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CREATIVE PERSON-CENTERED PSYCHOPHARMACOTHERAPY IN THE CONTEXT OF PRENATAL PSYCHIATRY - DILEMMAS AND CHALLENGES

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SUMMARY

The authors presented a psychopharmacotherapeutic approach to the treatment of women in the prenatal period that requires a personalized, person-centered treatment plan. Treatment should include care for the mental health of women of childbearing age, pregnancy planning, during the prenatal period, and then during the postpartum period. The authors highlighted creative psychopharmacotherapy which is the foundation of holistic and integrative treatment of mental disorders. They emphasize the significant role of the mother in the emotional development of the child, which begins while the child is still in the womb. Mothers who stop taking psychotropic drugs during pregnancy have an increased risk of recurrence of the mental disorder after childbirth because the mother's psychiatric illness is not a benign event and can cause significant morbidity for both the mother and her child, therefore, discontinuation or denial of medication during pregnancy is not always the safest option. For more serious disorders, such as schizophrenia, bipolar disorder, and severe depression, medications may be needed during pregnancy and lactation, despite complex evidence based on the effects of psychotropic medications on the fetus and newborn. Perinatal mental health has become a significant focus of interest in recent years. The randomized controlled examinations provide evidence of the effectiveness of psychological and psychosocial interventions at the individual level. It is necessary to make a new conceptual shift in the approach to maintaining the mental health of pregnant women and newborns, and that is to optimize the mental health of pregnant women, and not simply reduce the symptoms of mental disorders from which they suffer before conception, during pregnancy and after childbirth. Dilemmas and challenges of psychopharmacotherapeutic treatment in the prenatal period are intensified by the knowledge that the psychological difficulties of mothers can significantly affect the integrity of the safe relationship between mother and child, which is essential for the emotional, cognitive, and behavioral development of the child. Often, these problems existed before pregnancy or occurred during pregnancy, and they are often the deterioration of the mental state due to discontinuation of pharmacotherapy during this period.

The quality of the biopsychosocial milieu in the fetal period and childhood during the early neuroplastic development phase is one of the determinants of risk for diseases during the life cycle. For this reason, the mental health of pregnant women and mothers must be optimized. For many of these women, health is optimized with pharmacotherapy.

Key words: *creative person-centered psychopharmacotherapy - prenatal psychiatry - mental disorders*

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INTRODUCTION

Creative psychopharmacotherapy is the foundation of holistic and integrative treatment of mental disorders. According to many experts, psychopharmacotherapy on its own is generally not sufficient enough for a complete recovery (Jakovljavić 2013).

Pharmacotherapy which focuses on a person always includes an individualized approach because every patient is a one-of-a-kind individual who consists of body, mind, and soul. Sensitivity to different medications varies from one individual to another. Patients' active participation in the treatment is an essential part of person-centered pharmacotherapy which can significantly contribute to better treatment adherence. Patients are not only carriers of symptoms, diseases, or illnesses, they are primarily human beings, persons, and personalities with their power, autonomy, needs, values, desires, life purpose (Jakovljević 2014).

Modern psychiatry in the last century has proposed several aggregative biopsychosocial models as opposed to the predominant fragmented, reductionist, and dogmatic approaches. Postmodern psychiatric alternatives emerged as pluralism and integration. The holistic and integrative approach in medicine and psychiatry was built upon the assumption that human beings are, in health and sickness, complex systems with dynamic interactions of biological, psychological, social, energetic, informational, and spiritual processes (Jakovljević 2008, 2021).

Perinatal mental health is in a focus of interest for centuries and up until recently, this interest was mostly focused around postpartum psychosis and depression, with relatively little funding for individual-level treat-

ment research as well as investment in specialist services and public health interventions. However, that is starting to change (Howard & Khalifeh 2020).

Psychopharmacotherapeutic approach to the treatment of women in the prenatal period requires a personalized, person-centered treatment plan because it is a complex treatment that includes care for the mental health of the future mother, which is essential for the healthy development of the child. Treatment should include care for the mental health of women of childbearing age, pregnancy planning, during the prenatal period, and then during the postpartum period. In the literature, we find that 50% of pregnancies are unplanned (Erdeljić Turk & Vitezić 2017) and that the teratogenic potential of the drug is most pronounced from the 17th to the 60th day after conception in the phase of organogenesis (Bajs Jovanović et al. 2017). The effect of the drugs in the early and most sensitive stage of yet undiscovered pregnancy is often questioned (Erdeljić Turk & Vitezić 2017). In the basic recommendations on the use of psychopharmaceuticals we find that it is necessary to discuss in great detail if the therapy has a higher risk for the pregnant woman and/or child or does it have benefits, then when is it possible to choose non-drug therapy. Psychopharmaceuticals should be used at the latest gestational age, as short as possible and using the minimum dosage, monotherapy is preferred, drug selection should be individualized depending on the clinical picture and possible previous patient experience and in accordance with the classification of psychopharmaceuticals Food and Drug Administration (FDA) and it is necessary to achieve maximum possible cooperation with the patient and her family members (Bajs Jovanović et al. 2017).

This should be an incentive for clinicians to consider the aforementioned when planning psychotherapeutic treatment for women of childbearing age. An adequate treatment plan requires a good understanding of psychopharmacotherapy in the prenatal period.

After the appearance of atypical antipsychotics, the fertility of women with schizophrenic disorder had also increased. The potential short-term and long-term risks of using antipsychotics, as well as the risks of their omission in the treatment of psychotic mothers that would lead to potential deterioration of the mental state, pose a complex question in determining the optimal approach to treating women during pregnancy (Sikirica 2016).

Even though the data, gathered in the last 30 years, suggests that some drugs can be safely used during pregnancy, the knowledge on the risks of prenatal exposure to psychotropic drugs is still incomplete. Therefore it is very common for patients to stop or avoid pharmacological treatment during pregnancy (Anonymous 2020). Mothers that stop taking psychotropic drugs during pregnancy have a higher risk of relapse after childbirth (Feldman & Almeida 2019).

Perinatal mental health has become a significant focus of interest in recent years, with investments in new specialist mental health services in some high-income countries and inpatient psychiatric units for mothers and babies in a variety of settings. Perinatal mental disorders are among the most common morbidities of pregnancy and make an important contribution to maternal mortality, as well as detrimental outcomes for newborns, infants, and children. Randomized, controlled examination provides evidence on the efficiency of psychological and psychosocial interventions on an individual level, although it is still uncertain which women with perinatal mental disorders also need additional parenting support. The evidence base on the usage of psychotropic drugs in pregnancy is almost exclusively based on observation. Overall, there is little research on the spectrum of perinatal mental disorders, on how to improve access to treatment of women with psychosocial difficulties, and on the effectiveness of different service delivery models. There is an urgent need to expand generic psychiatric services to include conception care and further investment in public health interventions in addition to existing perinatal mental health services for both women and men, to reduce maternal and child morbidity and mortality (Howard & Khalifeh 2020).

THE ROLE OF THE MOTHER IN THE EMOTIONAL DEVELOPMENT OF THE CHILD

When we talk about psychopharmacotherapy in the context of prenatal psychiatry it is important to emphasize the significant role of the mother in the emotional development of the child (Hasanović 2021).

In this section, we will touch upon a few reasons why everything should be done in the field of psychiatry, both pharmacotherapeutic and psychotherapeutic in terms of stabilizing the mother's mental state during pregnancy and after childbirth, which will ensure that maternal care is optimal (Sikirica 2016). Considering that some mental disorders occur before or during the pregnancy, and the symptoms of the illness are discovered only after childbirth, and since we know the importance of the mother-child relationship early on for the emotional development of the child, it is important to carefully monitor the mental state of the mother during these sensitive phases.

The bond between the mother and child begins while the child is still in the womb. Assessment of fetal behavior provided a promising opportunity to understand the latent function of the developmental pathway of the fetal central nervous system (Hasanović 2021). After the assesment of the normal neurobehavioral development using a four-dimensional (4D) ultrasound, attempts were made to identify the functional characteristics of the fetus which can predict a range of developmental dysfunctions that accompany those characteristics (Kurjak et al. 2012).

The mother-child relationship takes shape during childbirth and develops throughout life, especially within the first years of the child's life. The relationship that the mother has with her child and her mental state will affect the child's self-image later in life, how it feels around itself and how it views the world (Kostić 2018). The child's earliest emotional experiences take place inside the family, therefore the relationship with the parents in early childhood is a model for forming future relationships. Even though the emotional development of the child partly depends on the innate predispositions, it largely depends on the compliance of the child's needs with the expectations and behaviors of the environment in which the child grows up. Crucial to a child's balanced emotional development is the earliest relationship with the mother. In the first few months of the child's life, her face gives the first and most important information about the emotional world with which the child will later on begin to harmonize (Laible & Thompson 1998). Bowlby's observations led him to believe not only that the child's relationship with the mother was important for later functioning, but also that the relationship was crucial to the child. Bowlby, along with his colleague James Robertson, observed that children experience great distress when separated from their mothers, even if they have been fed and cared for by others (Cassidy & Shaver 2008). Freud was the first to claim that the emotional connection between the mother and child is an important foundation for future relationships with other people (Berk 2015, Lipovac 2018). The child, through the process of breastfeeding, holding, and face to face contact, usually first develops attachment to the mother and only then to other caregivers (Ainsworth 1979).

If the mother's mental state is not adequate after the birth, either due to a depressive disorder or some other psychiatric disorder from the psychotic spectrum, it can negatively affect and interfere with the normal relationship between the child and the mother. Looking at the mother-child relationship through the prism of Bowlby's attachment theory which describes the particularity of the mother-child affectionate bond at that early stage of life to highlight the particularity of the child's tendency to seek relationships with others, for an object that adequately meets his needs. Through this connection with the mother, the child also develops the stability of his mental apparatus (Sikirica 2016).

Pregnancy and the postpartum period are associated with an increased risk of developing depressive symptoms in women. Postpartum depression affects approximately 10-15% of women and disrupts the mother-newborn interaction which is important for the development of the child. Maternal attachment, sensitivity, and parenting style are key to the healthy maturation of a child's social, cognitive, and behavioral skills, and depressed mothers often show less attachment, sensitivity, and sharper or disturbed parental behaviors, which can contribute to negative outcomes for the child (Brummelte & Galea 2016).

Current perinatal mental disorder classifications are confusing, which partly maintains the discussion on whether these disorders are unique in their causes and psychopathology, or are they the same as mental disorders in other periods of a woman's life. Recent evidence suggests that even within individual diagnostic constructs, there are different phenotypes of postpartum depression, with the potential need for different interventions and services (Putnam et al. 2017).

Although the research on children with parents who suffer from mental disorders is on the rise, few researchers have examined the long-term impact of parents' mental disorders on children who have reached adulthood. These children are exposed to a higher risk of weaker social, physical and mental health in comparison to children in families that have not been affected by parental mental disorders, and without existing protective factors, this risk can pass into adulthood (Patrick et al. 2019).

PSYCHOPHARMACOTHERAPY IN THE PRENATAL PERIOD

Pregnancy is a period in which the optimal application of psychopharmacotherapy is the most difficult and responsible to perform, in order to carry it out it is necessary to have complete knowledge and understanding of the individual characteristics of the pregnant woman, her illnesses, previous experiences of possibly taking psychopharmaceuticals, and in-depth understanding of every individual psychopharmaceutical. Women with a history of psychiatric disorders often come to counseling regarding taking psychotropic medications during pregnancy. Psychiatric disorders often appear for the first time during pregnancy. Many pregnancies are not planned and they can occur unexpectedly while women use psychotropic medication. A large number of women stop taking the medication after discovering their pregnancy, which can pose a significant risk. Many of them stop taking medication after learning they are pregnant, which can pose a significant risk. Decisions to initiate or maintain treatment during pregnancy must reflect an understanding of the risks associated with fetal exposure to a particular drug, but the risks associated with untreated maternal psychiatric illness must also be considered. Maternal psychiatric illness is not a benign event and can cause significant morbidity for both the mother and her child, therefore, discontinuation or denial of medication during pregnancy is not always the safest option (Anonymous 2020).

We find in the literature that the best way to prevent postpartum depression is to prevent prenatal depression, if prenatal symptoms are ignored, the risk of exposure to postpartum depression increases. If we overestimate the risks of drugs before childbirth and underestimate the mental health of the mother before childbirth, we could see an increase in postpartum depression and ultimately risk harm to both mother and child (Feldman & Almeida 2019).

Risks of using psychotropic drugs

Upon prescribing medication during pregnancy, the following risks associated with prenatal exposure should be considered: risk of teratogenesis, risk of neonatal toxicity, and risk of long-term neurobehavioral repercussions (Anonymousa 2020).

Medication that could harm the embryo/fetal development is called teratogen. The probability that exposure to a teratogenic drug leads to negative outcomes depends on several factors: drug dose and duration of exposure, gestational age during exposure, individual susceptibility to exposure, and cumulative exposure to teratogen (Erdeljić Turk & Vitezić 2017). The most pronounced teratogenic potential occurs in the period from 17 to 60 days after conception, during this period drug treatment is not recommended (Bajs Janović et al. 2017). Typical manifestations of teratogenesis are fetus death, growth retardation, organ malformations (morphological and/or functional), and carcinogenesis (Huić & Bilušić 2002). Neonatal toxicity or perinatal syndromes (sometimes referred to as "neonatal withdrawal") refer to the range of physical and behavioral symptoms observed in the neonatal period that can be attributed to drug exposure in the prenatal period. And if the data suggest that some drugs can be used safely during pregnancy if clinically justified, our knowledge of the long-term effects of prenatal exposure to psychotropic drugs is incomplete (Anonymous 2020).

Due to ethical restrictions, there is a small number of available data on the usage of psychotropic medication during pregnancy (Ranđić 2015). The US FDA is very careful and does not issue a permit for the use of this drug in pregnancy until there is enough information that a drug is not harmful. Nevertheless, based on substantiated data, the FDA has made certain recommendations by classifying existing psychopharmaceuticals according to the degree of risk to the child (Bilušić 2019).

Antipsychotics and pregnancy

The usage of antipsychotics during pregnancy and lactation poses a complex evaluation on the period and length of the therapy, dosage, and sensitivity of the fetus. Of antipsychotics in pregnancy, and it is generally advised to avoid pharmacological treatment and caution when prescribing drugs due to the risk of perinatal and neonatal complications caused by drugs. Mental disorder, on its own, is a risk factor during pregnancy and especially psychotic state. Maternal schizophrenia is associated with an increased risk of stillbirth, neonatal death, premature birth, decreased birth weight, and gestational age for children of schizophrenic mothers. The risk of perinatal psychosis is 0.1-0.25% in the general population and about 50% in women with a history of bipolar disorder. In the month after childbirth, the increase in the risk of psychosis is 30-50% (Bajs Janović et al. 2017).

First-generation antipsychotics are considered to have a minimal risk of teratogenicity but may cause extrapyramidal side effects, hyperprolactinemia, and fertility effects. Existing studies do not find an increased risk of large fetal malformations, but there is probably an increased risk of perinatal complications in the second and third trimesters of pregnancy. Possible withdrawal symptoms, unstable body temperature, extrapyramidal symptoms, respiratory problems, convulsions, and transient slowing of neurodevelopment are possible. Prospective studies of pregnancies on haloperidol do not show a significant increase in the incidence of malformations, even if taken in the first trimester, but there is a higher incidence of preterm birth and low birth weight. Phenothiazine (promazine, chlorpromazine, levopromazine, fluphenazine, thioridazine) are considered low-risk antipsychotics, but there is potential for hypotension, sedation, and anticholinergic effects. There are insufficient data on the use of fluphenazine in pregnancy (Bajs Janović et al. 2017). Although there is more information on the effects of the first generation of antipsychotics and some authors recommend them in the first line of psychosis therapy (haloperidol, promazine), the second generation of antipsychotics, especially quetiapine, olanzapine, and risperidone are used more often in pregnancy (Erdeljić Turk & Vitezić 2017).

Newborns exposed to the second generation of antipsychotics have a higher incidence of increased growth and birth weight compared to pregnancy on the first generation of antipsychotics. Clinical research studies do not find a higher incidence of large congenital malformations, but there is insufficient data. The percentage of placental passage for some of them is: olanzapine 72%, haloperidol 66%, risperidone 49%, quetiapine 24% (Bajs Janović et al. 2017).

In clinical practice, high-potential neuroleptics such as haloperidol, perphenazine, and trifluoperazine are recommended over low-potential agents in the treatment of pregnant women with psychiatric illnesses (Anonymous 2020).

The potential short-term and long-term risks of using antipsychotics, as well as the risks of their omission in the treatment of psychotic mothers that would lead to potential deterioration of mental state, represent a complex issue for the clinician in determining the optimal approach to treatment during pregnancy. General guidelines when choosing antipsychotics in pregnancy are to prefer non-pharmacotherapeutic procedures, monotherapy, and minimum effective dose (Sikirica 2016).

Antidepressants and pregnancy

In the treatment of depression in pregnancy, the greatest experiences are with tricyclic antidepressants (TCAs), which have been in use since the 1960s, and most users were amitriptyline and imipramine (Taylor et al. 2015). They are believed to have no pronounced

effect on the fetus throughout pregnancy and do not cause large fetal malformations. However, exposure to TCA in the third trimester may cause withdrawal symptoms among the newborn (agitation, irritability, and convulsions). Newborns exposed to TCA during pregnancy can develop neonatal toxicity in the form of restlessness and respiratory difficulties (Bajs Janović et al. 2017).

Selective serotonin reuptake inhibitors (SSRIs), with the exception of paroxetine, do not appear to be teratogenic nor do they cause large fetal malformations in pregnancy (Andrade et al. 2009). Paroxetine is associated with cardiac malformations, especially with higher doses, and if used in the first trimester. Studies have shown that the risk of developing a heart malformation is 1.5 to 2 times higher in children of women which took paroxetine than in children of women who took a different antidepressant. The most numerous are studies on the use of fluoxetine in pregnancy, and only one of them reveals a slight increase in minor malformations (Bajs Janović et al. 2017). By monitoring developmental changes in the kidneys, heart, and lungs, fluoxetine affects neonatal growth during pregnancy by being able to delay organ growth (Ghavamabadi et al. 2018).

The use of SSRIs in pregnancy is associated with reduced gestational age, miscarriages, and reduced birth weight. But depression carries almost the same risk of preterm birth and birth complications. Clinical manifestations may include transient and limited symptoms such as restlessness, tachycardia, hypothermia, vomiting, hypoglycemia, irritability, persistent crying, increased tone, difficulty feeding and sleeping, convulsions, and respiratory difficulties. SSRIs are generally considered the first line of choice for treating depression in pregnancy for safety and efficacy. In order to minimize the teratogenic risk, pregnant women should take the minimal dosage (Bajs Janović et al. 2017).

In a large cohort study, the treatment of psychiatric disorders of mothers with SSRIs in therapy during pregnancy was associated with a lower risk of preterm birth and cesarean delivery, compared with the offspring of mothers who were not exposed to drugs and had mental health problems but a higher risk of neonatal maladaptation, such as low Apgar score and monitoring the newborn in the intensive care unit. Research provides new evidence of the protective role of SSRIs during pregnancy for some detrimental reproductive outcomes, presumably by reducing maternal depressive symptoms. Divergent research suggests that clinical decisions about the use of SSRIs during pregnancy should be individualized, taking into account maternal psychiatric history and reproductive history (Malm et al. 2015). For mothers that breastfeed, the most evidence for the use of selective serotonin reuptake inhibitors (SSRIs) exists, and most recommendations exist for paroxetine and sertraline (Bačeković 2017).

Venlafaxine is not associated with an increased risk of congenital malformations, and duloxetine is associated with a risk of miscarriage (Vitale et al. 2016). Moclobemide, reboxetine, trazodone, bupropion, and mirtazapine are not recommended during pregnancy due to lack of data (Taylor et al. 2015). Bupropion may be an option for women who have not responded to fluoxetine or tricyclic antidepressant therapy, as up to date data has not shown an increased risk of malformations associated with bupropion (Anonymous 2020). Monoamine oxidase inhibitors (MAOIs) are not recommended during pregnancy, they should be avoided due to the suspicion of an increased risk of fetal malformations and the risk of a hypertensive crisis (Bajs Janović et al. 2017).

The usage of antidepressants during the second trimester of pregnancy is associated with a high risk of preeclampsia or gestational hypertension. Many depressions, which we label as postpartum, occur even before the childbirth. There is an increased risk of depression recurrence among women who had already had a depression phase and discontinued the treatment, and especially in pregnant women with bipolar disorder. Untreated depression as an independent factor can have negative consequences on pregnancy and childbirth.

Mood stabilizers and pregnancy

The risk of illness relapse during pregnancy if the medication that stabilizes the overall mood is discontinued is very high. One study found that women with bipolar disorder who were euthymic at conception and discontinued mood stabilizer therapy had twice the risk of relapse and were ill five times longer than women who continued to use mood stabilizers. The risk of postpartum relapse increases up to eight times in the first month after delivery (Taylor, Paton & Kapur 2009).

Lithium is completely equalized across the placenta. Although the overall risk of major malformations in infants exposed in utero has probably been overestimated, lithium should be avoided in pregnancy if possible. Slow discontinuation prior to conception is recommended in therapy because abrupt discontinuation is suspected to increase the risk of relapse. The postpartum relapse rate may be 70% higher in women who discontinued lithium therapy before conception. If termination is not successful during pregnancy, reenable and resume therapy. It is well known that the use of lithium during pregnancy is associated with heart malformations. The relative risk for Ebstein's anomaly is 10-20 times. The period of maximum risk for the fetus is two to six weeks after conception, before most women eve find out they are pregnant. The risk of atrial and ventricular septal defects may also be increased. When using lithium in the third trimester, due to changes in pharmacokinetics, an increased dose is required to maintain plasma lithium levels during

pregnancy, as total body fluid increases, but needs to return to pre-pregnancy levels immediately after delivery. Plasma lithium levels should be monitored during pregnancy and immediately after delivery. Cases of neonatal goiter, hypotension, lethargy, and cardiac arrhythmia have been described (Taylor et al. 2009).

Carbamazepine and valproate have a clear causal relationship with an increased risk of various types of fetal abnormalities, most commonly spina bifida. Both drugs should be avoided, if possible, and an antipsychotic should be prescribed instead. Valproate has a higher risk than carbamazepine. Where continued use of valproate or carbamazepine is considered essential, a small dose of monotherapy is recommended because the teratogenic effect is likely to be related to the dose of the drug. All patients should take folic acid (5 mg daily) for at least one month before conception (this may reduce the risk of neural tube defects). Carbamazepine use in the third trimester also are quires a vitamina Ka (Taylor et al. 2009).

Of all the drugs used to treat psychiatric disorders, the one with the greatest potential for congenital damage is valproate. This drug is often considered the last resort in the treatment of women of reproductive age, as the risk of teratogenicity is high in very early pregnancy, before most women realize they are pregnant (Anonymus 2010).

Data for lamotrigine indicate a low risk of fetal malformations when used as monotherapy, even though a significantly increased risk of cleft palate has been reported (Taylor et al. 2009). There is increasing information on the reproductive safety of lamotrigine, and this may be a useful alternative for some women. While other anticonvulsants are used in the treatment of bipolar disorder, there is limited information on the reproductive safety of newer anticonvulsants, especially gabapentin, oxcarbazepine, tiagabine, levetiracetam, zonisamide (Anonymous 2020).

Atypical antipsychotics are quite often used to control acute bipolar disorder symptoms. Although data on the reproductive safety of these newer drugs is limited, so far no study has indicated any teratogenic risk associated with this group of drugs (Anonymous 2020).

Anxiolytics and pregnancy

Anxiety disorders and insomnia often occur in pregnancy. Cognitive-behavioral therapy and sleep hygiene measures are preferred (Taylor et al. 2009). There are numerous reports of the use of benzodiazepines in pregnancy although they are known to have a number of side effects among the newborn. Benzodiazepines pass through the placenta and due to the immature liver of the fetus they are metabolized more slowly, accumulate, so the concentration in the fetus is several times higher when compared to the mother.

With the use of benzodiazepines in the first trimester there may be abnormalities of the palate, stenosis of the pylorus, and inguinal hernias, in the second trimester the anomalies are less frequent (heart defects and hand disorders), and in the third trimester there may be developmental delays, baby weight loss, hypotension of the newborn (floppy baby syndrome) and feeding difficulties (Taylor et al. 2009).

Since there is sufficient evidence that benzodiazepines increase the risk to the fetus, the following rules should be followed: In case of anxiety, dysphoria, and insomnia, apply professionally justified non-drug methods of treatment (psychotherapy, sociotherapy methods). If these methods are not effective, monotherapy should be applied, especially to choose an anxiolytic individually, to avoid application in the first and second trimester. It is recommended to use it as soon as possible, in the lowest possible dose, and to use anxiolytics with a shorter half-life (eg lorazepam, oxazepam) (Erdeljić Turk et al. 2017).

The use of benzodiazepines in early pregnancy is associated with miscarriage. To date, however, the association between benzodiazepine-specific exposure and the risk of miscarriage has not been investigated. An increased risk of miscarriage has been observed in early pregnancies with accidental exposure to short-acting and long-acting benzodiazepines. Insomnia, anxiety, and mood disorders predominate during pregnancy; clinicians should carefully evaluate the benefits and risks of prescribing benzodiazepines in early pregnancy as there are alternative non-pharmacological treatments (Sheehy et al. 2019).

Hypnotics and pregnancy

The association of zolpidem use in pregnancy, at usual clinical doses, with teratogenic effects has not been established. Cases of low birth weight and premature birth have been described. A case of neural tube defect has been described in a woman addicted to zolpidem who consumed high doses of zolpidem in the first trimester (Sharma et al. 2011). Systemic data on the reproductive safety of non-benzodiazepine agents such as buspirone and the hypnotic drugs zolpidem and zaleplon are not currently available. Therefore, these drugs are not recommended for use in pregnancy (Anonymous 2020).

The use of flurazepam in pregnancy should be avoided, the drug should be used only if the potential benefit to the mother outweighs the possible risk to the fetus (Mulabegović et al. 2014).

Nitrazepam may damage the fetus if taken during pregnancy. There is a risk of congenital anomalies when applied in the first trimester. The use of the drug in the last trimester can cause neonatal depression of the nervous system, respiratory depression, and hypotension, and hypothermia (Mulabegović et al. 2014).

CREATIVE PSYCHOPHARMACOTHERAPY IN OPTIMIZING THE MENTAL HEALTH OF PREGNANT WOMEN AND NEWBORNS

The correct answers to the question of how to define human life are complicated. Today's dilemmas consider respect for human life from birth to death including not only biology but also other sciences. Philosophy, theology, psychology, sociology, law, and politics evaluate this topic from different points of view. The integration of all of the above could result in a useful response. When we define life, it should not be understood as it is today, but as it was in its primordial form and as it will be in the future. Life, in the true sense of the word, begins when a chemical substance rises in a special way to an autonomous, self-regulating, and self-reproducing system. Life is connected with the living being and creates its own system as one invisible whole - it forms its individuality. One of the most important characteristics of living beings is reproduction. Reproduction is a means of creating new life by changing form from the old to the newly formed human being. Therefore, variability, individual development, and harmony characterize human beings. Individuality is the most important characteristic of human beings contained in new life, but in addition, every human life is shaped through evolution, characterized by phenotype, behavior, and ability to recognize and adapt. The human embryo and fetus develop into these characteristics (Kurjak et al. 2018).

There is no doubt that the embryo and fetus in the womb are biological human beings before birth. A newborn child is the same human individual in development that was in the mother's womb. Birth alone cannot give the nature of personality or human individuality. This is confirmed by the premature birth of babies who are truly human and almost as sustainable as those whose pregnancies last to the end. All known evidence supports that the human fetus will be a truly ontological human individual and consequently a de facto human being, although not by law (Kurjak et al. 2018).

Perinatal mental health has become a significant focus of interest in recent years, investing in new specialist mental health services in some high-income countries, and inpatient psychiatric units for mothers and babies in a variety of environments. In their paper, Howard and Khalifeh (2020) summarized and critically examined the epidemiology and impact of perinatal mental disorders, including new evidence of an increase in their prevalence in young pregnant women. As previously emphasized, perinatal mental disorders are among the most common morbidities of pregnancy they make an important contribution to maternal mortality as well as adverse outcomes of newborns, infants, and children. A review of current databases of evidence on interventions, including individual and public health ones, as well as service delivery models, found that randomized controlled trials provide evidence of the effectiveness of psychological and psychosocial interventions at the individual level, although it is not yet clear which women with perinatal mental health disorders need additional parenting support.

The effectiveness of psychological and psychosocial interventions can be monitored in over 49 randomized controlled trials (RCCs) that provide strong results and evidence for effective and cost-effective psychological and psychosocial interventions for the treatment of postnatal depression (Dennis & Hodnett 2007, Camacho & Shields 2018). In addition to the cognitive-behavioral therapy (CBT) modified for postnatal depression, which has been most frequently investigated, there is evidence of the clinical efficacy of a number of other interventions, including interpersonal therapy (IPT), listening visits, and exercise. There are uncertainties regarding efficacy, but there is consistent evidence of improved depressive symptomatology (Howard & Khalifeh 2020). RCCs interventions that use new modalities of telepsychiatric modalities, eg CBT via the Internet or behavioral activation, have also shown strong effects for perinatal depression in several countries (Milgrom et al. 2016, O'Mahen et al. 2013, Lau et al. 2017). There is a smaller but similar literature on the treatment of mental disorders during pregnancy, however, a lack of controlled studies for mental disorders other than depression is evident. Recently, small trials of self-care management for patients with antenatal depression have been conducted, and insufficient strong preliminary evidence on the effectiveness of interventions is evident (Milgrom et al. 2011, Trevillion et al. 2020). IPT intervention studies for perinatal anxiety disorders provide limited data (high levels of heterogeneity). IPT is effective in treating the symptoms of depression and appears to be promising as a method of treating anxiety and improving interpersonal functioning (Sockol 2018).

There is also evidence from small studies to suggest that CBT may reduce the symptoms of blood phobias and injections in pregnant women (Lilliecreutz, et al. 2010), PTSD and depression in mothers who have premature babies in neonatal intensive care units (Shaw et al. 2013, Koochaki et al. 2017) and postnatal obsessive-compulsive disorder (OCD) (Challacombe et al. 2017). In addition to the effect of psychotherapy on maternal depression, subsequent studies of the effects of psychotherapy on the newborn were performed, and the findings were inconsistent. Psychosocial interventions for perinatal depression have not only been effective in reducing maternal depressive symptoms, but have also led to improved infant growth, vaccine responses, and reduced diarrhea (Rahman et al. 2013). Treatment of major depression and anxiety during pregnancy with brief CBT intervention seems feasible and useful. In order to reliably detect clinically significant effects on infant outcomes, a higher RKS is likely to be needed (Milgrom et al. 2015).

Women need interventions tailored to pregnancy and later relationships with their child, but there seems to be no reason to question the effectiveness of treatments that are effective in other periods of a woman's life so that they would not be effective if applied in the perinatal period. Several different manuals for perinatal interventions have been developed, but some argue that the experience and flexibility of therapists are the most important aspects of psychological interventions (Fonagy & Luyten 2019).

Postpartum PTSD can negatively affect women's well-being, mother-child relationships, and child development. Furuta et al. (2018) systematically reviewed and evaluated the effectiveness of trauma-focused psychological interventions (TFPIs) for postpartum women through review and meta-analysis. They found no solid evidence to suggest whether TFPIs could improve women's recovery from clinically significant PTSD symptoms. They concluded that further larger studies are needed, distinguishing between low and high-risk groups, and with adequate monitoring, to determine which TFPIs are most effective and acceptable for the treatment of postnatal PTSD.

Chiorino et al. (2020) examined the impact of applied short EMDR (Eye Movements Desensitization and Reprocessing) treatment over conventional therapy and found that most treated women improved their post-traumatic symptoms of post-traumatic stress after just one treatment. EMDR resulted in being more effective than conventional therapy in reducing the proportion of women with post-traumatic stress symptoms at six weeks postpartum. Moreover, women treated with EMDR had fewer flashbacks and distress than women with conventional therapy. No significant difference was found between these two therapeutic interventions on the relationship between maternal and neonatal attachment and postpartum depression symptoms. Although preliminary, these findings suggest that brief EMDR intervention could be a viable and promising tool in the early treatment of post-traumatic stress associated with traumatic childbirth (Chiorino et al. 2020, Pašalić & Hasanović 2018).

Perinatal mental disorders are common and can adversely affect both maternal functioning and fetal and neonatal outcomes. For more serious disorders, such as schizophrenia, bipolar disorder, and severe depression, medications may be needed during pregnancy and breastfeeding, and there are more complex evidence based on the effects of psychotropic medications on the fetus and newborn. In addition, the neonatologist must be aware of the accompanying problems that women with mental disorders can have because they can also affect the newborn. A close relationship with family physicians and primary care, where there are mental health concerns, to ensure that the mother's mental health is optimal, is important for the mother and her infant (Khalifeh et al. 2015).

The evidence base for the use of psychotropic drugs in pregnancy is almost exclusively observation. There is little research on the full spectrum of perinatal mental disorders, on how to improve access to treatment for women with psychosocial difficulties, and on the effectiveness of different service delivery models. Existing research and clinical implications highlight the need to expand generic psychiatric services to include protection against conception, and further investment in public health interventions, in addition to perinatal mental health services, potentially for women and men. All of this can reduce the morbidity and mortality of mothers and children (Howvard & Khalifeh 2020).

Stika and Frederiksen (2007) commented on the lack of research on the safety and efficacy of drugs in pregnant women, saying: "A pregnant woman may be the last true therapeutic orphan. Due to ethical, medical-legal and fetal safety concerns regarding pregnant women, few pharmacokinetic, pharmacodynamic or clinical trials are conducted during pregnancy".

It is necessary to make a new conceptual shift in the approach to maintaining the mental health of pregnant women and newborns, and that is to optimize the mental health of pregnant women, and not simply reduce the symptoms of mental disorders they suffer from before conception, during pregnancy and after childbirth. Positive mental health is a separate construction, separate from the absence of disease, and is associated with improved birth outcomes and parenting practices that support favorable diet development (Phua et al. 2020). Emotional well-being is an overall positive state of emotional charge, life satisfaction, sense of meaning and purpose, balance, and ability to deal with personal goals (Feller et al. 2018).

Mental health professionals must insist on policies that improve the health of our patients during pregnancy and after childbirth when they are given the maternal role of a parent. Through partnerships with international visionary leaders, we must consolidate and share responsibility for advancing research into the treatment of pregnant women with psychiatric illness and other medical disorders. In doing so, we will appreciate the extraordinary gift of newborns by caring for the women who bring into the world and nurture our next generation. We need to adapt our pregnant women not to be like neglected orphans and take care of them through the mainstream health care with research and practice (Wisner et al. 2020).

CONCLUSIONS

Pregnancy is the period in which the use of psychopharmacotherapy is most difficult, for the clinician, the treatment in this period requires great responsibility, which requires knowledge of the individual characteristics of the pregnant woman, her illness, previous

experience with the therapy, and very detailed knowledge of each psychopharmaceutical and its teratogenicity. A personalized approach is necessary, and the active participation of the patient in the treatment is essential, and if necessary, the involvement of family members depending on the severity of the clinical picture.

For adequate treatment in the prenatal period, it is not enough to plan psychopharmacotherapy during pregnancy, but a much broader and holistic approach in the treatment of women of childbearing age is necessary, which should include pregnancy planning, especially when it comes to the use of psychopharmaceuticals. In addition to careful selection and planning of pharmacotherapy, psychotherapeutic, interpersonal, and family interventions are also necessary.

Dilemmas and challenges of psychopharmacotherapeutic treatment in the prenatal period intensifies the knowledge that the psychological difficulties of mothers can significantly affect the integrity of the safe relationship between mother and child, which is essential for the emotional, cognitive, and behavioral development of the child. Often, these problems existed before pregnancy or occurred during pregnancy, and often the deterioration of the mental state is due to the discontinuation of pharmacotherapy during this period.

The quality of the biopsychosocial milieu in the fetal period and childhood during the phase of early neuroplastic development is one of the determinants of the risk for diseases during the life cycle. For this reason, the mental health of pregnant women and mothers must be optimized. For many of these women, health is optimized with pharmacotherapy.

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Dina Šmigalović: conception and design of the manuscript, collecting data and literature searches, analyses and interpretation of literature, manuscript preparation and writing the paper; and gave final approval of the version to be submitted.

Mevludin Hasanović: made substantial contributions to conception and design, literature searches, participated in revising the manuscript and gave final approval of the version to be submitted.

Izet Pajević, Asim Kurjak & Miro Jakovljević: made substantial contributions to conception and design, and interpretation of data, participated in revising the manuscript and gave final approval of the version to be submitted.

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