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# Efficacy of Vitamin B6 on Pregnancy Outcomes: A Randomized Clinical Trial

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Author MK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors GK and PB managed the analyses of the study and updated data. Author PB managed the literature searches. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** Postpartum depression is a common and disabling disorder. A low level of vitamin B6 might theoretically causes symptoms of depression. The aim of this study was to investigate the effect of vitamin B6 on Pregnancy outcomes among the mothers at risk for postpartum depression during third trimester.
**Methods:** A single blind randomized clinical trial was conducted via using B6 and placebo on 86 at risk postpartum depression pregnant subjects at six selected health center in Isfahan, Iran with a simple random sampling method (Feb-July, 2016). The main inclusion criteria in this study was at least a risk factor of postpartum depression; evaluated by Hospital Anxiety-Depressive Scale, Social Support Appraisals Scale, Holmes and Rahe Life Change and Stress Evaluation Questioner. Data was analyzed applying SPSS20 and statistical tests (chi-square, t-test, Mann-Whitney, Fisher's exact test).

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**Results:** In case group after intervention mean depression score was (4.2±2.7) significantly lower than before intervention (10.4±1.4) (p<0/001) Control group mean depression score was no significant difference after (10.4±3.4) and before intervention (9.3±4.2) (p= 0.10).
Mean maternal weight gain (P=0.32), delivery type (P=0.56), infant birth weight (P=0.37), gestational age (P=0.31) were not significant difference between two groups.
**Conclusion:** Vitamin B6 may have a positive effect to decreasing of postpartum depression score, and no effects on another pregnancy outcome.

*Keywords: Postpartum depression; vitamin B6; pregnancy outcomes.*

## 1. INTRODUCTION

Postpartum depression is a common and disabling mental social disorder [1]. It may begin at most during the first four weeks after birth. Some studies that have reported up to 12 months after childbirth [2]. The prevalence of postpartum depression in the first few weeks after delivery is 13 to 20 percent [3]. The prevalence of postpartum depression was reported 22 percent in Iran [4]. Prenatal depression is also very important due to a negative impact on the mother, fetus, and newborn [5]. Prenatal depression is effective inability to self-care including nutrition, sleep, and attention to medical advice; moreover, about 50 percent of women depressed during pregnancy will experience postpartum depression [6]. Signs and symptoms of depression may be as mood changes, sleep and appetite disorders, psychosomatic disorders, fatigue, poor concentration, feeling of guilt and lack of enjoyment of work [7].

In this situation, the mother is not able to act as another and a wife and it may lead to suicide or infanticide in severe untreated cases [8]. Due to the lack of understanding of the grief and depression after childbirth, about 80 percent of women who are diagnosed with this type do not report the case to their doctor [9]. Important risk factors for postpartum depression are previous history of psychiatric disorders, poor marital relationships, unwanted pregnancy, anxiety and depression during pregnancy, lack of social support, and stressful life events [10].

Mothers experienced adverse pregnancy outcomes are more liable to emotional stress during future pregnancies [11]. Weight and age at the birth are two important factors in the perinatal mortality and disturbances that may bring risk of disability and reduce quality of life; hence, considering predisposing factors as well as its prevention is very important [12].

There is a hypothesis about the association between serum concentration of vitamin B6 and depressive symptoms [13]. It is supposed that vitamin B6 has a medical assistance role in different states of neurotransmitter disorders [13]. Production of serotonin and catecholamine depends on the presence of pyridoxal phosphate derivative PLP [13]. Vitamin B6 has a cofactor role in the metabolism of essential enzymes, amino acids, carbohydrates, and fats [14]. Vitamin B6 and depression symptoms are related through role of vitamin B6 as a cofactor in monoamine transmitter and a facilitator of tryptophan and serotonin pathway [15].

Shibata et al. noted in a study that the concentration of pyridoxal-5- phosphate decreases significantly in the second and third trimester of pregnancy compared to the first trimester values [16]. The concentration values back to the first trimester of pregnancy a month after delivery. In addition, results of the study by Shrim et al. showed that taking vitamin B6 in the first trimester of pregnancy has no adverse effects on the mother and baby, even at high doses [17]. The role of vitamin B6 supplement has been approved as a treatment for mood disorders before menstruation [18]. Vitamin B6 dose intake in this study show equivalence to nausea and vomiting treatments during the first trimester. Intake doses prescribed for nausea and vomiting treatments were 25 mg three times a day [19]. Mother's psychological change increases in the third trimester of pregnancy for the approaching childbirth and the postpartum period [20]. Hence, the time of intervention has been selected in the third trimester of pregnancy [16,20]. With respect to the prevalence of postpartum depression and its consequences, this study examines the impact of vitamin B6 on pregnancy outcomes of mothers at risk for postpartum depression in the third trimester of pregnancy.

## 2. METHODS

The present study is a single blind randomized clinical trial, approved by Isfahan University of

medical sciences ethics committee, registered at IRCT with a unique code.

Subjects studied were 28 weeks pregnant referred to six randomized selected health centers of Isfahan (Iran) for prenatal care from February until July 2016. These randomized selected health centers were ethnically, culturally, socioeconomically, and number of clients pregnant women homogeneous. Research subjects have participated in the study thorough knowledge of objectives of the research and voluntary consent. In each research process, they have been free to leave the study. Inclusion criteria were: having at least a risk factor for postpartum depression; previous history of psychiatric disorders, poor marital relationships, unwanted pregnancy, anxiety and depression during pregnancy, lack of social support, and stressful life events; pregnant mother's physical health, sever major depressive disorder (MDD) absence, and no obstetric complications in the current pregnancy. Exclusion criteria consist of prenatal depression in third trimester and unwillingness to continue the study at any time. The main eligibility was being a mother at risk for postpartum depression at 3th trimester. Participants were healthy pregnant mother without any systemic diseases or obstetric complications in the current pregnancy, and lack of major depressive disorder (MDD). In this study, sample size for each group was determined according to the sample size obtained from the formula comparing the two communities. This sample size included 20 percent loss in the 39 sample per group [21]. Ninety-five percent confidence interval and power of test 80 percent is estimated. Simple random sampling, qualifying inclusion in the study are placed in two groups, 43 subjects of the Case group and 43 subjects of the Control group. In this study, the participants did not know their own groups. Babanazari and kafi stated, the length of the questionnaire designed may affect the results of research due to the pregnant mother physiological condition [22]. In this study, we used the shortest forms that hold suitable validity and reliability during pregnancy period. The research tools include:

Research questionnaires contain information about demographic characteristics, taking a complete psychiatric, medical and midwifery history, a complete physical exam and checking routine tests including CBC, TSH, BUN, Cr, UA, UC, Hb and FBS. Subjects were interviewed to assess risk factors for PPD by using Hospital Anxiety-Depression Scale (HADS), Social Support Appraisals Scale (SS-A), Holmes-Rahe Life Change and Stress Evaluation Questioner (HRLCSEQ). Previous history of psychiatric disorders, poor marital relationships, and unwanted pregnancy were assessed by Yes or No questionnaire.

The outcomes of interest were depressive symptoms, maternal weight gain in the last trimester of pregnancy, infant birth weight, delivery type, infant sex, gestational age using the health records of maternal care after childbirth. Edinburgh Postpartum Depression Scale (EPDS) used to evaluate the rate of depression before and after the intervention. Unexpected adverse fetal and neonatal outcomes (e.g., stillbirth, preterm labor, death of infant, congenital anomalies) affect PPD. Unexpected outcomes may be confounding variable. Participants with unexpected outcomes were excluded.

The Hospital Anxiety and Depression Scale (HADS) is a self-administered scale consisting of 14 items split across anxiety and depression subscales, each with a four-point ordinal response format. To reduce the risk of a false positive bias, the scale does not assess symptoms of anxiety and depression related to physical disorder, such as fatigue and insomnia [23]. HADS assesses current anxiety and depression during pregnancy that has 14 items and two sub-tests of anxiety and depression. Each item is graded in Likert four item scale (0-3). In a psychometric study internal consistency of the test was calculated using Cronbach's alpha for sub-test of anxiety (0.78) and subtest of depression (0.86) [24]. Cut-off point in Iran has been regarded less than 11 [24]. Social Support Appraisals Scale (SS-A) including 23 questions and five responses for each question with respect to Likerts five-item scale were scored (0-1) [25]. The correlation of sub-tests to total test has been used for calculating the validity of the questionnaire; in this regard, the coefficients of 0.76, 0.55, and 0.74 was obtained for correlation of overall social support to sub-tests of friends, family, and acquaintances that all are significant at the level of 0.0001. Cut-off point has been regarded less than 11 [26]. In addition, Holmes and Rahe Life Change and Stress Evaluation Questionnaire (HRLCSEQ) has been used. It has 41 items. The minimum value scored for an item is 11 and the maximum value is 100. A person may have more than one item; individuals with scores above 150 when entered the research. In

the client obtaining the score 300 or higher will be referred to a psychiatrist due to critical situation. The reliability of the instruments is calculated using Cronbach's alpha and classification method; the results are 0.72 and 0.64, respectively. It indicates acceptable reliability of the questionnaire [27]. We obtained data that were routinely collected during the physical examination, laboratory data, information about medical and midwifery history in health records of maternal care. Edinburgh Depression Scale has been applied to measure depression scores before and after intervention in research Subjects [28]. Edinburgh Depression Scale (1970) is a standard and applicable tool in the pregnancy and after the delivery. In this research, maximum sensitivity is 78 percent and its specificity is 75 percent. A cutoff score of 13 is regarded for depression in Iran [28].

Each case group consisted of forty-three subjects; each subject received two 40 mg B6 pills daily from 28th week of pregnancy to the end of pregnancy. After the childbirth, they received one 40 mg B6 pill daily for a month. Likewise, forty-three subjects in the control group received two placebos daily from 28 weeks of gestation to the end of pregnancy. After childbirth, they received one placebo daily for a month. Placebo is starch tablets simulated to vitamin B6. The subjects were reminded to consume pills every two weeks by phone. Postpartum Depression Inventory was filled by subjects 6 weeks after the childbirth.

Data analysis has been performed using SPSS software version 20; accurate examinations have been conducted using independent t-test, paired t-test, chi-square, Mann-Whitney, and Fisher's exact test.

## 3. FINDINGS

Ten women were excluded and referred to psychiatrist because of probable major depression. Eighty-six pregnant mothers whom were diagnosed at risk of PPD participated in this study from February until July 2016. Two subjects of case group and one subjects of control group were excluded with their own demands. A subject in the case group with preterm labor and another from the control group, due to the infant death were excluded. The final analysis comprised 81 subjects (flow diagram).

Research findings, especially independent t-test, showed that there was no significant difference between demographic characteristics and obstetrical history including age (P=0.23), age of spouse (P=0.93), body mass index (P=0.80), parity (P =0.81) and number of children (P=0.12) in the two groups. Chi-square test showed that the income status has no significant difference between the two groups (P=0.49) (Table 1).

The findings related to the distribution of risk factors for postpartum depression including Chi-square test showed that the two groups have no significant difference in terms of poor marital relationships (P=0.39) and unwanted pregnancy (P=0.80). Moreover, Fisher's exact test represented that the two groups have no significant difference in terms of previous history of mental disorders (P=0.20). Therefore, the groups are homogeneous (Table 2).

**Table 1. Comparison demographic variables between the case and control groups**

| Variable | | Case group | | Control group | | P- value | Test |
|---|---|---|---|---|---|---|---|
| | | Mean | Standard deviation | Mean | Standard deviation | | |
| Age | | 28.2 | 4.6 | 29.6 | 5.8 | 0.23 | Independent t-test |
| Husband's age | | 33.2 | 5.2 | 33.3 | 5.2 | 0.93 | |
| BMI | | 25.1 | 3.04 | 24.9 | 2.7 | 0.80 | |
| Pregnancy number | | 2 | 1.1 | 1.9 | 0,8 | 0.81 | |
| Child number | | 1.5 | 0.9 | 1.2 | 0.4 | 0.12 | |
| **Variable** | | **Number** | % | **Number** | **%** | **P- value** | |
| Education | Below high school | 9 | 24.3 | 15 | 36.5 | 0.36 | Mann-Whitney test |
| | High school | 19 | 51.4 | 17 | 41.5 | | |
| | University | 9 | 24.3 | 9 | 22 | | |
| Job | Housewife | 32 | 82.1 | 36 | 92.3 | 0.18 | Chi-square test |
| | Working | 7 | 17.9 | 3 | 7.7 | | |
| Income | Acceptable | 31 | 83.8 | 31 | 77.5 | 0.49 | |
| | Unacceptable | 6 | 16.2 | 9 | 22.5 | | |

Paired t-test indicated that mean score of depression of mothers in the Case group has significantly been lower after intervention (P<0.001). In the control group, no significant difference has been observed between the two periods (before and after intervention (P<0.10) (Table 3). Table 4 illustrates results of two cases of pregnancy outcomes for mothers and babys. It implies lack of a significant statistical difference of mean birth weight (P=0.37) with gestational age (P=0.31) and delivery type (P=0.56) in the Case group and control group. However, the mean birth weight, gestational age, and percentage of normal childbirth in case group are to some extent higher than control group. Besides, results showed no significant difference in mean maternal weight gain between the two groups of pregnant women in the third trimester (P=0.32).

**Table 2. Comparison postpartum depression risk factors between experimental and control groups**

| Variable | Case group | | Control group | | P- value | Test |
|---|---|---|---|---|---|---|
| | Number | % | Number | % | | |
| Previous history of psychiatric disorders | 5 | 12.5 | 2 | 4.9 | 0.20 | Fischer exact test |
| poor marital relationships | 11 | 28.2 | 8 | 20 | 0.39 | Chi-square test |
| Unwanted Pregnancy | 12 | 30 | 11 | 27.5 | 0.80 | |
| | **Mean** | **Standard deviation** | **Mean** | **Standard deviation** | **P- value** | **T-test** |
| Anxiety | 7.6 | 3.2 | 8.3 | 3 | 0.35 | |
| Social Support | 17 | 3 | 16.4 | 3.8 | 0.43 | |
| Stress | 162.1 | 60.8 | 162.3 | 80.8 | 0.99 | |
| Depression | 5.1 | 2.8 | 5.9 | 2.9 | 0.23 | |

**Table 3. Comparison the mothers' depression score before and after intervention with each the group**

| Depression score | Paired t-test | | After intervention | | Before intervention | |
|---|---|---|---|---|---|---|
| Group | P | T | Standard deviation | Mean | Standard deviation | Mean |
| Case group | <0.001 | 12.71 | 2.7 | 4.2 | 1.4 | 10.1 |
| Control group | 0.1 | 1.69 | 3.4 | 10.4 | 4.2 | 9.3 |

*Case group (P-value <0.05)*
*Control group (P-value >0.05)*

**Table 4. Comparison the pregnancy outcome after intervention between the two groups**

| | Control group | | Case group | | Chi-square test | |
|---|---|---|---|---|---|---|
| | % | Number | % | Number | $\chi^2$ | p |
| C/S | 46.3 | 19 | 40 | 16 | 0.33 | **0.56** |
| NVD | 53.7 | 22 | 60 | 24 | | |
| Infants sex | % | Number | % | Number | $\chi^2$ | p |
| Boy | 56.1 | 23 | 47.5 | 19 | 0.80 | **0.37** |
| Girl | 43.9 | 18 | 52.5 | 21 | | |
| Total | 100 | 41 | 100 | 40 | | |
| | | | | | Independent t-test | |
| | Standard deviation | Mean | Standard deviation | Mean | t | p |
| Maternal weight gain (Kg) | 1.4 | 3.7 | 1.3 | 4.02 | 0.99 | **0.32** |
| Gestational age (week) | 1.1 | 38.5 | 1.3 | 38.8 | 1.01 | **0.31** |
| Birth weight (Kg) | 354.4 | 3140.3 | 384.5 | 3216.4 | 0.90 | **0.37** |

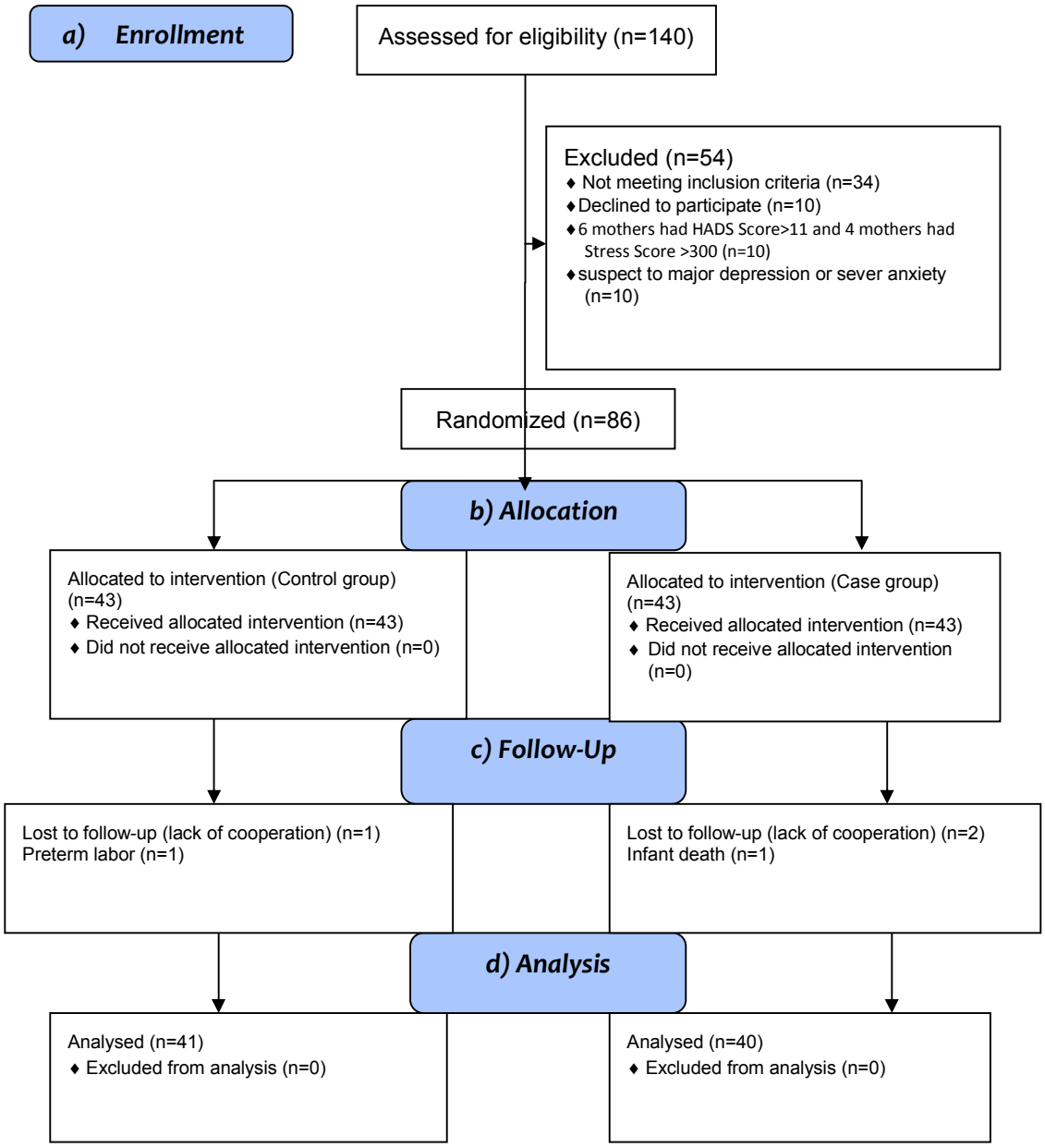


**Figure 1. Consort 2010 flow diagram**

## 4. DISCUSSION

The findings indicated that the mean of depression scores has reduced significantly in the case group after intervention. In this research, vitamin B6 reduced depression scores in mothers at risk for postpartum depression. The research findings in this regard are consistent with the results of studies about the association between serum vitamin B6 concentration and symptoms of depression [13,29]. For example, the results of study conducted by Hvas expressed that there is a relationship between pyridoxal-5 phosphate serum and symptoms of depression [13]. Another research confirmed the impact of vitamin B6 on symptoms of depression in older adults [29]. Nanri et al. stated that there is a relationship between serum pyridoxal concentrations and depressive symptoms among adults [15]. The study by Miakye et al. implies that there is no relationship between mothers' postpartum depression and amounts of vitamin B6 dietary; our finding is inconsistent with the results of their study [30]. In Miakye's study,

history of mental disorders and socio-cultural factors were not controlled; these factors may have disturbed the results of their study. Valentina et al. reported that there is no significant relationship between geriatric depression score and history of heart disease after taking low-dose vitamin B6 [31]. Our finding is also inconsistent with the Valentina's research [31]. Low-dose vitamin B6 and the statistical population factors are effective in the results of Valentina's research. In order to evaluate pregnancy outcomes, this research showed that vitamin B6 has no impact on the outcomes of pregnancy including birth weight, gestational age, and the amount of mothers' maternal weight gain in their third trimester. Miakye et al found no relationship of mean birth weight and with the amount of vitamin B6 intake through diet and mothers' postpartum depression. The results of this research are in line with the findings in this respect [30].

Bae et al. found that there is no significant difference for outcomes of pregnancy, birth weight, gestational age, and maternal weight gain during pregnancy in two groups of mothers with low depression and mothers with high depression [32]. This finding is consistent with the results. In Shrim's study, consumption of high doses of vitamin B6 in the first trimester of pregnancy has no impact on fetal malformations and birth weight. Our results are consistent with this finding in terms of birth weight [16]. According to studies conducted in the available resources, this study is the first interventional study that investigates the impact of vitamin B6 on pregnancy outcomes. Further studies are required to confirm and evaluate the results of present research.

## 5. CONCLUSION

The results indicated that the administration of vitamin B6 at the third trimester of pregnancy may be effected against postpartum depression; but it has no influence on another pregnancy outcomes. These results are preliminary. Further studies especially with more samples for a more complete assessment of pregnancy outcomes are warranted to get more results. However, further confirmtion of these finding is needed.

## 6. LIMITATIONS

Dietary intake of vitamin B6 and plasma pyridoxal 5'-phosphate (PLP) concentrations were not controlled.

## CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

## ETHICAL APPROVAL

This study approved by ethics committee of Isfahan University of Medical Sciences (IR.MUI.REC.1394.3.970) and received approval cod of Iranian Registry of Clinical Trials (IRCT201203229322N1).

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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