007/s00737-020-01093-1

Toor, R., Wiese, M., Croicu, C., & Bhat, A. (2024). Postpartum Psychosis: A Preventable Psychiatric Emergency. Focus, 22(1), 44–52.

https://doi.org/10.1176/appi.focus.20230025

Tsokkou, S., Kavvadas, D., Georgaki, M.-N., Papadopoulou, K., Papamitsou, T., & Karachrysafi, S. (2024). Genetic and Epigenetic Factors Associated with Postpartum Psychosis: A 5-Year Systematic Review. Journal of Clinical Medicine, 13(4), 964. https://doi.org/10.3390/jcm13040964

Meltzer-Brody, S., Howard, L. M., Bergink, V., Vigod, S., Jones, I., Munk-Olsen, T., ... & Milgrom, J. (2018). Postpartum psychiatric disorders. Nature reviews Disease primers, 4(1), 1-18. https://doi.org/10.1038/nrdp.2018.22

Sit, D., Rothschild, A. J., & Wisner, K. L. (2006). A review of postpartum psychosis. Journal of women's health, 15(4), 352-368. https://doi.org/10.1089/jwh.2006.15.352

Sanadi, R., Raj, E. A., Kuppusamy, C. V., Arasappa, R., & Chandra, P. S. (2026). Navigating postpartum psychosis: perspectives, needs, expectations and experiences of women and their families–a systematic review. Archives of Women's Mental Health, 29(2), 40. https://doi.org/10.1007/s00737-025-01669-9

Camoni, L., Bernardini, C., & Gigantesco, A. (2026). Antepartum and Postpartum Mental. Telepsychotherapy and Mental Health Services: Evidence-based Therapeutic Approaches, 295.

Özdilek, R., Aksoy, S. D., & Dincel, Y. (2026). Effect of Postpartum Mood Education on Maternity Blues and Postpartum Depression in Mothers: A Randomized Controlled Trial. Journal of Holistic Nursing, 08980101261435463. https://doi.org/10.1177/08980101261435463

Wenzel, E. S., Frye, R., Roberson-Nay, R., & Payne, J. L. (2025). The neurobiology of postpartum depression. Trends in Neurosciences. https://doi.org/10.1016/j.tins.2025.05.005

Raji, H., Dinesh, S., & Sharma, S. (2025). Inside the impulsive brain: a narrative review on the role of neurobiological, hormonal and genetic factors influencing impulsivity in psychiatric disorders. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery, 61(1), 4. https://doi.org/10.1186/s41983-024-00930-9

Naoi, M., Wu, Y., Maruyama, W., & Shamoto-Nagai, M. (2025). Phytochemicals modulate biosynthesis and function of serotonin, dopamine, and norepinephrine for treatment of monoamine neurotransmission-related psychiatric diseases. International journal of molecular sciences, 26(7), 2916. https://doi.org/10.3390/ijms26072916

Mallick, K., Ruwatia, R., Mondal, A. C., & Banerjee, S. (2026). Neurosteroids in Neurological and Psychiatric Disorders: Therapeutic Implications. CNS & Neurological Disorders-Drug Targets. https://doi.org/10.2174/0118715273411580251203115939