Overview of metabolomic aspects in postpartum depression

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Abstract

Along with the typical biochemical alterations that occur during pregnancy, certain metabolic changes might be associated with the development of several psychiatric disorders, including postpartum depression (PPD), which is the most common type of psychiatric disorder during pregnancy or first postpartum year, and it develops in about 15 % of women. Metabolomics is a rapidly developing discipline that deals with the metabolites as the final products of all genetically controlled biochemical pathways, highly influenced by external and internal changes. The aim of this paper was to review the published studies whose results suggest or deny a possible association between the fine regulation of the metabolome and PPD, enabling conclusions about whether metabolomics could be a useful tool in defining the biochemical pathways directly involved in the etiology, diagnosis and course of PPD. Beside numerous hormonal changes, a lot of different metabolic pathways have been discovered to be affected in women with PPD or associated with its development, including alterations in the energy metabolism, tryptophan and amino acid metabolism, steroid metabolism, purine cycle, as well as neurotransmitter metabolism. Additionally, metabolomics helped in defining the association between PPD and the exposure to various endocrine disrupting metabolites during pregnancy. Finally, metabolome reflects different PPD therapies and exposure of fetus or breastfed infants to pharmacotherapy prescribed to a mother suffering from PPD. This review can help in creating the picture about metabolomics' broad application in PPD studies, but it also implies that its potential is still not completely used.

Keywords: metabolites; biomarkers; therapy; hormones; xenobiotic

Introduction

Depressive disorders are a group of severe psychiatric disorders that have been listed as diseases with the highest prevalence in the world for the last thirty years (GBD, 2018), with their prevalence being higher in women than in men (Albert, 2015). Postpartum depression (PPD) is the most common type of psychiatric disorder occurring during peripartum period, and it develops in about 15 % of women (Gaillard et al., 2014). Although the majority of women suffering from PPD show mild symptoms for a shorter period of time, a certain percentage of women experience more severe symptoms of depression, whose treatment requires psychotherapy and/or pharmacological intervention (Brummelte and Galea, 2010). In PPD a population-based variability was noticed (Villegas et al., 2011), together with a history of depression, anxiety and adverse life events, younger age and smoking, which were suggested as PPD risk factors (Guintivano et al., 2018; Verreault et al., 2014). The early recognition of PPD onset is extremely important because the lack of adequate psycho- and/or pharmaco-therapy can have dramatic consequences, both for the mother and the entire family (Koutra et al., 2017). It was shown that children of mothers with PPD, especially of those which were not adequately treated, have increased rates of delay in intellectual and motor development (Goodman et al., 2011), increased reactivity to stress (Muzik and Borovska, 2010) and pronounced vulnerability to mental health problems, especially depression, later in life (Murray et al., 2011). Postpartum depression is considered as one of the subtypes of major depressive disorder (MDD) and currently the main criterion for distinguishing PPD from MDD is the period of onset. The Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) (APA, 2013) defines PPD as a major depressive episode with peripartum (during pregnancy or up to four weeks postpartum) onset. However, very often the postpartum period is considered as twelve months after delivery (Stuart-Parrigon and Stuart, 2014). In any case, both types of depression share similar symptoms, but certain differences have been observed that mostly depend on the period of PPD development. Thus, depression occurring in the later postpartum period may be more similar to MDD occurring outside of the perinatal period (Batt et al., 2020). Additionally, late- and early-onset PPD differ by socio-economic correlates, life events and associated psychiatric disorders (Tebeka et al., 2021)

The postpartum period is characterized by numerous hormonal changes, including a drop in progesterone and estrogen levels, which are often involved in mood changes (Standeven et al., 2020). Postpartum depression is further characterized by elevated levels of cortisol, a glucocorticoid steroid hormone secreted in response to stress (Seth et al., 2016). In addition to hormonal, amino acid metabolism is extremely important in pregnancy and the development of PPD. For example, low tryptophan levels are characteristic for PPD (Duan et al., 2018), while polymorphisms of genes involved in the tryptophan-serotonin synthetic pathway can affect stress sensitivity during pregnancy and the postpartum period (Duan et al., 2018). Although the existence of certain molecular mechanisms involved in the development of PPD is evident, there is still a large number of unknown facts, resulting in the unclear etiology of the disorder, prolonged diagnosis procedure, with the prediction of the PPD development or better treatment very difficult to accomplish.

Metabolomics is a fairly young and rapidly developing discipline that deals with the metabolome. The human metabolome includes the final products of all genetically controlled biochemical pathways, highly influenced by environmental (external and internal) changes. Metabolites profiling provides an opportunity to identify a large number of molecules whose different representation in the investigated

disorder reflects the disorder related changes in certain biochemical pathways. This way conclusions can be drawn about the etiology of the investigated disorder and its biological indicators can be defined (Beger et al., 2016). Therefore, metabolomics is becoming a useful tool for discovering new potential diagnostic/prognostic indicators, as well as therapeutic targets, in clinical practice, including neuropsychiatry (Konjevod et al., 2021, 2019; Nedic Erjavec et al., 2018).

According to the literature data, summarized in Table 1, it is evident that metabolomics already found its application in PPD related studies. Different research groups used different approaches to test specific hypotheses. Some of them aimed to find reliable and easily obtainable biomarkers that ideally could help in early and precise diagnosis, therapy response monitoring and outcome prediction. Usually, this type of study starts with the untargeted, non-hypothesis driven, approach, which later helps to generate hypothesis for further targeted steps. Additionally, different biological problems require different research techniques. Metabolomics is strongly supported by the development of high-throughput technologies such as nuclear magnetic resonance (NMR) spectroscopy or mass spectrometry (MS), which, especially after coupling with separation techniques such as gas (GC) or liquid (LC) chromatography, is a very powerful analytical technique. And finally, in different studies various types of biological samples can be used. Namely, metabolites can be detected in all kinds of biological matrices, but usually the samples of choice are the ones requiring less invasive sampling procedures, such as peripheral blood (plasma, serum), urine, feces or breast milk or, more invasive, cerebrospinal fluid (CSF).

The aim of this paper was to review the published studies whose results suggest or deny the connection between the fine regulation of the metabolome and PPD, enabling conclusions about whether metabolomics could be a useful tool in defining the biochemical pathways directly involved in the etiology, diagnosis and course of PPD. Table 1 represents the overview of papers, discussed in this review and dealing with the metabolomics aspects of depression developing in the peripartum period. More details about PPD associated changes in abundances of specific metabolites are provided by Suplementary table 1.

Materials and methods

The study was performed in line with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021). PRISMA flow diagram on literature review strategy is shown by Figure 1. A systematic literature search was done by reviewing databases Medline, Web of science and Scopus for English language studies published in the period from January 2010 until April 2023. Keywords for literature search were: metabolomics, metabolome, metabolite, postpartum/peripartum/antenatal depression. Additionally, reference lists of published review articles were reviewed to identify other eligible studies. All articles were screened according to title and abstract after which a full text review was conducted for eligible studies. Only original research articles were included, while conference abstracts and studies without clearly described methodologic procedures or studies in which depression was not exclusive to postpartum period were not included.

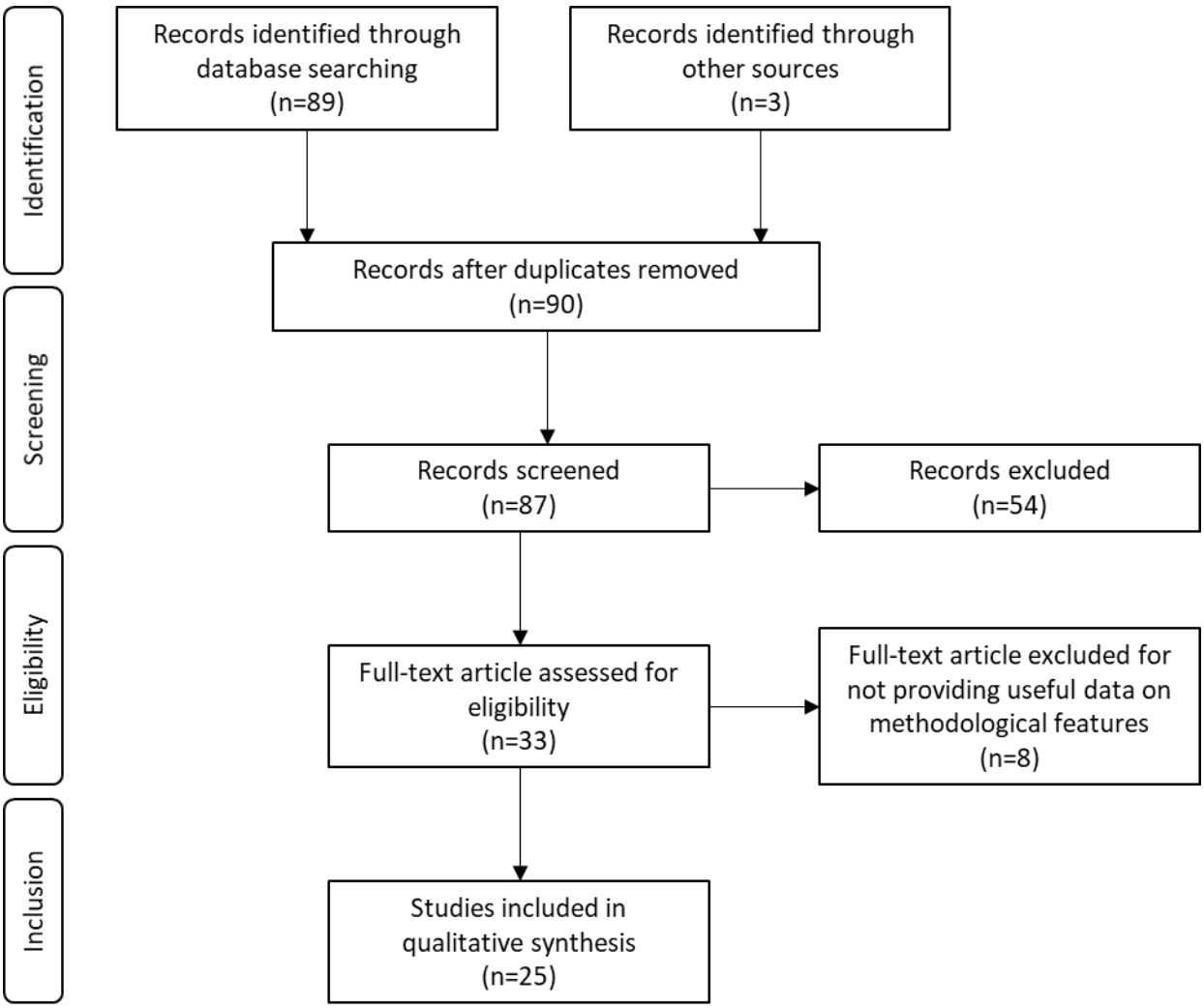

Figure 1. PRISMA flow diagram on literature review strategy

Table 1. Overview of the literature data dealing with metabolomics aspects in PPD, with summarized reported information about subjects, type of biological sample, methods and main metabolomic changes associated with PPD in humans.

Study	Total number of included subjects	Biological sample	Metabolomics method	PPD associated metabolic feature
Targeted metabolomics approach				
Accortt et al., 2021	89	Serum	LC-MS	Vitamin D Metabolite Ratio
Borgsted et al., 2022	82	CSF Blood serum	LC LC-MS	Serotonin; Estrogen
Deligiannidis et al., 2016	56	Plasma	LC-MS	Steroid hormones; γ-aminobutyric acid
Greco et al., 2022	105	Urine	LC-MS	Xanthine; Hypoxanthine
Jacobson et al., 2021	149	Urine Serum	LC-MS GC-MS	Phtalate metabolism; Steroid hormones
Kim et al., 2021	221	Breast milk	LC-MS	Phthalate metabolism
Papadopoulou et al., 2019	20 (1st cohort) 15 (2nd cohort)	Serum	LC-MS	Glutathione-disulfide; Adenylosuccinate; Adenosine triphosphate
Pařízek et al., 2014	44	Blood Umbilical cord blood	GC-MS	Steroid hormones
Rampono et al., 2011	10 mother-infant pairs	Breast milk Blood plasma	LC	Antidepressant metabolism
Rogers et al., 2016	49	Urine	GC-MS	Cortisol
Sha et al., 2021	163	Plasma	LC-MS GC-MS	Tryptophan-kynurenine pathway
Sha et al., 2022	114	Plasma	GC-MS LC-MS	Tryptophan-kynurenine pathway
Sit et al., 2011	21 mother-infant pairs	Serum Umbilical cord blood	LC	Antidepressant metabolism
Teshigawara et al., 2019	132	Plasma	LC	Tryptophan-kynurenine pathway

Study	Total number of included subjects	Biological sample	Metabolomics method	PPD associated metabolic feature
Veen et al., 2016	133	Serum	LC-MS	Tryptophan-kynurenine pathway
Untargeted metabolomics approach				
Bränn et al., 2021	24	Plasma	GC-MS	Threonine; Glycerolipids
Henriksson et al., 2019	50	Plasma	GC-MS	Glucose; Lactate; Pyruvate
Kortesniemi et al., 2021	150	Breast milk	^{1}H-NMR	Fatty acids; Caprate; Hypoxanthine; Lactate
Laketic et al., 2022	99	Serum	^{1}H-NMR	Amino acids
Lin et al., 2017	92	Urine	GC-MS	Formate; Succinate; 1-methylhistidine; α-glucose; Dimethylamine
Yu et al., 2022	531	Plasma	GC-MS	Tricarboxylic acid; Amino acids; Nucleic acids
Zhang et al., 2019	80	Urine	LC-MS	4-hydroxyhippuric acid; Homocysteine; Tyrosine
Wu et al., 2019	66	Plasma	LC-MS	Lipids

CSF cerebrospinal fluid; LC liquid chromatography; GC gas chromatography; MS mass spectrometry; ^{1}H-NMR proton nuclear magnetic resonance

Metabolomics as a tool for studying hormonal changes associated with postpartum depression

Comparable to many psychiatric disorders, identifying the biological factors and mechanisms leading to development of PPD has been a complex and ambiguous task. Metabolomics approach allows simultaneous monitoring of several biological systems and pathways and their interplay by detecting the low fold changes of many metabolite levels with higher sensitivity than traditional immunochemical and colorimetric methods (Bränn et al., 2021). Since biological changes accompanying psychiatric and brain-related disorders, including PPD, are usually far less prominent in peripheral samples compared to central nervous system, the ability to detect subtle changes in easy obtainable biological fluids, makes the metabolomic studies a promising new tool in identifying and understanding the molecular mechanisms underlying PPD (Papadopoulou et al., 2019).

Significant physical changes in pregnancy and postpartum period affect metabolic, immunological, neurotransmitter and hormonal systems, which combined with other clinical, psychological and sociological factors could contribute to higher susceptibility to PPD (Bloch et al., 2005; Mitchell et al., 2011). Most of the theories on PPD etiology are based on dramatic and rapid changes in hormone levels during pregnancy, childbirth and breastfeeding (Bloch et al., 2005, 2003). The significant decrease of corticotropin-releasing hormone (CRH) and reproductive hormones such as estradiol and progesterone and their neuroactive metabolites after childbirth and the delivery of placenta, has been shown to affect the neuronal circuits (Schiller et al., 2015) and contribute to the postpartum depressive symptoms (Kikuchi et al., 2021). The conducted metabolomics studies also showed the association of reproductive and hypothalamic-pituitary-adrenal (HPA) axis related hormones with PPD (Borgsted et al., 2022; Deligiannidis et al., 2016; Parízek et al., 2014; Rogers et al., 2016; Sha et al., 2021).

It has been reported that changes in testosterone levels, obtained in the maternal blood, but not in the umbilical cord blood, as well as fetal estrogen levels, could be associated with the PPD symptoms and etiology (Parízek et al., 2014). The levels of testosterone, androsterone and its metabolites (androstenedione, 5α-androstane-3α, 17β-diol) 4 weeks prior to childbirth were significantly higher in mothers who later developed PPD. Additionally, significant differences in the levels of these hormones and metabolites in the maternal blood were observed after childbirth depending on the presence and severity of depressive symptoms (Parízek et al., 2014). This indicates that changes in steroidogenesis possibly leading to postpartum depression can be detected at least 4 weeks prior to childbirth. On the other hand, estrogens (estradiol, estrone and estriol) and 16α-hydroxy-progesterone from umbilical cord blood were significantly higher in depressive subjects compared to mothers who did not develop PPD (Parízek et al., 2014). It has been proposed that significant decrease in the estrogen levels after child birth can contribute to the mental changes by affecting the neurotrophins systems, as well as expression, density and activity of monoamine receptors, especially dopaminergic and serotonergic (Borrow and Cameron, 2014; Bossé et al., 1997; Cardona-Gomez et al., 2004; Finocchi and Ferrari, 2011), while progesterone and its neuroactive metabolites have modulatory effect on γ-aminobutyric acid (GABA) A receptors (Costa et al., 1995).

Recent studies also suggested possible relationship between reproductive hormones and neurotransmitters' systems (Borgsted et al., 2022; Deligiannidis et al., 2016). Antepartum levels of serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA) in CSF were associated with higher mental distress and anxiety symptoms in healthy pregnant women, at a trend level (Borgsted et al., 2022). Lower antepartum to postpartum estrogen levels, and higher postpartum estrogen concentration were associated with more severe anxiety and depressive symptoms, although no direct link between 5-HIAA

and estrogen concentracions has been observed (Borgsted et al., 2022). Higher plasma levels of peripartum progesterone and pregnanolone, both pro-neuroactive steroids, have been observed in women at risk of developing PPD, based on their current depressive and anxiety symptoms, compared to the healthy subjects (Deligiannidis et al., 2016). Moreover, pregnanolone levels positively correlated with the Hamilton depression (HAM-D) and Hamilton anxiety (HAM-A) rating scales scores. In contrast, peripartum GABA concentrations in plasma were lower in women at risk of developing PPD compared to the control subjects and negatively associated with HAM-D and HAM-A scores (Deligiannidis et al., 2016).

Estrogen and progesterone levels in plasma were also associated with the levels of inflammatory factors and metabolites included in the tryptophan-kynurenine pathway, during which neuroactive metabolites, such as quinolinic and kynurenic acid, both binding to glutamate receptor N-methyl-D-aspartate, are generated (Sha et al., 2021). Estrogen levels were positively associated with interleukin (IL) 6, and negatively with the levels of kynurenic acid, kynurenine and picolinic acid, while progesterone negatively correlated with the inflammatory factor IL-1β, quinolinic acid and nicotinamide, and positively with kynurenine, IL-6, nicotinamide and IL-2 (Sha et al., 2021). These results suggest that estrogen and progesterone favor the activity of separate branches of kynurenine pathway, but also affect the immune system in opposite direction, where estrogen could contribute to a higher pro-inflammatory response and progesterone exhibits anti-inflammatory effects, although both hormones positively correlated with long-term depressive symptoms post-partum (Sha et al., 2021).

In addition to its role in stress response, inflammation and metabolism, hormones included in the HPA axis (CRH, adrenocorticotropic hormone (ACTH), and cortisol), and their metabolism have been implicated in several psychiatric disorders, including depression, anxiety and psychosis (Kortesniemi et al., 2021; Lopresti and Drummond, 2013; Rathi et al., 2022). During pregnancy, placental CRH significantly affects HPA axis, leading to the increased cortisol production, which has been linked with postpartum depression and weight change, indicating possible shared biological mechanism (Chai et al., 2022; Lopresti and Drummond, 2013; Molyneaux et al., 2014), since it has been reported that women who retain weight two or more body mass index (BMI) units 6 months after childbirth, have significantly higher risk of depression and anxiety (Bliddal et al., 2015). Recent study, which monitored the levels of total cortisol metabolites in urine, depressive symptoms and weight change at 1 week, 1 month, 3, 6 and 12 months postpartum, did not confirm the direct link between higher BMI and postpartum depression (Rogers et al., 2016). Women who had more severe depression symptoms 12 months postpartum had greater total cortisol metabolite secretion; however, this was not associated with the weight loss. Meanwhile, lower activity of 11ß-hydroxysteroid dehydrogenase type 1 (11b-HSD-1), which produces cortisol, and 5a-reductase, an enzyme converting cortisol to its tetrahydrometabolites and testosterone to dihydrotestosterone, have been associated with enhanced weight loss but not with depression in any time point, indicating that cortisol metabolism is associated with postpartal distress and weight change through different pathways linked to the HPA axis (Rogers et al., 2016).

Metabolic changes leading to PPD

Along with the typical biochemical alterations that occur during pregnancy, certain metabolic changes might be associated with the development of several psychiatric disorders, including PPD (Yu et al., 2022). Numerous metabolic pathways have been discovered to be changed in women with PPD or associated with its development, including alterations in the energy metabolism, tryptophan and amino acid metabolism, steroid metabolism, purine cycle, as well as neurotransmitter and hormonal metabolism (Yu et al., 2022).

Changes in the energy metabolism, often manifested through alterations in the tricarboxylic acid (TCA) cycle during pregnancy, might be associated with PPD development, and might influence the cognitive and behavioral development of the offspring as well (Henriksson et al., 2019; Laketic et al., 2023; Yu et al., 2022). Additionally, changed levels of adenylosuccinate and adenosine triphosphate (ATP), as the primary energy source for many cellular and metabolic processes, identified in women with PPD, support the implications of changes in energy metabolism in PPD (Papadopoulou et al., 2019). Furthermore, inflammation is thought to be a major factor in the development of PPD and depression in general, and it may be linked to the changes in energy metabolism through a variety of metabolic pathways (Laketic et al., 2023).

Energy metabolism changes can be identified also through alterations in amino acid metabolism. Such changes, including arginine biosynthesis, valine, leucine and isoleucine biosynthesis, threonine catabolism, alanine, aspartate and glutamate metabolism were reported in women with PPD compared to control group (Bränn et al., 2021; Laketic et al., 2023; Yu et al., 2022; Zhang et al., 2019). Kynurenine and an essential amino acid tryptophan are metabolites crucial for fetal development during pregnancy. Therefore, changes in the tryptophan metabolism are common physiological processes in pregnancy. Metabolites that take part in the tryptophan-kynurenine metabolic pathway have different biological functions, including inflammation, neuroactivity and immunoregulation (Sha et al., 2022). However, increased levels of stress hormones and inflammatory processes encourage tryptophan metabolism through the neuroregulatory kynurenine pathway at the expense of serotonin (Duan et al., 2018), which indicates that increased regulation of kynurenine pathway represents a risk for the development of PPD (Duan et al., 2018). Moreover, kynurenine is a precursor for several other neuroregulatory metabolites, such as quinolinic acid, 3-hydroxykynurenine and kynurenic acid, which might influence glutamatergic and serotonergic neurotransmission (Duan et al., 2018). Increased levels of kynurenic acid, kynurenine, as well as kynurenine/tryptophan and kynurenic acid/kynurenine ratios were found in women with PPD compared to non-depressed women (Teshigawara et al., 2019). Elevation of plasma kynurenine by inflammatory cytokines during pregnancy might affect and induce vulnerability to develop PPD symptoms (Teshigawara et al., 2019). Likewise, increased levels of inflammatory cytokines and quinolinic acid were significantly associated with the severity of depressive symptoms during pregnancy and postpartum (Sha et al., 2022). However, study by Veen and colleagues (2015) reported decreased levels of kynurenine in women with postpartum psychosis and PPD (Veen et al., 2016).Furthermore, 3-hydroxyanthranilic acid was decreased in the postpartum period in women with PPD compared to non-depressed women (Teshigawara et al., 2019). Although role of 3-hydroxyanthranilic acid in the PPD is still not clear, it is assumed that it is involved in anti-inflammation and neuroprotection which indicates that decreased levels of 3-hydroxyanthranilic acid might represent potential risk factor for developing PPD (Teshigawara et al., 2019).

Alterations in purine metabolites were also reported in women with PPD. Elevated levels of xanthine and hypoxanthine during pregnancy have been associated with the development of depressive symptoms (Greco et al., 2022). The purine cycle plays an important role in the regulation of oxidative stress, which is considered to be an underlying mechanism associated with depression (Greco et al., 2022). Furthermore, several studies have reported an association between the decreased levels of prenatal vitamin D and PPD symptoms (Accortt et al., 2021). Vitamin D has a major role in bone metabolism, but it is also associated with the inflammatory processes and mood disorders. It has been shown that women with PPD had significantly lower vitamin D, measured as the vitamin D metabolite ratio (VMR), which corresponds to the ratio of 24,25(OH)2D and 25(OH)D, compared to women without PPD (Accortt et al.,

2021). Therefore, reduced levels of vitamin D are somehow associated with an increased risk of developing PPD (Accortt et al., 2021). However, the association between a deficiency of vitamin D and PPD symptoms is still not clear and further studies are necessary.

Metabolomic biomarkers of PPD

Despite its high prevalence, PPD remains underdiagnosed and undertreated, partly due to the lack of objective biomarkers for early detection and monitoring of the disorder. Recent studies, also mentioned in Table 1, have used metabolomics to investigate the metabolic changes associated with PPD and to identify potential biomarkers. These studies have focused on various biological samples, including urine, plasma and serum, and have identified several metabolites that have been significantly altered in women with PPD compared to respective control subjects. These metabolites may be involved in the pathophysiology of PPD and could serve as potential biomarkers for this common and debilitating disorder.

Several studies have identified urine metabolites that have the potential to serve as biomarkers for the diagnosis of PPD. For instance, Lin et al. found 22 metabolites that were altered in women with PPD compared to the healthy control subjects (Lin et al., 2017). Dimethylamine, formate, 1-methylhistidine, succinate, and α-glucose have been identified as potential biomarkers for PPD, along with seven significantly altered metabolic pathways (D-glutamine and D-glutamate, glyoxylate and dicarboxylate, phenylalanine, taurine and hypotaurine, propanoate and pyruvate metabolism, as well as TCA cycle) (Lin et al., 2017). Similarly, Zhang et al. distinguished 10 urine metabolites that may facilitate the diagnosis of PPD, suggesting that PPD may result in changes in amino acid, bacterial, as well as neurotransmitter metabolism (Zhang et al., 2019). Relatively high sensitivity and specificity were observed for some of the potential biomarkers, including homocysteine, 4-hydroxyhippuric acid and tyrosine (Zhang et al., 2019). Additionally, Greco et al. were the first to report a potential association between purine metabolites, specifically hypoxanthine and xanthine, and depressive symptoms in pregnant women, implying the involvement of oxidative stress in the pathophysiology of depression (Greco et al., 2022).

Some investigations have focused on identifying metabolites that are differentially expressed in blood plasma of women experiencing depression during pregnancy or postpartum. Wu et al. identified 35 differentially expressed lipid metabolites in women with PPD compared to depression not associated with pregnancy (Wu et al., 2019). Cholesterol sulfate (CS) and 1-(2E,4E-octadecadienoyl)-sn-glycero-3-phosphocholine (PC (18:2(2E,4E)/0:0)) were found to be significantly correlated with an increased risk of severe PPD (Wu et al., 2019). Cholesterol sulfate can serve as a substrate for the synthesis of pregnenolone sulfate (PregS), an endogenous excitatory neurosteroid known to have antidepressant effects (Ritsner et al., 2010). Thus, the synthesis of PregS may be obstructed in women with PPD, leading to increased plasma CS levels. PC (18:2(2E,4E)/0:0) was also found to be a potential biomarker for PPD, with significantly higher levels in this group of subjects (Wu et al., 2019). Previous studies have shown that children and adolescents with major depression have increased levels of PC in their plasma (Zhou et al., 2019) and magnetic resonance spectroscopy imaging has revealed a correlation between PC (18:2(2E,4E)/0:0) and depression-related brain regions like the hippocampus (Biedermann et al., 2015). Furthermore, a study by Bränn et al. identified two separate groups of women with PPD symptoms (Bränn et al., 2021). The first group exhibited elevated levels of fatty acids, amino acids and glycerol-phospholipid metabolites, alongside reduced levels of sugars and sugar acids. These findings suggest possible impairment of kidney function, which may be attributed to oxidative stress, even after childbirth (Bränn et al., 2021). The second group demonstrated elevated levels of both fatty and sugar acids, a metabolic profile commonly observed in the individuals with the metabolic syndrome (Lent-Schochet et al., 2019) and associated with depression

(Ghanei Gheshlagh et al., 2016). The study found differences in several metabolites, including erythronate, glyoxylate, urea and uric acid, suggesting the existence of different subtypes of PPD (Bränn et al., 2021). In addition, five metabolites (erythritol, glycerol, 2-hydroxybutanoic acid, phenylalanine and threonine) were consistently different in both groups compared to the control group (Bränn et al., 2021). In addition, Yu et al. reported significant differences in 37 metabolites between women with and without PPD during pregnancy and the 1-month postpartum period, with disruptions observed particularly in the TCA cycle (Yu et al., 2022). Combined usage of machine learning and multivariate statistical analysis helped in identifying potential biomarkers for predicting PPD during pregnancy, including cytosine and erythrulose. This study has found a significant decrease in cytosine, one of the four primary nucleotide bases of nucleic acids, during pregnancy (Yu et al., 2022). Cytosine plays a crucial role in regulating the biosynthesis of pyrimidine nucleotides and disruption of pyrimidine metabolism has been linked to antidepressant treatment response (Park et al., 2016) and depression in female students (Zhao et al., 2020)**.** Erythrulose, an important metabolite in "Tetrose metabolism" (Batt et al., 1960), has been also identified as a potential risk factor for PPD (Yu et al., 2022). The levels of erythrulose display opposite changes in women with PPD, increasing significantly during pregnancy and decreasing postpartum (Yu et al., 2022). It inhibits glucose breakdown and ATP production for the TCA cycle (Racker et al., 1959) and its association with oxidative phosphorylation or defects in the ATP production in PPD may be responsible for impaired ATP release, which has been observed in patients with major depression (Martins-de-Souza et al., 2012), as well as animal models of depression (Illes et al., 2020).

In addition to investigations of potential biomarkers for PPD in urine and plasma, several studies have focused on identifying PPD biomarkers PPD in serum samples. In one study three serum metabolites were found to exhibit altered levels in women with PPD as compared to control subjects (Papadopoulou et al., 2019). These metabolites were identified as adenylosuccinate, ATP and glutathione-disulfide, and were all elevated in the PPD group (Papadopoulou et al., 2019). Glutathione is an essential endogenous antioxidant compound and its ratio with glutathione disulfide serves as a prognostic factor for oxidative stress (Freed et al., 2017) and increased oxidative stress is frequently observed in patients with major depressive disorder (Black et al., 2015; Dowlati et al., 2010; Lindqvist et al., 2017). Adenylosuccinate is involved in nucleotide biosynthesis (Gooding et al., 2015) and ATP is the primary source of cellular energy involved in numerous cellular processes. ATP derived from astrocytes has been shown to impact depression-like behaviors, and mice vulnerable to chronic social defeat had lower levels of ATP in their brains (Cao et al., 2013). Moreover, a positive associations between self-reported depression and several metabolites, such as alanine, glucose, leucine, lactate and phenylalanine, were reported (Laketic et al., 2023). These metabolites contribute to the glycolysis and the TCA cycle, both of which play crucial roles in the energy production (Laketic et al., 2023). Increased energy demands, that have been linked to depression (Østergaard et al., 2018), could explain the observed differences in metabolite levels. This notion is supported by the growing body of evidence indicating a relationship between depression and mitochondrial dysfunction, oxidative stress and ultimately inflammation (Gardner and Boles, 2011; Gu et al., 2021; Sharma and Akundi, 2019).

Metabolic biomarkers could provide objective and non-invasive measurable indicators of the disorder, which could improve early detection and personalized treatment. Despite the potential of metabolomics, there are several challenges associated with the identification and validation of metabolomic biomarkers, including sample collection and processing variability, the need for large and diverse cohorts and the lack of standardized analytical methods and data analysis pipelines. Nevertheless,

the identification and validation of the metabolomic biomarkers could lead to improved diagnosis and treatment of PPD, which could have significant positive impacts on maternal and child health.

Revealing the role of xenobiotic exposure in PPD by metabolomic approaches

Xenobiotics are toxic or harmless exogenous metabolites, such as drugs, dietary supplements, pollutants, solvents, cosmetics, tobacco smoke and lead/heavy metals, that are metabolized and eventually eliminated via different routes (Johnson et al., 2012; Mitchell et al., 2020). One of them is bisphenol A (BPA), a compound largely synthesized as part of epoxy resins and different food/drink plastic packages. Bisphenol A has various adverse effects on the hormonal, immune and reproductive systems and metabolic processes (Tchen et al., 2022). Similarly, BPA analogue, bisphenol F (BPF) also showed adverse effects on the hormonal regulation and inflammatory response (Tchen et al., 2022). Consequently, exposure to these metabolites might cause the development of various psychiatric disorders, including PPD, due to their neurotoxic effect and influence on the brain, behavior and neurodevelopment of the offspring. A recent study showed that exposure to the BPA and BPF among pregnant women were associated with C-21 steroid hormone, lysine, and lipoate metabolism (Tchen et al., 2022). Altered metabolites and their corresponding metabolic pathways associated with BPA and BPF exposure are involved in various biological processes, including inflammation, stress response, energy storage and neural development (Tchen et al., 2022) which are all processes that might be altered in PPD. For example, C-21 steroid biosynthesis is associated with the synthesis of various hormones, including estrogens, progesterone and androgens, while altered cortisol levels are positively associated with the BPA exposure (Tchen et al., 2022). All these metabolites were observed to be altered in women with PPD. Likewise, BPA exposure was associated with alterations in the cysteine metabolism (Tchen et al., 2022), metabolic pathway altered also in women with PPD, as well as with tyramine, metabolite found to be associated with depression (Tchen et al., 2022). Therefore, exposure to bisphenols during pregnancy was shown to be linked to the alterations of xenobiotic metabolism, amino acid and steroid metabolism, indicating changes in various biological processes, such as stress response, inflammation, reproduction and neural development (Tchen et al., 2022).

Moreover, perfluorooctane sulfonic acid and methyl-perfluorooxtane sulfonamide acetic acid were found to be associated with higher depression scores (Aung et al., 2023). Per- and poly-fluoroalkyl substances affect levels of CRH and consequently stress response (Aung et al., 2023), that might lead to PPD development. Furthermore, study by Jacobson et al. (2021) showed that urinary concentrations of di-n-octyl phthalate and diisononyl phthalate were associated with reduction of progesterone levels in pregnant women, while di-n-octyl phthalate was associated with PPD (Jacobson et al., 2021). Since di-n-octyl phthalate was associated with hormonal changes and more severe PPD symptoms, these results suggest that endocrine disrupting chemicals could cause hormonal disruptions that may lead to the development of PPD symptoms (Jacobson et al., 2021). Similar study showed that altered levels of phthalate metabolites are not directly associated with greater risk for PPD development (Kim et al., 2021). Levels of the mono-(2-ethyl-5-hydroxyhexyl) phthalate and ethylparaben were increased in the breast milk of women with PPD, but this result was not statistically significant (Kim et al., 2021). In addition to findings showing that exposure to phthalate metabolites is positively associated with anxiety and depression, due to their involvement in altered lipid and hormonal metabolism, oxidative stress and dysfunction in neurotransmission and mitochondrial processes (Kim et al., 2021), there are also evidences that such exposure during pregnancy might lead to the PPD development.

Metabolomics in postpartum depression therapy

Unrecognized, and hence untreated, PPD can seriously affect mother–child interactions, infant development and interactions with other family members. Therefore, it is important to detect and treat depression during pregnancy or postnatal period as early as possible to avoid harmful consequences. Therapeutic interventions in PPD include psychotherapy, pharmacotherapy, neuromodulation and hormonal treatments. Mild PPD treatment is usually based on psychosocial and psychological interventions, but in case of severe PPD or when there is no sufficient response to psychological treatment, antidepressant drugs may be required (Stewart and Vigod, 2019). The first choice antidepressant pharmacotherapy in PPD includes the selective serotonin reuptake inhibitors (SSRIs), while other antidepressants are usually chosen in case of remission or SSRI treatment resistance (Stewart and Vigod, 2019).

Both SSRIs and serotonin and noradrenaline reuptake inhibitors (SNRIs) can cross the placenta and the blood-brain barrier and are also excreted in the milk, with different antidepressants resulting in different fetal exposure (Kaufman et al., 2022). Metabolomics approaches can be used for testing the exposure of breastfed infants to pharmacotherapy prescribed to a mother suffering from PPD. The usual measure of infant drug exposure are drug concentrations in breast milk or infant serum, with latter being more accurate, since all antidepressants can be detected in breast milk, but are not always spotted in the infant serum. A group of authors (Sit et al., 2011) investigated whether the cord-to-maternal antidepressant concentration ratio could be associated with abnormal perinatal events and preterm birth. They used reversed-phase high-performance liquid chromatography (HPLC) to measure citalopram, sertraline, nortriptyline and fluoxetine/norfluoxetine levels in serum samples of mothers treated with SSRIs during pregnancy and umbilical cord blood samples collected at delivery. The main results of the study indicated no association between occurrence of complicated perinatal events and cord-to-maternal antidepressant concentration ratios or maternal depression levels. However, exposure to short half-life antidepressants resulted in more perinatal events when compared to fluoxetine exposure. Additionally, no association between preterm birth and cord-to-maternal metabolite concentration ratios was reported (Sit et al., 2011). Another study (Rampono et al., 2011) provided data on the exposure of breastfed infants to the SNRI antidepressant desvenlafaxine consumed by their mothers. Authors used HPLC to quantify desvenlafaxine in milk during 24 hours after taking the medicine. Additionally, desvenlafaxine was also quantified in mothers' and infants' plasma samples. The results showed that the maximum concentration of desvenlafaxine in milk occurred 3.28 (2.44–3.79) h after dosing and relative infant dose was acceptably low, 6.8% (5.5–8.1%) of the weight-adjusted maternal dose (Rampono et al., 2011).

Metabolomics can help us to explore how certain therapeutic approaches affect different biological pathways. A study (Qiu et al., 2021) performed on an animal model of PPD (corticosterone treated rat dams) described how the treatment with SSRI fluoxetine may affect metabolites in the tryptophan-kynurenine (TPK) metabolic pathway, which is altered in MDD and PPD (Maes et al., 2011). In order to quantify plasma TPK metabolites, authors used isotope dilution liquid chromatography coupled with tandem mass spectrometry. Results indicated that PPD animal model reflects TPK profiles in MDD and PPD, while fluoxetine treatment showed limited effects on TPK metabolites suggesting that TPK metabolic pathway is not targeted by fluoxetine, but could serve as potential therapeutic target for some other, novel PPD therapeutics (Qiu et al., 2021). The same SSRI was used in another study that aimed to

investigate how fluoxetine treatment during pregnancy and lactation modulates the mother gut microbiome and metabolome in a rat model relevant to depression (Ramsteijn et al., 2020). A targeted metabolomic approach using ultra-performance liquid chromatography was applied to quantify fecal metabolites in a rat model of maternal vulnerability during pregnancy and lactation. Fecal microbiome diversity was found to be significantly different between pregnancy and lactation, while fluoxetine treatment altered fecal amino acid concentration, which correlated negatively with the relative abundance of bacterial taxa *Prevotella* and *Bacteroides* (Ramsteijn et al., 2020). Since the microbial metabolites contribute to homeostasis and development, authors concluded that the effects of SSRIs on the maternal microbiome might have health consequences for mother and her offspring (Ramsteijn et al., 2020).

Whenever a psychiatrist has to recommend an antidepressant drug, a various number of factors, including the primary and comorbid diagnoses, overall symptom severity, suicide risk, personal and family medical history, previous treatments efficacy and patient's tolerability and compliance with the treatment plan, should be considered (Gelenberg, 2010). In PPD, the treatment plan is additionally complicated by the fact that the pharmacotherapy could affect fetus during gestation or an infant during lactation period. As was already mentioned, the untreated PPD is often associated with pronounced developmental and mental health problems (Goodman et al., 2011; Murray et al., 2011; Muzik and Borovska, 2010). On the other hand, there are also negative effects of antidepressant treatment during pregnancy, including spontaneous abortions, preterm births, decreased child's body weight, intrauterine growth retardation and increased birth deaths (Oyebode et al., 2012). In another words, one should weigh the risks of fetus/infant drug exposure with the risk of untreated maternal PPD. Ideal PPD pharmacotherapy should be fast-acting with limited adverse effects for both mother and child. Although various pharmaco- and psycho- therapies are available nowadays, they are often understudied, which leads to their underutilization. Bearing in mind the heterogeneous phenotypic presentation of PPD, studies focusing on the biology behind the phenotypes and therapeutic interventions, may help in personalizing the care for the mothers and their infants.

Conclusion

Metabolomics can provide almost a real time insight into the biological processes affected by such a complex condition as pregnancy, which potentially can cause even more complex psychiatric disorder such as PPD. By detecting metabolites whose disruption is associated with PPD, one can make conclusions about the whole biochemical pathways associated with this disorder. Although still developing and often technically demanding, metabolomics is a very useful discipline whose targeted and untargeted approaches can help with revealing the biological background, reliable biomarkers, treatment and course of PPD. This knowledge is of crucial importance for developing faster, more accurate and precise diagnostic procedures followed by the well-timed, more effective and personalized therapy, resulting in reducing the negative or even fatal consequences of PPD for mothers, children and their families, but also society in whole. This review may help in creating the picture about metabolomics' broad application in the PPD studies, but it also implies that its potential is still not completely exploited. With this in mind, it is worth to mention that, by reviewing the published literature dealing with this topic, one can notice that some important aspects of metabolomics studies are still neglected. As it was already mentioned, the

metabolome is influenced not only by endogenous (genetic, gut microbiota), but also environmental factors. Environmental factors include diet, lifestyle and xenobiotic use, such as medication therapy, which can significantly affect obtained results and add to non-specific variations. Hence, this is something that definitely should be considered as confounding variables in future studies dealing with metabolic features of PPD.

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