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Peripartum depression: current considerations on classification, biological importance, and therapeutic potential of neuroactive steroids

Peripartalna depresija: aktuelna razmatranja o klasifikaciji, biološkom značaju i terapijskom potencijalu neuroaktivnih steroida

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Introduction

Various research results indicate that peripartum depression (PED) occurs in 13–19% of mothers, although there is no precise data [1, 2]. Extensive epidemiological studies of PED have not been conducted in Serbia, and the results generated on smaller samples (n = 195, n = 120) showed that postpartum depression occurred in 11% [3], i.e., 23.3% [4] of women, respectively. The estimate is that 50% of women with depression during pregnancy or postpartum are not diagnosed or treated [5]. If not diagnosed or treated, in addition to the negative effect of the disorder on the patients, PED can negatively impact the child's health and lead to dysfunctional dynamics in the whole family. In extreme cases, outcomes of untreated peripartum depression can be suicide or infanticide [6]. Suicidality is increased in women during the peripartum period [7, 8], and a recent study [8] demonstrated that the prevalence of suicidality in individuals with depression or anxiety occurring in the year preceding or following birth increased significantly from 2006 to 2017. Maternal suicide accounts for up to 20% of all postpartum deaths, representing one of the leading causes of maternal mortality in the perinatal period [6]. Untreated PED can compromise the attachment process in mother-infant dyad, cause the cessation of breastfeeding, lead to infant neglect and abuse, imposing a series of short- and long-term adverse effects on the child [9]. In this paper, we will put a spotlight on current dilemmas regarding diagnostic criteria for PED through classification systems, their applicability in an everyday clinical practice setting, as well as new evidence on the biological importance of neuroactive steroids and their potential for the development of new pharmacotherapeutic options.

Postpartum depression or peripartum depression?

In the International Classification of Diseases (ICD-10), the tenth revision currently in use in the Republic of Serbia, "Mental and behavioral disorders associated with the puerperium (starting within six weeks of birth)", represents a distinct category. Within this category, PED and postnatal depression could only be classified as a subcategory of mild mental and behavioral disorders, which is not elsewhere classified. It represents a spectrum of mood changes in the postpartum period (PP), including transient postpartum sadness, postpartum depression (POD), and postpartum or puerperal psychosis [10]. With this, ICD-10 excludes the possibility of diagnosing POD in patients whose symptomatology fulfills the criteria for moderate or severe depression with or without psychosis. In such patients, in everyday clinical practice, clinicians usually diagnose major depression without any determinant regarding pregnancy. National Guidelines for the Treatment of Depression issued by the Ministry of Health of the Republic of Serbia in 2013 recognize depression during pregnancy and POD as distinct clinical entities with recommendations for its treatment [11].

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Contrary to ICD-10, The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), offers more precise criteria for depression related to pregnancy and/or delivery, placing it as one of the specifiers of major depressive disorder – "with peripartum onset". This specifier can be added to the diagnosis of a major depressive episode regardless of its severity as long as symptoms that meet the diagnostic criteria for depression occur during pregnancy or four weeks after delivery [12]. DSM-5 has made a major step forward in the classification of peripartum mood disorders, given that a growing body of research evidence indicates that nearly 50% of peripartum depressive episodes have their onset during pregnancy [13, 14].

The Eleventh Revision of the International Classification of Diseases (ICD-11), which is effective as of January 1st, 2022, recognizes as a distinct diagnostic category "a syndrome associated with pregnancy or the puerperium (commencing within about six weeks after delivery) that involves significant mental and behavioral features, most commonly depressive symptoms" [15]. The name of this clinical-diagnostic entity – "postpartum" or "postdelivery" depression, has become rooted both among healthcare professionals and the general population. An increasing number of studies indicate that approximately 50% of peripartum depressive episodes have their onset during pregnancy, most often in the third trimester, and can deteriorate significantly in PP [13, 14, 16]. The international perinatal psychiatric consortium for POD conducted a large study examining the heterogeneity of a sample of 6,556 women with POD. Among the patients with the most severe symptomatology (n = 730), 67% had the onset of symptoms during pregnancy [14]. A study [17] conducted in 2019 on a sample of 2,466 participants from a large population cohort in Sweden examined the timing of the onset of PED and its association with various risk factors. This study showed that 60.6% had no depression, 8.5% had developed depression during pregnancy, 10.9% had depression with early postpartum onset, 5.4% with late postpartum onset, and 14.6% had chronic depression. There is also evidence that suggests that PED may occur within 12 months after delivery [17, 18]. Research data indicate that the peak time of the onset of PED symptoms occurs between the second and third postpartum month [19].

Insufficiently comprehensive diagnostic criteria for PED may have several implications for everyday clinical practice. Although progress is made through new revisions of the DSM-5 and ICD-11 classification systems, there appears to be a large discrepancy between narrow time windows proposed by diagnostic criteria and a growing body of evidence indicating a much broader time range for the manifestation of the disorder. That can lead to the failure of documenting this disorder with unreliable prevalence, especially in developing countries that do not have screening programs for peripartum depression. That may also contribute to underdiagnosing and, thus, undertreatment and insufficient research on this disorder. The lack of sufficiently comprehensive diagnostic categories can be an issue for both physicians and patients who develop mood disorder symptoms in the peripartum period. It may mislead the physician to a different therapeutic approach, and in administrative terms, it may limit patient access to certain specialized programs or new therapeutic options for peripartum depression. That can especially be a problem in countries with restricted healthcare budgets, where health insurance funds are forced to additionally restrict the criteria for reimbursement of certain medicines compared to official diagnostic criteria or the registered indication of the drug due to the high prices of innovative drugs.

The abovementioned imperfections of current classification systems must not be a barrier to the detection and treatment of peripartum depression. The term peripartum depression, accepted by DSM-5 classification, can be a strong signal for both clinicians and the general population that pregnant women can also develop mood disorder that requires treatment.

It is a widespread belief in the general population, and among clinicians as well, that pregnancy is a protective factor when it comes to mental health, but the situation is different. Research data indicate that many psychopathological manifestations occur during pregnancy for the first time [20]. Only 25% of women who develop symptoms of PED report symptoms to their physician. In addition, there is a tendency to minimize these symptoms both by the mothers themselves and healthcare workers, attributing them to physiological consequences of childbirth [21]. More intensive and comprehensive strategies for raising awareness and psychoeducation about this disorder are necessary. Furthermore, the diagnostic approach for PED should be more proactive and incorporate an extensive network of healthcare professionals who engage with pregnant women and women in the PP. There are currently no official programs or recommendations for screening for PED in the Republic of Serbia. Experiences from developed countries show that screening for PED led to an increase in diagnosis and treatment of the disorder only when specialized treatment was available. Moreover, some data show that screening for PED in the presence of an appropriate treatment program improves the treatment outcomes [22]. One study [23] showed that even when screening was mandatory, it did not lead to higher rates of treatment for POD – it led to high screening rates, but there were low rates of transition to treatment programs. One large cohort study [24] conducted in the USA on pregnant women (n = 97,678) examined the rates of screening and treatment before, during, and after the implementation of a universal perinatal screening program for depression in one obstetric clinic. Not only did this study show a significant increase in screening rates but also an increase in the number of women treated for depression. The authors emphasized that the main advantage of such a program was the well-established cooperation of obstetric clinics with healthcare professionals in the field of mental health. The authors also point out that, in this case, well-established and easily accessible ways of referring patients within the health system contributed to improved treatment outcomes.

Considering the great importance of diagnosing and treating PED, the development of a targeted national screening program for PED is imposing itself as a necessity. Furthermore, there is an unmet need for the development and implementation of well-established clinical pathways with well-defined steps – from suspected PED identified by screening to evaluation and evidence-based treatment in specialized mental health services. Given the number of different medical specialties that come into contact with women during the peripartum period, there is a big responsibility of each professional association to address the problem of PED in their guidelines and recommendations. However, great strides can be made at the individual level, including general practitioners, obstetricians, gynecologists, nurses and technicians in gynecological services, community nurses, pediatricians, as well as employees in mental health services. Their engagement and proactive approach in screening for PED and timely referral add great value to the overall management of the disorder.

Current considerations on the biological importance of neuroactive steroids in the development of peripartum depression

A plethora of biological and psychosocial research has demonstrated that the etiology of PED is multifactorial, with complex yet not completely understood underlying pathophysiology that leads to a myriad of different phenotypes [14, 25]. Here, we scrutinize recent research on the role of neuroactive steroids in the development of the disorder and the implications they have on the development of new pharmacological options for PED. We particularly focused on recent research on the interplay of perinatal neuroactive steroids perturbations with the hypothalamic-pituitary-adrenal (HPA) axis, gamma-aminobutyric acid (GABA)-mediated neurotransmission, and neuroinflammation.

Studies have demonstrated that basal cortisol concentrations increase during pregnancy, reaching their peak in the last weeks. In days and weeks after delivery, there is a decrease in corticotropin-releasing hormone (CRH) and cortisol concentrations, and that decrease was related to the development of depression with postpartum onset. It has also been shown that lower cortisol concentrations registered in women with POD are maintained for up to 12 months after delivery [26]. The inability to suppress the induced activation of the HPA axis during pregnancy and the PP is considered to play a dominant role in the pathogenesis of PED [27]. Some nonclinical studies [28, 29] have shown a critical role for K+/Cl- co-transporters – (KCC2) in GABA-mediated regulation of CRH neurons in the paraventricular nucleus of the hypothalamus and subsequent regulation of stress-induced HPA axis activation. These studies have demonstrated the role of chloride homeostasis in regulating the physiological stress response. Data from nonclinical studies indicate that HPA axis suppression during pregnancy and the PP is mediated by normal maintenance of KCC2 expression in the paraventricular nucleus of the hypothalamus. On the contrary, selective loss of KCC2 in neurons with CRH results in the inability to suppress the HPA axis during pregnancy and PP, which was related to anxiety and depression-like behavior in mice. A recent study [29] directly linking the HPA axis and PED in mice showed that chemogenetic "silencing" of CRH neurons in the periventricular nucleus of the hypothalamus might improve abnormal postpartum behavior observed in mice with selective KCC2 loss. These data suggest that regulation of KCC2 activity is a potential target for developing new pharmacological options for peripartum depression.

As indicated above, there is a functional connection between GABA transmission and HPA axis dysfunction, and studies have shown that disrupted GABA signaling results in the absence of HPA axis suppression in PED [29–31]. During pregnancy and in the PP, there are significant changes in the concentrations of neuroactive steroids – metabolites of steroid hormones that manifest their effects in the central nervous system [32]. It has been shown in animal models that the neuroactive metabolite of progesterone, allopregnanolone, exerts anxiolytic and antidepressant effects that are considered to be mediated, at least partially, by its ability to potentiate GABA receptors by positive allosteric activity [33].

The GABA system adapts to changes in the concentrations of neuroactive steroids during pregnancy [34, 35]. Allopregnanolone concentrations increase during pregnancy and reach their maximum during the third trimester [36–38], followed by a steep drop in concentration after delivery [39]. As neuroactive steroid concentrations increase during pregnancy, GABA type A ($GABA_A$) receptors downregulate. Under physiological conditions, postpartum concentrations of neuroactive steroids lead to the re-expression of $GABA_A$ receptors. It is hypothesized that in PED, the level of $GABA_A$ receptor expression does not return to the previous one, leading to impaired neuroplasticity of $GABA_A$ receptors and the absence of a homeostatic mechanism that maintains the ideal level of $GABA_A$ transmission in response to fluctuating neurosteroid concentrations [34, 35]. These findings on the role of neuroactive steroids and $GABA_A$ receptor regulation in the pathophysiology of POD represent an important basis for developing innovative therapeutic options for PED.

Another important mechanism that shed light on the area of the pathophysiology of PED in this research is the interrelationship of neuroactive steroids, neuroinflammation, and tryptophan catabolism. In physiological conditions, pregnancy is characterized by a balance between inflammatory and anti-inflammatory mechanisms [40]. These mechanisms progress towards the preponderance of a "proinflammatory state" while approaching end-of-term pregnancy [40] leading to increased immune regulatory processes, partly via immune mechanisms and partially via increased HPA-axis activity and progesterone levels [41]. As discussed, these mechanisms could be disrupted after delivery leading to increased serum levels of proinflammatory cytokines. Although the overall data from studies are not convincing [40], some of them significantly

and positively associated increased levels of interleukin (IL)-6 [42–44], IL-1β [42], tumor necrosis factor (TNF)-α [43], and IL-8 [44] with depressive symptoms in postpartum women. It is implicated that increased levels of proinflammatory cytokines activate and shift tryptophan metabolism towards its degradation via the kynurenine pathway, which limits serotonin production and leads to an imbalance of neurotoxic and neuroprotective tryptophan catabolites that compromise glutamatergic neurotransmission contributing to depressive and anxiety symptoms in women with POD [44]. Furthermore, besides neuroinflammation, there is some evidence that both progesterone and estrogen have their role in regulating tryptophan degradation by suppressing two important enzymes of the kynurenic pathway – indoleamine 2,3 dioxygenase (IDO) [45] and tryptophan decarboxylase (TDO) [46]. These mechanisms could be important in PED since the placenta exhibits high expression and activity of these kynurenine pathway enzymes [47] and knowing that there is a dramatic drop of estrogen and progesterone after childbirth that could potentially contribute to increased tryptophan catabolism with already described effects.

The pharmacotherapeutic potential of neuroactive steroids in peripartum depression

Currently, pharmacotherapeutic interventions in PED, as well as in other disorders related to women's hormonal transition phases, mainly consist of off-label use of monoaminergic antidepressants approved for the treatment of major depressive disorder [11, 48–52]. To date, no drug in the Republic of Serbia nor the European Union has received regulatory approval for PED. This situation created a huge unmet need for developing specific, effective therapies for treating peripartum depression. The development of new therapeutics for PED was primarily determined by progress in elucidating the complex pathophysiology of the disorder, but also the delicacy of conducting clinical trials in this population of patients.

The already mentioned role of allopregnanolone in the positive allosteric modulation of GABA receptors was the scientific basis for the development of brexanolone, the first specific therapy approved by the United States Food and Drug Administration (FDA) for the treatment of POD in adults in 2019 [53]. Due to the poor oral bioavailability of allopregnanolone and its rapid metabolism, an analog of allopregnanolone – brexanolone, whose intravenous application achieves stable serum concentrations, has been developed [54]. The exact mechanism of action of brexanolone is not completely clear. However, it is considered that brexanolone offers women with POD comparable concentrations of allopregnanolone with concentrations of endogenous allopregnanolone in the third trimester of pregnancy, providing additional time for physiological adaptation to abruptly reduced concentrations of endogenous allopregnanolone. In addition, since it acts as a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors, it thus exhibits acute anxiolytic and antidepressive effects [55]. Brexanolone was registered based on efficacy and safety studies in one open-label proof of concept study, one double-blind placebo-controlled phase 2 study, and two double-blind, placebo-controlled phase 3 studies [54–56].

Both phase 2 [54] and two-phase 3 studies [56] enrolled patients whose onset of PED was during the third trimester of pregnancy or within four weeks of delivery. Enrolled patients had severe depressive episodes at the start of treatment in phase 2 and the first phase 3 study and moderately severe depression in the second phase 3 study. In all three studies, brexanolone was administered as a continuous intravenous infusion for 60 hrs, with dose titration.

In phase 2 study [54] (n = 21), brexanolone showed a significant effect compared to placebo in the reduction in Hamilton Depression Rating Scale–Depression (HAM-D) overall score at 60 hrs post-infusion. In phase 3 studies with a larger number of patients (n = 122, n = 104), considerably smaller yet statistically significant effects were demonstrated [56]. In phase 2 study and the first phase 3 study, the achieved effects of the drug on the reduction of HAM-D scores were sustained until day 30 (longest follow-up). In the second phase 3 study, there was no difference between brexanolone and placebo on day 30 on the reduction of HAM-D scores [54, 56]. A pooled safety analysis from placebo-controlled studies on 140 patients with POD who received brexanolone showed that adverse events (AEs) leading to dose reduction or discontinuation of therapy were related to excessive sedation (loss of consciousness, syncope, somnolence, dizziness, fatigue), infusion site reactions, changes in blood pressure, or infusion pump dysfunction. Due to serious AEs in the form of sedation, somnolence, and loss or altered state of consciousness, FDA approved brexanolone with significant restrictions. The drug may be administered only in specialized and certified institutions with trained health care staff with the obligation of risk assessment and risk mitigation strategy implementation and constant patient monitoring for hypoxia using a pulse oximeter with an alarm for all 60 hrs of continuous drug administration. The drug has not been tested on pregnant women and should not be used during pregnancy [57].

Presented data suggest that treating patients with PED with this drug would be possible only in carefully selected cases, with extreme caution. Given that the longest follow-up in brexanolone studies was only 30 days, it is still unclear what the long-term treatment outcomes are. Gathering these data outside controlled clinical studies in everyday clinical practice would be very valuable for making more informed therapeutic decisions. Another pitfall that could hinder the widespread use of brexanolone in everyday clinical practice is the need for its administration in the inpatient setting, even if the presenting patient symptomatology does not require hospitalization. That would lead to early mother-infant separation with a tendency to its short and long-term implications. The manufacturer of brexanolone is currently developing another compound for the treatment of POD – zuranolone, with recently completed phase 3 clinical trial [58], which we appraise below. Zuranolone is an oral formulation with a similar pharmacological profile as brexanolone,

exerting its action as a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors. While brexanolone is identical to allopregnanolone, zuranolone has a neuroactive steroid base that has been chemically modified to increase its oral bioavailability. In this phase 3, double-blind, placebo-controlled study (n = 153), zuranolone was administered orally once a day in patients with severe POD. Zuranolone improved symptoms of depression compared to placebo on day three, and the improvement was sustained until the forty-fifth day (longest follow-up), even with dosing cessation after 2 weeks. In this trial, zuranolone led to rapid and sustained improvements in anxiety as well as improved global and maternal functioning compared with the placebo, despite the relatively high placebo response observed in this trial. Zuranolone was well-tolerated. The same percentage of treatment-emergent AEs was recorded in both groups, with three patients in the zuranolone group (sedation, n = 1; confusional state, n = 1; migraine, n = 1). In the zuranolone group, one patient discontinued because of an AE (intermittent sedation). The most common AEs in the zuranolone group were somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, sedation, and nausea. Unlike brexanolone, zuranolone in this outpatient randomized clinical trial did not lead to any notable or clinically significant changes in vital signals or electrocardiograms. No evidence for increased suicidal ideation or suicidal behavior was observed compared with the baseline, measured by the Columbia-Suicide Severity Rating Scale. These data from the zuranolone study are very encouraging considering the oral route of administration in the outpatient setting, fast response, and rapid achievement of remission with a favorable safety profile. Furthermore, in addition to improvement of clinician-rated measures of depression, anxiety, and global functioning, an important differentiator for zuranolone is the evidence of improved maternal functioning at day 45 recorded as a patient-reported outcome measure. What we see as the downside of presented data is the lack of long-term treatment outcomes as well as the safety of the drug in breastfeeding mothers. Moreover, what may narrow the indication field of use for this drug is the fact that zuranolone is currently investigated only in patients with severe POD, while patients who require treatment mostly have mild and moderately severe POD. With all the available data for these two innovative neuroactive steroid $GABA_A$ receptor-positive allosteric modulators, it seems more likely that zuranolone, if approved by health authorities, has greater potential than brexanolone to become the new standard of care for patients with severe PED with broader adoption in clinical practice.

Conclusion

The research data show that PED may occur during pregnancy, most often during the third trimester and within one year after delivery. Complex interactions of neuroactive steroids, neuroinflammation, and neurotransmitters represent an area of intensive research in an attempt to elucidate the biological basis of PED but also an area that stimulates the development of new pharmacotherapeutic options. Data from late-stage clinical trials of brexanolone and zuranolone are promising but more evidence from everyday clinical practice on long-term safety, efficacy, and functional outcomes would better inform new therapeutic algorithms for peripartum depression. There is still an urgency to do research both on underlying pathophysiology and the development of new medications for PED since this area is lagging far behind other affective and other mental health disorders.

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