THE RELATIONSHIP OF VITAMIN B6 (PYRIDOXIN) AND POSTPARTUM DEPRESSION: A SCOPING REVIEW

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ABSTRACT

Introduction: Postpartum depression (PPD) is one of the mental disorders that has a negative impact on a mother's feelings after birth and causes them to lose interest in living their daily lives, primarily due to the chemical imbalance in the brain. Vitamin B6, or known as pyridoxine, is believed to be one of the chemicals in the brain which is involved in emotional regulation. However, the mechanism of action is unknown. Thus, the aim of this study is to review the influence of vitamin B6 and its relationship with the onset of PPD. **Methods:** Keywords "vitamin B6" and "vitamin B" and "pyridoxine" and "nutrition" and "PPD" and "perinatal depression" were employed in PubMed, SpringerLink, BioMed Central Journal and ScienceDirect. The screened articles were chosen based on their suitability for the topic of interest and published in English between 2000 and2023. The articles were chosen in accordance with PRISMA, and their eligibility was determined using inclusion and exclusion criteria. **Results:** A total of 3404 articles had been obtained initially and the resulting five articles met the criteria. It was revealed that the relationship between deficiency of vitamin B6 and PPD is still ambiguous. Two articles suggested the intake of vitamin B6 to an adequate level can be helpful to reduce the risk of PPD. In contrast, there are three studies that proposed that low vitamin B6 levels are not associated with PPD, hence increasing its intake during this period is found to be irrelevant. **Conclusion:** In conclusion, this review indicates that further investigation is warranted to determine the exact effect of vitamin B6 and its mechanism of action in emotional regulation. It is hoped that this benefits the mothers in prevention and treatment of PPD, thus improving the quality of their life.

KEYWORDS: postpartum depression, pyridoxin, vitamin B6

INTRODUCTION

Postpartum depression (PPD) is characterised by newly given birth mothers who experienced mood swings and other depressive symptoms. It is the period after birth when the mothers are in their most vulnerable state, especially during the first month after childbirth (Cernadas, 2020). The PPD symptoms are observed around a month after birth and could be prolong due to factors such as financial difficulties or low level of awareness regarding health and safety after pregnancy and birth (Cernadas, 2020). Women with a history of depressive and anxiety disorders, as well as those who experienced premenstrual syndrome (PMS) are most likely to develop this type of depression after childbirth. In addition, women who have obstetric risk factors such as emergency caesarean section, lack of social

support and experience of domestic violence, as well as mothers with unhealthy lifestyles, including lack of exercise, are also prone to develop PPD (Hanna, 2022). Although the exact cause of PPD remains undefined, multiple factors such as genetics, hormones, psychology, as well as social life have been observed to contribute to its development (Mughal et al. 2022).

It is well known that the pathophysiology of PPD is attributed to the dysregulation of reproductive hormones, such as oestradiol and progesterone. Apart from that, changes in the specific components of the endocrine system, such as the hypothalamic-pituitary-adrenal axis (HPA) have also been suggested in the onset of PPD. These changes lead to the under-secretion of catecholamines, resulting in an inadequate stress response Moreover, the central nervous system also plays a significant role in the onset of depression. Depression can occur when there is a disturbance in certain parts of the brain responsible for regulating stress and emotions (Mughal et al., 2022). According to Kris-Etherton et al. (2021), it was reported that inadequate nutrition can cause mood disorders due to a lack of nutrients that play crucial roles in the neuroendocrine system. For example, important nutrients including tryptophan, vitamin B6, vitamin B12 and folic acid are necessary to produce neurotransmitters such as serotonin and dopamine, which are mainly involved in mood regulation (Kris-Etherton et al., 2021). Crucial micronutrients such as vitamin D, fatty acid, and vitamin B during pregnancy and after birth period have a significant role in the onset of PPD. These micronutrients deficiencies have been observed to affect the psychoneuroimmunology of the mothers, which may cause them to develop PPD during this vital and fragile period (Ellsworth-Bowers and Cowin, 2012).

One of the crucial vitamins that could affect the balance of neurotransmitters in the nervous system is vitamin B6 (Berkins, 2021). Vitamin B6 is "the generic name for six compounds with vitamin B6 activity: pyridoxine, pyridoxal, pyridoxamine and their respective 5′-phosphate esters, pyridoxal 5′ phosphate (PLP)and pyridoxamine 5′ phosphate (PMP) which are the active coenzyme forms of vitamin B6". Similar to other vitamins in the B vitamin family, vitamin B6 acts as a coenzyme in a variety of physiological processes, and most of them are protein metabolisms. Therefore, the vitamin B6 deficiency has a significant physiological effect such as the onset of depression and anxiety in general. Meanwhile, in a study by Berkins et al. (2021) about the association between vitamin B6, B12 and folate deficiency and depression among vegetarians, they observed that there are positive associations between these nutrients' deficiency and the mood disorder, which proves that under-intake of vitamin B6 lead to depression. To date, the relationship of vitamin B6 with specific depression like PPD is unknown. Therefore, this review aimed to explore the relationship between vitamin B6 and PPD. The findings are hoped to be a motivation towards more clinical and non-clinical investigation as a strategy to prevent or lower the risk of PPD.

METHODOLOGY

Identification of Relevant Studies

This study aimed to gather a comprehensive selection of pertinent articles from various databases, including PubMed, SpringerLink, BioMed Central Journal and ScienceDirect. The study employed keyword searches; vitamin B, vitaminB6, pyridoxine, nutrition, postpartum, depression, PPD, perinatal depression. Search results were enhanced by combining terms with the Boolean operators AND, OR, and NOT. Furthermore, this scoping review was conducted according to the Joanna Briggs Institute (JBI) methodology for scoping reviews (Peters et al., 2020). The JBI methodology of scoping review is a method of evidence synthesis, and this methodology follows the established methodological guidance, Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) guidelines (Munn et al., 2022).

The selection of papers that were involved in this study followed the inclusion and exclusion criteria. The articles that were qualified to be included in this review were the papers that mainly or in an aspect of mentioning the relationship between vitamin B6 and PPD. The articles that were chosen were limited to only being published from 2000 until 2023 and should be written in English only. Apart from that,

the papers had to be full paper publication and publication types such as index and non-index journals were also included. Meanwhile, the articles which did not pertain to the topic of vitamin B6 and PPD, published before the year 2000, articles that could not be accessed in full-text and articles that were not written in English were excluded from this review.

Selection of Relevant Studies

The screening of the articles was divided into two phases. The first stage was by searching the keywords on the databases and screening based on the titles and abstracts of the articles to filter out any ineligible papers to be included in this study. Next, any duplicates found from the articles were removed. The second stage was by evaluating the articles in full-text form to verify that the articles fulfil the inclusion criteria to participate in this scoping review and must be excluded if they meet any of the exclusion criteria. The final articles that were selected were further included in the study and have undergone data extraction.

Data Selection

After the articles were approved to be included in this study, the data related to the effect of vitamin B6 imbalance which led to PPD to occur as well as data regarding the use of vitamin B6 to reduce the risk of PPD were extracted. The data was either numerical, such as level of vitamin B6 in plasma among postpartum mothers, or in words taken from the articles. The data extraction, or charting of the data, was done in a charting table to record the key information of the source including the author, reference and findings of the research objectives and questions. The key information that was recorded in the charting table include authors, title, year of publications, the origin of the study, study designs, results, and key findings related to this scoping review.

RESULTS AND DISCUSSIONS

A comprehensive search resulted in the identification of 3404 articles that were deemed relevant to the study. The number of articles remaining after the screening for duplicates was 2297, and a total of 60 articles remained after the screening based on the titles. After the abstract screening, a total of 15 articles remained. These articles were then assessed based on their full text to determine which articles would be included in the result. A few articles were removed due to not fulfilling the inclusion criteria and as a result, five articles met the established criteria for inclusion in the analysis. Figure 1 illustrates the procedures involved in selecting relevant articles based on PRISMA-ScR 2009 Flow Diagram.

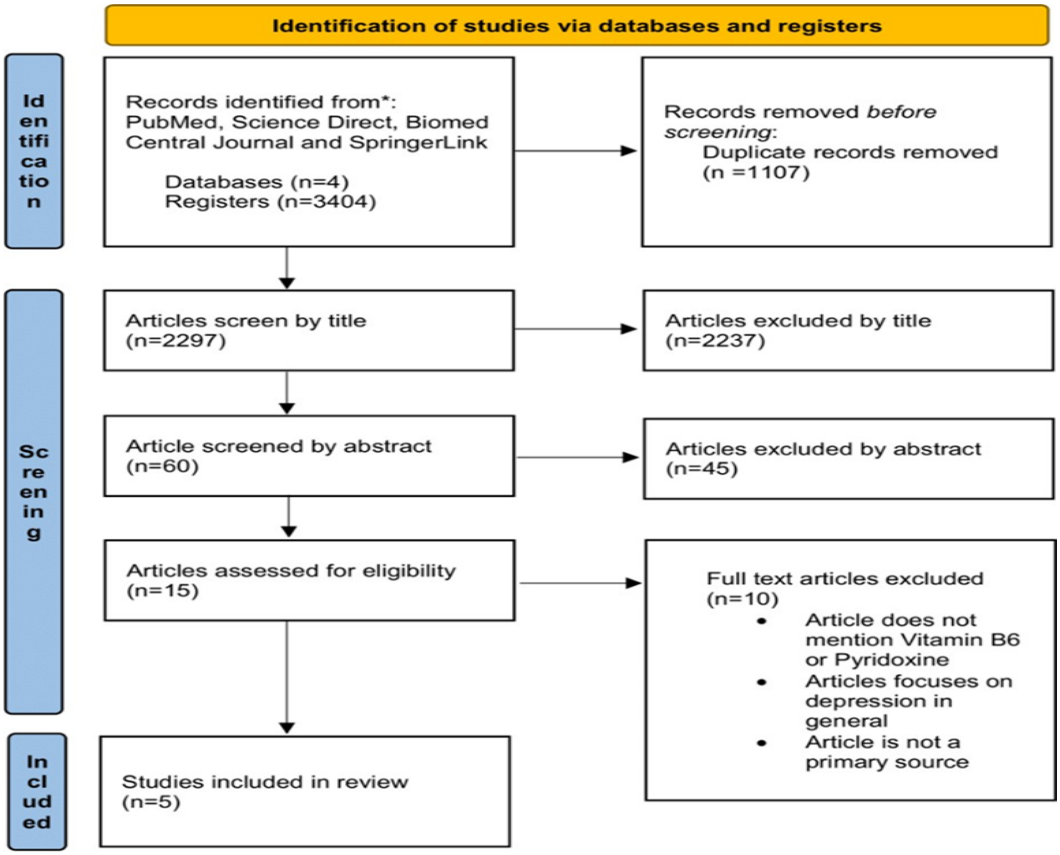

Figure 1 Selection of Articles based on PRISMA-ScR 2009 Flow Diagram

The Relationship of Vitamin B6 and PPD

According to Table 1, two out of five articles concluded that vitamin B6 has a significant influence on the onset of PPD (p<0.001), while the remaining three articles found no prominent association between vitamin B6 and PPD (p>0.05). All five articles emphasize the importance of nutrition among postpartum mothers regarding depression, considering the fragile period faced by the mothers during this time. The findings from the two articles regarding vitamin B6 and PPD are characterised by the decreased intake or level of this micronutrient among postpartum women, which led to the occurrence of PPD (Khodadad et al., 2021, Qiu et al., 2020). In addition, Qiu et al. specifically mentioned that fluoxetine (FLX) treatment could significantly disrupt the metabolism of vitamin B6, eventually inducing postnatal depression.

Meanwhile, it can be observed in another three articles where the inadequate intake of this vitamin does not contribute to the factor of postnatal depression. One of the studies concluded that the intake of pyridoxine pre-pregnancy and during pregnancy did not affect the occurrence of perinatal depression, while another study showed that subjects who consume vitamin B6 lower than the recommended range did not have a significant relationship with PPD. Additionally, one of the studies mentioned that there is no inverse relationship discovered between the intake of pyridoxine with the risk of PPD. To conclude, two of the articles, which consist of one randomised controlled trial and one preclinical experiment agreed that there is a significant relationship between vitamin B6 and PPD, meanwhile the other three articles which were all cohort studies disagreed with the relationship between vitamin B6 and PPD.

Table 1 Details of Selected Articles

Author/ Year	Title	Country	Study Design /sample size	Relationship with PPD
Miyake et al. 2006	Dietary folate and vitamins B12, B6, and B2 intake and the risk of Postpartum depression in Japan: the Osaka Maternal and Child health Study	Japan	Prospective Cohort Study (n= 865)	An inverse relationship between the intake of folate, cobalamin, or pyridoxine and the risk of PPD was not observed.
Khodadad et al., 2021	Can Vitamin B6 Help to Prevent PPD? A Randomised Controlled Trial	Iran	Randomised Control Trial; case group (=41), control group (n=40)	Vitamin B6 has a positive effect on reducing PPD scores among mothers at risk for PPD.
Blunden et al.,2012	Postpartum depressive symptoms: The B-vitamin link	United Kingdom	Cohort Study (n=2856)	Vitamin B6 intake before and during pregnancy is not associated with postpartum depressive symptoms.
Qiu et al., 2020	Postpartum fluoxetine increased maternal inflammatory signalling and decreased tryptophan metabolism: Clues for efficacy	Canada	In vivo Preclinical experiment, (n=47)	The changes in vitamin B6 metabolites because of fluoxetine treatment may be a representation of disrupted vitamin B6 metabolism.
Leung et al., 2013	Prenatal micronutrient supplementation and postpartum depressive symptoms in a pregnancy cohort	Canada	Cohort Study (n=475)	Vitamin B6 showed a nonsignificant trend with PPD although the subjects in this study consumed this vitamin lower than the recommended intake.

The Effect of Imbalance of Vitamin B6 In Mothers During Postpartum Period

The level of vitamin B6 is observed to be closely associated with PPD. The occurrence of PPD in relation to vitamin B6 is attributed to its inadequate level among postpartum women during this period, as has been proven in the article by Qiu et al. (2020). As has been proposed by several previous studies regarding the association of vitamin B6 with depression and anxiety, it can be confirmed that a similar mechanism is implied to PPD. Vitamin B6 plays a significant role in the production and biosynthesis of important neurotransmitters including serotonin and dopamine. Therefore, the insufficient levels of this vitamin among postpartum women are indeed an associated factor with PPD. According to Qiu et al. (2020), the fluoxetine treatment significantly decreases the plasma concentration of tryptophan as well as the components of pyridoxine, which proves that the metabolism of vitamin B6 is disrupted in the study. This is due to the role of pyridoxine as the important coenzyme for tryptophan metabolism. Hence, decreased levels of vitamin B6 plays a part in causing PPD to occur.

The Use of Vitamin B6 to Prevent the Onset of PPD

Based on the results obtained in a study by Khodadad et al. (2021), it is proved that vitamin B6 possesses an ability to reduce the chance of PPD onset among postpartum women. In the study, the Edinburgh postnatal depression scale (EPDS) was used to assess depression rates prior to and 1.5 months after the last intervention (day of pregnancy) as the primary outcome measure. From the statistical analysis provided by Khodadad et al. (2021), the mean post-intervention depression score of the case group is 4.2, which is significantly lower than the control group who has the mean of 10.4 ($p < 0.01$). This shows that vitamin B6 can be used to reduce the risk of PPD among the mothers. According to a study by Hanna et al. (2022), vitamin B6 has been observed as one of the supplements that is helpful in treating patients with depression, behavioural issues as well as migraine headaches. This is due to vitamin B6 being prominently involved in the production of neurotransmitters. Thus, it is suggested that vitamin B6 as one of the potential treatments for PPD. Due to the decreased level of vitamin B6 during pregnancy as well as during the postpartum period, increasing the intake of vitamin B6 is helpful to decrease the risk of PPD (Khodadad et al., 2021), especially in a population where nutritional deficiencies are prominent. Despite that, findings from a few papers involved in this study conflicted with this opinion.

According to Hvas et al. (2004), low levels of vitamin B6 may be associated with the onset of depression due to it being a coenzyme, particularly in the pathway of tryptophan-serotonin. Apart from that, low intake of vitamin B6 also has been found recently to be related to depression and anxiety in a study by Kafeshani et al. (2019). Hence, the effect of decreased levels of vitamin B6 in inducing depression in general has been known. Regarding PPD, which is also considered one of the types under the umbrella term of depression, its association with vitamin B6 also has been understudied due to there being less papers being published on this topic.

One of the papers included in this review, by Khodadad et al. (2021) specifically studied the ability of vitamin B6 in preventing the onset of PPD among postpartum mothers in a randomised control trial study. It was found that the group that was given vitamin B6 had a reduced depression score post-intervention while there was no significant difference in the placebo group post-intervention. In the same study, the level of pyridoxal 5'-phosphate, which is the active form of pyridoxine was specifically mentioned to be lowered during the second and third trimesters of the pregnancy and returned to its normal level when it reached the first month of the postpartum period. This may prove how the reduced level of plasma vitamin B6 may induce postnatal depression, as well as proving that vitamin B6 had the capacity to lower the risk of postnatal depression among women. According to the authors, this study was perhaps considered as the first study to investigate the effect of vitamin B6 on PPD prevention due to there being no other studies available at the time studying this topic. Meanwhile, the main limitations of this study were the confounding factors such as uncontrolled dietary vitamin B6 intake and physical activity.

Additionally, one of the studies included in this review done by Qiu et al. (2020) titled 'Postpartum fluoxetine increased maternal inflammatory signalling and decreased tryptophan metabolism: Clues for efficacy', supported the significant relationship of pyridoxine with PPD by studying the relationship of postpartum fluoxetine, maternal inflammatory signalling and tryptophan metabolism. Findings showed that the vitamin B6 influences the efficacy of FLX treatment during the postpartum period. The FLX treatment was found to decrease the plasma levels of tryptophan as well as the levels of pyridoxine components in the subjects. Due to the role of vitamin B6 as an essential coenzyme in the metabolism of tryptophan, therefore the metabolism of vitamin B6 was also disrupted by FLX. In addition, it was found that the disturbance of vitamin B6 metabolism due to the FLX treatment may cause the inefficiency of this treatment in treating depressive symptoms during postpartum, which also proves that the lower levels of vitamin B6 may induce depression in the postpartum period. This study was able to prove their hypothesis right, as well as identify two possible mechanisms that affected the treatment of PPD by FLX, one of them being the disruption of metabolism of tryptophan and vitamin B6. This study also suggested for further research on vitamin B6 as a biomarker for PPD in the future.

As mentioned in a study by Kris-Etherton et al. (2021) on nutrition and behavioral health disorders, vitamin B6 is involved in a lot of physiological processes in the human body, one of it is the production and synthesis of neurotransmitters. Therefore, the deficiency of vitamin B6 has been closely associated with the onset of mood disorders including depression. A severe deficiency of vitamin B6 can cause a few other conditions and some of it being mood disorders and cognitive decline. Additionally, they also mentioned that adequate levels of vitamin B6 can reduce the level of plasma homocysteine, which reduces the risk of depression. This fact is supported by Bremner et al. (2021), which showed that high concentration of plasma homocysteine may indicate insufficient methyl transfer reaction which causes inadequate synthesis of neurotransmitters, and eventually lead to depression.

Interestingly, findings from three articles showed that there was no significant relationship between vitamin B6 and PPD. Miyake et al. (2006) concluded pyridoxine (B6) along with folate (B9) and cobalamin (B12) intake was not related to the risk of PPD as observed in the subjects. From the questionnaire, 21 out of 865 participants were found to develop PPD. However, there was no significant relationship between vitamin B6 and PPD. These studies had a few methodological strengths including low possibility of recall bias or bias due to the relatively high rate of follow up, which was 86.3% and the participants came from the same residential background. However, this methodology could not control other confounding factors such as family psychiatric history and participants' lifestyle. Apart from that, the self-perception without clinical diagnosis from professional was one of the main weaknesses of this study.

Other findings were determined by Blunden et al. (2012) which supported the contradiction with the positive effect of vitamin B6 on PPD. The cohort study on PPD symptoms with vitamin B came up with a summary of there was no association between the intake of vitamin B6 during and after pregnancy with the symptoms of PPD. From this study, it was found that the dietary intake of vitamin B6 before, early and after pregnancy has no significant relationship with PPD. The results obtained from this study can be supported with a few strengths including using the largest sample size to date to study the relationship between nutritional status with postpartum depressive symptoms. Another cohort study by Leung et al. (2013) on prenatal micronutrient supplementation and postpartum depressive symptoms concluded a similar outcome. Among the 475 participants who managed to complete the EPDS questionnaire, 59 of them were found to have PPD. It was found that vitamin B6 was one of the vitamins that were consumed by the participants 90% above the recommended dietary allowance (RDA). It was also found that participants with low EPDS score consumed more vitamin B6 than participants with high EPDS score. However, vitamin B6 intake has no significant relationship with PPD. Further actions to support their initial findings were executed including the establishment of temporal relationship between supplement intake with postpartum depressive symptoms, as well as the repeated collection of supplement intake to ensure the valid average intake of the nutrients of the participants in this study.

CONCLUSION

In a positive note, vitamin B6 has shown to induce a therapeutic effect on reducing and preventing the risk of PPD during pregnancy and postnatal period in two selected studies. In contrast, three cohort studies disagreed with the positive relationship between pyridoxine and the onset of PPD. Thus, the relationship between vitamin B6 and PPD is still ambiguous because of the contradictory between the two opinions. Therefore, more studies focusing on the population of mothers who are prominently facing deficiencies of nutrient access, for example, in geographical regions which has high poverty rate or on mothers who are struggling with eating disorders, can be explored. Other important but under-studied micronutrients can be considered since it may also become one of the contributing factors to PPD. Importantly, understanding the mechanism of action of vitamin B6 or other nutrients and PPD may lead to prevention of this disease and improve the quality of life among mothers.

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