

Postpartum depression: A systematic review of the genetics involved

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Abstract

Postpartum depression is one of the most prevalent psychopathologies. Its prevalence is estimated to be between 10% and 15%. Despite its multifactorial etiology, it is known that genetics play an important role in the genesis of this disorder. This paper reviews epidemiological evidence supporting the role of genetics in postpartum depression (PPD). The main objectives of this review are to determine which genes and polymorphisms are associated with PPD and discuss how this association may occur. In addition, this paper explores whether these genes are somehow related to or even the same as those linked to Major Depression (MD). To identify gaps in the current knowledge that require investigation, a systematic review was conducted in the electronic databases PubMed, LILACS and SciELO using the index terms "postpartum depression" and "genetics". Literature searches for articles in peer-reviewed journals were made until April 2014. PPD was indexed 56 times with genetics. The inclusion criteria were articles in Portuguese, Spanish or English that were available by institutional means or sent by authors upon request; this search resulted in 20 papers. Genes and polymorphisms traditionally related to MD, which are those involved in the serotonin, catecholamine, brain-derived neurotrophic factor and tryptophan metabolism, have been the most studied, and some have been related to PPD. The results are conflicting and some depend on epigenetics, which makes the data incipient. Further studies are required to determine the genes that are involved in PPD and establish the nature of the relationship between these genes and PPD.

Key words: Genetics; Single nucleotide polymorphisms; Molecular; Postpartum depression; Genes

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Core tip: *5HTT* and *5HTTLPR* were the most studied gene and polymorphism, respectively. *5HTTLPR* is associated with postpartum depression (PPD) in the majority of papers, but epigenetics must be considered. *TPH1* and *TPH2* polymorphisms are related to peripartum depression. *COMT* and *MAOA* polymorphisms were also risk factors for PPD. Once again, only when epigenetic was analyzed, an association with *BDNF* polymorphism was possible. *MTHFR*, *CYP2D6* and *PER2* polymorphisms were not related to this mood disorder. Polymorphisms of oxytocin, steroids and estrogen genes were positively correlated with PPD.

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INTRODUCTION

Historically, pregnancy and puerperium have been considered periods that protect women from mental disorders. It is now known that the opposite is true: those periods confer a higher risk of appearance and recurrence of mental disorders and should therefore be a public health concern. Postpartum depression (PPD) is one of these disorders. Epidemiological papers demonstrated that the prevalence of postpartum depression is between 10% and 15%^[1-3].

The adverse impacts of PPD are not limited to mothers; PPD also affects other family members and influences family dynamics. Recent studies have shown that PPD can also lead to significant language, cognitive and emotional processing problems in children^[4-6]. Psychopathologies in children may not be restricted to the first years of life; it is possible to find manifestations, such as conduct disorder, that persist even until adolescence^[7]. The partners of women with PPD also tend to have depression more frequently than expected^[8,9].

Psychological and social changes mark the transition to motherhood. Those changes, together with clinical history and obstetrical aspects, may be related to PPD. Self-esteem, childcare stress, life stress, social support, marital relationship, infant temperament, marital status, socioeconomic status, unplanned/unwanted pregnancy^[10], previous psychiatric disorder^[1,10], method of childbirth, and previous abortion^[11] are the main findings associated with PPD.

In addition, biological changes are related to PPD. According to some investigations, these changes may be partly genetically determined. A study conducted in England evaluated 44 pairs of sisters who had unipolar

depression and found that those pairs in which one sister fulfilled the PPD criteria according to DSM-IV, 42% of the other sisters developed PPD after giving birth. For those who had no family history of depression, the rates dropped to 15% ($P = 0.01$). In this study, the evidence of a genetic influence is even greater when the PPD period was restricted for 6 to 8 wk postpartum^[12]. Another study, conducted in Australia, involved the interview of 838 pairs of adult twins about their postpartum experiences. The authors reported that genetic factors explained 25% of the variance in the occurrence of PPD^[13]. Over the last decade, many studies have been devoted to verifying the impact of this type of genetic variation in PPD, and it is thus important to know the concept of Single Nucleotide Polymorphisms (SNPs). SNP is a genetic variation that affects only one base pair in the DNA sequence. These variations in DNA sequence can affect the individual response to diseases, bacteria, viruses, chemicals, pharmaceuticals. To be considered an SNP, the variation should occur in at least 1% of a given population.

The present report aims to assess molecular studies associated with PPD and highlight the most studied genes and polymorphisms.

RESEARCH

The present paper is a systematic, integrative review that includes several studies with different methodologies to answer questions about the relationship between genetic factors and the development of postpartum depression. For guidance, the following questions were raised: Are there genes or polymorphisms that are more related than others to postpartum depression? What is their relevance? Are Major Depression (MD) and Postpartum Depression the same or different disorders? Is PPD only a temporal variant of MD?

This study consisted of a search of all articles describing a clear relationship between genetics and postpartum depression that were indexed in PubMed, LILACS and SciELO published before April 2014.

To accurately answer the questions that guided this review, the abstracts were read and classified during a selection process. If, after reading the abstract, there was reasonable doubt about the inclusion or exclusion of the paper, the whole article was read. The same procedure was adopted when abstracts were not available. Thereafter, a reverse search was carried out.

The following inclusion and exclusion criteria were used.

Included: papers in Portuguese, Spanish or English in the researched databases, with index terms "postpartum depression" and "genetics", which assessed the genes and polymorphisms related to PPD. For this purpose, the following algorithms were used: ("Depression, Postpartum"[Mesh]) AND ("Genetics"[Mesh] OR "genetics"[Subheading]).

Excluded: review articles and animal models; articles that were not available by CAPES (Brazilian governmental agency that sponsors studies) and not provided by authors upon request; those that researched another postpartum psychopathology, finding or result; and those that did not address genetics involved in PPD.

RESULTS

The LILACS and SciELO searches did not result in any article fulfilling the criteria. The PubMed search resulted in 56 papers. After reading the abstracts, 36 were excluded: 6 reviews^[14-19], 2 papers that were not available by CAPES and not sent by the authors upon request^[20,21], 5 animal models^[22-26], 12 investigating another postpartum psychopathology (psychoses and bipolar)^[27-38], 3 evaluating the children^[6,39,40], 1 on breastfeeding^[41] and 7 that did not address the genetic factors involved in PPD^[12,13,42-46]. A reverse search resulted in no additional items. Finally, a sample was formed^[47-66].

The 20 selected studies were conducted in 10 different countries. Sweden^[48,50,53] and the United States of America^[49,57,64] had three publications each (15%). Germany^[56,61], China (Taiwan)^[55,60], Spain^[51,58], Canada^[63,66], the United Kingdom^[54,65] and Brazil^[47,62] had two papers each (10%). Israel^[59] and Netherlands^[52] had one paper (5%) each (Table 1).

Of the selected sample, the *5HTT* gene was the most studied^[48-50,52,56-58,66]. Genes associated with tryptophan metabolism^[55,60,61,66] and Catechol-O-methyl transferase (COMT)^[48,52,62,66] were the next most researched. Monoamine Oxidase (*MAO*) gene was studied in three of the articles included in this review^[48,52,66], and the Brain-Derived Neurotrophic Factor (*BDNF*) gene was studied in two articles^[47,50]. Two articles analyzed genes that are not commonly evaluated in depression studies: the Methylene tetrahydrofolate Reductase (*MTHFR*) gene^[54] and the *CYP2D6* gene^[53]. One article was about circadian gene *Per 2*^[50], and one was about the oxytocin gene (*OXT*) and oxytocin receptor gene (*OXTR*)^[63]. Costas *et al.*^[51] assessed 44 genes involved in pathways that are hypothetically related to the etiology of postpartum mood disorders, that is, those included in the HPA axis, in the effects of stress in the prefrontal cortex, and in the regulation of sex hormones. Looking for an association between PPD and the HPA axis, Engineer *et al.*^[65] tested the glucocorticoid (*GR*) and type 1 corticotropin-releasing hormone (*CRHR1*) receptor genes. Based on the results of Costas' paper, Pinssoneault *et al.*^[66] researched the *ESR1* gene both as a principal outcome and under the additive power of other genes: *COMT*, *TPH2*, *MAOA*, *5HTT*, dopamine receptor D2 (*DRD2*), serotonin receptor 2A (*HTR2A*) and dopamine transporter (*DAT*). An Israeli study evaluated peripheral blood mononuclear cell (*PBMC*) gene expression^[59]. Finally, an American study analyzed 417 microsatellite markers in linkage studies and

chromosomes 1 and 9 by Genome-Wide Association Studies (GWAS)^[64].

The most studied polymorphism was the 5-HTTLPR, which was addressed in eight articles^[48-50,52,56-58,66]; some of these articles also analyzed other polymorphisms in the 5HTT, such as STin2 VNTR^[57,58] and rs140700^[51]. The remaining studied polymorphisms were those of *TPH 1* and 2^[55,60,61,66], *COMT*^[48,52,62,66], *MAO*^[48,52,66], *BDNF*^[47,50], *CYP2D6*^[53], *MTHFR*^[54], *Per 2*^[50], *OXT/OXTR* genes^[63] and *GR/CRHR1* genes^[65]. Pinssoneault *et al.*^[66] adopted a different strategy: in addition to looking for polymorphisms of the estrogen receptor alpha gene (*ESR1*), they looked for associations with the polymorphisms already cited in this report (*MAOA*, *COMT*, *TPH2*, *5HTTLPR* SNPs) besides those of the genes *HTR2A*, *DAT* and *DRD2*^[66]. Segman *et al.*^[59] used a different approach, analyzing not polymorphisms but 3142 active transcripts, whereas Mahon *et al.*^[64] studied 16.916 SNPs through GWAS (Table 1).

DISCUSSION

The data regarding *5HTT* gene polymorphisms were variable. Doombos *et al.*^[52] performed the only study that found an independent relationship between PPD and the 5HTTLPR polymorphism whereby subjects with the 5HTTLPR long allele variable developed PPD. Binder *et al.*^[49] and Sanjuan *et al.*^[58] found a significant association between 5HTTLPR and PPD only at 8 wk postpartum, but the results became nonsignificant in a posteriori analysis, suggesting that the findings were dependent on the evaluation time point. The remaining 5HTTLPR studies also depended on covariates to achieve statistically significant associations with PPD: unfavorable environments^[57]; previous psychiatric history, maternity stressors and *COMT*-Val158Met allele^[48]; autumn or winter delivery^[50]; stressful life events^[56]; and a gene-gene interaction with *ESR1* TA repeat^[66].

The *TPH* gene study showed a significant difference in genotype frequency for the T27224C polymorphism between standard groups and those with comorbid depression and anxiety, with risk analysis showing that the C allele conferred a strong protective effect for depression and anxiety. This finding suggests that the *TPH1* gene has an important role in the pathogenesis of postpartum mental disorders^[60]. Similarly, one of the *TPH2* gene studies attested that the C2755A polymorphism could be considered a risk factor for depression. The C2755A polymorphism occurred only in women with peripartum major depression and anxiety disorders ($P = 0.043$) and exhibited a dominant gene action ($P = 0.038$) with an estimated disease risk of 1.73. Hence, despite its small sample size, this study suggests that *TPH2* represent a population-specific risk factor for peripartum major depression^[55]. A recent study supports that conclusion; it found that a haplotype block in the promoter region of *TPH2* showed significant associations with

Table 1 Genes and polymorphisms associated with postpartum depression

Article	Ref.	Country	Instrument	Genes	Polymorphisms
CYP2D6 genotypes and depressive symptoms during late pregnancy and postpartum	Josefsson <i>et al</i> ^[53]	Sweden	EPDS	CYP2D6	CYP2D6*1 (wild type), CYP2D6*3, CYP2D6*4
Association of tryptophan hydroxylase gene polymorphism with depression, anxiety and comorbid depression and anxiety in a population-based sample of postpartum Taiwanese women	Sun <i>et al</i> ^[60]	China	SADS	TPHI	T3840A, A12517C, A20004C, C347T, T27224C
Mood changes after delivery: role of the serotonin transporter gene	Sanjuan <i>et al</i> ^[56]	Spain	EPDS/DIGS	5HTT	5HTTLPR, STin2 VNTR
The development of peripartum depressive symptoms is associated with gene polymorphisms of MAOA, 5-HTT and COMT	Doornbos <i>et al</i> ^[52]	Netherlands	EPDS	MAOA, 5HTT, COMT	MAOA, 5HTTLPR, COMT Val158Met
Population-specific functional variant of the TPH2 gene 2755C>A polymorphism contributes risk association to major depression and anxiety in Chinese peripartum women	Lin <i>et al</i> ^[55]	China	SADS	TPH2	T-703C, T-473A, A90C, C2755A, C10662T, G93329A
Genome-wide linkage and follow-up association study of postpartum mood symptoms	Mahon <i>et al</i> ^[61]	United States	DIGS		417 microsatellite markers in linkage studies / 16,916 SNPs in the 1 and 9 chromosomes for GWAS. 3142 active transcripts set
Blood mononuclear cell gene expression signature of postpartum depression	Segman <i>et al</i> ^[59]	Israel	EPDS	PBMC gene expression	5HTTLPR
A serotonin transporter gene polymorphism predicts peripartum depressive symptoms in an at-risk psychiatric cohort	Binder <i>et al</i> ^[69]	United States	SCID / HRSID-17	5HTT	
Association study of 44 candidate genes with depressive and anxiety symptoms in post-partum women	Costas <i>et al</i> ^[51]	Spain	EPDS/DIGS	44 genes involved in pathways hypothetically related to the etiology of postpartum mood disorders: HPA axis, effects of stress in the prefrontal cortex, and regulation of sex hormones	388 SNPs
An association study between the Val66Met polymorphism of the BDNF gene and postpartum depression	Figueira <i>et al</i> ^[47]	Brazil	EPDS	BDNF	BDNF Val66Met
Postpartum depression symptoms: a case-control study on monoaminergic functional polymorphisms and environmental stressors	Comasco <i>et al</i> ^[50]	Sweden	EPDS	COMT, MAOA, 5HTT	COMT Val158Met, MAOA uVTNR, 5HTTLPR.
Role of mother's genes and environment in postpartum depression	Mitchell <i>et al</i> ^[57]	United States	CIDI-SF	5HTT	5HTTLPR, STin2 VNTR
Val66Met functional polymorphism: effect of season of delivery	Comasco <i>et al</i> ^[50]	Sweden	EPDS	BDNF, 5HTT, PER2	BDNF Val66Met, PER2 SNP 10870 (G and A), 5HTTLPR (L and S)
Folic acid supplementation during pregnancy may protect against depression 21 months after pregnancy, an effect modified by MTHFR C677T genotype	Lewis <i>et al</i> ^[54]	England	EPDS	MTHFR	C677T
The 5-HTTLPR polymorphism modulates the influence on environmental stressors on peripartum depression symptoms	Mehta <i>et al</i> ^[66]	Germany	EPDS	5HTT	5HTTLPR

Genetic variants in the tryptophan hydroxylase 2 gene (TPH2) and depression during and after pregnancy	Fasching <i>et al</i> ^[61]	Germany	EPDS	TPH2	rs11178993, rs6582071, rs11178997, rs7955501, rs17110536, rs4760814, rs7300641, rs4760820, rs10879354, rs1487275, rs10879358, rs11615016, rs17110747, rs1872824 COMT Val158Met
Postpartum depression symptoms associated with Val158Met COMT polymorphism	Alvim-Soares <i>et al</i> ^[61]	Brazil	EPDS	COMT	
Interaction between oxytocin genotypes and early experience predicts quality of mothering and postpartum mood	Mileva-Seitz <i>et al</i> ^[61]	Canada	CES-D	OXT, OXTR	OXT: rs2740210, rs4813627 / OXTR: rs237885
Association of glucocorticoid and type 1 corticotropin-releasing hormone receptors gene variants and risk for depression during pregnancy and post-partum	Engineer <i>et al</i> ^[61]	United Kingdom	EPDS	GR, CRHR1	GR: BclI, ER22/23EK/CRHR1: sl876828, rs242939, rs242941
Association study of the estrogen receptor gene ESRI with postpartum depression - a pilot study	Pinsonneault <i>et al</i> ^[61]	Canada	MINI, SCID, EPDS and/or MADRS	ESRI, COMT, TPH2, DRD2, HTR2A, DAT, MAOA, 5HTT	ESRI: TA repeat rs2077647, rs1801132, rs3798577, rs988328, rs1884051, rs3020327, rs9340958, rs3020434 / HTR2A: rs6314, rs6311 / DAT: rs27072, rs6347, In8VNTR / 5HTTLPR/MAOA: rs1137070, pVNTR/TPH2: rs7305115 / DRD2: rs2828265 / COMT: rs4680

EPDS: Edinburgh Postnatal Depression Scale; SADS: Schedule for Affective Disorders and Schizophrenia; DIGS: Diagnostic Interview for Genetics Studies; SCID: Structured Clinical Interview for DSM-IV; HRSD-17: 17-item Hamilton Rating Scale for Depression; CID-I-SF: Composite International Diagnostic Interview-short form; CES-D: Center for Epidemiological Studies Depression Scale; MADRS: Montgomery-Asberg Depression Scale; TPH: Tryptophan hydroxylase; 5HTT: Serotonin transporter; MAOA: Monoamine oxidase A; COMT: Catechol-O-methyltransferase; PBMC: Peripheral blood mononuclear cell; BDNF: Brain-derived neurotrophic factor; PER2: Period circadian clock 2; MTHFR: Methyltetrahydrofolate reductase; OXT: Oxytocin; OXTR: Oxytocin receptor; GR: Glucocorticoid receptor; CRHR1: Type 1 corticotropin-releasing hormone receptor; ESRI: Estrogen receptor alpha; DRD2: Dopamine receptor D2; HTR2A: Serotonin receptor 2A; DAT: Dopamine transporter.

depression values during pregnancy and 6-8 mo after pregnancy^[61]. This last paper also showed that the SNP rs10879354 had a significant association with depression throughout the postpartum period. A gene-gene interaction with *ESRI* gene was not found^[66].

Four papers focused on the COMT genes^[48,52,62,66], with three of them also focusing on the MAOA gene^[48,52,66]. COMT-Val158Met allele polymorphism was one of the main risk factors for PPD^[48,52,62], despite not being an independent risk factor^[48,52,66]. Previous psychiatric contact, maternity stressors and the time of the evaluation (6 wk or 6 mo postpartum) influenced the relationship^[48]. Similarly, the interaction with MAOA - L polymorphism was associated with more pronounced depressive symptoms than when the COMT-Val158 Met allele was considered alone^[52]. MAOA rs1137070 and COMT rs4680 polymorphisms were found to have an additive effect plus *ESRI* in producing PPD^[66].

Figueira *et al*^[47] and Comasco *et al*^[50] did not find any linear correlation between PPD and the BDNF ValMet polymorphism. The correlation showed a trend toward significance among Met allele carriers^[47,50]. There was a cumulative and significant effect of the presence of Met allele and autumn/winter delivery^[50].

The C677T polymorphism was also studied in a study that focused on the association between MTHFR and PPD. Its results indicated that low folate levels do not appear to be a significant risk factor for peripartum depression but may be a factor for non-gestational-related depression, especially in women with the MTHFR C677T TT genotype^[54]. The study on CYP2D6 showed that in a sample that included 45 women reporting symptoms of depression only during pregnancy, 56 women reporting symptoms of depression only after pregnancy and 44 women reporting symptoms of depression both during and after pregnancy, there were no differences in CYP2D6 genotyping and depressive symptoms^[53].

Circadian genes did not appear to have a "family" effect. Despite the correlation between postpartum depressive onset in bipolar disorder and Per3 4/4 homozygotes^[37], the circadian gene *Per 2* was not related to PPD^[50].

As in Major Depression^[67], the *OXTR* gene appears to be related to perinatal depression. Its SNP rs237885 was associated with pre-natal, but not post-natal, depression scores^[63]. There was also a correlation between OXT SNPs rs2740210 and rs4813627 and depression score 6 mo after delivery. However, this finding seems to be mediated by mother's early life quality of care because the association was not retained in the regression model. That is, these appear to be separate effects

rather than causally linked outcomes^[63].

Costas *et al.*^[51] studied 44 genes that are hypothetically linked to depression and, after correcting for multiple tests, did not find a significant relation between any of the SNPs tested and PPD. Nevertheless, a post hoc analysis showed that a combination of three SNPs of the protein kinase C beta gene (*PRKCB*): rs198183, rs381901 and rs2051684, achieved statistical significance (global $P = 0.0001596$)^[51], turning it into a potential target.

The GR polymorphism BclI, but not the ER22/23EK, showed a positive association with high EPDS score and, therefore, PPD. This correlation was also positive for the minor allele rs242939 SNP of the *CRHR1* gene, with the particularity that a relation with prenatal EPDS score could also be found in this case^[65]. This result supports Brummelte and Galea's statement that there are changes in all aspects of the HPA system (ACTH, CRH and cortisol) during pregnancy and the postpartum period. Women who are susceptible to HPA axis dysregulation may be particularly vulnerable for developing stress-related disorders at this time^[68].

Two variants in the *ESR1* gene, the TA repeat and rs2077647, were statistically associated with EPDS scores and PPD^[66], suggesting that estrogen-linked molecular mechanisms could also be involved in PPD genesis. Conversely, gene-gene interactions detected with encoding serotonergic signaling proteins (5HTT and HTR2A) reinforce serotonin's contribution to PPD.

Segman *et al.*^[59], analyzing *PBMC* gene expression and its 3142 active transcripts, found a signature of 73 active transcripts showing 1.5-fold or higher significant association with PPD. Of those, a subsample of 57 transcripts remained significant in the secondary analysis. Despite the small sample size of the study, both the 73 and 57 differential transcript sets (but not the 3142) correctly distinguished PPD patients from controls. This capability could be used as a prognostic tool, allowing for the initial screening of mothers who are at higher risk for PPD development.

Finally, Mahon *et al.*^[64] used linkage and GWAS techniques and found that the chromosomes 1q21.3-q32.1 and 9p24.3p22.3 were associated with postpartum depressive mood. The authors suggest that Hemicentin 1 (*HMCN1*) and Methyltransferase like 13 (*METTL13*) genes on chromosome 1 contain polymorphisms that confer vulnerability for PPD, highlighting the notion that specific studies of those genes should be attempted^[64]. These results must be watched with caution because bipolar patients with postpartum depressive onset were mingled in the sample. However, a study published last month also confirmed that an *HMCN1* polymorphism (rs2891230) is associated with PPD diagnosis in a population without bipolar diagnosis^[69].

Despite the substantial number of genes and polymorphisms reviewed here, there are still others that need testing. For instance, Maguire *et al.*^[24] noticed a relationship between GABAA receptor plasticity during pregnancy and PPD and proposed an animal model

using GABA α R δ subunit deficient mice. Therefore, GABAergic genes may also be potential targets^[24]. Another important genetic mechanism involved in Major Depression and not tested in PPD studies is the course of inflammation genes. Because functional allelic variants of the genes for IL-1 β and TNF- α increase the risk for depression and are associated with reduced responsiveness to antidepressant therapy^[70-72], their influence under PPD would be interesting to measure.

Overall, all of the articles selected had large sample sizes, thus rendering reliable results. Some of the differences found for the same polymorphism may be attributed to different methods used for PPD diagnosis, as observed in table 1. Another important point to note is that it seems, as in other psychiatric disorders, that genetic influence appears not to be sufficient by itself to cause the disorder. The development of psychiatric disorders is often dependent on epigenetics, and an environmental trigger is often required for these diseases to develop^[48,50,57].

Riecher-Rössler *et al.*^[73] stated that there is no doubt that sex and gender, with their biological and psychosocial correlates, strongly affect mental health, given the marked difference regarding the prevalence, symptoms, risk factors and outcomes of psychiatric disorders between the sexes. Nevertheless, using PPD as an example, the author shows that such influence is necessary to ensure better clinical care and not to justify the existence of a distinct diagnostic entity. It was possible to demonstrate that the factors used to define "true" or "valid" psychiatric disorders: descriptive validity (the same symptoms), construct validity (the same risk factors) and predictive validity (the same course) are not satisfied in PPD^[73]. MD and PPD apparently share the same genetic background because PPD seems to be linked to MAO, COMT, 5HTT and other pathways usually related to MD. In our opinion, this strengthens the possibility that they are the same disorder with a temporal variant^[74,75]. However, there are not sufficient published data to determine whether there is a specific etiological factor that is capable of differentiating those two disorders. Further studies are needed to nullify this hypothesis, and for that, other candidate genes must also be researched.

CONCLUSION

This review summarizes the representative findings in the literature regarding the genetics involved in Postpartum Depression.

The main conclusion of this review is that similar genes tend to be studied in Postpartum Depression and that these genes have a similar pattern to those already associated with Major Depression in the literature.

The relationship between molecular genetics and PPD is an extremely current issue. The oldest article selected was from 2004, and the newest was from 2013. However, there is still little research in this area

compared with other psychiatric disorders, and it deserves further study due to its importance in terms of public health.

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