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REVIEW ARTICLE

# Lucky gene 5-HTTLPR and postpartum depression: A systematic review

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## Abstract

**BACKGROUND:** Postpartum depression (PPD) should be given more attention for its increasing incidences, severe complications and complex pathogenesis. Previous studies of PPD have mainly been focused on the social contributions to its etiology such as age, marriage and economic status, whilst less attention has been given to inner biological factors. Currently, emerging researches have endeavored to explore 5-HTT related pathogenesis of PPD.
**OBJECTIVE:** This report was aimed at proffering updates on some research advancements in the field of PPD through the reviewing published papers concerning postpartum depression, with prime focus on the role of 5-HTT.
**SEARCH STRATEGY:** This review report dug into articles containing both PPD and 5-HTTLPR. Web of Science, Pubmed and CNKI (National Knowledge Infrastructure) were employed for searching relevant publications.
**SELECTION CRITERIA:** There was a strong association between 5-HTTLPR polymorphism and the pathogenesis of PPD, with established evidence showing that L allele (Long allele) in 5-HTTLPR was associated with reduced susceptibility to PPD.
**LIMITATIONS:** All things considered, sufficient clinical experiments are needed to ascertain the feasibility of our theoretical statements. In addition, relevant articles are comparatively scarce presently.

## INTRODUCTION

PPD is defined as an episode of major depressive disorder (MDD) occurring either during pregnancy or within the first 6 months postpartum (Kim *et al.* 2016). It is one of the most common complications during both prenatal and postpartum period, with a prevalence of 10% to 15% in women of childbearing age. It is becoming a popular disease amongst women of all races, ages, parities, and socioeconomic groups, with almost every woman encountering a certain degree of this form of depression at some time during this period. However, around 50% of patients with significant depressive symptoms are recognized (Gaynes *et al.* 2005; Gjerdingen & Yawn 2007).

Untreated and unresolved PPD leads to some kind of ramifications for the affected individual, their infant as well as their relationship with family members. This can be very severe and subsequently cause social conflicts. Thus, the universal screening for PPD is an interesting approach, with several psychiatrists and obstetricians making recommendations regarding universal PPD screening during maternity or early childcare (Ellis *et al.* 2016). While published reports only provided summary assessments, they failed to assess program design, context, setting, or components as well as potential factors influencing either success or failure. Nevertheless, reports have indicated that programs pertaining to future studies should be based on present successful programs and their identified facilitators whilst avoiding identified barriers of maternal outcomes.

Previous studies have postulated hormonal imbalance, especially estrogen and progesterone, to be the cause of PPD. However, the exact mechanism has not been elucidated (Choi *et al.* 2016). Presently, risk factors of PPD include past episodes of depression, weakness in personality, lack of social support, undesirable marriage, family disputes, unexpected life events, maternal complications in perinatal period along with poor economic status. During pregnancy, elevated estrogen and progesterone levels in women last for a comparatively long period. Since estrogen has a variety of nerve regulation function, its fluctuations or continuous deficiency as well as sudden withdrawal after birth could culminate in emotional depression (Almeida *et al.* 2012). Also, thyroid function during pregnancy is affected by various factors. After birth, thyroid hormone level changes, and thyroid dysfunction has been associated with PPD. Again, there exist abnormal metabolism of neurotransmitters and altered function of receptors. Specifically, abnormal brain neurotransmitters are from the synaptic cleft and their functional activities. During these process, neurotransmitter involved with serotonin (5-HT), dopamine (DA), norepinephrine (NA) can be produced. Besides, PPD could be related to a variety of social factors, for instance, previous episodes of depression and family genetic history (Shea *et al.* 2017).

We do hope this review enhances our understanding of PPD, subsequently leading to promising new directions in the pathology, nosology as well as treatment of this malady.

## NEW ADVANCEMENTS OF PPD RESEARCHES

As stated earlier on, PPD has complex causes and complications, with certain areas particularly understudied.

*Pain intensity*

Firstly, some researchers have demonstrated PPD to be associated with higher pain intensity. Additionally, relationships between depression and expected, perceived and recalled labor pain were also examined (Affonso *et al.* 2000; Sullivan *et al.* 2001; Bjelanovic *et al.* 2009). During pregnancy, hormonal changes often cause all kinds of somatic symptoms coupled with bodily changes. These changes, for instance, include alterations in sleep, appetite, weight, energy and concentration. All these could be stressful, especially for mothers carrying their first child (Mohr *et al.* 2010).

*PPD in father*

Another new direction has to do with resolving incidences of PPD in fathers. Given the implications of clinical depression in men both during pregnancy and postpartum periods, further systematic approaches of investigations in both direct and indirect predictors of elevated depressive symptoms in men during this period of time is necessary (Wee *et al.* 2011). Though we barely are aware of the possibility of fathers being patients of PPD, it has been documented that on average 1 in 14 fathers suffer from PPD (Gürber *et al.* 2017). One neglected observation has to do a husband's knowledge about PPD and his behavior towards his wife suffering from PPD. Owing to husbands' poor knowledge about PPD, their attitude towards their wives' might play a crucial role in the initiation of PPD.

*Trace elements*

Although the etiology of PPD is unclear, there are increasing evidences suggesting psychoneuro-immune connection. Complex interactions between hormones, neurotransmitters and trace elements, for instance zinc and magnesium, acts on synaptic neurotransmission in the brain (Duarte *et al.* 2008; Nikseresht *et al.* 2012). In light of these, acute administration of combined treatment with Zn, Mg, and Vitamin B1 on postpartum day 3 has been shown to improve depressive symptoms and anxiety-like behaviors. Also, there has been recent indications that alterations in zinc, magnesium and NMDA receptor complex in the hippocampus could potentially be involved in the pathophysiology of suicide-related disorders like depression, which further leads to functional NMDA receptor hyperactivity (Sowa-Kućma *et al.* 2013).

## RISK FACTORS FOR PPD

Presently, emphasis is being placed on identifying predictive factors during the antenatal period for PPD (De Tychey *et al.* 2008). In the past however, emphases were placed on only on the mother's poverty level, psychiatric history, partner absence as well as stressful life events (Shapiro *et al.* 2012).

*Personality features*

Personality traits, especially neuroticism, might be responsible for the increasing prevalence of depression among females. According to a previous study, high-perfectionism is a personality dimension associated with major PPD. The inclusion of perfectionism assessment, together with other factors, might be con-

sidered in order to improve the detection of women at risk of PPD, early intervention might be of beneficial (Gelabert *et al.* 2012).

*Nutrition*

There has been new trait suggesting that micronutrient deficiencies might contribute to the development of PPD. For prevention or treatment of PPD, it would be important to inveigle more clinicians to treat pregnant and postpartum women with dietary modification or micronutrient supplements. These interventions would be relatively inexpensive, and women reluctant to take anti-depressant medication might be more willing to use dietary supplements (Freeman 2009). Nonetheless, the link between nutrition and PPD is in its infancy. Present evidence has not been strong enough to safely prevent or treat PPD with dietary interventions or supplements alone (Kendall-Tackett 2010). As such, further research concerning the link between micronutrients and PPD would be imperative before clinicians can design the right diet and supplementation plans to prevent and treat PPD (Groer & Morgan 2007). How these deficiencies influence 5-HTT and hypothalamic-pituitary-adrenal (HPA) axis is an intriguing direction for research from a PPD perspective (Groer & Morgan 2007).

*Pathogenesis*

Over the past few decades, there has been significant spread of awareness by professionals and the general public on the importance of maternal perinatal mental health, with acknowledgement of the prevalence and morbidity related to psychiatric illness during pregnancy and postpartum (Gavin *et al.* 2005; Gaynes *et al.* 2005). Currently, a line of evidence from both human and animal models infer that dysregulations in hormone, abnormalities in hypothalamic-pituitary-adrenal axis (HPA axis) and contributions from genetics and epigenetics factors together play key roles in the development of perinatal reproductive mood disorders (Zou & Crews 2005). Investigations into both human and animal models of PPD shows much promise for future identification of the underlying pathophysiology and subsequent early identification, timely prevention and appropriate treatment for women with potential danger of PPD (Cooper *et al.* 2007). Simultaneously, exploring on the best way to counsel pregnant women concerning the risks of untreated major depressive disorder versus the risks of psychopharmacologic treatment during pregnancy and lactation is worth looking into (Beck *et al.* 2006; Oberlander *et al.* 2009; Warburton *et al.* 2010).

## IMMUNE MEDIATORS PLAY IMPORTANT ROLE PPD EARLY DIAGNOSIS

Alterations of immune signals in depression have been investigated since the 1980s. Cytokine genes have been demonstrated to be expressed in the brain, with accumulating data supporting the hypothesis that signals mediated by immune molecules could underlie the biology of some subtypes of MDD (Segman *et al.* 2010). In that context, it is important to note that immune mediators are part of molecular signature of postpartum depression, leading to early diagnosis (Licinio 2010).

*Endocrinic link*

The general finding concerning this area is that elevated stress hormones act via specific immune cell receptors to activate macrophages, inhibit Th1 cell activity and activate Th2 axis. Depressed mothers have been found to exhibit impairment in cellular immunity in comparison to non-depressed mothers, along with susceptibility symptoms of infection (Vedhara & Irwin 2005). Other results from studies have evidenced Th1/Th2 ratio to be curtailed in both serum samples and whole blood ex vivo culture supernatants, suggesting suppression of cellular immunity in depressed mothers (Maes *et al.* 2000). Serotonin autoimmunity has been associated with increased physiosomatic symptoms, including malaise and neurocognitive symptoms (Yang *et al.* 2017), along with increased serum neopterin and lysozyme, coupled with increased plasma TNF-α and IL-1 in normal individuals in similitude to depressed patients without the 5-hydroxytryptamine (5-HT) autoimmunity (Anderson & Maes 2013). Subsequently, women diagnosed with PPD have higher levels of CRH, ACTH and cortisol prior to and during episodes of depression in comparison to women who do not develop PPD (Maes *et al.* 2012). Furthermore, reports have evidenced women diagnosed with PPD to demonstrate a cytokine-driven hyperactivity of the HPA axis when compared with those who do not develop PPD. This was substantiated through significant differences in slopes of the relationships between cytokines and HPA axis hormones in non-depressed women in juxtaposition to those diagnosed with PPD (Corwin & Pajer 2008).

*Inflammatory response system*

Activation of the inflammatory response system (IRS) might be involved in the pathophysiology of anxiety states and major depression. In pregnant women, there have been indications of immune activation as well as immunosuppression as confirmed by some researches. Other researches have suggested the pathophysiology of postpartum anxious blues might differ from that of depressive blues. Women with postpartum depressive symptoms have been evidenced to exhibit significant elevated serum IL-6R concentrations both at the end of pregnancy and in early puerperium, suggesting an increase in IL-6 signaling. In conclusion, women with anxiety and depressive symptoms in the puerperium are characterized by IRS activation and reduced anti-inflammatory activity in the serum. As such, IRS activation might play a role in the etiopathology of postpartum depression.

Additionally, other studies have been focused on increased inflammatory potential, which suggested the decrement in endogenous anti-inflammatory compounds together with curtailed omega-3 polyunsaturated fatty acids in postnatal period causes an inflammatory environment (Sylvén *et al.* 2013). The latter might result in the utilization of peripheral inflammatory products, especially kynurenine, in driving other central processes to produce postnatal depression (Saleh *et al.* 2013). Again, elevations in thyroid stimulating hormone linked to thyroid autoimmunity has been proposed as a parturition measure to predict succeeding PPD (Anderson & Maes 2013).

*Roles of 5-HTT and 5-HTTLPR on PPD*

The 5-HTT gene is a promising avenue for genetic research, with a high likelihood that this gene affects risk of depression and other psychiatric conditions. Three carefully conducted studies reported associations between the 5-HTT genotype and PPD (Shapiro *et al.* 2012). A previous study suggested a significant association between 5-HTTLPR (serotonin-transporter-linked polymorphic region) gene polymorphism and onset of depression after PM implantation. Recent study has proved that SS genotype might be one of the susceptible genes in postpartum depression (Xu *et al.* 2014). In line with other researches, it has been demonstrated the L allele (long allele) carrier status has been associated with heightened risk of depressive symptoms in postpartum when SLE (stressful life events) were experienced during pregnancy (Munafo 2012). There is an increasing evidence the interaction of 5-HTTLPR with childhood adversities and SLE augment the risk for MDD. Also, the genetic correlation of depression has been confirmed. According to family studies by Gershon and Weissman in the 1990's, the risk in first-degree relatives of patients with depression was 2–3 times than that of the general population (Munafo *et al.* 2006). Again, Levinson suggested depressive heritability reached 40–50% in 2006. Herein, we hypothesize that 5-HTTLPR polymorphisms of L/L gene homozygote might be a protective factor for depression, especially among females. The L allele might also be a protective factor of depressive symptoms (Xu *et al.* 2014).

Moreover, a previous finding also proposed the role of BDNF gene in the development of PPD symptoms, potentially being mediated by season of delivery. The researchers of this study indicated no gene–gene interactions, however, a cumulative effect was detected with carriers of greater number of 5-HTTLPR S and BDNF Val66 Met Met alleles having higher EPDS scores when delivered during autumn/winter (Comasco *et al.* 2011). Moreover, there has been strong evidence of some women being genetically more reactive to the environment, subsequently resulting in a crossover of risks of PPD for most reactive groups. The biological susceptibility model posits that some individuals have greater genetic reactivity to stress, leading to worse outcomes in poor environments, but better outcomes in rich environments (Mitchell *et al.* 2011). Also, Jose Luis Ivorra demonstrated that 5-HTTLPR polymorphism moderates the influence of a mother's anxiety on infant irritability. Their results evidenced a linear relationship in the irritability scores of infants with the 5-HTTLPRs allele with that of their mothers' anxiety of caregiving at 8 and 32 weeks, whereas the irritability of infants carrying the HTTLPR ll genotype was independent of their mothers' anxiety (Sanjuan *et al.* 2008). The authors subsequently speculated that both mothers' confidence or anxiety about rearing and several infant polymorphisms are possible risk factors in screening of abnormal emotional development (Ivorra *et al.* 2010). Again, G×E interactions have been suggested to become particularly noticeable from longitudinal study designs in specific physiological or social challenging periods (Doornbos *et al.* 2009).

## CONCLUSION

There still need to be more investigative studies conducted on PPD pertaining to its unknown causes and complications. This report presented a systematic review on research advancements and risk factors of PPD, coupled with analysis on the important role played by 5-HTT and 5-HTTLPR. We surmise that gene-environment interaction contributes to PPD pathogenesis as well as interactions with endocrine and inflammatory responses. Additionally, we have evinced the L allele in 5-HTTLPR to be associated with lower risk for PPD. This review, thus, provides a theoretical foundation for the clinical diagnosis and treatment of PPD.

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***Conflict of interest***

*The authors declare no conflict of interest*

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