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REVIEW

The role of catechol-o-methyltransferase in postpartum depression

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ABSTRACT

The global prevalence of postpartum depression is increasing annually. This condition has been associated with polymorphisms in the catechol-O-methyltransferase (COMT) enzyme, which plays a critical role in the degradation of catecholamines. Therefore, a literature review was conducted to examine the influence of COMT enzyme variants on postpartum depression, with a focus on specific time periods and genetic variants implicated in the disorder. The review methodology involved a systematic search of articles on the PubMed database using the keywords "catechol-O-methyltransferase," "postpartum depression," and "role of COMT in postpartum depression." Inclusion criteria required full-text availability in either Indonesian or English. Four relevant studies were identified that investigated the relationship between COMT enzyme variants and postpartum depression. Evidence suggests that the COMT Val158Met polymorphism may affect the risk of postpartum depression in the context of elevated estrogen levels, as high estrogen concentrations are known to downregulate COMT expression. Additionally, certain single nucleotide polymorphisms (SNPs), including rs2020917 (TT genotype), rs737865 (GG genotype), and the COMT rs4680 Met variant allele, have been shown to modulate the influence of COMT on postpartum depression independently of estrogen levels, possibly through interactions with other enzymatic pathways.

Keywords: catechol-o-methyltransferase, polymorphism, postpartum depression

INTRODUCTION

Postpartum depression (PPD) is a mental health issue that frequently arises in the community and serves as a significant contributor to maternal distress and health complications.[1] Each year, postpartum depression impacts around 10-15% of adult mothers, with 20-50% of those affected experiencing depressive symptoms that persist for over six months.[2] According to the World Health Organization (WHO), around 20% of mothers in low- and middle-income countries suffer from PPD. In high-income areas, the presentation of PPD has almost doubled.[3] Based on research by Syamantha conducted on mothers aged 15-54 with babies aged 0-6 months, in Indonesia, the prevalence of depression six months after giving birth is 4.0%, namely 5.7% in urban areas and 2.9% in rural areas.[4]

PPD is also associated with other factors, such as stressful life events, stress in raising children, and prenatal anxiety, which influences postpartum depression. In addition, a history of previous depressive episodes, marital conflict, and being a single parent are also risk factors for postpartum depression.[2] The occurrence of PPD is linked to genetic factors that previously have been correlated with major depressive disorders, including catechol-O-methyl transferase (COMT) and Monoamine Oxidase (MAO). COMT is an enzyme that breaks down catecholamines, such as epinephrine, norepinephrine, and dopamine. Variations in the COMT gene are a risk factor for PPD and have been found to be contributing to the higher rates of postpartum women with depression.[5] COMT polymorphisms are associated with PPD because polymorphisms of this enzyme can cause decreased activation of COMT itself.[6]

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The literature review aims to discuss the influence of the COMT enzyme on PPD and to determine the period and the existence of specific genetic variants of COMT that influence depression in postpartum women.

METHOD

The method used in this literature review is to use data from the Google search engine via the PubMed website with the MeSH (team) database. The articles searched used three keywords: "catechol-o-methyltransferase," "postpartum depression," and "role of COMT in postpartum depression." These keywords were adjusted to the inclusion criteria, namely that the article could be accessed entirely in both Indonesian and English.

After collecting articles through the database, adjusted based on the keywords and inclusion criteria determined by the researcher, all the articles will be read. All articles will be summarized and presented in a table containing "author/year," "methods," and "discovery." At the end, an analysis and discussion of these articles will be carried out so that a conclusion can be drawn.

RESULTS

From the search results, four articles were obtained that met the requirements. The results of the four articles are included in the table below.

Table 2. Studies related to the effects of COMT on postpartum depression

Author/Year	Methods	Discovery
Comasco, et al/ 2016	One hundred seventy postpartum women. 29 of them experienced postpartum depression, and 141 women were used as controls. The women examined were estimated to experience depression after 69 ± 11 days postpartum.	This research shows that postpartum women experience a decrease in PPI (Prepulse Inhibitor), and there is no effect of COMT on PPI early after giving birth. The COMT gene has components similar to estrogen and interacts with sex hormones and the gonads, so the effect of the COMT Val 158 Met hormone on PPI occurs if high levels of estrogen are involved. No impact of COMT on PPI was observed during the phase of low estrogen levels.
Ma, et al/ 2019	591 Chinese women who underwent cesarean section. PPD was diagnosed using an Edinburgh Postnatal Depression Scale (EPDS) score of greater than 10, measured 42 days after a cesarean section. The research was carried out by analyzing the genotypes rs2020917, rs737865, rs933271, rs2075507, and rs4633 from COMT and the SNP site rs6323 from the MAOA gene.	This study indicates that women with a combination of low activity variants of MAOA and COMT met alleles exhibit higher EDPS scores, especially at the 36th week of pregnancy and the 6th week postpartum, but not at the start of pregnancy or the 12th week postpartum.
Doornobos, et al/ 2009	Nine pregnant women were asked to complete Edinburgh Postnatal Depression Scale (EPDS) during pregnancy and after childbirth. The participants were evaluated at the 16th and 36th weeks of pregnancy, as well as at the 6th and 12th weeks postpartum. The study aims to analyze related polymorphism in MAOA, COMT and 5-HTT.	This research demonstrates that women with a combination of low-activity variants of the MAOA and COMT met alleles experience an increase in EPDS scores at the 36th week of pregnancy and 6 weeks postpartum, but not at the start of pregnancy or 12 weeks postpartum.
Comasco, et al/2011	Two hundred fifty-seven women at six weeks and six months postpartum. The research was conducted based on the Edinburgh Postnatal Scale (EPDS).	This research shows that there is a relationship between postpartum depression and COMT Val 158 Met at six weeks postpartum but not at six months postpartum. This depression is linked to the relationship between genes-environment, COMT val 158 met and MAOA, mental history, and postpartum stress.

DISCUSSION

PPD is depression that commonly occurs in women after giving birth with symptoms such as poor mood, anhedonia, sleep and eating disorders, and decreased social interest.[7] PPD can be influenced by several factors, including genetic, neuroendocrine factors, partner support, age, parity, maternal education and a previous history of depression.[8] Other factors associated with PPD are the presence of genetic polymorphisms of Hematopoietic and Myeloid Nuclear Differentiation Factor 1 (HMNC1), Catechol-O-Methyltransferase (COMT), Monoamine Oxidase T (MAOT), protein Kinase C Beta (PRKCB), Estrogen Receptor 1 (ESR1), sodium bicarbonate cotransporter 1 (SLCA4) which is influenced by certain environmental condition.[9]

COMT (Catechol-O Methyltransferase) is located on chromosome 22q11, two of which are involved in the regulatory function of dopamine. The COMT enzyme functions to degrade catecholamine hormones by transferring the methyl group from s-adenosylmethionine to the 3,4 dhydrobenzene (catechol) group of the molecule, which causes inhibition of dopamine activation in the synaptic cleft. The action of COMT is widespread in neurons and non-dopaminergic glia.[10] The various genotypes in COMT SNP are SNP rs4680 with the genotype variant AA/AG/GG, SNP rs4633 with the genotype variant CC/CT/TT, SNP rs2020917 with the genetic variant TT/CT/CC, SNP rs2239393 with the genotype variant AA/AG/ GG, SNP rs737865 has the TT/CT/CC genetotype variant, SNP rs174699 has the CC/CT/TT genotype variant, and SNP rs5993883 has the GG/GT/TT genotype variant.[11]

The most common SNP in the COMT gene is COMT Val158Met variant (rs4680), which causes a change in the nucleotide base from G to A at codon 158 (rs4680), which causes a change in the amino acid valine (Val) to methionine (Met). Changing the amino acid to the met allele causes a decrease in enzyme activation of COMT, thereby reducing the degradation of catecholamine hormones.[6] In one study, it was also found that there was an interaction between COMT and the MAOA hormone, which could influence symptoms of PDD.[12] MAOA is an enzyme found in the mitochondria and located on the X chromosome. It plays a role in breaking down catecholamine neurotransmitters such as norepinephrine, serotonin, and dopamine.[13]

In other research, it was also found that the COMT hormone can influence pepulse inhibition (PPI) in postpartum depression.[14] Prepulse inhibition (PPI) refers to the reduction of the startle reflex response to a startling stimulus when a weak prepulse stimulus precedes it. This measure is used to evaluate sensorimotor gating in various species, including humans and rodents. A decrease in PPI, which is believed to indicate a dysfunction of sensorimotor gating, has been observed in individuals with psychiatric conditions (schizophrenia, bipolar disorder, and post-traumatic stress disorder).[15] In PDD, the effect of COMT on PPI occurs when there are high estrogen levels, while it is not found in phases with low estrogen levels, as in the early follicular phase or postpartum. This occurs because PPI is affected by sex and gonadal hormones, and COMT contains elements such as estrogen.[14]

Besides its function in catecholamine metabolism, COMT also plays a role in the metabolism of estradiol and estrogen. Estradiol is initially converted into catechol estrogens by cytochrome P450 enzymes. Subsequently, catechol estrogens are inactivated through o-methylation by COMT.[16] A polymorphism in COMT can lead to reduced COMT activity and a decreased inactivation of catechols, resulting in higher estrogen levels. This increase in estrogen can affect PPI.

During pregnancy, estrogen levels (estradiol, estriol, and estrone) continue to rise and peak in the third trimester, mainly because of these hormones produced by the placenta. With placenta expulsion during delivery, levels of estrogen and progesterone decrease sharply, reaching pre-pregnancy levels on the fifth day postpartum. Estrogen hormone levels 3 - 6 months after giving birth will return to normal before pregnancy.[17] Estrogen reduces the expression of the COMT gene by inhibiting its transcription through two estrogen response elements found in the COMT promoter.[16]

In Comasco's study of 170 postpartum women, 29 were diagnosed with PDD, while the remaining 141 women served as controls, and non-Caucasian women were excluded to account for genetic variability. The participants, who were approximately 69 ± 11 days postpartum, completed the Montgomery and Asberg Depression Rating Scale (MADRS-S), The State-Trait Anxiety Inventory (STAI), and the Edinburgh Postnatal Depression Scale (EPDS). They also provided information on their medical and obstetric history, alcohol use, smoking, medications taken since delivery, sleep duration before the test, and details about their pregnancies. Genotype analysis was performed for COMT Val158Met (rs4680), SNP OXTR rs237885, and rs53576 using Kbioscience Allele-Specific Polymorphism assay (Kaspar), which involves competitive allele-specific PCR and bi-allelic SNP assessment. The genotype frequencies for COMT rs4680 were A/A 45 (35.7%), G/A 59 (46.8%), and G/G 22 (17.5%). The study found that COMT did not impact PPI in the early postpartum period. However, sex and gonadal hormones do affect PPI, and COMT has response elements that interact with these hormones. The influence of the COMT genotype on PPI seems to depend on estrogen levels; high estrogen levels during pregnancy were associated with effects on PPI, while no such effect was observed during periods with low estrogen levels, such as the follicular phase or early postpartum period.[14]

In a study by Ma et al., 591 Chinese women who had undergone cesarian sections and scored 10 or higher on Edinburgh Postnatal Depression Scale (EPDS) at 42 days after cesarean operation. The research involved examining genotypes for COMT at rs2020917, rs737865, rs933271, rs2075507, and rs4633, as

well as SNP rs6323 of the MAOA gene using Sequenom mass array SNP analysis. Logistic regression was employed to identify potential risk factors for PPD and to explore the interaction between genetic and environmental influences. The study found that the incidence of PPD in this group was 18.1%. Logistic regression analysis revealed that COMT polymorphisms rs2020917 (TT genotype) and rs737865 (GG genotype), along with severe stress during pregnancy and domestic violence, were significant risk factors for PPD. In contrast, maternal polymorphisms with rs737865 AG + AA genotype and rs2020917 CT genotype + CC genotypes were associated with a lower risk. The concluded that the COMT rs2020917TT and rs737865GG genotypes, along with stress during pregnancy and domestic violence are key risk factors for PPD.[7]

In research by Doornbos et al., nine pregnant women were asked to complete the EPDS score at 16 and 36 weeks of pregnancy, as well as 6 and 12 weeks postpartum. The study focused on analyzing polymorphisms related to MAOA, COMT, and 5-HTT. The COMT val158met (rs4680) polymorphism was assessed using allelic discrimination with the Biosystems 7500 real-time polymerase chain reaction (PCR) tool. The study found a notable interaction between the development of depressive symptoms and polymorphisms in 5-HTT, MAOA and COMT, and MAOA × COMT. Specifically, women carrying both the MAOA low activity variant and the COMT met allele showed improved EPDS scores at 36 weeks of gestation and six weeks postpartum, but not during early pregnancy or 12 weeks postpartum. COMT met allele affects activity in the pre-frontal cortex and limbic system in response to negative stimuli and stress-related endocrine responses. In animal models, reduced COMT activity increases stress responses and pain sensitivity. Lower activity of both MAOA and COMT diminishes the ability to manage stress-induced catecholamine release.[18]

In the research conducted by Comasco et al, involving 257 women at six weeks and six months postpartum, the EPDS was used to evaluate the depressive symptoms. The study found a link between PPD and the COMT Val 158 Met variant at six weeks postpartum, but not at six months. The research also highlighted significant gene-gene interactions with PPD. Specifically, in women with low MAOA activity, the COMT met allele was associated with PPD symptoms. Conversely, the high activity variant of MAOA was significantly linked to PPD symptoms only when paired with the COMT met allele. Similarly, the short of 5HTT was significantly associated with PPD symptoms when combined with the COMT Met allele. The COMT-Val158Met variant was associated with PPD symptoms, particularly in the context of a history of psychiatric disorders and maternity stressors. By six months postpartum, hormonal levels had returned to normal, suggesting biological, hormonal, and genetic factors may be less influential compared to environmental and social factors at this later stage.[12]

CONCLUSION

The Cathecol-O-Methyl Transferase (COMT) Val158Met enzyme can influence the incidence of postpartum depression when there are high estrogen levels because high estrogen levels will cause a decrease in the expression of the COMT enzyme. However, there are SNP variants and interactions of specific alleles with other enzymes that cause the COMT enzyme to influence postpartum depression, even if low estrogen levels are found. In the COMT SNP rs2020917 (TT genotype) and rs737865 (GG genotype), it was found that the effect of the COMT enzyme on postpartum depression, even though estrogen levels were low at 42 days postpartum, is because COMT rs737865 will cause a mutation from A to G and the rs2020917 polymorphism allele will mutate from C to T, causing transcription of the gene to increase, and causing NE to increase.

In COMT rs4680, low-activity variants of MAOA and COMT met alleles were found, indicating the occurrence of postpartum depression at six weeks postpartum due to the low activity of these two enzymes, causing a reduced capacity to neutralize the release of catecholamines. This was confirmed in other studies where it was found that there was postpartum depression if there was the influence of MAOA, both low and high activity, only if the COMT met allele was present. The COMT met allele affects the pre-frontal cortex and limbic activity in response to unpleasant or emotionally harmful stimuli and the endocrine stress response.

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