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Untangling the knot of Postpartum Depression: What do we know and what is yet to be discovered?

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Abstract

There is an enormous research data concerning the postpartum depression (PPD) etiology, symptomatology and treatment, however, the known prevalence among the women suffering with depressive symptomatology after the childbirth is still high (6.5% to 20% of the new mothers). Furthermore, it is estimated that 50 % of the cases are not even detected, leaving a great percentage of women in their most vulnerable times without treatment. Having in mind these high numbers, along with the known catastrophic consequences that PPD may have on both mother and her child, one cannot ask himself: what are we missing? This literature review aims to critically discuss the many faces of PPD, the neurological and hormonal research progress throughout the years as well as the challenges and certain limitations of the research regarding the PPDs problematics. Implications for future studies will be made which will possibly fill the gaps in the existing knowledge about PPD and its' complicated nature.

Key words: postpartum depression, endocrinology, estrogen, progesterone, allopregnanolone, HPA-AXIS, serotonin.

What is postpartum depression?

New mothers are often describing the first contact with their baby as a magical, life changing experience, colored with emotions of unconditional love and happiness. However, this is not the case for all women. Some of the mothers are not able to feel that powerful bond with their newborn even a several months after delivery. Since the earliest medical literature, cases of postpartum depression (PPD) have been documented and studied, yet centuries later, many questions are still unanswered.

Prior to the 19th century, postpartum psychiatric disorders were mainly seen as "female madness" with major focus on hysteria, mania and psychosis. This hypothesis was essentially postulated by Hippocrates, B.C., and it was based on the biological events happening during and after the pregnancy that resulted in agitation, mania attacks and delirium (Sparks, 2013). In other words, Hippocrates hypothesized that the depressive symptoms which occur after a delivery of a child may be a consequence of the blood collecting at the breasts or may be an effect of a suppressed fluid that comes from the uterus after giving birth, if it flows to the head (Brockington, 2005). In the 13th century, influenced by this theory a female physician Trotula de Ruggiero proposed that the "postpartum madness" occurs due to increased moisture in the womb which leads to filling the brain with water (Sparks, 2013). Furthermore, in the period of Middle Ages, postpartum mental illness was associated with the devil and the treatment was nevertheless barbaric, subjecting the women to exorcism (Tasca, 2012). It was also claimed that women who were showing signs of melancholy or hysteria were witches or victims of a witchcraft (Sparks, 2013).

In the 19th century, although the term postpartum madness still persisted, the idea that there is a connection between the natural process that the female reproductive organs were involved in and postpartum depressive symptoms were embraced. The observations of the French psychiatrist Louis Victor Marcé, led to a meaningful discovery about the connection between the immune response and the endocrine system and "postpartum insanity", although he as well used different types of a barbaric treatments, such as applying leaches to the women's' vulva (Osborne, 2018). At the same time, Jean-Etienne Esquirol (1883) hypothesized that the prevalence of the PPD was much bigger in the general population compared to the prevalence known from the records of the

mental hospitals. Furthermore, he was also one of the first psychiatrists believing in the separate diagnosis of PPD and suggested two distinct phenotypes of the disease, puerperal and lactational. The first category, was defined as diagnosis occurring in the first 6 weeks after delivery, and the second, the lactational category was defined as depressive symptomatology occurring after the 6th week in the postpartum period. The interest on PPDs' problematic continued to rise throughout the history, leading to new meaningful discoveries in terms of etiology and pathology, yet, PPD was first recognized by the psychiatric community in 1994 in the fourth edition of the Diagnostic and Statistical Manual (DSM IV) (Sparks, 2013).

Today, according to the latest research, PPD affects approximately 6.5% to 20% of the mothers, although it is estimated that 50% of the cases are still undetected which leaves a significant percentage of women who suffer from PPD but do not get treatment (Mughal et.al., 2022; Hutchens & Kearney, 2020). Despite of the fact that we no longer live in the Middle Ages and a great progress in terms of scientific discoveries was made, the stigma and the shame are still prevalent among women who face difficulties in the postpartum period. One of the main causes for these feelings that occur in mothers facing emotional difficulties in the period after giving birth are the cultural expectations (Whiffen, 1992). Not being able to "properly" meet the needs of the baby, or not being able to feel the pleasure and joy of motherhood, women are often scared that they will be perceived as bad mothers (Whiffen, 1988a, Whiffen, 1992). Other reasons for not reporting the symptoms and seeking an adequate help are fear of separation from the baby, stigmatization as mentally ill, inadequate social support or even not being able to recognize the symptomatology since many of the symptoms are related to the new responsibilities which arise for the new mothers (Edwards & Timmons, 2005). The above-mentioned factors, further lead to hiding the difficulties that they face from the society and even from their closest family members which often results in worsening symptomatology.

The increasing body of literature in the past years provide significant findings, leading us one step closer to better understanding of this ruthless disease. The first step towards untying the knot of postpartum depression is looking at what is already known. Therefore, we present the types of postpartum depressive disorders, the potential factors leading to it as well as its underlying symptomatology. The significant catastrophic impact that PPD may have on the development of

the child will also be discussed in order to get the whole picture of the consequences that may arise if PPD is not detected and adequately treated.

Types of Postpartum depressive disorders

Due to the many challenges that arise in the postnatal period, the emotional difficulties that women face may vary in their duration and intensity, hence, in the literature three types of postpartum depressive reactions have been described. Most frequent depressive reaction is the maternity "blues" which occurs within the first 10 days postpartum and it is characterized with mild depressive transient symptomatology such as anxiety, irritability and tearfulness (Whiffen, 1992; Riecher-Ro¨ssler & Hofecker Fallahpour, 2003). Although, the symptomatology of the maternity blues is milder and it usually resolves without any treatment, it is crucial to be followed, since if not taken seriously, it can progress into postpartum depression (Paykel et al. 1980; Kendell et. al., 1981). The second one, is the postpartum psychosis, which is defined with hallucinations and agitation during the first three months following the delivery of the baby (Altshuler et. al., 1998). Other detected symptoms in the postpartum psychosis are cognitive disorganization, bizarre behavior, homicidal ideation as well as risk of infanticide (Wisner et al., 1994; Brockington et. al., 1981; Friedman et. al., 2012). The third depressive reaction is the postpartum depression, which is most often defined as an episode of major depression which occurs during the pregnancy or in the postpartum period, with duration of symptoms at least 2 weeks, without any psychotic features (Cox, Murray, & Chapman, 1993; O'Hara, 1995, 1997; Watson et al., 1984). The present literature review will focus on the third depressive reaction, postpartum depression, looking more thoroughly into its' multifaceted nature. So how does PPD look like and why is it so important to be recognized at the very beginning?

Diagnostic criteria

DSM V and ICD 11 are most commonly used diagnostic manuals around the world by many clinicians and researchers in the field of psychiatry. DSM-V is published by the American Psychiatric Association and serves as a standard reference for the diagnosis and treatment of mental health conditions, whereas the ICD-11 is the latest version of the World Health Organization's (WHO) international standard manual for health conditions. As it was said before, Major Depressive Disorder with postpartum onset was first recognized in the fourth edition of the DSM in 1994 and it was defined as onset of symptoms within the first four weeks after delivery.

In the fifth edition of the DSM (DSM V) the specifier for the Postpartum Depression was extended and the specifier with peripartum onset was added. So, according to DSM V, postpartum depression is defined as "major depressive disorder with onset of symptoms during pregnancy and/or within the first four weeks postpartum" [American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Association; 2013.]. The International Statistical Classification of Diseases and Related Health Problems, on the other hand, does not take into account the peripartum onset of depression and classifies the postpartum disorders as "episodes occurring within 6 weeks postpartum that cannot be classified elsewhere" (code F53, mental and behavioral disorders associated with the puerperium, not elsewhere classified). [World Health Organization. ICD-10: the ICD-10 Classification of Mental and Behavioral Disorders: clinical descriptions and diagnostic guidelines. World Health Organization; 1992]. Despite the fact that both of these manuals are almost always used in clinical settings to classify and diagnose, many researchers argue that both have some flaws regarding the PPD definitions and their use. The most significant criticism is directed at the onset of PPD according to the guidelines in DMS-V and ICD-11. In the next chapters we would go more into details about this ongoing discussion, the scientific data behind it and the potentially better proposals regarding this matter.

Table 1

Comparison between the classificatory systems for perinatal psychiatric disorders

ICD- 10	DSM-IV	DSM-5	ICD-11
Mental and behavioral disorders	1.Mood disorders Major depressive disorders Bipolar I disorder Bipolar II disorder 2. Schizophrenia and other psychotic disorders 3. Brief psychotic disorder	1.Mood disorders Major depressive disorders Bipolar I disorder Bipolar II disorder 2. Schizophrenia and other psychotic disorders 3. Brief psychotic disorder	Mental behavioral and neurodevelopmental disorder (also, under complications predominantly related to puerperium) Mood disorders (depression, bipolar disorders; qualifier – current episode perinatal)
F53: Mental disorders associated with the puerperium, not elsewhere classified Not meeting criteria for other mental disorders because of - Insufficient information - Additional features making classification elsewhere inappropriate	Puerperal code – Postpartum-onset specifier: Can be applied to major depressive, manic, or mixed episode; or mixed episode in major depressive disorder; Bipolar I disorder, or Bipolar II disorder; or to brief psychotic disorder	Puerperal code – Peripartum-onset specifier: Can be applied to major depressive, manic episode; Bipolar I disorder, or Bipolar II disorder; or to brief psychotic disorder	Mental or behavioral disorders associated with pregnancy, childbirth and the puerperium, not elsewhere classified Syndrome associated with pregnancy or the puerperium (Commencing withing about 6 weeks after delivery)
Only when commencing within 6 weeks of delivery	Onset of episode within 4 weeks postpartum	Onset of the symptoms in pregnancy or 4-week postpartum	

ICD: International Classification of Disease, DSM: Diagnostic and Statistical Manual of Mental Disorders
Note: From "Will the DSM-5 and ICD-11 "Make-over" Really Make a Difference to Women's Mental Health?" by Parameshwaran, S., & Chandra, P. S., 2018, *Indian Journal of Social Psychiatry, 34*(Suppl 1), S79-S85(Doi: 10.4103/ijsp.ijsp_34_18).

Symptomatology

Regarding the clinical picture of PPD, it can be said that is similar to major depression disorder (MDD), since the symptomatology correlate to a great extent. Sad, depressed mood, anhedonia, restlessness, diminished interest or pleasure in everyday activities, sleep disturbances, weight loss or weight gain, impaired concentration and suicidal ideations are common symptoms that occur in women who suffer from PPD, as well as, in women who suffer from MDD experienced in other times in women's life (Cooper et. al., 1988, Bernstein et. al., 2008; Lux & Kendler, 2010; Hoertel et. al., 2015). However, studies show that some of the symptoms are more prevailing in PPD, such as, confusion, emotional liability, psychomotor lethargy and disorientation (Dean & Kendell, 1981; Bernstein et. al., 2008). Additionally, the literature suggests that PPD is often characterized with anxiety, ruminative thoughts and panic attacks, guilt and agitation which further points out the comorbidity of PPD with anxiety (Pitt 1968; Pawluski et. al., 2007; Hamilton, 1960; Hopkins et al., 1989; Hendrick et al., 2000). For example, Hendrick et al., (2000) in their study compared symptoms and treatment responses in women with PPD and women who suffered from MDD and who hadn't delivered a child two years prior to the study. None of the women in both groups had a history of depression. Regarding the symptoms, the results revealed that mothers had a significantly higher symptomatology of anxiety compared to the women with major depression disorder in other times of their life. Moreover, they also found that the group with PPD had a more severe symptomatology than the MDD group (Hendrick et al., 2000). Although these results were in line with the findings of O'Hara et. al. (1990), the data across the literature are inconsistent. Whiffen and Gotlib (1993) in their study found that women with MDD suffer more severe symptoms than new mothers with PPD (Hendrick et al., 2000). This is also in line with the research which show that the risk of suicide is significantly lower in PPD than in MDD in other periods of life (Pitt, 1968; Bernstein et. al., 2008). Researchers are explaining this with the fact that most of the new mother have higher motivation to live because of their newborn child (Bernstein et. al., 2008).

Maybe one of the most characteristic symptoms of PPD is associated with the relationship of the mother with the infant. New mothers who suffer from PPD are struggling with the demands that are proposed by the new role which often results in development of negative feelings like

irritability and hostility toward the baby and poor child care. For example, Bettes (1988), was examining the effects of PPD on motherese which is a "baby talk" that most often mothers use in order to get infants attention and expose them to language. The results that were obtained from this study suggested that mothers suffering from PPD had significantly lower reaction time (RT) in responding to the infant vocalization, did not use exaggerated intonation which is specific for motherese and had more variable utterances and pauses (Bettes, 1988). Similarly, Fleming et. al. (1988) in their study compared the maternal attitudes of mothers who suffer from mild postpartum depression and non-depressed mothers. They obtained self-report measures from the mothers during the last month of the pregnancy and at 1 and 3 months postpartum. Also, by videotaping the nursing and the breastfeeding at 1 and 3 months postpartum they were observing the behavioral interactions between the mother and the infant, scoring the maternal behaviors like affectionate contact, caretaking activities, vocalization to the infant, the visual orientation of the mother toward the infant and if the mother was rocking or jiggling the infant. The obtained data suggests that compared with non-depressed mothers, mothers with mild depression showed reduced maternal feelings and affectionate behavior and they were less likely to respond to the infants' vocalization at 1 and 3 months (Fleming et. al., 1988). Other studies also indicate that women with PPD are perceiving the infants' cry as less salient which leads to less appropriate and sensitive responsiveness (Esposito, 2017; Schuetze & Zeskind, 2001). All things considered; it can be concluded that PPD is a major threat not only to the mothers' well-being but to the child development as well, further highlighting the importance of early detection and treatment. In this context the knowledge and awareness regarding the possible risk factors is mandatory in order to be able to recognize and closely monitor women who are more vulnerable of developing depressive symptoms in the postpartum period.

Risk Factors

The tremendous hormonal and neurobiological changes that are occurring in the postnatal period together with the new responsibilities are requiring significant adaptational skills from the women making them extremely vulnerable. This and the fact that it is a time when women are more susceptible to depression than usual, the researchers are considering the postpartum period as a risk factor by itself for developing depressive disorders (Brockington & Kumar, 1982; O'Hara et. al., 1982). However, even if the postpartum period is a risk factor by itself and PPD is a potential

threat to all the women, not everyone is experiencing depressive symptomatology and unfortunately some mothers are far more likely to experience the disorder. The evaluation of the articles revealed that the risk factors for postpartum depression are heterogenous and can be divided into five categories: psychiatric, obstetric, biological and hormonal, social, and lifestyle risk factors (Ghaedrahmati et. al., 2017).

With the help of the animal studies and the growing data of etiological research in the domain of PPD, several biological and endocrinological theories were proposed, explaining the possible causes of PPD. Furthermore, these theories differ and while some suggest that the main reason for PPDs' symptomatology is the hormonal withdrawal which occurs after delivery, others "blame" the rapid alternations of the hormones which take place throughout the prolonged postpartum period (Wisner et al., 2002; Bloch et. al., 2000; Burke et. al., 2017). Another point of view which is also prominent in the literature is the specific sensitivity of some women to hormonal changes, which may explain the reason why only subset of women suffers from the depressive symptoms during the pregnancy or after delivery (Cooper et al. 1995; Payne et al. 2009; and Bloch et al., 2000). These theories will further be explained in more details since the focus of the present literature review is more on the biological aspects of PPD.

One of the greatest predictors for PPD are a history of major depression (MDD) and generalized anxiety disorder (GAD) not specifically related to child birth (O'Hara & Swain, 1996; Beck, 2001; Josefsson, 2002). Additionally, data suggests that existing depressive and anxiety symptomatology during pregnancy is strong risk factor for depression in the postpartum period (O'Hara & Swain, 1996; Beck, 2001; Josefsson, 2002). Other clinical psychiatric factor is a family history of depression and other psychiatric illnesses. However, the results from different studies for this variable are inconclusive, meaning some of the studies didn't find any significant correlation between PPD and family history of depression or found only a small effect size (O'Hara & Swain, 1996; Josefsson, 2002).

The term obstetric factors is an umbrella term for pregnancy and delivery complications such as preeclampsia, hyperemesis, premature labor, caesarean section, instrumental delivery, premature delivery, etc., (Robertson et. al., 2004). Forman et. al. (2000) in their study didn't find any significant correlation between pregnancy or delivery complications, and postpartum depression. Similar results obtained few more independent studies suggesting that obstetrical

factors are not strong predictors for PPD, (Johnstone et al., 2001; Josefsson, 2002; Warner et. al., 1996). However, other authors suggest that these results may be influenced by other external factors so they must not be taken for granted (Robertson et. al., 2004). On the other hand, Blom et al (2010) were exploring the correlation between several perinatal complications and PPD. According to the results, more than two perinatal complications were highly correlated with development of depressive symptomatology in the postpartum period. A little older study by Boyce and Todd (1992), also found high correlation between emergency caesarean section and PPD at three months after delivery. Yet again, conclusions regarding the correlation between obstetric risk factors and PPD cannot be made, since when a number of not controlled confounding variables may mediate this relationship.

The social factors are very strong predictors of PPD and include social support from the family members, friends as well as the support from the partner. During this sensitive period, studies show that that women who feel isolated and do not receive support from the loved ones are in greater danger for developing postpartum depression (Escribà-Agüir & Artazcoz, 2011; Landman-Peeters et. al.,2005). O'Hara and Swain (1996) in their Meta-Analysis indicated that poor social support during pregnancy was significantly corelated with high levels of depressive symptomatology in the postpartum period. In this meta-analysis the role of the baby's father was also highlighted as an important social factor (O'Hara and Swain 1996). In addition to this, Ludermir et. al. (2010) found significant association between partner violence and occurrence of severe symptoms of postpartum depression. More specifically, the results suggested that partners' physical, psychological and sexual violence were strong predictors of PPD (Ludermir et. al. 2010). What is interesting is that psychological violence showed significant correlation to postpartum depression even without the presence of physical or sexual violence, further highlighting the importance of prevention and treatment of psychological violence (Ludermir et. al. 2010).

Other social factors worth mentioning are social-economic factors such as professional career, income and education, which were found that had small but significant role in the occurrence of PPD (Chien et. al., 2012; Bartley, 1994; Patel, 1999; Huang, 2015). Additionally, also important strong risk factors are stressful experiences which are happening during pregnancy. These life events include death in the family, divorce or getting fired and can trigger depressive symptomatology in the postpartum period even if the women had not had any history of MDD

(Robertson et. al., 2004). Further significant variables are qualitative nutrition, sleep and physical activity which to some extant can prevent depressive symptomatology (Chatzi et. al., 2011; Zinga et. al., 2005; Daley et. al., 2007). In other words, the data shows that a lot of aspects can influence the occurrence of PPD, so it is extremely important to conduct more studies looking into combined effects of the psychosocial and biological variables in order to get a clearer picture of the profiles of women in risk of developing depressive symptoms in these vulnerable times.

Although, most of the possible causes of PPD are stable over cultures, there are some risk factors that differ. For example, in some cultures, like China and India, the disappointment of the spouse with the gender of the baby can trigger PPD, especially if the baby is a girl and these results were not obtained in Western cultures (Patel et. al., 2012; Lee et. al., 2000). Studies also show that polygamy which is legal in some African countries can be a significant risk factor for developing postpartum depression (Adewuya et al., 2005b; Fatoye et al., 2006). Asian cultures have specific traditional activities in the postnatal period, such as going back to their family home for two months or not being able to leave the home for 30 days after childbirth meanwhile receiving support from the closest family members (Bhugra and Bahl, 1999; Holroyd et al., 1997). Although these activities are primarily practiced to help the women to recover, it was shown that they may be potential factors leading to PPD (Chee et al., 2005; Leung et al., 2005a,b).

Even though when it comes to the possible risk factors of PPD there still are uncertainties within the literature, it can be concluded that history of MDD, GAD, social support, partner violence and stressful life experiences are strong predictors which increase the chances in women for PPD diagnosis. The well-being of the mother, as it is already mentioned, is crucial for the healthy development of the newborn. That being the case, it is extremely important for the clinical practitioners to be aware and recognize these threats so that the undetected cases of PPD drop. Moreover, routine screenings in women, especially for these vulnerable categories can be highly beneficial for early detection and intervention, for the mother, her infant and the whole family (Buist et.al., 2002).

Consequences on Child Development

As it is already known, the experiences and relationships within the first few years are most crucial for the social as well as the neurodevelopment of the child. Most dominant contact of the baby is the one with the parents, so it can be said that the child's development is mostly dependent

on the quality of this relationship, which is significantly disturbed if the mother is suffering from PPD. For example, it was shown that infants of mothers with PPD compared to infants of healthy mothers, showed significantly more negative expression and protest behaviors (Field, 1984). Other studies also suggested that infants of depressed mothers are exhibiting less positive affect and expressions and more withdrawn and avoidance behavior toward the mother (Cohn et. al., 1986; Field et al., 1990; Murray et al., 1996a).

Furthermore, the symptoms of PPD have impact not only during the first months of baby's life but later in life as well. Children at the age of two with pre and postanal depressed mothers showed difficulties in social-emotional development measured by the Ages and Stages Questionnaire: Social- Emotional (ASQ:SE) (Junge et. al., 20107). Alvarez et. al. (2012) hypothesized that children of mothers with PPD will have less adaptive behaviors and development compared to children of non-depressive mothers. Children of school age were assessed on few development outcomes such as ego-resiliency, self-esteem, peer social competence, intelligence, school adjustment, internalizing behavior problems, and externalizing behavior problems which in previous studies were shown to be significant for better adjustment during the school years as well as predictive variables for adaptive functioning in the later years. The findings from this study suggest that children with depressed mothers had signifyingly lower abilities to cope with stressful situations related to the educational requirements, had lower ego-resiliency and had more difficulties in adapting to the social life and their peers (Alvarez et. al., 2012).

It has been also found that PDD in mothers is closely correlated with the cognitive abilities of their female children. Namely, Alvarez et al, (2012) hypothesized that children whose mothers suffered from PPD in the past will have more adverse developmental outcomes compared to the children from the control group. The results from this study demonstrated that the young female children achieved lower scores on the verbal intelligence test measured with Peabody Picture Vocabulary Test-Revised (PPVT-R), (Alvarez et. al., 2012). This data proposes that a long-term healthy relationship between mothers and their daughters is important for the proper development of the language skills.

Similarly, Aoyagi et. al. (2019) conducted a study which examined language expressive skills in infants and young children (up to 40 months) whose mothers were suffering from early or late onset PPD. Using the expressive language subscale of Mullen Scales of Early Learning

(MSEL; Mullen, 1995) they suggested that infants from 18 months and older obtained significantly low scores but only in mothers with late onset PPD group further explaining the results that late onset PPD which occurs after the first month following child birth influences brain regions which play a key role in development of expressive language skills (Aoyagi et. al., 2019). Similarly, Stein et. al. (2008) were assessing mothers with PPD at 3, 10 and 36 months and their children's' language skills at 36 months. Although, they didn't find direct correlation between these two variables, results revealed that mothers who were depressed at the 10-month assessment in the postpartum period showed significantly poorer caregiving which further resulted in poorer language skills exhibited by their child at 36 months. In other words, the authors suggested indirect relationship between poor language skills and PPD which was mediated by the quality of the caregiving (Stein et. al., 2008).

However, results from the literature are inconsistent when it comes to the association between mothers with PPD and child's language skills. For example, both Murray (1992) and Cornish et al, (2005) were examining the relationship between several aspects of the cognitive and language development of the infants (up to 1 year old) and maternal PPD. Both of these studies did not find any significant correlation between these two variables (Murray, 1992 & Cornish et al, 2005). However, it was argued that these results are due to the fact that they were assessing infants from 4 to 12 months old in who the expressive language skills dramatically start to develop after the first year (Aoyagi et. al., 2019). Even though the results from studies are to some extant ambiguous, the effects of the irritability, reduced sensitivity, hostility and liability of the mothers with PPD towards their child leave scars on the development of the infant either on their further cognitive abilities or social-emotional life.

The poorer care and not adequate responses to the infants' needs, further can have negative effect on the neurodevelopment of the child, which highlights the importance of prevention - if possible, early detection and intervention which will include both mother and child. Cognitive behavior therapy as well as dyadic interventions such as Toddler-parent psychotherapy (TPP) and Infant Massage were shown to improve PPD symptomatology as well as enhance mother-infant relationship, yet more research need to be made which will focus on the therapies that are most helpful for the neurodevelopment of children of mothers who suffer from PPD (Drury et. al, 2016). Moreover, the authors also suggest that novel therapies and approaches are needed. They propose

alternative therapies that target caregiving behaviors influenced by PPD, such as sleep, nutrition, and play where the mutual benefit for the child and the mother will be granted. Finally, Drury et al, emphasize the need for more research in this domain, because as they say the PPD is not only destroying the mother-child relationship and may have a negative impact of the psychosocial and cognitive development of the child, but "the impact of PPD may span generations" (Drury et. al, 2016).

Aim of the current literature review

Taking into account the consequences of PPD on mothers, their children and the whole family, as well as the high expected prevalence of PPD in women (6-20%), it imposes a strong impact over the general wellbeing and thus it is of high importance to unravel the mystery of PPD. Over the past decades, significant progress has been made in terms of research and clinical care, however, even with the development of the methods and the techniques of the research in the field of neuropsychology and psychiatry a lot of answers in context of PPD remain unanswered. The aim of the present article is to critically address the current progress as well as the challenges and certain limitations of the research regarding the possible phenotypes of PPD. What will follow below is a review of the hormonal and neurological studies which give us a better understanding of the symptomatology and behavior of mothers who suffer from PPD and could provide a better insight on the dilemma which is a matter of debate for many years. Is PPD homogenous disorder or are there several phenotypes? The literature on the indicated question is still ambiguous, however the importance of finding the answers is of great significance for identifying the best possible treatment. Implications for future studies will be made in order to fill the gaps in the existing knowledge about PPD and its' complicated nature.

PPD in search for definition

MDD and PPD – same or different disorders?

The biggest debate when it comes to PPD problematic is if it is significantly different disorder from major depression occurring in other times of women's life. Having in mind that MDD is one of the most important risk factors of PPD, one' could ask themself if PPD is just another depressive episode in women suffering from major depression. As for the other psychiatric disorders in general, professionals who work in the field of maternal health have divided opinions regarding this matter. According to some, PPD and MDD are etiologically the same, while others argue that there are significant differences which differentiates them into two separate disorders (Batt et. al. 2020). Another view is that women who experience their first depressive episode in the postpartum period are phenotypically different from women with postpartum depressive episode who also have a history of major depression (Cooper et. al. 1995). In the light of this debate, PPD and MDD are compared in terms of prevalence, symptoms and their intensity, hormonal events as well as neurological abnormalities.

Although there are few studies suggesting that PPD is more prevalent when compared to MDD because of the specific timing of onset, the overall data shows no significant differences (Augusto et. al., 1996; Cox et al., 1993). Augusto et. al. (1996) compared childbearing women with women with matched age, who had not delivered at least two years prior to the study. Their findings suggested that the rate of depression in the postpartum period is almost twofold in comparison with the control group. However, neither the pregnant women nor the controls have been controlled for past episodes of MDD. Furthermore, all the participants were given the Edinburg Postnatal Depression Scale (EPDS) meaning that it may not captured the symptoms (if any) in the controlled group. That being said, we must be mindful when drawing conclusions from this data, since many studies do not confirm this correlation (Augusto et. al., 1996).

Contrasting results obtained Hoertel et. al. (2015) who in order to compare the prevalence in peripartum, postpartum and non-postpartum population, conducted a study using a nationally representative sample from the United States. No significant differences were found between postpartum women and women of reproductive age who were not in the peripartum phase (Hoertel

et. al., 2015). Additionally, compared to peripartum women, non-child-bearing women showed significantly higher prevalence of all depressive criteria, except for worthlessness and guilt (Hoertel et. al., 2015). Similar results were obtained in another study where pregnant women were compared with matching controls (O'Hara et. al., 1990). No statistically significant differences were found between pregnant and non-pregnant group, neither for postpartum women and the controls (O'Hara et. al., 1990). The review of the literature implies that although the postpartum period is followed by significant triggers for depressive symptomatology, the prevalence of the postpartum depression is not higher than the prevalence of depression in other period of women's life, yet, this conclusion must be taken with caution since studies suggest that there is still a great percentage of underdiagnosed women suffering from PPD.

As it was already mentioned, in contrast to MDD, PPD is characterized not only with depressive symptomatology, but anxiety manifestations as well. Agitation, obsessive thoughts, irritability and panic attacks are common symptoms that are reported from PPD patients, however that is not the case for women suffering from major depression (Pitt, 1968). The milder clinical picture of PPD as well as the lower rate of suicidal ideations is another verification of the distinction of PPD and MDD (Pitt, 1968; Whiffen & Gotlib, 1993). However, it can be argued that neither all the patients suffering from MDD present homogeneous symptomatology (Lux & Kendler, 2010). Furthermore, few studies challenge the above-mentioned data with contradictory findings, implying that the clinical manifestation of depression during pregnancy and the postpartum period is not significantly different from non-postpartum depression (Hoertel et. al., 2015; Cooper et. al., 1988). On the other hand, Jolley and Betrus (2007) present a critique on these findings, arguing that studies which are using standardized MDD screening tools, which was the case in both of these studies, couldn't record the specific symptoms of PPD (Jolley & Betrus, 2007). Overall, the literature is not cohesive when it comes to the differences in symptomatology of PPD and MDD, so a conclusion about PPD as a distinct entity cannot be made solely based on the data of studies assessing the symptoms of these two disorders.

The neurological research concerning PPD are rare compared to the numerous data of MDD which can be found in the literature. Despite of that, there are several neurological findings which may support the hypothesis that PPD and MDD are distinct disorders. For example, Pawluski et. al. (2017) in their literature review stress the importance of the neurobiological

mechanisms which act as mediators in the relationship between the mothers' wellbeing and child's development. Comparing fMRI studies, they emphasize the differences in brain activation patterns found in population with postpartum depression and women suffering from major depression. Based on the literature findings, in contrast to individuals with MDD, women with PPD show hypoactivity in the medial affective and limbic regions during resting-state activity and functional paradigms involving emotional cues, further implying that these differences may differentiate PPD from MDD (Pawluski et. al., 2017).

As another example, Hamilton et. al. (2012) conducted a metanalyses regarding the neural activity and neural response to positively and negatively valanced stimuli in MDD population compared to healthy control groups. The results suggested that the MDD subjects compared to the control group in studies using negative valanced stimuli showed enhanced activity in the amygdala, insula, and dorsal anterior cingulate cortex and lower response in the dorsal striatum and dorsolateral prefrontal cortex (Hamilton et. al., 2012). Silverman et. al. (2011) in their neuroimaging study analyzed the neuronal response on 17 women suffering from PPD at 6-8 weeks postpartum while preforming neuropsychological linguistic paradigm. Blunted amygdala response was observed in response to threat-related linguistic stimuli, showing different patterns of activation regarding negative stimuli compared to results in studies with MDD patients (Silverman et. al., 2011). Moses-Kolko et al., (2010) in their study using emotional face matching task hypothesized that negative emotional faces will be correlated with altered amygdala activity (hyperactivity of the amygdala) in PPD patients when compared to mothers without depressive symptomatology. The results did not support this hypothesis since it was demonstrated that more severe PPD cases were correlated with blunted amygdala response on negative stimuli which is in line with the results from the previously mentioned study (Moses-Kolko et al., 2010). It was also found that mothers who showed more hostility towards their child exhibited decreased amygdala activity (Moses-Kolko et al., 2010). The amygdala is believed to be a part of a so called "maternal caregiving brain network", since it is part of emotional regulation systems and plays important role in modulating the social behavior (Amaral, 2003; Pawluski, 2017). Numerous studies with healthy mothers showed significant amygdala activation when processing their own babies' stimuli (especially faces) which further highlights the importance of the amygdala in the mother-infant bond and its' involvement in postpartum depressive symptomatology (Leibenluft et al., 2004; Strathearn & Kim, 2013). However, the data concerning the different patterns of activation of

AMG in PPD an MDD patients must be taken with caution since the discrepancies in the conceptual definitions and methodologies of different studies do not allow us to make an inference if PPD is different disorder.

In our knowledge, only one study directly investigated common and distinct neuronal mechanisms of PPD, MDD and healthy controls using fractional amplitude of low frequency fluctuations (fALFF), regional homogeneity (ReHo), weighted degree centrality (DC) and functional connectivity (Cheng et. al., 2022). The data which was analyzed in this study was collected from 77 women matched in age, without prior episodes of MDD, from who 26 were diagnosed with PPD, 22 with MDD and 29 healthy women. None of the patients received treatment prior or during the study. According to the results women with PPD and women suffering from major depression both showed abnormalities regarding the neuronal mechanisms compared to the healthy controls. Significant increase in fALFF in the left temporal pole (LTP) was observed in both PPD and MDD patients when compared to controls, which further suggest difficulties in emotional regulation, common for both of the disorders. Even though similarities were noted, there were also few significant differences between the three groups. In other words, PPD patients showed decreased activity in fALFF in the left posterior middle temporal gyrus (pMTG_L) and left supplementary motor areas (SMA__L). Statistically significant reduced functional connectivity (FC) between pMTG and precuneus (Pcu) as well as between left and right subgenual anterior cingulate cortex (sgACC_L) was also observed in patients with PPD. The above-mentioned results further imply disruption within the default mode network (DMN) in mothers with PPD which may be linked to the impaired emotional control and difficulties in processing of positive and negative emotional stimuli. In regards with the ReHo, PPD patients demonstrated increased homogeneity in the left thalamus (THA_L) and sgACC_L when compared to MDD patients, who on the other hand had significantly increased ReHo in comparison to the control group. The authors further explain these results suggesting that the over-suppression of THA_L in PPD patients in comparison with the MDD and the control group leads to emotional deregulation in new mothers with depressive symptomatology. The findings of this study signify the neurobiological differences in PPD and MDD patients further providing better knowledge of neural mechanisms which may lead to better diagnosis and treatment for mothers with PPD. However, since this is a unique study which directly compares the neuronal responses of these two

vulnerable groups, task-based research with bigger samples is necessary in order to reveal the bigger picture underlying the PPDs' neuropathology and its differences with MDD.

Initial argument of the theories supporting the view that PPD should not be defined with the diagnostic criteria for major depression disorder is the empirical data from hormonal studies suggesting that there are biological differences in women with PPD when compared with women suffering from MDD (Lancet Psychiatry, 2015). The hormonal fluctuations happening during pregnancy and in the period after delivery are making the women more vulnerable to depressive symptomatology. However, although these hormonal changes are dramatic during the postpartum period, they do not affect all the women equally further suggesting that there is a subset of women who are more vulnerable to these dramatic hormonal fluctuations (Bloch et al., 2000; Cooper et al., 1995). In line with this, is the study of Kettunen et al. (2014) who were aiming to explore if PPD is a homogenous disorder. Although they were not assessing hormonal factors in PPD, they suggested that women with PPD may differ between themselves. In other words, they compared mothers with PPD who had history of depression with mothers who had their first episode in the postpartum period. The results suggested that women with "pure" PPD exhibited less severe symptomatology, and although "pure" PPD was rarer, it was demonstrated that there is a subset of women who are specifically vulnerable to the biological changes occurring in the postnatal period (Kettunen et al. 2014). The previously stated, further points out the difference between PPD and non-PPD women and hence, the possible uniqueness of the postpartum depression. However, more studies should focus on directly comparing the hormonal factors of PPD and MDD in order to allow us to make inferences about the possible distinctiveness which may further have impact on the pharmacological treatment for this specific population.

So, is PPD a separate disorder? The literature does not offer one simple answer. The obtained data from the studies so far, leaves no room for a generalization or a conclusion regarding this matter, since the results are conflicting and vague. The existing evidence are supporting the two different viewpoints, making it almost impossible for the researchers and clinicians to agree when it comes to defining PPD. Additionally, whether same or different, agreeing on one definition on PPD is crucial for the prevention, early identification of the disease, predicting the outcome and providing the best possible treatment.

The worldwide used diagnostic manuals DSM V and ICD 10 define PPD as a part of major depression disorders using postpartum specifier, in order to emphasize the specific temporal period in which it occurs. Having said that, since PPD is still in search for definition and the point of view when it comes to the PPDs' onset, course and duration also vary. As it was already stated, according to DSM V the onset may range from pregnancy to 4 weeks after delivery, ICD defines the onset within 6 weeks postpartum and data from some studies implies that it can prolong even up to 12 months after childbirth. The lack of consent on PPDs' definition has serious implications in the research area as well as in the clinical practice. This may further have an effect on the prevalence and the fact that many women around the world are still underdiagnosed. The catastrophic impact that PPD may have on the mother and her child are additional motive for further research to solve the puzzle and fill in the blanks with one goal: consensus in defining PPD.

The heterogeneity of PPD

At the bottom of the problematic of finding agreement and constructing one definition of PPD lie several factors. As it was earlier said, researchers around the world when conducting a study regarding PPD, use distinct time frames for the onset as well as different diagnostic criteria. Although fewer in prevalence, studies have shown that depressive symptomatology can occur not only during the first weeks after a delivery, but throughout the pregnancy and later in the postpartum period as well, making it more difficult for postulating a diagnosis and consequently providing an adequate treatment. That being the case, some researchers often differentiate three subtypes of PPD: peripartum, early and late onset postpartum depression.

Peripartum (perinatal, antenatal) depression is defined as a depressive episode with symptoms occurring during the pregnancy (O'Hara, 1986; Becker et. al. 2016). Further, many of the professionals, in the literature, differentiate between early and late-onset postpartum depression. Early onset PPD is more prevalent and refers to a depressive episode which symptoms emerge in the first 4 to 6 weeks in the postnatal period (O'Hara, 1986; Munk-Olsen et al. 2006) . On the other hand, it was found that some mothers are starting to face emotional difficulties later suggesting another "subtype" of PPD – late onset postpartum depression, which is mainly characterized with onset of symptoms starting from 3 months to a one year after delivery (Evans et. al. 2001; Munk-Olsen et al. 2006). Since there is lack of a consensus in regards to the onset of PPD many studies are using the terms peripartum (antenatal, perinatal) and postpartum as

synonyms and the postpartum period is often not differentiated between early and late onset. In this part of the literature review, the three terms will be seen as different entities in order to compare and contrast the similarities and possible differences between them. As we will see in the following section, these distinctions are important since they may be associated with different risk factors and symptoms, which will further result in more targeted and tailored approach to treatment. From research point of view, this distinction will help the researchers in designing more effective studies and interventions which in return will contribute in the development of targeted prevention and treatment strategies.

Looking at the widely used international diagnostic classificatory systems DSM V and ICD 10 it can be noted that the onset criteria for diagnosis are to rigorous and not in accordance with results of scientific studies showing the extended time period in which PPD may occur. This results in heterogenous data obtained from research focusing on the time of onset of PPD regarding the prevalence and incidence of the three "subtypes", since studies use various definitions and focus on different time points in which PPD may occur (O'Hara et al., 2014). The systematic review conducted by Gavin et al., (2005) summarized the data of studies conducted between 1980 and 2004, concerning the point and period prevalence and incidence of women suffering from major and minor depression during pregnancy and the period including 1 year after delivery. Overall, 28 cross-sectional, cohort and case control studies were included which were assessing general U.S. population of women of childbearing age from developed countries. The point prevalence which tells us about the proportion of the women with minor and major episode of PPD at a specific time point, in this review was 11% in the first trimester, 8.5% at the rest of the pregnancy, further increasing in the postpartum period, reaching 12.9% in the third month after delivery and then again drops to lower range in the fourth throughout the seventh month (9.9% - 10.6%). The period prevalence (measuring the prevalence of a broader interval of time) according to the data of the studies included in this review for major and minor PPD was: 18.4% during pregnancy and 19.2% up to the 3rd month in the postpartum period. When looking for major depression only, the percentage was smaller. In other words, 12.7% of women were suffering from major depressive episode during the pregnancy and 7.1% during the first three months in the postpartum period. The incidence data for major and minor postpartum depressive new episode was 14,5% for the pregnant women as well as the women suffering from depression during the first 3 months after delivery (Gavin et. al. 2005). Munk-Olsen et al., (2006) observed that although the highest risk for hospital

admission was from 10 – 19 days in the postpartum period, the risk of depressive symptomatology was significant through the first five months as well. However, they didn't assess the risk of hospitalization in pregnant women (Munk-Olsen et. al. 2006). According to some authors, these data regarding the prevalence and incidence of PPD, proposes that the specifier of the onset of PPD should be extended (Wisner et al., 2010).

Looking at these results it can be noted that PPD is most prevalent during the first three months in the postpartum period. However, we cannot exclude the occurrence of depressive symptomatology in the pregnancy or in the later postpartum period based on the lower prevalence rates which may be due to several factors. Firstly, as we will see in the next part, the hormonal fluctuations are most prominent during this period. Next are the psychosocial factors including stressors such as infant care and sleep deprivation which are more challenging during the first few months due to adaptation of the mother to her new role. The diagnostic criteria for PPD and the focus of research studies can also influence the reported prevalence rates. It can be said that most of the studies highlight the early postpartum periods, leading to more data on early-onset PPD. Late-onset PPD is relatively less studied, contributing to the perception of lower prevalence. Lastly, since there is not defined strict time period for PPD, different clinicians and researchers define it differently, which may further result in different diagnosis. Some may define it as late onset PPD, while others as major depression, so which is the right?

Many studies have focused on targeting and differentiating the potential risk factors for the three "subtypes" of PPD. However, the results between studies differs and while some of the data shows differences in risk factors for depressive symptomatology between different times of onset of PPD, others show that the predictors for PPD are same between antenatal depression, early and late onset PPD. For example, Stowe et al., (2005) aimed to evaluate the onset of the depressive symptomatology in mothers diagnosed with PPD. The risk factors related to different onset timing were also explored. Hence, they assessed 315 women from Emory Women's Mental Health Program from who 209 fulfilled the criteria for inclusion in the study and were further divided into three groups regarding the onset of the depressive episode, antenatal depression, early onset and late onset PPD. They defined early onset postpartum depressive episode as onset of symptoms within the first six weeks, and late onset PPD as onset of the disorder after 6 weeks in the postpartum period. All of the 209 women who were included in the study were in their first

postpartum year, didn't take any medication for the current depressive episode and were able to provide information about the specific timing of onset of the depressive symptomatology. According to the data, in 11,5% of the participants the onset of depressive symptomatology started during the pregnancy, 66,5% of the women reported early onset PPD and the rest 22% noted that the depressive symptoms started later in the postpartum period. Furthermore, when it comes to the risk factors, several differences between the groups were noted. Firstly, single mothers were more likely to show depressive symptomatology during pregnancy but not in the postpartum period. Secondly, late onset PPD was significantly corelated with previous history of major depression but not with previous episodes of PPD. Authors suggest that this difference may further imply that late onset PPD is a distinct syndrome when compared with antenatal and early onset postpartum depression (Stowe et. al. 2005).

Similarly, as the previous study, Tebeka et. al., (2021) aimed to identify and assess the risk factors which occur in early and late onset PPD. Women with PPD were divided in two groups according to the onset of the symptomatology. 250 women exhibited early onset PPD and 235 women were identified in the late-onset group. The groups were defined by assessing the participants at 8 weeks and 1 year after delivery. Childhood abuse, history of depression as well as stressful life situations were risk factors associated with both early and late onset PPD. One significant difference was in the early maternal postpartum events which were more prominent in the late onset group. Women from this group were also more likely to be unemployed. Early onset women in comparison with late onset group were more likely to report chronic physical disease. These results highlight the risk of the occurrence of a postpartum depressive symptomatology which is present even after the 6th week in the postnatal period underlining the importance of clinical screening of new mothers throughout the whole first year after delivery (Tebeka et. al. 2021). Also, these studies suggest that early and late onset PPD may present different subtypes of postpartum depression, however, this interpretation must be taken with caution since there were there are many overlapping risk factors.

The literature of PPD suggests that antenatal depression is a significant risk factor for depression in the postpartum period. Bennett et. al., (2004) in their systematic review tried to estimate the prevalence of postpartum depression during the 1st, 2nd and 3rd trimester. According to the results of the statistical analyses of the 23 studies included in the review 7,4% of the women

suffered from depressive episode during the first trimester. Significant increase of the depressive symptomatology was noted in the second (12,8%) and third trimester (12,0%) of the pregnancy suggesting that maybe late pregnancy may be a risk factor for PPD, since it is challenging period in the woman's life. Further support of these results is the study of Leigh and Milgrom (2008) who were investigating the risk factors of antenatal, postnatal depression and parenting stress. The prevalence of antenatal depression was 16.9% during the last trimester of pregnancy and 11.2% in the early postpartum period. Incidence of antenatal and postnatal depression was not measured nor a follow up for late postpartum depression was made. Regression analyses revealed that antenatal depression is the strongest predictor for PPD as well as the most dominant mediator between postpartum depression and other risk factors further suggesting the important its important role and the significance of early screening during the pregnancy which will provide prevention, better outcome and treatment (Bennett et. al., 2004).

Rich-Edwards et al., (2006) also aimed to study the risk factors in antenatal and postnatal depression of pregnant women selected from Project Viva, a prospective cohort study of pregnancy outcomes and maternal and child health. 1278 women completed the Edinburgh Postnatal Depression Scale (EPDS) in the antenatal and postnatal period, from who 31% suffered from antenatal and postnatal depression. The prevalence of women with depressive symptomatology in only the postpartum period was 6%. Previous depressive episode was strongest predictor for antenatal depression. However, for postnatal depression, antenatal depressive symptomatology was the most significant risk factor, once again highlighting the importance of screening for depressive symptomatology during the pregnancy and not only in the postpartum period (Rich-Edwards et al. 2006).

Another study also hypothesized that different risk factors are significant for early onset PPD when compared with PPD occurring later in the postpartum period (Munk-Olsen et al., 2006). Early-onset postpartum depression was defined as onset of symptoms in the first four weeks after delivery and late-onset as depressive episode with beginning of the symptomatology between the 5^{th} and 12^{th} week postpartum. In regards to the risk factors, the authors were measuring the differences between the two groups in age, emotional support, psychiatric history and parity (Munk-Olsen et al., 2006). Similar results as the study of Munk-Olsen et al., (2006) were obtained in relation to the onset of PPD (Mori et al., 2011). In other words, the prevalence of early onset

PPD was higher (11%) when compared to late onset PPD (4%). History of previous episode of depression or anxiety was risk factor for both early and late onset PPD. When it comes to the emotional support, the results showed that it is a significant risk factor for early onset PPD and although the relationship between the variables emotional support and late onset PPD was not significant, authors suggest that there was a trend which implied that the lack of support is associated with higher risk of depressive symptoms later in the postpartum period. The statistical analyses revealed that younger and older age (<25years, >35 years) were significant risk factors for late onset PPD, however this relationship was not found for early onset PPD. On the other hand, statistically significant relationship was observed between parity and depressive symptomatology only within first 4 weeks after delivery. Authors suggest that these results further imply the possible distinctive aetiology between early and late onset PPD, highlighting the onset of symptoms as an important factor which should be further more thoroughly explored (Mori et al., 2011).

As well as the previous study, Howell et al., (2009), analyzed the possible risk factors associated to depressive symptomatology occurring at different timepoints in the postpartum period. Two-item version of the Patient Health Questionnaire (PHQ-2; Kroenke et al. 2003) was used for assessing the participants at two time points: baseline (2 weeks after childbirth) and at 6 months postpartum. 563 mothers were included in the sample, further divided into four groups based on the depressive symptomatology and its time of emergence: the never, the always, the late onset and in the remission group. The group never, was presented by 52% of new mothers who didn't show any symptoms during the both times of screening, the always group presented 14% mothers who screened positive for PPD at 2 as well as 6 months postpartum, late onset group consisted of 10% of women who showed depressive symptomatology only at the second screening and the final group were women at remission (24%) who manifested depressive symptoms at the 2 months, however these symptoms were not evident at 6 months postpartum. The risk factors assessed in this study were also divided into three categories: demographic and fixed characteristics (age, race, marital status, education, income, parity, delivery type and past history of depression.), situational triggers of depression (physical symptoms, functional limitations, infant characteristics, demands from the social context, infant colic, infant illness, and infant gender) and buffers of depression (social support and social criticism). Regarding the demographic and fixed characteristics, the never group showed similarities with the remission group, however,

both differed from always and late onset group. In other words, women in the first two groups reported no history of past depressive episode and were more likely to be white when compared to the second two groups where women were from more diverse ethnicity (non-white) and were more likely to have experienced depressive symptomatology in the past. On the other hand, significant differences were observed between the never group compared to the other three groups concerning the situational triggers which were more pointed up in mothers who showed depressive symptomatology only at the first screening and mothers in the always group. More specifically, the remission group exhibited lower self-efficacy and was triggered by more physical symptoms and infants with colic. The always group was mostly affected by physical symptoms. Interesting results were obtained regarding the buffers of depression i.e., the social support and criticism. Except of the never group, all other three groups were influenced by the lack of social support. Moreover, the late onset group reported satisfactory social support at the 2-month screening which declined over time suggesting that even though these women had history of depressive episode in the past, didn't showed any depressive symptoms at baseline, further implying that the social support may act as a mediator between past history of depression and late onset PPD (Howell et al., 2009). Authors suggest that the results of the cited study point out the necessity of a multifaceted approach of the clinical management which will prepare the mothers for their new role by educating them how to identify their somatic or depressive symptomatology and equip them with useful skills for managing and overcoming the difficulties with which they are facing (Howell et al., 2009).

Similar findings as the previous study were obtained in the study of Se´guin et al., (1999) who focused on the relationship between PPD and stressful life conditions as a possible risk factor in women of low socioeconomic status. The participants, 68 women, who originated from a household income below the poverty level as established by the Canadian Council of Social Development were assessed with Beck Depression Inventory (BDI) at several points during the pregnancy and the postpartum period. At six months postpartum 38.2% of the women were suffering from depressive symptomatology, from who more than half did not show any signs of PPD during the previous screenings which were at the last trimester of the pregnancy, third and ninth week after delivery. Similar as the previous study, it was discovered that social support is positively correlated with PPD at 6 months postpartum. In other words, women who reported higher level of support at the 3-week screening were less likely to develop depressive

symptomatology in the later postpartum period. Furthermore, since social support is multifaceted construct, authors noted that during the early postpartum period instrumental support was more significant for the women, however, new mothers required more emotional support from their partners and families in the later postpartum period (Se´guin et al., 1999). All this being said, these results are emphasizing the importance of screening for PPD not just in the early postpartum period, but in the following period as well. Additionally, identifying the risk factors and protentional triggers is from crucial importance for possible prevention of the disorder, and better multifaceted approach in regards to the treatment of the postpartum depressive symptomatology. Increasing the social support in this vulnerable time, helping the mothers increase their self-efficiency and providing them knowledge about the physical and psychological changes which occur in this period are significant steps which should be taken in the fight with PPD.

Properly identifying risk factors for PPD is crucial for early identification and better outcomes for the mother and subsequently the child's development. Having in mind the possible triggers may even help in prevention of the women who according to the data are in danger for developing PPD. Women with history of depression, obstetrical complications, stressful life events and who were abused in their childhood should be additionally followed during the pregnancy and in the first year after delivery. Although, the data of the risk factors for PPD does not give us an unreasonable doubt to advocate about different subtypes of PPD, it gives us evidence that the risk of PPD is not present only within the first few weeks. Even though early onset PPD is far more prominent in the population, screening in the later periods after delivery is more than necessary in order to spot, protect and give treatment to all the women facing the emotional difficulties in this sensitive period.

In order to further investigate the heterogeneity of PPD, few studies have focused on the specific symptomatology which may occur during the pregnancy or the postpartum period. For example, in order to reveal clinical subtypes of postpartum depression, Postpartum Depression: Action Towards Causes and Treatment (PACT) Consortium (2015), analyzed the diversity of PPDs' symptomatology (Guintivano et al., 2018). In this study, PPD was defined as major depressive non-psychotic episode which occurs in the first 12 months after child delivery, without prior episode of other psychiatric psychotic disorder. The data was obtained from the PACT Consortium and contained 17 912 records of mothers with depressive symptomatology and

controls who completed either (EPDS), the Hamilton Depression Rating Scale 17 item (HAM-D-17) or the structured clinical interview for DSM, fourth edition (SCID). For the purpose of examining the validity of the clinical subtypes of PPD, latent class analysis (LCA) was used. Furthermore, two-tier approach was applied, where in tier one 6556 women were included who were screened with EPDS only, including the ones that were struggling with depressive symptomatology during the pregnancy or after delivery. Tier two on the other hand, analyzed 4245 women suffering from PPD, diagnosed with either SCID or one of the measures which were previously mentioned (EPDS score ≥ 10; HAM-D-17 ≥ 8). 2537 of the women were included in two-tier analyses. The statistical analyses revealed three latent classes of PPD in the two-tiers, with strong positive LCA entropy (0,925). The first class in tier one was constituted of women who didn't report and depressive or anxious symptomatology in pregnancy nor in the postpartum period. The second and third class were represented by mothers who were suffering from postpartum depressive symptomatology, however, the two classes differed between themselves in terms of symptoms severity, the onset of the PPD, suicidal ideations and comorbidity with anxiety. In other words, the third class was characterized with more sever symptomatology, suicidal thoughts, panicky and crying behaviors. In tier one, the third class also more often reported history of mood and anxiety disorders. In the second tier, the first class had fewer women with sever PPD symptomatology who had another psychiatric comorbidity. In the second as well as the first tier, the third class had the most severe cases of PPD with most prominent suicidal ideations when compared to the other two classes. Speaking of the timing of onset of the PPD episode, women in the third class in both of the tiers reported symptomatology onset during the pregnancy, while in women in the second class the symptoms onset was the first four weeks after delivery. These results further suggest that women with antenatal depression compared with women whose depressive episode begins in the postpartum period, show worse clinical picture and more negative outcomes, which highlights the importance of properly defining the timing of the onset of PPD which has high prognostic value. Authors also suggest that more studies on this matter are needed, since the timing of onset may present a valuable marker for biological research of PPD (Guintivano et al., 2018).

Using the same database from PACT, Putnam et al., (2017), aimed to identify different subtypes of PPD as well as differentiate them by the time of symptom onset using the National Institute of Mental Health (NIMH) research domain criteria (RDoC) functional constructs. RDoC

is a research framework which aims to promote innovative research strategies not in order to replace the current diagnostic manuals but to contribute in better understanding of the mental illnesses which will further result in improved diagnosis, prevention and better treatment solutions (National Institute of Mental Health). Seven international sites from PACT were included for data analyses, in which the subjects were 663 women (19-40) suffering from perinatal or postnatal depression. The obtained results from the statistical analyses suggested existence of five subtypes of PPD: severe anxious depression, moderate anxious depression, anxious anhedonia, pure anhedonia and resolved depression. These subtypes were differentiated by the nature and severity of the symptomatology as well as the time of onset of the symptoms (onset during the three trimesters during pregnancy or in three different postpartum periods). The first type, severe anxious depression was described with very severe symptomatology of depression and anxiety which was significantly higher than the other subtypes, however there was no statistically significant correlation between this subtype and anhedonia. The data showed that women with depressive symptomatology during the first trimester and in the postpartum period had most severe symptomatology, so correspondingly severe anxious depression was characterized with onset of symptoms in the first trimester or after 8 weeks in the postpartum period. Second, women with moderate anxious depression had similar onset of symptoms, however, the intensity of the symptomatology was significantly less severe. Most of the women with anxious anhedonia had onset of depressive symptoms during the first four weeks after delivery and were characterized with severe depressive but not anxious symptomatology. Pure anhedonia subtype was approximately represented in all the perinatal and postnatal periods except during the first four weeks in the postpartum. The final 5th type, resolved depression was catheterized with onset of symptoms in the third trimester of pregnancy and had significantly lower score on all depressive dimensions. These findings further suggest of the necessity of the novel approaches when it comes to the solving the mystery of PPD since according to all the gathered evidence it is complex and heterogeneous disorder. The authors imply that more research is needed which will concentrate on the different causes, pathophysiological and biological mechanisms in order to identify the best treatment and to improve the diagnosis of PPD, since as we mentioned earlier, the postpartum depressive symptomatology is often overlooked (Putnam et al., 2017).

The obtained data from research investigating the risk factors and depressive symptomatology during pregnancy and in the early and late postpartum period so far suggests that

probably these may not represent distinct types of PPD. However, this data holds significant importance as it demonstrates that PPD is not a uniform disorder. As it was shown in the previously mentioned studies, the onset of symptoms can vary from pregnancy to the late postpartum period, highlighting the need for screening at multiple time points (Gavin et. al. 2005 & Munk-Olsen et al., 2006). Accurate diagnosis of depressive symptoms in the late postpartum period is crucial, not only for the well-being of the mother but also for the infant, as it has been observed that these symptoms may be linked to the language development of the child. As we can note, many of the studies define early and late onset in different time points which may be the reason for the unconclusive results and that is one more reason for one conclusive definition of PPD. Yet, agreement for the possible times of onset is not important only for the research but for the clinical practice as well. Expanding the onset period of PPD will help to detect even women whose symptoms were still not developed during the early period after delivery (Wisner et al, 2010). On the other hand, capturing the onset of the antenatal depression and providing an appropriate treatment on time will reduce the cases of PPD, since as it was already mentioned, antenatal depressive symptomatology is one of the most important risk factors (Bennett et al., 2004). Future studies should focus on exploring the correlation between the risk factors and the hormonal events which emerge during the pregnancy and in the postpartum period in order to examine the possible differentiation between prenatal and early and late onset postpartum depression.

Endocrinology and PPD

Despite the many psychosocial events that are happening in the period of pregnancy and postpartum, women are also facing with profound biological changes from which the dramatic decrease of several steroid hormones are the most striking ones. These endocrine alternations are unique for this time period and provide the woman with adaptive preparations for the childbirth (Tal & Taylor, 2021). Furthermore, these hormonal shifts are not only responsible for the physical changes that occur during pregnancy but also play a vital role in the emotional and psychological adjustments that women undergo as they transition into motherhood (Soma-Pillay et al., 2016). However, research data show that some of these changes may be at the bottom of the mood problems and depressive symptomatology at this specific vulnerable period in women's life. Thereby, in this part of the literature review, hormonal shifts during pregnancy and the postpartum period will be explored, as well as their impact on both the physical and emotional aspects of motherhood, and their connection to PPD.

During the pregnancy there is a continuous increase of hormone plasma concertation, which is followed by a major drop at delivery, and the women stay in this hypogonadal state until the restoration of the menstrual cycle which varies depending on if the woman is lactating (Bloch et al., 2003). These hormonal fluctuations influence the production and regulation of neurotransmitters such as serotonin, dopamine, and gamma-aminobutyric acid (GABA), all of which play critical roles in maintaining stable moods (Sari & Susanti, 2023). Knowing this, the hormonal withdraw theory was postulated, which basically suggests that the rapid decline in estrogen and progesterone levels following childbirth can disrupt mood-regulating mechanisms in the brain, potentially contributing to postpartum blues and depressive symptomatology (Bloch et al., 2000; Galea et al., 2001). As a result, researchers, while searching for the biomarkers of PPD, have been focused on several steroid hormones, including estrogen, progesterone and cortisol.

Furthermore, data from the literature has shown that these hormonal alternations occur in all pregnant women, however only some of them are affected and show depressive symptomatology (Soares & Zitek, 2008). That being said, researchers speak about a subset of women who are specifically vulnerable to the withdrawal of these hormones. For example, Cooper

et. al. (1995) in their study hypothesized that women with PPD may differ between each other regarding the previous history of depression. In other words, the authors were comparing women with PPD whose first episode onset was after the birth of their first child and postpartum women with already exciting history of MDD. The participants were primiparous women who were divided in three groups based on their depression status: 34 women who faced depressive symptomatology for the first time in the postpartum period, 21 women with a history of MDD and recurrence of the symptomatology in the postpartum period and 40 women who constituted the control group and didn't show any symptoms of PPD nor had any past affective difficulties. This was a longitudinal study where the participants were assessed at several time points during the course of 5 years. According to their results, in comparison to women with history of MDD, women whose first episode of depression was at postpartum period had an elevated risk for future PPD. On the other hand, women with history of MDD although didn't have increased risk of PPD, they were at higher risk for following MDD outside the postpartum period. Their finding suggests that there is a possibility that there are two nosologically distinct subtypes of women with PPD, as well as, women whose first major depression episode was after the birth of their first child are more vulnerable to the reproductive and hormonal changes that happen after delivery (Cooper et. al., 1995).

Payne et al. (2009) in their review also talk about subtype of depression known as "reproductive depression" which develops in women with hormonal sensitivity as a result of a gonadal hormone changes that occur during the specific reproductive events in women's reproductive life. This subtype of depression includes menarche, perinatal depression, premenstrual dysphoric disorder (PMDD), and depression in the perimenopausal period (Payne et al. 2009). Using evidence from correlational and genetic studies the authors discuss about the link between the reproductive subtype of depression, female gonadal steroids and the neurotransmitter system. They also propose the possible role of neuro-steroids, however pointing out the necessity for future studies carefully examining the possible connection (Payne et al. 2009). In the following section, the complex possible role of the gonadal steroids in the PPDs' problematic will be explained, followed by the description of the involvement of oxytocin in the pregnancy and the postpartum period and its connection with PPD. Lastly, we will talk about the involvement of the HPA axis, and how does the alternations in the HPA axis reactivity during pregnancy corelate with PPD.

Gonadal steroids

Estrogen – "The major female sex hormone" & Progesterone – "The pregnancy hormone"

Estrogen and Progesterone are steroid hormones, highly involved in brain functioning as well as regulation of the female reproductive health. Estrogen represents an umbrella term for 3 major hormones, estradiol, estriol, and estrone, which are actually a biologically active forms of estrogen from which estradiol (E) as a most dominant form, drastically fluctuates in various reproductive phases in women's life span such as pregnancy and menopause (Douma et al., 2005). It was shown that although all the three forms of estrogen gradually increase throughout the pregnancy, E concentrations during the second half of the pregnancy was 2,5 times higher compared to estriol or estrone concentrations and by the last trimester E levels increased 50 times (Tulchinsky et al., 1972). After delivery there is a significant drop in E which concentrations are back to normal after several days in the postpartum period (Hendrick et al., 1998).

On the other hand, progesterone and its metabolite – allopregnanolone are also extremely important for sustaining healthy pregnancy by reducing the blood pressure, maintaining the cervical integrity (Schiller et al., 2014). In contrast to estrogen which levels are highest during the ovulation phase, progesterone levels rise only during the luteal phase of the menstrual cycle, yet, both of these hormones increase thorough the pregnancy (Vink et al., 2017). However, it is demonstrated that during the gestational period, progesterone and consequently ALLO levels are a lot higher when compared to estradiol, with progesterone reaching 200–2000 nmol/l (Sundström-Poromaa et al., 2020). In addition to this, data from studies show that there is a significant fluctuation in progesterone levels within subjects during the midluteal phase as well as significant variability between women, making it hard for the researchers to postulate a progesterone standard value for research and clinical purposes (Mesen & Young, 2015). At the end of the pregnancy there is a functional withdrawal of this steroid hormone and its metabolite ALLO, preparing the women for labor, after which there is a sudden drop in its concertation (Hill et al., 2011). This withdrawal of progesterone lasts for 2-3 h postpartum, before its luteal phase levels are achieved (Hill et al., 2011). ALLO luteal levels are reached roughly five days in the postpartum period (Hill et al., 2011). For several years, it was widely believed that the withdrawal of estrogen and progesterone is implicated in the etiology to the depressive symptomatology in the postpartum period (Hendrick et al., 1998; Douma et al., 2005).

In line with this hypothesis, are animal studies confirming the "hormone withdrawal" hypothesis postulated for PPD. Galea et al., (2001) examined this hypothesis in female Long-Evans rats who were subjected on estradiol and progesterone injections for 23 days in order to stimulate pregnancy. The rats were divided in three groups: pregnant- who were receiving estradiol and progesterone daily during the "pregnancy" for 23 days, pregnant + EB – prolonged receiving estradiol in the "postpartum period" (after the 23th day) and control group who were not injected with any hormone. Forced Swim Test (FST) and Open Field Test (OFT) were used in order to examine depressive symptomatology in rats. It was demonstrated that in comparison with control and pregnant + EB groups, rats in the pregnant group were showing significantly more depressive behaviors on FST and OFT, further confirming the withdrawal hypothesis of PPD in rodents, meanwhile suggesting that prolonged intake of estrogen can reduce the depressive symptomatology (Galea et al., 2001). Similarly, Stoffel and Craft (2004), stimulated hormonal pregnancy for 22 days in several rats and then compared their behavior with controls using FST and elevated plus-maze. The obtained results showed that there is a significant relationship between estrogen and progesterone withdrawal and depressive behaviors since it was shown that rats in the "pregnancy" group showed depressive-like behaviors on the FST after the 22th day, when the hormonal withdrawal started to taking place (Stoffel & Craft, 2004). Despite the fact that these results are in favor of the hormone withdrawal hypothesis, inferences must be made with caution since although many times animal model studies can help us in the direction of thinking, they still differ from clinical human studies.

Although animal studies can surely provide valuable insights into biological mechanisms, human studies are crucial for understanding human health and behavior directly. This being the case, in order to understand and explore the possible correlation between PPD and hormonal changes, we need as much as possible human studies including participants with diverse background, age as well as diverse history of mental and physical health. Bloch et al. (2000) in their study postulated that there is a possibility that a subgroup of women developed PPD as a result of their sensitivity to reproductive hormone changes which happen after some reproductive events such as childbirth. The participants in this study were sixteen women which were divided in two groups based on their history of postpartum depression (8 with history of PPD and 8 without history of PPD). In order to test their hypothesis, the authors simulated supraphysiologic levels of gonadal steroids by adding supraphysiologic doses of estradiol and progesterone for 8 weeks and

then withdrawing the both steroids to a hypogonadal state. According to their results none of the participants in the control group were affected by the hormonal changes, while five out of eight women with history of PPD developed significant mood symptoms throughout the withdrawal phase. These findings suggest that childbirth may represent specific biological trigger for women that are sensitive to the fluctuations of the levels of the gonadal steroids' estradiol and progesterone (Bloch et. al., 2000).

Research data is confusing and diverse when it comes to the problematic of the hormonal withdrawal hypothesis. Some authors like O'Hara (2001) believe that PPD is a result of drastic decrease in the levels of estrogen and progesterone in PPD women when compared with healthy mothers in the postpartum period, however, others, don't agree with this notion since many studies failed to find significant difference in the concentration of these hormones in PPD and healthy postpartum population (O'Hara et al., 2011). O'Hara et al., (2001) in their study measured the hormonal levels and the depressive symptomatology in women in their 6th week of the postpartum period. The authors in this study found significant relationship between levels of estradiol and PPD, yet, this relationship was not observed in regards to progesterone (O'Hara et al., 2001). On the other hand, Klier et al. (2007), assessed 105 women in order to examine the relationship between depressive symptomatology in the postpartum period and the level of estrogen and progesterone in the first five days after delivery. In order to examine the depressive status of the patients, they were tested with the German version of SCID (semi-structured clinical interview) 5 days in the postpartum period, the SDS Zung self-rating depression scale in the 38th week of pregnancy and the first 10 days after delivery and additionally tested with EPDS at six months postpartum. The concertation of estrogen and progesterone were measured by taking blood sample during the last trimester of pregnancy and in the first 5 days after giving birth. The data from the statistical analyses suggested that women with depressive symptomatology in the postpartum period did not have significantly different levels of estrogen and progesterone compared to women without PPD in the first 5 days after delivery (Klier et al., 2007). These results differ from findings in other studies; however, the authors suggest that these discrepancies are probably due to the fact that they measured the levels of the hormones during the first 5 days in the postpartum period in contrast with O'Hara et al., (2001) who were measuring the hormonal levels in the 6th week after delivery.

Although the data from the previous study do not show statistically significant differences between hormonal concentrations in PPD and non-PPD women, it further supports the hypothesis about specific population of women more biologically sensitive to hormone withdrawal proposed by Cooper et. al. (1995), Payne et al. (2009) and Bloch et al., (2000). Consistent with these findings are the results from clinical studies suggesting that treatment with estradiol has a positive impact on PPDs' symptomatology. For example, Gregoire et al., (1996) in their controlled trial study, aimed to examine the possible beneficial effect of transdermal estrogen for treatment in women with severe PPD. The participants were women with non-psychotic PPD, which onset was during the first 12 weeks after delivery measured by EPDS and clinical psychiatric interview (SADS). In order to measure the efficacy of transdermal estradiol therapy the women were randomly assigned in active and placebo group. The whole experiment lasted 6 months, during which the patients in the active group were told to apply two patches in order to get 17β-estradiol 200 μg daily, and change them two times in a week for the first 3 months, after which they were instructed to additionally take 10 mg of dydrogesterone because of the high risk of endometrial hyperplasia. The placebo group were given the same instructions, only they took a placebo patches and tablets. Every month during the 6-month period women were assessed with EPDS and SADS in order to compare the baseline scores with scores obtained after treatment in both of the groups. The statistical analyses showed that there is significant difference between the active and placebo group in the EPDS and SADS scores suggesting that the treatment with transdermal estrogen is successful weapon in the battle with PPD. Furthermore, the results also showed that the desired effects are reached during the first month which is a lot faster when compared with traditional antidepressants additionally implying the superiority of transdermal estrogen (Gregoire et al., 1996).

Another evidence for the fast and efficient effect of 17β-estradiol is the study of Ahokas et al., (2001). In their study they assessed 23 women with PPD according to ICD-10 criteria, at baseline and every week during the 8-week course period with the Montgomery-Asberg Depression Rating Scale (MADRS). The baseline measurements of serum estradiol concentrations showed that all the women were in hypogonadal state. The patients were treated with 17β-estradiol which resulted in improving the MADRS scores during the first week and remission in 19 of the patients at the end of the second week (Ahokas et al., 2001). Taken together, these two studies suggest that estradiol is successful treatment in the "subgroup" of women who are significantly

vulnerable to the hormonal changes happening in the postpartum period and develop depressive symptomatology. These result are also in line with research suggesting the efficiency of estradiol treatment in other depressive disorders with reproductive nature such as premenstrual dysphoric disorder and perimenopausal depression (Moses-Kolko et al., 2009).

Looking into progesterone, the researchers in the latest period have mostly been focused on its metabolite allopregnanolone (ALLO), according to who, this metabolite has the leading role in postpartum depression. As it was previously stated a metabolite of progesterone, ALLO modulates GABA-A receptors and its' levels vary significantly during the time of menstrual cycle, pregnancy and postpartum period, significantly increasing in plasma during the luteal phase of the women menstrual cycle and late pregnancy (Burke et al., 2018; Bixo et al., 1997; Genazzani et al., 1998). Being a positive allosteric modulator of GABA – A receptors, ALLO slows the rate of recovery of this receptor from desensitization and increases the rate of entry into fast desensitized states, thus acting as anxiolytic (Tsutsui & Haraguchi, 2020). However, studies show that besides the anxiolytic and sedative properties, ALLO can also act as anxiogenic. For example, it was suggested that women who suffer from premenstrual syndrome (PMS) had significantly lower concentrations of this metabolite than the controls during the luteal phase of the menstrual cycle. Results also shown that in the follicular and luteal phase the concentration of progesterone were lower in the experimental group (Monteleone et al., 2000). Similar results obtained Rampkin et. al., (1997) with the exception that they didn't find significant differences between the PMS and the control group regarding the serum progesterone level. However, the obtained results implied that there was a significantly smaller ratio of the ALLO to progesterone in the PMS group (Rampkin et al., 1997). These results further lead to the hypothesis that there is a group of women that may suffer from insufficient production of ovarian neuroactive steroids in the luteal phase, which further leads to inability to enhance GABA-A inhibition in the period of ovulation or other psychological or physiological stressful situations resulting in changes in the mood, anxiety and depression (Rampkin et al., 1997; Monteleone et al., 2000).

As it was already said, levels of ALLO fluctuate not only during the menstrual cycle but also during pregnancy as well as in the postpartum period. According to the results of many studies, the levels of ALLO rise during pregnancy continuously, while after the delivery there is a rapid drop within a few days (Luisi et. al., 2000; Nappi et. al., 2001). Nappi et. al. (2001) were

investigating if ALLO and progesterone may be a biomarker for maternity blues. They were also measuring the correlation between serum ALLO and progesterone in the postpartum period. The obtained results showed that the levels of the serum ALLO were lower in the postpartum period than in the pregnancy, and that women who were experiencing postpartum blues had significantly lower levels were than the euthymic women. The levels of the progesterone although not significantly, were also lower. They interpreted their results in light of ALLO rather than progesterone itself taking more complex part in the postpartum mood disorders (Nappi et. al., 2001). So, the question that rises is if ALLO itself has a leading role not only in postpartum blues but in PPD as well and if that is the case, does the lower levels of concentration of ALLO are the cause or the changes that are rapidly happening during the pregnancy and delivery and in the postpartum period?

Oborne et. al. (2017), hypothesized that women whose levels of ALLO were lower during the second and third trimester will develop postpartum depression after delivery. By measuring progesterone and ALLO in the second and third trimester in 60 pregnant women with history of mood disorder their results showed that there is a significant relationship between PPD and ALLO. In other words, their findings suggest that women whose ALLO levels were lower in the second trimester were more likely to develop PPD. However, they didn't find any significant relationship between third trimester ALLO and PPD, which was explained by the fact that the hormones were measured earlier than the third trimester highest point (Oborne et. al., 2017). Although future research is needed, according to the findings of the cited study, ALLO levels in pregnancy may be a valuable indicator of depressive symptomatology in the postpartum period.

Similarly, Hellgren et al. (2014), hypothesized that higher levels of ALLO in late pregnancy would lead to fewer anxiety and depression symptoms. 96 women in late third trimester filled out Montgomery-Åsberg Depression Rating Scale (MADRS-S) and the Spielberger State-Trait Anxiety Inventory (State and Trait versions, STAI-S and STAI-T, respectively). Roughly two weeks before their delivery date the participants also provided informed consent and blood sample. Six weeks after the delivery the Swedish version of the Edinburgh Postnatal Depression Scale (EPDS) was sent to the participants to be filled and returned via mail. This research findings suggested significant negative correlation between concurrent self-rated depression score and late pregnancy serum allopregnanolone, however no significant relationship was found between

allopregnanolone and postpartum depressive symptoms. They explain these results with the possibility that the lower levels of ALLO after delivery has bigger influence after the first few days which explains the maternity blues, but not that big difference after several weeks (Hellgren et al., 2014). However, both, depressive symptomatology during pregnancy and maternity blues, increase the risk for postpartum depression, so these are important evidence for the role of ALLO in PPD, emphasizing the lower levels of this metabolite as a potential biomarker of PPD.

Other authors in their review propose that the affective changes that are happening after delivery are a result of the fluctuations in the levels of ALLO rather than the absolute concentration in hormonally sensitive women (Burke et. al., 2017; Gordon et. al., 2015). This hypothesis was based on research that showed that the symptoms of premenstrual dysphoric disorder (PMDD) are mitigated when the levels of ALLO are stabilized from the follicular to the luteal phase of the woman's menstrual cycle by blocking the conversion of progesterone to its 5α-reduced neuro-steroid metabolite (Schiller et al., 2014). Moreover, Martinez et al. (2016) tested the hypothesis that changes in mood may be triggered by the changes in ALLO in susceptible women. Their preliminary evidence showed that there is a negative correlation between depressive symptoms in women with history of premenstrual dysphoria (PMD) and PPD and circulating levels of ALLO, which was also supported by studies with animal models (Martinez et al., 2016). Furthermore, it was shown that extended withdrawal of ALLO modifies GABA receptors which further is causing for ALLO to act as an anxiogenic after its reintroduction (Smith et al., 2006). The authors claim that this also may be the explanation of the late onset PPD. In other words, after delivery of the baby ALLO levels remain low since the hypothalamic pituitary-ovarian (HPA) axis is suppressed due to lactation. After the prolonged withdrawal, in the later postpartum period due to resumption of menstruation, ALLO fluctuations resume with mid-luteal peaks (Burke et. al., 2017). Knowing this, they hypothesized that late onset PPD is a result of resumption of ALLO levels after a period of prolonged withdrawal which alters GABA – A (Burke et. al., 2017). These evidence, also support the assumption about the involvement of ALLO in PPD and reproductive mood disorders, but with the exception that they are pointing out the importance of the changing levels of ALLO during woman's reproductive life and encourage the further exploration of its mechanisms.

Last but not least indication about the involvement of ALLO in PPD, are the treatment trials of a synthetic formulation of ALLO, brexanolone, in women with moderate to severe PPD

symptomatology. This double-blind, randomized, placebo-controlled trials of three studies showed that brexanolone injection may significantly contribute in remission rates in women with PPD. In other words, the results showed that compared to placebo groups, women in the experimental group had reduced depressive symptomatology, as well as, there was a rapid onset of action of the brexanolone injection and durable treatment response (Kanes et al., 2017, Meltzer-Brody et al., 2018). This is the first drug ever that is approved by the FDA specifically for PPD, however it is indicated that the usage of this drug is permitted only in the postpartum period, and not during the pregnancy.

Taken together, the depressive symptoms that arise during the postpartum period may occur due to a direct effect of changes in the level of the ALLO, indirect effect due to changes in receptor concentration or configuration or due to the effect of the mediating factors like changes in the immune system or HPA axis. The literature indicates that ALLO may be the key factor in the etiology of the mood disorders in the postpartum period, however, more studies are needed examining the relationship between ALLO and other hormones, social variables and risk factors in order to know its exact position and role in the PPDs' maze.

Neuropeptide

Oxytocin – "The love hormone"

OT is nonapeptide hormone synthetized in the supraoptic and paraventricular nuclei (SON and PVN) of the hypothalamus and secreted by the posterior pituitary into the bloodstream (Kim et al., 2014; Uvnäs-Moberg et al., 2020; Scantamburlo et al., 2007). Besides the hypothalamus, OT receptors are also found in other brain regions such as bed nucleus of the striae terminalis (BNST), central and medial nuclei of the amygdala, septum, hippocampus and medial preoptic area (MPOA), (Scantamburlo et al., 2007; Kim et al., 2014). The various locations of the OT receptors in the human brain suggest its role as neurotransmitter and its implication in maternal behavior as well as anxiety and depressive disorders (Scantamburlo et al., 2007; Kim et al., 2014).

When it comes to the oxytocin (OT) and its relationship with PPD the interest was not as strong as it was for the other hormones. However, the relationship between OT, its facilitation in child birth and breastfeeding, stimulated the researchers to further explore the possibility of its involvement in this ruthless disease and to investigate the possible beneficial effects when used in

therapeutic purpose (UvnäsMoberg et al., 2020). Furthermore, another indication of the possible association between these two variables are animal and human studies reporting the relationship between OT and major depression and anxiety. For example, Scantamburlo et al., (2007) aimed to explore the relationship between plasma levels of OT and mood disorders. 25 patients with MDD were assessed on the 17-item Hamilton Depression Rating Scale (HDRS) and State-Trait Anxiety Inventory (STAI). Using Pearson product–moment correlation the results revealed that patients with higher anxiety and depression scores had lower plasma levels of OT further suggesting negative relationship between OT levels and mood disorders. As we know, depression and anxiety play the key role in PPD symptomatology, so the correlation between these mood disorders and OT may further imply the involvement of OT in PPD.

Another evidence for the OT-PPD correlation, as it was already mentioned, is the association between OT and lactation. Uvnäs -Moberg et al., (2020) conducted a systematic review regarding the plasma levels of oxytocin in response to breastfeeding and the impact of various medical interventions such as caesarean section, epidural analgesia and infusion of synthetic oxytocin on oxytocin production. Given the purpose, they selected 29 articles which met several inclusion criteria like "population of breastfeeding women who had at least two measurement of plasma levels of oxytocin in response to breastfeeding", studies written in English, German, French, Japanese and "Peer- reviewed original research/data" (Uvnäs -Moberg et al., 2020). The summarized results revealed several important findings for the present review. Firstly, data from the included studies suggested that although oxytocin levels dropped in the first few days after delivery, positive relationship between breast-feeding or breast stimulation and OT levels was observed. Secondly, the OT levels were also positively associated with duration of the lactation as well as the quantity of milk production however, this relationship was compromised by another variable – stress, implicating the importance of stress on lactation. In line with these is the data suggesting that in women who did not breast feed and used other alternatives, OT levels did not increase. Another important finding was that caesarean section and epidural analgesia had negative impact of OT levels which was restored with OT infusion (Uvnäs -Moberg et al., 2020). As previously mentioned, stress, caesarian section and non-breastfeeding are mentioned in several studies as several important risk factors for PPD. This being said, the question which arises is: What is the role of OT in this complex chain?

In this context, another important review to mention is the one of Galbally et al., (2011) explaining the correlation between OT and mother-infant bond. According to the 8 included studies higher levels of OT were associated with stronger mother-infant relationship. For example, one of the included studies was examining the relationship between OT levels in the three trimesters during pregnancy and in the early postpartum period. The results suggested that OT levels varied dramatically during pregnancy across sample so it's almost impossible to set up a standard value of OT during pregnancy which was also the case in several other studies, however, it was shown that women whose levels rose during pregnancy had higher scores on the maternal–fetal attachment scale (MFAS). In other words, stronger mother-infant bond was observed in women whose levels of OT were not static during pregnancy (Galbally et al., 2011). Having in mind all of the above-mentioned data, the relationship between OT and PPD is worth for further explanation.

Animal studies support the idea that OT hormone may play a significant role in the PPD symptomatology. Studies with animal models suggest that OT levels are closely related to breastfeeding, stress regulation, anxiety and depressive symptoms and maternal behaviors (Kim et al., 2014). For example, it was demonstrated that rats with lesions of the PVN, female mice with reduced OT neurons in the PVN and female OT knockout mice were exhibiting impaired maternal carer-giving behavior (Insel and Harbaugh, 1989; Ragnauth et al., 2005; Takayanagi et al., 2005). Moreover, another study by Pedersen and Prange (1979) demonstrated that female virgin rats which were administered 0.4 μg of oxytocin by intracerebroventricular injections started to demonstrate maternal care-giving behaviors towards foster pups (Pedersen and Prange, 1979). The valuable insight provided by the animal studies in regards to OT-PPD relationship, is worth further exploring through epidemiologic research in order to be able to generalize and thus directly apply these findings in the medical practice.

Although, human studies investigating the possible association between OT levels and PPD are limited, the data from the existing ones imply the possible association and inverse relationship between OT levels and PPD symptomatology. For example, Stuebe et al., (2013) examined if the breastfeeding duration and neuroendocrine changes during feeding the baby are corelated to the PPD symptomatology. Several neuroendocrine markers were assessed: The OT levels were measured in 47 breast-feeding women at baseline, several times during the feeding of the baby and

after women were finished with the breast feeding, progesterone and estrogen-measured at baseline, 10minutes during and after the feeding, and cortisol, corticotropin releasing factor (CRF), free Thyroxine (T4), and total T4 only at two time points which were baseline and after the mothers breast-fed their babies. EPDS, Spielberger State and Trait Anxiety Inventory were used to assess the depressive and anxious symptomatology in the third trimester and at 2 and 8 weeks after delivery. The statistical analyses revealed that women with lower levels of OT were significantly more prone to higher scores on the EPDS at the three time points when measured, however for the other hormones this was not the case. Namely, statistically significant inverse relationship was found only between total T4 and PPD at the 8th postpartum week which was also in line by other studies showing that total T4 in pregnancy I positively corelated with depressive symptomatology in the postpartum period. The authors interpreted these results in regards to the neuroendocrine changes happening during lactation and how these changes are connected to the PPD symptomatology such as depression and anxiety (Stuebe et al., 2013).

Similarly, Skrundz et al., (2011) investigated the possible connection between prenatal levels of OT and depressive symptoms during the postpartum period. The participants were 73 women recruited during their third trimester of pregnancy who did not have had any current problems with the mental health or severe medical complications. 16 of the participants had a history of MDD episode at least 2 years prior the current study. OT measures were collected during the last trimester of the pregnancy and EPDS was also administered in order to divide the participants into a risk-for PPD group (rPPD) and a no-risk-for PPD group (nPPD). The scores from the first assessment on EPDS were also used as control scores in order to be compared with the scores obtained after 2 weeks in the postpartum period. During the initial visit the mothers were also assessed on Computer Assisted Personal Interview (CAPI) in order to check the current mental health status as well as possible previous episodes of mood disorders. The obtained results suggested that mothers who had lower levels of OT during the last months of pregnancy, had higher scores on the EPDS in the postpartum period confirming the results of the previous study. The authors explain this inverse relationship by pointing out the meaningful role of OT in the maternal behavior such as “positive affect and gaze in interactions” and lack of these types of behaviors in mothers with PPD (Skrundz et al., 2011). Furthermore, one of the important roles of OT is lowering the intensity of the stress reactivity which insinuates the possible interaction

between OT levels, amygdala reactivity and HPA-axis in challenging times such as pregnancy and postpartum period (Cox et al., 2015).

On the other hand, Guintivano et al., (2018) did not find statistically significant relationship between OT levels and PPD symptomatology in women with PPD compared to controls. They assessed 1517 racially diverse women in the 6th week after delivery with the MINI International Neuropsychiatric Interview (MINI-Plus, version 6.0) in order to determine the PPD status and several other self-assessment measures to check for depressive symptomatology (EPDS) and adverse life events such as past trauma, abuse and every-day stress levels. Subsequently, the participants were divided in two groups: women with PPD symptomatology and controls. During the first visit, plasma OT levels were also taken and analyzed with enzyme-linked immunosorbent assays (ELISA). The obtained results showed that there is no significant difference between the two groups when it comes to the correlation between OT levels and PPD symptomatology. However, as it was said earlier, many studies show that there is no significant difference between hormonal levels in women suffering from PPD and controls, yet, there is a chance that women with PPD are more vulnerable to the changes that occur during pregnancy and postpartum. This further implies that although the results from this study show that women with and without PPD symptoms do not differ in terms of plasma OT levels, OT may still have impact on the group of mothers more sensitive to the normal perinatal fluctuations in reproductive hormones (Guintivano et al., 2018). One limitation to this study is that they collected the sample of plasma OT at only one time point and they did not control it and synchronized it with the breast-feeding period as it was in the other studies, nor the breastfeeding status was controlled (Thul et al, 2020).

Cox et al., (2015) conducted a study in which they explored the relationship between three variables: OT levels, stress reactivity and breast-feeding women. Namely, they were interested if the breast-feeding status was relevant variable in the OT levels and the HPA axis relationship. The participants were 47 women, recruited in their third trimester. After delivery they were separated in two groups breast-feeding (39) and non-breastfeeding (8) group. The women were assessed on the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) and the Spielberger State and Trait Anxiety Inventory (STAI), (Spielberger, 1983) at three time points: at the enrollment, at 2 weeks and 8 weeks in the postpartum period. At the 8th week, participants were assessed on a modified version of The Trier Social Stress Test (TSST) after feeding their newborns. The

neuroendocrine measures like Oxytocin (OT), Corticotropin-releasing hormone (CRH) and cortisol (CORT) during the 8th week were also collected from the participants at baseline and several time points during the feeding of the baby, the TSST administration and measures from the post-stress recovery. In search for the answer of this question they obtained a few meaningful results. Statistically significant positive relationship was observed between levels of OT and breastfeeding status during the administration on TSST. In other words, breastfeeding women had higher OT levels compared with non-breastfeeding mothers while feeding the baby. Also, in breast-feeding women, lower heart rate and lower cortisol levels were observed during the TSST assessment when compared to non-breastfeeding women. When it comes to the symptomatology of PPD, the results showed that depressive symptoms were indeed corelated to the OT levels, CORT levels as well as the rate of the heart-beat. Namely, depressive symptomatology was negatively corelated with OT levels and positively corelated with the heart-beat rate. Breast-feeding women with PPD symptomatology higher levels of OT were corelated to higher levels of CORT during the administration of the TSST. These results imply that during stressful situations in depressed mother there is a complex interplay between HPA axis, OT levels and stress among breast-feeding women who suffer PPD symptomatology, further suggesting the power of the depressive symptoms which can apparently modify the OT-CORT relationship (Cox et al., 2015). The authors suggest that future studies are needed to further confirm the involvement of the HPA axis and OT, since these results clearly hint possible connection between these two variables and PPD symptomatology (Cox et al., 2015).

Although many studies suggest that OT may promote motherly like behaviors, studies in regards to OT as a therapeutic agent for PPD show contradictive results. It was shown that intranasally administered oxytocin modulates neural responses and increases the responsiveness to infant crying by decreasing anxiety and enhancing empathy in new mothers (Riem et al., 2011). However, in this study, the women were not suffering from PPD. Another research examining the relationship between synthetic oxytocin (synOT) and depressive symptoms in the early and late postpartum period, obtained interesting results. 260 women in the postpartum period who were assessed on EPDS at the last trimester of pregnancy (T1) and at 6th (T3) and 9th (T4) week in the postpartum period. Scores of Maternity Blues Questionnaire were also obtained during the visit in the 1st week (T2) after delivery. The participants were divided in two groups determined by the administration of synOT intrapartum: women who received synOT and controls. It was shown that

although administered synOT during labor did not have any significant correlation with the mood symptoms and maternal behavior in the early postpartum period or correlation with baby blues, it decreased the risk for developing clinical symptoms of PPD in the later postpartum period (Riem et al., 2011). The authors further explain that this finding might be due to subjective birth experience: mothers who were administered synOT during child-birth had more pleasant experience compared to other women for who the labor was negative experience (Riem et al., 2011). However, authors also suggest that these results must be taken with caution since this study was observational and causality cannot be established (Takács et al., 2018).

On the other hand, Mah et al., (2013) not only they did not obtain the same results as the previous study, but the results were inverse. They hypothesized that administrated nasal OT will have positive impact on the mother-baby relationship in mothers suffering from PPD. In this research the participants were 25 depressed women in their 1st year of postpartum period whose score on the EPDS was 12 or higher. The design was double-blind, placebo-controlled meaning that the participants were divided in both groups: half of the women were administered 24 IU OT during their first visit while the other half were administered placebo nasal spray. The second visit was a week after where the placebo group from the first week received 24 IU OT and the other group was administered placebo. The current mood was assessed with Self-Assessment Manikin and The Five-Minute Speech Sample was administered for evaluation of expressed emotions. Contrary to their hypothesis, the results showed that mothers in the experimental group described their infants in a more negative manner than the mothers in the placebo group. Furthermore, when it comes to the current mood, mothers who were administered with intranasal OT had lower scores on the Happy to sad scale on the Self-Assessment Manikin. One aspect that was shown to be enhanced with the OT administration was that mothers perceived the relationship with their child improved (Mah et al., 2013). Authors explained that these results might be due to the small sample (Mah et al., 2013). Another possible explanation for these results is the study by Jonas et al., (2009) who examined the effects of intravenously or intramuscularly infused OT during labor on maternal release of oxytocin in response to breastfeeding. It was demonstrated that the women who were administered exogenous OT had decreased endogenous OT levels which may be the explanation on the results of the study of Mah et al., (2013).

Similarly, as for the other hormones, the connection between oxytocin and PPD is not very clear. Both animal and clinical studies report contradicting data making it almost impossible to conclude the role and the involvement of OT in the complexity of this disorder. One of the main reasons for these inconclusive results is lying in the different methodologies which are used in the studies as well as the different definitions of PPD. However, this is not a problem just in regards to the relationship between PPD and OT, but in general when it comes to PPD research, which is why it will be elaborated in more details later. That being said, although causalities and general conclusions cannot be made regarding the regarding the impact of OT on PPD, it is important to note that the literature suggest that probably there is a correlation although we cannot determine the nature nor the direction of this relationship. Furthermore, there is evidence that OT levels are corelated with other meaningful neuroendocrine variables like the hormones of the HPA axis and although OT may not be directly corelated to PPD, there is a big chance that it participates in the interplay and it plays an important role (Cox et al., 2015).

Steroid hormone and HPA-AXIS

HPA-AXIS and Cortisol – "The stress hormone"

One of the most meaningful human behaviors from evolutionary point of view is known as the "fight or flight" response which is a physiological reaction to an event or a situation that is perceived as harmful, stressful or even life-threatening. This human reaction is regulated by the function of the hypothalamic–pituitary–adrenal (HPA) axis, a major neuroendocrine system which is describing the interplay between the hypothalamus, pituitary gland, and the adrenal glands (Smith & Vale, 2006) . Under stressful conditions, the HPA-axis is stimulated, leading to a cascade of events such as releasement of the corticotropin releasing factor (CRH) from the hypothalamus, further stimulating the pituitary gland to secrete the adrenocorticotropic hormone (ACTH) into the bloodstream which in turn elicits secretion of cortisol from the adrenal glands giving the body sufficient amount of energy to deal with the source of the stressor (Glynn et al., 2013; Garcia-Leal et al., 2017; Saxbe, 2008). That being said, data from research implies that mood disorders especially depression and anxiety might be a result of alternations of the HPA axis reactivity which may occur due to hyper or hypoactivation of this complex system (Kasckow et al., 2001; Vreeburg et al., 2009; Varghese & Brown, 2001). Furthermore, other disorders such as posttraumatic stress

disorder (PTSD) or chronic fatigue syndrome are also characterized by attenuated HPA-axis functioning and altered cortisol awakening response (CAR) highlighting the role of HPA-axis in stress related disorders. (Neylan et al., 2005; Meinlschmidt et al., 2010).

As it was previously stated, the pregnancy is a period in women's life represented by a dramatic neuroendocrine alternation, which occurrence on one hand is preparing the new mother for delivery throughout the nine months of pregnancy and on the other hand, these changes act as a protective shield towards the baby's healthy development (Meinlschmidt et al., 2010). Studies show that the functioning of the HPA-axis during pregnancy is not an exemption of these alternations, resulting in increase of ACTH, CRH and cortisol concentration over the course of pregnancy, leading to highly enhanced levels of HPA hormones in the maternal blood at the end of the gestation period (Meinlschmidt et al., 2010; Garcia-Leal et al., 2017). Data has also shown that the pregnancy period is also characterized with enhanced cortisol awakening responses (CAR) which is explained as an abrupt increase in cortisol secretions during the first 30minutes after awaking (Heim et al., 2009; Neylan et al., 2005; Meinlschmidt et al., 2010). In the literature, these changes are explained as an adaptive mechanism which results in decreased physiological as well as psychological stress responses in pregnant women during this vulnerable time (Glynn et al., 2013). Inversely, in the immediate postpartum period there is an abrupt reduction in the ACTH, CRH and cortisol levels resulting in period of HPA-axis hypoactivation and a blunted CAR response, which may be prolonged weeks or even months after delivery, until it returns in its pre-pregnancy state (Garcia-Leal et al., 2017).

In light of these evidence, researchers started hypothesizing about the HPA-axis possible involvement in the depressive symptomatology of the postpartum period. Numerous studies provide evidence regarding the dysfunction of this neuroendocrine system and its connection to PPD. Moreover, significant amount of data suggests attenuated CAR response in PPD patients, further encouraging researchers to investigate this relationship more thoroughly. For example, Meinlschmidt et al., (2010) aimed to investigate if psychological stress and HPA reactivity in the postpartum period is associated with CAR in the last month of the pregnancy. The salivary cortisol samples were taken from 22 women in their 36th week of pregnancy as well as 8 weeks after delivery three times during the day: 0, 30, 45, and 60 min after awakening. The Trier Social Stress Test (TSST) was administered in order to test the HPA-axis responses to a

psychosocial stressor followed by mood questionnaire constituted by three scales, termed elevated versus depressed mood, wakefulness versus sleepiness, and calmness versus restlessness and the German version of the State-Trait Anxiety Inventory. The obtained results suggested that mothers with higher CAR during pregnancy had lower the plasma ACTH, plasma cortisol, and salivary cortisol responses to the TSST at 8 weeks postpartum, however, this relationship was not found at 6 weeks postpartum, nor it was found any significant relationship between CAR and psychological stress response. The participants in this study were healthy mothers without any mental health problems which may explain the lack of correlation between CAR and psychological stress responses. However, the significant negative relationship between CAR and HPA-axis functioning provides a better insight in maternal stress reactivity and implies the possible role of this neuroendocrine system in the etiology of PPD (Meinlschmidt et al., 2009).

Taylor et al., (2009) compared 21 women with and 30 women without depressive symptomatology in the postpartum period in order to examine if there is a different pattern in the diurnal output of saliva cortisol. These two groups were also compared to third control group – healthy non-pregnant women represented by 21 female students. In order to examine the status of depression, EPDS was administered to all of the postpartum participants at two time points: during the 4^{th} and 6^{th} – 8^{th} week after delivery. During the second time the new mothers were also asked to provide diurnal saliva samples, while in non-pregnant participants the samples were collected at the 10^{th} day of their menstrual cycle. All of the women provided samples at few time points during the day: immediately after waking up, 30 minutes later, 3 hours and 12 hours after. Compared to the non-PPD and non-pregnant group, participants in the depressed postpartum group had significantly higher cortisol levels immediately after waking up, yet, there was no increase of the cortisol levels 30 minutes after. On the other hand, although the cortisol levels in non-depressed postpartum and non-pregnant women was lower at the first time point (at waking up), they had significant rise in cortisol in the first 30 minutes after. However, this significant differences between the groups were not observed during the other two time points of the day (3 and 12 hours after waking up). In the interpretation of the data, the authors imply that the pattern of the diurnal cortisol pattern which was found in this study in women with PPD, is similar to the pattern found in patients with Post Traumatic Stress Disorder (PTSD) and chronic fatigue syndrome. These results also suggest differences in the HPA -axis function between PPD and melancholic depression, providing possible evidence in the argument of the PPD/MDD problematic. Namely,

while it was shown that melancholic depression is characterized with increase of the cortisol outputs, in PPD patients in this study this was not the case (Taylor et al., 2009). Although this interpretation cannot be taken for granted since there is not direct comparison between PPD/MDD patients in this study, the results imply possible valuable distinction and give a direction for new research area, which may help solving the mystery a hundred years old.

Very similar research design was used by de Rezende et al (2016) who wanted to investigate if the dysregulation of the HPA-axis in women with PPD found in the previous study persists longer than eight weeks after delivery. Aiming to inspect this relationship, the authors recruited 104 women from who 37 were women suffering from PPD, 42 were healthy postpartum women and 25 were controls – healthy non-postpartum women. The participants had no any medical conditions, were not taking any treatments that might affected the levels of cortisol and had not experienced any mental health issues other than anxiety. The salivary cortisol levels were taken exactly the same as the previous study with one inconsistency which was measuring the diurnal output of saliva cortisol at approximately the sixth month after delivery in postpartum women and between 5 and 8 days after their menstrual period in non-postpartum women. Center for Epidemiologic Studies Depression Scale, the Beck Anxiety Inventory (BAI) and the Perceived Stress Scale (PSS-14) were used in order to assess the mental health of the participants during pregnancy and Hamilton Rating Scale for Depression (HAM-D) and the EPDS were used to assess the severity of the depressive symptomatology. At awaking, statistically significant difference was observed between controls and postpartum women in general, implying that at six months postpartum there are alternations in the functioning of the HPA – axis regardless of the status of depression. However, the obtained data revealed that the reduction of the diurnal variation of cortisol was significantly lower in women with depressive symptomatology compared to the other two groups further suggesting that although all postpartum women have altered HPA-axis functioning, in women suffering from PPD these alternations are more dramatic (de Rezende et al., 2009). Taken together, the results from these two studies clearly highlight the involvement of the neuroendocrine system in PPD, not only in the early but in the late postpartum period as well, emphasizing the need of the PPD screening even in the later postpartum period. More studies regarding the involvement of the HPA-axis in PPD are needed which will further investigate its functioning in patients whose symptoms occur later in the postpartum period in order to examine the similar of different patterns of activation between early and late PPD.

As in the other cases, the HPA-axis is not an exemption, and contraindicative findings can also be found. For example, Hellgren et al., (2013), were examining the relationship between HPA-axis reactivity and ongoing or previous history of depressive episode in pregnant women. The CAR measurements were taken in the same way as in the previous studies, between 35th and 39th week in the pregnancy period. Depressive symptomatology was measured at the same time while using EPDS. The number of the sample was 134 women who were further divided into three groups based on the EPDS scores: never depressed pregnant women (n = 57), pregnant women with history of depression (n = 39), and depressed women during the current pregnancy (n = 38). According to the results, there was not significant relationship between CAR and current or past depressive symptomatology (Hellgren et al., 2013). Similar results were also obtained by Shea et al., (2007) whose goal was also as the previous study through CAR to investigate the relationship between HPA-axis and depression and anxiety in pregnancy. According to the results, CAR did not distinguish pregnant women with depression from controls. Although these studies do not support the hypothesis concerning the relationship between HPA-axis dysregulation and depressive symptomatology, they differ from the previous studies in the variables they were measuring. Namely, while latest studies were exploring the relationship between HPA-axis and antenatal depression, previously mentioned studies were focused on the depressive symptomatology during the early and late onset of the postpartum period (Shea et al., 2007). As it was stated earlier, there is an assumption that postpartum depression may differ from prepartum depression, which is in line with the cited studies.

The involvement of the HPA-axis and its hormones in stressful situations, along with the involvement in pregnancy and the postpartum period provides a solid ground for further exploring its relationship with PPD. Several assumptions can be made according to the previously cited studies. The altered CAR in pregnancy is probably a good indicator for the depressive symptomatology in the postpartum period (Meinlschmidt et al., 2010). Moreover, it was shown that CAR is probably related to the late rather than the early onset PPD (Chai et al., 2020). However, CAR is not a good indicator for depression during pregnancy (Chai et al., 2020). These results further imply that the HPA-axis may be the key difference between antenatal depression and early and late onset PPD, which is why researchers need to focus on further exploring this hypothesis which will lead to better detection and differential diagnosis. Although these are very valuable studies for pointing up direction for future research, inferences cannot be made. The

methodological challenges that researchers face while measuring hormonal concentration together with the methodological discrepancies across studies and not enough replication studies, prevents us to draw conclusion regarding this matter.

The animal and human studies regarding the involvement of hormonal alternations in PPD show that some hormones play a crucial role in its etiology. However, due to the difficulties that researchers are facing in the methodology of these experiments and research, it is hard to draw a conclusion and get a consensus regarding this matter. Namely, the complexity of the hormonal systems, the fluctuations of the hormones throughout the day and across the menstrual cycle, the accuracy and precision of hormone assays, the involvement of multiple confounding variables, the complex interactions of the hormones with each other are just a several challenges that can get in the way when doing a hormonal study. So, is it the withdrawal of the gonadal hormones the main culprit for PPD, or the alternations of ALLO during and after the pregnancy? Is CAR a good predictor for depressive symptomatology after delivery and if the answer is yes, how can we predict the antenatal depression? Or is it simply the vulnerability of some women of the hormonal alternations the main reason which lies behind this ruthless disease, together with the biological, psychological, and social factors, since we know that this is a multifaceted condition? And lastly, how can we examine the interplay of these factors in order to get a comprehensive understanding of this condition? In order to get answers of these questions, or at least get closer to the answers, more replication studies are needed which are essential in order to ensure the reliability, validity, and generalizability of the findings of the hormonal studies.

General Discussion

In the present review we addressed the current progress and challenges in the PPDs' key factors regarding the clinical and research practice. It can be agreed that PPD is complex disorder, which has a major impact not only on the mothers' well-being but on the whole family as well. Furthermore, the negative consequences of this cruel disorder can be observed in the brain development of the child in its early years and beyond, compromising the language abilities, the social and emotional development and the coping skills in stressful situations. This, together with the fact that PPD is widely prevalent among the general population, it attracted the attention of the researchers many years ago.

In the past, studies mostly focused on its social and psychological factors which may alter the quality of the maternal care and the symptomatology which occurs as a result of these factors. The results of the empirical studies showed that there are several strong risk factors contributing to the depressive symptomatology in the postpartum period such as a history of mood disorder, inadequate social support from the partner and family members, partner violence, stressful experiences during pregnancy and after delivery (O'Hara & Swain, 1996; Escribà-Agüir & Artazcoz, 2011; Ludermir et. al. 2010; Robertson et. al., 2004). Moreover, the imposed changes in the lifestyle of the mothers due to the new role like the disturbed sleep and appetite patterns are also contributing to the mood changes in the postnatal period. Finally, as significant causes are also considered the delivery type, breastfeeding of the baby and obstetrical complications during pregnancy (Robertson et. al., 2004). All these possible risk factors may result in anxiety, sad and depressed mood, emotional liability and lack of motivation in a period which is supposed to be filled with happy and loving emotions, yet, in mothers with PPD these emotions are often replaced by negative feelings towards their newborn and in some cases even suicidal ideations.

Lack of agreement between studies is observed in PPD vs MDD debate. Psychological as well as neurological research cannot seem to find a common ground regarding this question. Arguments from the scientific population are made on both sides, with some researchers claiming that these two disorders are the same, while others propose their differentiation in the clinical as well as the research practice (Batt et. al. 2020). The etiology of PPD nor MDD is known, so one

conclusion cannot be drawn which further results in difficulties in defining PPD, its time frame and the possible "subtypes". This consequently leads to difficulties in the research area, where the different definitions, measurements and time frames which are used further lead to obstacles in the clinical practice, screening and diagnosis of the patients.

On the other hand, the involvement of the biological systems in the etiology of PPD became a topic of interest in the recent years. In the past, very few studies have been focused on the role of the neuronal and endocrinological factors and their contributions in the depressive symptomatology of the postpartum period. With the evidence from animal studies showing the connection between neuroendocrinological changes, the pregnancy, postpartum period and maternal behavior, the hormonal events started to attract a considerable attention. Today, an-ever increasing body of literature shows that the hormonal changes during pregnancy and the postpartum period are important factors in the mother-infant boding and the mood changes which could alter this relationship. In line with this are evidence of studies of healthy pregnant women which show that the endocrine changes occurring in the pregnancy and postpartum period influence the structure as well as the function of the brain. For example, it has been shown that compared to nulliparous women, pregnant women *showed* reductions in the grey matter (GM) volume after delivery in several brain regions associated with the cerebral cortex, mainly involved in the social processes (Hoekzema et al, 2017). The gray matter volume changes were so obvious that the authors suggested that an MRI session could easily differentiate women with and without children. These GM reductions were evident even in the 2-year follow-up of the study suggesting that these reductions are probably adaptive mechanism helping the new mothers to easily adjust of their new role, emphasizing the involvement of the brain in the maternal attachment (Hoekzema et al, 2017).

Besides the changes in the structure of the brain, functional changes in pregnancy and postpartum period are also observed regarding memory and cognition, however, the results concerning these alternations are contradictory. The literature is mostly consistent in the changes of the social cognition such as improved facial recognition, better encoding of facial expression signaling threat and negative emotions, further supporting the neuroplasticity of the brain in the pregnancy and postpartum period as a service to motherhood (Pawluski et al., 2021). Furthermore, Rehbein et al., (2021) were assessing the influence of the gonadal hormonal changes on the grey

matter architecture in women in their second trimester of pregnancy and the correlation of these changes with the cognition and affect. The pregnant women with extreme levels of estradiol (extreme E2) were compared to nulliparous women who received 12 mg of E2 valerate (high E2 group) and nulliparous women with low E2 levels (control group). The results regarding the structural brain changes showed significant differences between extreme E2 and high E2 groups in the grey matter, more specifically the left putamen, significantly reduced in the extreme E2 group. Pregnant women compared to the other two groups, showed significant functional changes such as a reduction in processing speed, cognitive flexibility and higher positive affect. Authors imply that these results are in line with previous studies, further supporting the role of neuroplasticity of the brain in favor of quality maternal caregiving (Rehbein et al., 2021). Taken together these results demonstrate the importance of the interplay between the neurological and endocrinal factors in the maternal behavior, mood and cognition, hence implying their involvement in the well-being of the new mothers.

In addition to this, are the cited studies investigating the relationship between hormonal alternations and PPD. The review of the animal and human research suggests that there is distinct "subtype" of women practically vulnerable to the hormonal fluctuations occurring in the perinatal and postnatal period. Two hypotheses can be meet in the literature regarding this matter. The first hypothesis states that PPD is a result of the withdrawal of the sex hormones estrogen and progesterone which occurs immediately after delivery, while the second one implies that the alternations of the hormones in the pregnancy, in the early and late postpartum period are causing the depressive symptomatology (Bloch, et. al, 2005; Halbreich & Kahn, 2001). The data concerning these two hypotheses is contradictory and while some researchers support the first hypothesis, others, the depressive symptomatology are attributing to the fast hormonal fluctuations which are happening in the women's body during this beautiful but exhausting times (Halbreich & Kahn, 2001). The different findings may be due to the different PPD phenotypes, however more research are needed to have a clearer picture about the hormonal events and their influence of the mental health of the new mothers.

Furthermore, the alternations of OT are also implied to be a possible factor in the PPD occurrence, since OT is wildly involved in delivery and breastfeeding. Although many studies found significant relationship between OT levels and mood disturbances in the postpartum period,

there are also studies which did not find any association (Stuebe et al., 2013; Skrundz et al., 2011; Guintivano et al., 2017). However, the correlation between OT and the HPA axis which is also associated with depressive symptomatology in the postpartum period further supports the link between PPD and OT. Additionally, more rigorous studies are needed to confirm the direction of this relationship.

Finally, synthesizing the existing data from the literature regarding the involvement of the HPA-axis in PPD, it can be indicated that stressful situations such as the child-birth experience may attenuate the HPA-axis functioning which may further influence the occurrence of the depressive symptomatology (Taylor et al, 2009). As it was already explained, the HPA axis activation has an impact on cortisol secretion, so the hypo-activity of the HPA axis in the postpartum period results with lower levels of cortisol and altered CAR (Neylan et al., 2005). Furthermore, some studies suggest that compared to healthy postpartum women, mothers suffering from PPD have higher cortisol levels at walking up, yet, reduced CAR and decreased variation of the cortisol levels during the day (Taylor et al, 2009). However, this pattern was significant only for the depressive symptoms in the postnatal period, while correlation between cortisol fluctuations and depressive symptoms in the antenatal period was not observed, implying the possible distinctions in these "subtypes" of reproductive depression (de Rezende et al, 2009).

Reviewing the empirical evidence, it is clear that there are still critical challenges regarding the PPD etiology. Although the scientific research made great progress during the past several decades, looking into the preceding data, it can be argued that more questions arise than answers are resolved on the already existing dilemmas. However, the essential and ultimate question which is the starting point in resolving all the other problematics is: What are the conceptual and operational definitions of PPD? Here are two very important aspects which should be in the main focus of the researchers: conceptual definition – explaining the meaning of the concept, in this case PPD, while operational definition which tells us how to measure this concept. As we can see from the cited studies, so far, the researchers have not agreed on neither conceptualization nor the operationalization of PPD. These discrepancies in the research data, are causing complications in agreement of the PPDs' etiology and consequently resulting in underdiagnosed patients, difficulties in the screening and providing the best possible treatment. Therefore, in the following

section, arguments regarding the lack of agreement will be discussed as well as directions for future studies will be proposed in order to take one step closer in unraveling the PPD mystery.

Frist and extremely important steps are overcoming the discrepancies and upgrading the definition of PPD in the worldwide used diagnostic manuals such as DSM V and ICD 10. Several articles direct critiques towards these classificatory systems regarding the conceptualization of PPD. As aforementioned, the range of PPDs' onset differs between DSM V (from pregnancy to 4 weeks postpartum) and ICD 10 (from delivery to 6 weeks in the postpartum period), however researchers criticize both of these time-frames suggesting that this time period for PPD diagnosis is too short and does not fit the time period that is seen in the research and clinical practice (Moraes et al., 2017). Progress has been made in the DSM V with the inclusion of the depressive symptomatology during the pregnancy with adding the classifier with peripartum onset, however the scholars do not think that is enough, since studies show that the period of PPD may be prolonged from 6 months to a 1 year postpartum. O'Hara and McCabe, (2013) in their review further suggest that although the evidence regarding the onset and duration of PPD are varying, extension should be considered since there are lack of evidence for the 1-month time frame as well (O'Hara & McCabe, 2013). On the same page regarding this problematic are also Sharma et al., (2014) implying that without adequate specifiers there could be delay or missed cases in the diagnosis of PPD (Sharma et al., 2014).

Furthermore, the results from the hormonal studies also support this notion. For example, as it was previously stated, levels of ALLO fluctuate during pregnancy and in the postpartum period with the start and ending of lactation, indicating the role of these fluctuations in the etiology of PPD in vulnerable women and further implying the possible explanations of late onset PPD. Moreover, even if the late onset PPD has not distinct etiology, the symptomatology of the patients' needs to meet the full MDD diagnostic criteria in order to be diagnosed as PPD patients. However, Wisner et al., (2010) ask a well-grounded question: "Does within 4 weeks refer to the onset of symptoms that evolve into an episode of MDD or to onset of the full syndrome?". In other words what happens to the patients whose symptomatology occurs during the early stages of the postpartum period but does not meet the diagnostic criteria until the 7th month in the postpartum period? It is very possible that proper diagnosis in these patients may be missed if DSM V criterions are followed (Wisner et al., 2010). Another possible argument is that many first-time

mothers are unaware of the specific symptoms in the early postpartum period since they are often mixed up with the responsibilities that come with the new role, which further results in missed PPD diagnosis (Sharma et al., 2014). Thus, the argument of the DSM V workgroup regarding the lack of compelling evidence on the prolongation of the time frame for PPD diagnosis is not valid enough (Segre & Davis, 2013).

Similar critique is directed to the ICD 10, suggesting that in its definition for PPD it includes only "a small proportion of postnatal episodes" (Austin, 2010). Sharma et al., (2014) are also proposing the need for distinguishing between prepartum and postpartum onset since according to data from studies, there are different fluctuations and hormonal concentrations, sleep patterns and immune system functions which distinguish these two periods (Sharma et al., 2014). Separating these two vulnerable periods will help to highlight the occurrence of the symptomatology not only after the delivery of the baby but during the pregnancy as well, underlining the importance of early screening and detection. The inconclusive PPD definition is further obstructing not only the work of the clinical practitioners but also the work of the researchers in examining the PPD etiology.

Second important reason behind the discrepancies in the results of the PPD studies is the lack of agreement in the operationalization of this variable. In the introduction several widely used scales and test for PPD screening were mentioned, however it was shown that there is a significant variability across studies in the methods that researchers use in order to measure depressive symptomatology in the postpartum period, with EPDS being the mostly often used screening scale. Further, it was shown that while in some studies only one instrument was used, other studies used a combination of several instruments. According to Boyd and Somberg (2005) the existing variability across studies is probably due to the fact that there is "a lack of consensus about the utility and psychometric properties of screening measures in both clinical and research settings" (Boyd & Somberg, 2005). The authors reviewed several screening instruments such as BDI-II, EPDS, PDSS and CES-D and reported that the variability of the mentioned measures is inconsistent among studies. For example, the sensitivity values across studies regarding EPDS were varying from 22.2% to 96% and for the specificity values from 68% to 94% (Ukatu et al., 2017; Beck et al., 2001). Variability in the psychometric properties across studies was found for the other scales as well like for the specificity of BDI-II which varied from 45.3% to 100% (Ukatu

et al., 2017). Variability and sensitivity are crucial concepts in research and data analysis, especially in the field of science, so consistent psychometric properties of the instruments are important in order to conduct rigorous and credible research.

Furthermore, articles differed in the postulated cut-off scores with most discrepancies found in studies using EPDS. The recommended cut-off according to the authors of the scale Cox et al., (1987) it is ≥10 for English speaking population, however Matthey et al., (2013) reported that many researchers use unvalidated cut-off scores. Some of the reasons for the discrepancies which they stated were that many of the researchers misunderstood the original EPDS guide, used same cut offs in scoring pre and postpartum depression or did not validate the scores for different cultures and populations. Regarding the last, it is suggested that EPDS cut-off vary among cultures for the sake of the specificity and sensitivity of the questionnaire, however it is shown that the validated scores are not always used by the researchers (Matthey et al., 2006). Further, Matthey et al., (2006) analyzed the impact on the usage of unvalidated scores when measuring pre and postnatal depression and concluded that this resulted in decrease of the percentage in the postnatal period compared to the antenatal period which is leading to false conclusions. Authors suggest that these mistakes should not be made since it prevents comparison and leads to discrepancies amongst studies (Matthey et al., 2006).

Additionally, studies also differ in the timing of testing of PPD. In their review Moraes et al., (2017), found that from 22 analyzed studies 43% were screening PPD during the first 3 months, 19% from 4 to 6 months, 38% from 7months to the first postpartum year. These data points out 2 meaningful issues. Firstly, among the literature there are a lot more studies examining the early postpartum period compared to the late postpartum period. Similar results report Ukatu et al., (2017), where 75% of the studies were examining PPD symptomatology during the first 6 months postpartum. Secondly, these results may be due to the fact that researchers use different conceptual definitions with regards of the time frame of PPD. Moreover, many of the studies use perinatal and postnatal depression as synonyms, or does not distinguish the early from the late postpartum period leading to difficulties in comparing studies and reaching one cohesive conclusion (Batt et al., 2020; Ukatu et al., 2017).

Lastly, important discrepancy among the screening instruments is the symptomatology of PPD which they are measuring. As previously mentioned, it was fond that PPD symptomatology

is atypical and differs from the depressive symptoms occurring in other time of women's life with prevailing anxiety, irritability and emotional liability (Jolley & Betrus, 2007). Thus, it is questionable how much the screening scales measuring the MDD symptomatology can detect PPD. Furthermore, scales such as BDI-II measure changes in the sleep patterns, eating habits and fatigue which are "normal" for the women in the postpartum period due to the new responsibilities (Jolley & Betrus, 2007). Consequently, EPDS and PDSS were developed in order to escape measuring the somatic symptoms typical for this period (Boyd & Somberg, 2005). However, these scales due to their variability in specificity and sensitivity are not validated as diagnostic tools for PPD. Furthermore, Cox et al., (1987), the authors of EPDS stated: "The EPDS is not a substitute for this clinical assessment, and a score just below the cut-off should not be taken to indicate the absence of depression, especially if the health professional has other reasons to consider this diagnosis" (Cox et al., 1987). This being said, it can be concluded that although EPDS is most commonly used scale in the research area as well as in the clinical setting, discrepancies across studies can be detected in the psychometric properties of the instruments, timing of measuring of PPD and the symptomatology that different scales are measuring, further implying the need for better standardization of the most commonly used tests as well as greater consensus in the scientific community regarding the screening scales used in PPD detection (Moraes et al., 2017). A better collaborative approach is recommended for future studies in the scoring, period of screening and the combination of tools which will result in more comparable results and hopefully, less discrepancies in the findings regarding PPD percentage, risk factors, etiology and treatment (Ukatu et al., 2017).

Implications for future studies

From the present literature review it can be noted that the data from the included studies, in many cases is contradictory and conflicting. As it was mentioned in the prior section, one reason for these discrepancies is the differences in the methodology between studies. In the last years the replication studies are not very popular in the psychological science or as Martin and Clarke (2017) said "the psychology is undergoing a replication crisis". In their review, they stated several reasons for this phenomenon. Firstly, they talked about "publication bias" which basically means that the null findings of the replication studies are often not published or not even submitted for publishing.

As a second reason for the "replication crisis" the authors imply the aversion of the scientific journals toward the replication studies, since they are not original and not enough interesting. However, the replication studies are crucial in order to enhance the strengths of the original research, as well as the reliability and generalizability of the findings (Martin & Clarke, 2017). With this being said, the researchers must be encouraged to replicate studies in order to get a clearer picture about PPD, its risk factors and possible biomarkers.

In the case of PPD and solving the mystery behind it, more longitudinal studies are needed which will help in the dilemmas concerning the different PPD phenotypes, the occurrence of PPD with late onset and differentiation of the distinct risk factors behind these phenotypes. Furthermore, more longitudinal hormonal and neurological studies comparing mothers with and without PPD may help us to get a step closer to finding a valid biomarker for PPD. Tracking the development of the disease from pregnancy to the extended postpartum period will further provide knowledge regarding the trajectories of the symptoms, when they peak, decline, or remain persistent. With establishing the causality and temporality of PPD, researchers will be able to determine the sequence of the events which is crucial in tracking the evolution of various factors and symptoms. Longitudinal studies further facilitate examination of the individual variations of the symptomatology, further leading to better personalized treatment and support.

Lastly, multidisciplinary approach is needed in the research practice in order to gain more comprehensive understanding in PPDs' etiology. PPD is a multifaceted condition influenced by a combination of biological, psychological, and social factors. The interplay of these factors contributes to the complexity of PPD, and a comprehensive understanding of the condition requires considering all these entities. Having said that, researchers from different fields should ally together in order to gain better understanding of how psychosocial factors interact with biological causes of PPD (Yim et al., 2015).

Conclusion

In the present literature review, epidemiological and etiological studies were discussed in order to find the gaps in the existing literature and identify the questions which are still not answered regarding PPD and its complex nature. It can be concluded that PPD is a multifaceted condition and although in the past years a valuable data is obtained bringing us one step closer to providing a better quality of life for mothers suffering from this cruel disease, we still have a long

way to go. The need for unanimity among the scientific community as well as clinical practitioners regarding the definition of PPD is the essential first step that needs to be taken. Furthermore, classifying PPD as a separate disorder, distinct from MDD, may be beneficial in the research practice in order to focus on the possible different PPD phenotypes. In the clinical setting this distinction may ease the screening, prevention and treatment of PPD. Taking these steps, together with providing more longitudinal studies and replicational data may provide us with knowledge helpful in the untying the knot of postpartum depression.

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