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Article

Postpartum depressive symptoms: the B-vitamin link

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ABSTRACT

Objective This study examined longitudinal relationships between maternal red-cell folate status and dietary intakes of vitamins B_6, B_{12} and folate before and during pregnancy and subsequent postpartum depressive symptoms.

Study design and setting Within a cohort study of women aged 20–34 years (the Southampton Women's Survey) dietary data were obtained before pregnancy and at 11 and 34 weeks' gestation. Red-cell folate was measured before pregnancy and at 11 weeks' gestation. We derived relative risks of postpartum depressive symptoms using an Edinburgh Postnatal Depression Scale (EPDS) score of $\geq$ 13 administered from 6 months to 1 year postpartum.

Results No significant differences were found between those with postpartum depressive symptoms (n = 905) and those without (n = 1951) in relation to red-cell folate concentration or dietary intake of folate, vitamin B_{12} and vitamin B_6, before or during pregnancy. A prior history of mental illness (relative risk (RR) 1.83; 95% confidence interval (CI) 1.53–2.19) was associated with postpartum depressive symptoms, and women who breastfed until 6 months were less likely to experience postpartum depressive symptoms (RR 0.68; 95% CI 0.55–0.84).

Conclusion This study suggests that folate status and dietary folate, B_6 and B_{12} intakes before and during pregnancy are not associated with postpartum depressive symptoms. A history of mental illness, however, was a strong risk factor.

Keywords: B-vitamin intake, folate status, postpartum depression

Introduction

Postpartum depression is a depressive disorder of significant mortality and morbidity, affecting 10–15% of women between 2 weeks and 1 year after giving birth.[1] It has wide-reaching consequences, and is associated with adverse outcomes for the mother, child and family. Pregnancy is a time when women routinely engage with health services and is a crucial time to address mental health needs.

The efficacy of interventions that may reduce the risk of postpartum depression, such as antidepressants, is frequently weighed against known or unknown risks to the developing fetus. Several nutritional variables have been studied in relation to depression and it is known that pregnant women are susceptible to the effects of low nutrient intake due to increased demands. It is also known that the effects of B-group vitamin deficiencies commonly include mood disturbances.[2] However, interventions for postnatal depression do not routinely include the use of nutritional supplements because of a lack of evidence of their efficacy, although their safety profiles may be more widely accepted than that of antidepressants. Our study aims to contribute to the understanding of causal relationships between nutritional factors and postpartum depression with a view to informing research into whether nutritional supplements are likely to be effective in the prevention and treatment of postpartum depression.

Background

The main aetiological factors of importance in postpartum depression are thought to be psychosocial rather than biological – of particular importance are a personal history of depressive disorder and social adversity, e.g. unemployment, lack of support from a partner or family.[3] Nevertheless, the pathophysiology of postpartum depression has also been linked to dysfunctions in hormone regulation, hypothalamic–pituitary–adrenal axis abnormalities, genetics and epigenetic factors.[4]

The B-group vitamins have been implicated in the development of depression via the metabolism of neurotransmitters. The active metabolite of folate is involved in the methylation of homocysteine, an amino acid, and in the production of methionine which is required for several important signal-transduction pathways involving monoamine neurotransmitters.[2] High levels of homocysteine have been found in depressed patients in association with folate deficiency.[5] Likewise, a deficiency in vitamins B_{12} and B_6 has been shown to be associated with hyperhomocysteinaemia.[6] Vitamins B_6 and B_{12} are also cofactors in the production of serotonin from tryptophan and the intermediate neurotransmitter S-adenosylmethionine, respectively.[2]

In cross-sectional studies across a range of populations, a correlation has been found between the prevalence of depressive symptoms and low folate and vitamin B_6 status, including a poorer antidepressant response in those with a lower folate status.[7–9] This has led to debate over whether the relationship is causal or consequential.[10] Two recent longitudinal studies examined the relationship between folate status and the incidence of depression. Kendrick *et al*,[11] using data from the Southampton Women's Survey (SWS), found that red-cell folate concentration was not associated with subsequent depressive symptoms noted in general practice records over 2 years among women of reproductive age. Kim *et al*[12] found that low serum folate concentrations (and raised homocysteine) were significantly associated with the incidence of late-life depression at 2–3-year follow-up. Folate has also been found to have a role as an augmenting antidepressive agent and one study found this to be particularly the case for women when folate was used as an adjunct to fluoextine.[13]

There are few studies specifically examining the relationship between folate status and postpartum depressive symptoms. Those that used serum folate as a measure had very small samples and conflicting conclusions.[14,15] Miyake *et al*,[16] in the largest study measuring dietary folate intake as a predictor of postpartum depressive symptoms on the Edinburgh Postnatal Depression Scale (EPDS), found no associations. We aim to contribute to the evidence by looking at folate status and dietary intake data longitudinally in a large cohort of women who go on to become pregnant.

Methods

The SWS was established in 1998 and recruited 12 583 women aged 20–34 years who were not pregnant at the time of interview. Those who subsequently became pregnant were followed through the pregnancy and their children were followed through infancy and childhood. The SWS has been shown to be generally representative of England and Wales as a whole.[17] The results of this study should therefore be broadly generalisable to women of this age in England and Wales.

Between 1998 and 2002 all general practitioners (GPs) in Southampton were asked to help recruit women to the study. A letter and a leaflet explaining the study were sent to each woman, followed by a telephone call. Seventy-five percent of the women contacted agreed to take part and were interviewed by a research nurse following written consent. Blood samples were subsequently obtained from all the women. From March 2000, all women recruited to the study were asked at the initial interview to complete the 12-item version of the General Health Questionnaire (GHQ-12) to assess current symptoms of anxiety and depression. In total, 5051 women completed the GHQ-12 and had their baseline red-cell folate concentration measured by microparticle enzyme immunoassay using an Abbott IMX machine (Abbott, Columbus, USA). The coefficients of variation for the assays were < 10%. In those women who subsequently became pregnant, red-cell folate concentration was measured at around 11 weeks' gestation. Red-cell folate concentration is a reliable biological indicator of tissue folate stores and hence folate status over time.[18]

Research nurses administered food frequency questionnaires at baseline and at 11 and 34 weeks of pregnancy, and questions on dietary supplement use were used to obtain estimates of folate and vitamins B_6 and B_{12} intake. Food frequency questionnaires used in the SWS have been validated against detailed food diaries.[19] Except for a sample involved in a separate substudy, dietary data were not collected during pregnancy for those women who delivered after the end of 2005, hence there is a variation in the number of women completing questionnaires at different stages of pregnancy.

The GHQ-12 is a short screening instrument of 12 questions with good sensitivity for depression and anxiety.[20] Women were categorised as having 'case-level' symptoms of depression if their total score was $\geq$3, referred to here as 'GHQ caseness', where answers to questions indicating a lower likelihood of anxiety or depression were given a score of 0 and those indicating a higher likelihood were given a score of 1. Women were also asked whether they had a prior history of mental health problems requiring treatment, and demographic data were obtained about their smoking status, alcohol intake, socio-economic status and educational attainment.

EPDS scores were obtained for 2856 women who became pregnant. Our outcome measure, the EPDS, is the most widely used screening tool for postnatal depression and is used up to 1 year postpartum.[21] It consists of 10 questions asking women how they felt in the last 7 days. However, it was adapted in the SWS and women were asked to describe, using the same questions, how they had felt in the worst 2 weeks since the baby was born. Each question was given a score from 1 to 3, where higher scores indicate a higher likelihood of depression. A score of 13 or above is considered to indicate probable depression, although this is not synonymous with a diagnosis of postpartum depression.[21] At a cut-off point of $\geq$13 the EPDS has been found to have a sensitivity of 0.91 (95% CI 0.84–0.99) and a specificity of 0.91 (95% CI 0.88–0.94) for postpartum depression, with a positive predictive value of 57% and a negative predictive value of 99%.[22] Of the 2856 women in the sample, 1976 were interviewed at approximately 6 months postpartum and a further 621 were interviewed at approximately 1 year postpartum. In order to ensure that bias was not introduced by analysing women completing the EPDS at differing time intervals, we repeated the analyses using only those interviewed at 6 months and found that the results showed no significant differences. Our adaptation of the EPDS asking about the worst period since the baby was born inevitably raises the likelihood of identifying depressive symptoms. Our findings do not therefore reflect probable depression as identified by standard use of the EPDS; hence our use of the term depressive symptoms throughout. The term 'EPDS caseness' referred to in the results indicates a score of $\geq$13 on the EPDS.

In order to assess whether the longitudinal predictive effects of low folate status on depressive symptoms found in previous studies reflect a mechanism of delayed recovery from depression, for those with a prior mental health history we also compared the mean red-cell folate concentrations of those who scored $\geq$13 on the EPDS with those who did not.

Variables were analysed using Poisson regression with robust variance in STATA v. 10.0. A forward stepwise method was used to develop the multiple regression model. Logistic regression is less appropriate for use when the prevalence of the outcome variable is common, as it is here. Ideally, binomial regression would be used but as it does not always converge, therefore, Poisson regression was used because it provides similar results.[23] Adjustment was made for significant confounding variables in the multivariate model. All nutrient variables were positively skewed, and so were described using geometric rather than arithmetic means. Predictive effects were expressed as relative risks for all variables. A cut-off score of 13 was used for analysis of the EPDS response, because the EPDS score is not clinically validated for use as a continuous variable.[21]

Results

A total of 2856 women completed the EPDS postpartum within the time frame described. GHQ scores were available for 1686 women (59%) and red-cell folate concentrations were available for 2110 (74%) women at baseline and 1559 (55%) women in early pregnancy. The numbers of women completing dietary intake questionnaires were 2855 (99%), 1828 (64%) and 2252 (79%) at baseline, early pregnancy and late pregnancy, respectively. The lower numbers in the early pregnancy phase were due to some women not being seen at this stage because of delays in women making contact with the SWS when they became pregnant, either because they discovered the pregnancy or booked with their GP too late to be included. There is no reason to assume that these women were likely to have had significantly different folate status in early pregnancy and, indeed, baseline folate status did not differ significantly between those who were and those who were not seen in early pregnancy.

The number of women scoring >13 on the EPDS was 905 (32% of the sample), compared with 1951 (68%) women with lower scores. Based on the previously quoted positive and negative predictive values of 57% and 99%, respectively, this corresponds to an estimated prevalence of postpartum depressive symptoms of 18% in our sample.

Table 1 summarises the characteristics of the study population and compares those who had an EPDS score $\geq$13 with those who did not. Table 1 shows that prior history of mental illness, case-level symptoms on the GHQ at baseline, smoking status, alcohol status, breastfeeding to 6 months, receipt of benefits and perceived financial strain were all significantly associated with EPDS postpartum depressive symptoms in univariate analysis. Additionally, women with EPDS scores $\geq$13 were on average 0.33 years younger at delivery of their baby than women with lower scores ($P = 0.03$).

Table 2 gives the mean daily intakes of folate, and vitamins B_6 and B_{12} for the whole sample and for those with EPDS $\geq$13 and <13, showing that there were no significant relationships with any of these variables.

Red-cell folate concentrations ranged from 172 to 2604 nmol/L at baseline and from 224 to 2778 nmol/L in early pregnancy. At baseline, only 30 women (1.44%) were classified as having marginal folate status (< 350 nmol/L) according to a definition based on the National Diet and Nutriton Survey 2004.[24] These values are applicable to the general non-pregnant population. In pregnancy, only five women had marginal status (0.32%) based on the same values. Internationally accepted normal values for red-cell folate in pregnancy are not established.

Table 3 gives the final multiple regression model which included all confounders shown in Table 1 as being predictors of EPDS score of 13 or more. Those that did not remain significant after adjustment in the multivariate model were eliminated. Table 3 shows that a prior history of mental illness and caseness on the GHQ were significantly associated with having a score of 13 or more on the EPDS, whereas breastfeeding until 6 months appeared to decrease the risk.

Discussion

Folate status and dietary intakes of folate and vitamins B_6 and B_{12}, both before and during early and late pregnancy, did not predict postpartum depressive symptoms as assessed using the EPDS. Likewise, a lower red-cell folate concentration prior to or during early pregnancy was not found to differ significantly between those with a prior history of mental health problems as assessed by the GHQ who subsequently had postpartum depressive symptoms as assessed by the EPDS, and those who did not have postpartum depressive symptoms. Postpartum depressive symptoms were, however, associated with a prior history of mental illness and by depression or anxiety assessed using the GHQ before conception.

It is known that low folate status is associated with the prevalence of case-level symptoms on the GHQ in the SWS cohort.[11] However, the relationship may be consequential rather than causal, because lower red-cell folate concentration did not predict GP-recorded depressive symptoms on 2-year follow-up. Likewise, we found no longitudinal relationship between early pregnancy red-cell folate concentration and the incidence of postpartum depressive symptoms.

Our folate status and vitamin intake data assess average dietary intake for a large cohort of British women who go on to become pregnant. Such data are not widely available and could be used in comparisons with other countries where similar non-mandatory fortification policies exist. It is interesting to note that the percentage of women in our sample with marginal folate status at baseline and early in pregnancy in both those scoring $\geq$13 on EPDS and those scoring less was < 5%. This corresponds with the percentage found in women in the general population according to the latest National Diet and Nutrition Survey.[24]

Table 1 Characteristics of the study population, including confounding variables and risk factors of interest in relation to an EPDS score of >13

Variable	*n*	EPDS >13, *n*	%	RR	95% CI	*P*
Prior treatment for mental illness						
No	1169	274	23	1		
Yes	514	256	50	2.12	1.86–2.43	< 0.0001
Highest educational qualification						
Degree or above	645	188	29	1		
A levels or HND	1058	338	32	1.1	0.94–1.27	0.2
GCSE level	1071	348	32	1.06	0.98–1.14	0.2
None	74	30	41	1.12	1.01–1.23	0.03
GHQ caseness						
No	1208	291	24	1		
Yes	478	240	50	2.08	1.82–2.38	< 0.0001
Smoked before pregnancy						
No	2077	608	29	1		
Yes	777	297	38	1.31	1.17–1.46	< 0.0001
Smoked in pregnancy						
No	2167	646	30	1		
Yes	419	176	42	1.41	1.24–1.60	< 0.0001
Alcohol consumption before pregnancy						
≤14 units/week	2307	710	31	1		
>14 units/week	549	195	36	1.15	1.02–1.31	0.03
Alcohol consumption during pregnancy						
≤4 units/week	1377	436	32	1		
>4 units/week	856	268	31	0.99	0.87–1.12	0.9
On benefits						
No	2444	750	31	1		
Yes	412	155	38	1.23	1.07–1.41	0.004
Perceived financial strain						
Living comfortably or doing alright	1121	311	28	1		
Just about getting by	450	171	38	1.37	1.18–1.59	< 0.0001
Finding it difficult or very difficult	111	46	41	1.22	1.08–1.38	0.001
Breastfeeding at 6 months						
No	1277	448	35	1		
Yes	538	132	25	0.70	0.59–0.83	< 0.0001
Folic acid supplements in pregnancy						
No	80	28	35	1		
Yes	2486	785	32	0.9	0.67–1.22	0.5
≥400 μg/day folic acid in pregnancy						
No	1677	536	32	1		
Yes	361	116	32	1.01	0.85–1.19	0.9
B vitamins in pregnancy						
No	1117	366	33	1		
Yes	1449	447	31	0.94	0.84–1.06	0.3

Table 2 Geometric means and relative risks of nutritional variables categorised according to EPDS score <13 or >13

Nutritional variable	All women		EPDS score <13		EPDS score ≥13			
	Geometric mean		Geometric mean		Geometric mean		RR*	*P*
	n	95% CI	*n*	95% CI	*n*	95% CI	95% CI	
Baseline								
Red-cell folate (nmol/L)	2084	786 772–800	1432	783 767–801	652	791 765–817	1.00 1.00–1.00	0.5
Folate intake (μg/day)	2855	333 328–338	1950	330 324–336	905	339 329–348	1.00 1.00–1.00	0.06
Vitamin B_6 intake (mg/day)	2855	2.56 2.51–2.61	1950	2.53 2.47–2.58	905	2.64 2.55–2.73	1.02 0.94–1.12	0.6
Vitamin B_{12} intake (mg/day)	2855	5.36 5.27–5.47	1950	5.33 5.21–5.46	905	5.43 5.26–5.61	0.99 0.90–1.10	0.9
Early pregnancy								
Red-cell folate (nmol/L)	1559	2413 2365–2461	1055	2414 2357–2473	504	2409 2323–2497	1.00 1.00–1.00	0.9
Folate intake (μg/day)	2038	623 612–634	1386	628 615–641	652	612 593–631	1.00 1.00–1.00	0.2
Vitamin B_6 intake (mg/day)	2038	2.92 2.84–2.99	1386	2.93 2.85–3.02	652	2.88 2.76–3.00	0.88 0.75–1.04	0.1
Vitamin B_{12} intake (mg/day)	2038	5.68 5.55–5.81	1386	5.68 5.52–5.84	652	5.7 5.47–5.93	0.97 0.92–1.03	0.3
Late pregnancy								
Folate intake (μg/day)	2429	404 396–413	1663	402 393–412	766	410 395–426	1.00 1.00–1.00	0.1
Vitamin B_6 intake (mg/day)	2429	2.89 2.83–2.95	1663	2.89 2.82–2.96	766	2.89 2.79–2.99	0.90 0.76–1.06	0.2
Vitamin B_{12} intake (mg/day)	2429	6.12 6.01–6.24	1663	6.07 5.94–6.21	766	6.23 6.02–6.45	1.05 0.98–1.12	0.1

* Relative risk of having an EPDS score ≥13 associated with an increase of 10 units in the nutritional variable.

Table 3 Final multivariate model of statistically significant predictors of having an EPDS score >13 after adjustment for confounding variables

Variable	Relative risk	95% CI	*P*
Caseness on GHQ-12	1.84	1.53–2.20	< 0.001
Prior mental health condition	1.80	1.50–2.15	< 0.001
Breastfeeding until 6 months	0.65	0.52–0.81	< 0.001

The most striking difference in the data between baseline and early pregnancy was that the mean red-cell folate concentration in the overall sample was higher in early pregnancy than at pre-pregnancy baseline, reflecting the increase in folate intake resulting from folic acid supplementation. In our sample, 96.1% of pregnant women reported taking folic acid supplements at 11 weeks compared with none at pre-pregnancy baseline. The median intake from supplements in early pregnancy was 377 μg/day (interquartile range: 213–400 μg/day). It is possible that the number of folate-deficient women in our sample was too low to show an effect of folate deficiency on EPDS outcome. However, examining red-cell folate concentration as a continuous variable we did not find a relationship with EPDS score.

The results for the dietary intake data concur with other studies in postpartum depression looking at dietary data which have found no significant relationships with intake of these B-vitamins.[16] However, there may be a need for further research correlating serum assays of B-vitamins before and during pregnancy with postpartum depressive symptoms in order to further explore and establish this relationship.

Consistent with the literature, we found a negative effect of previous mental illness on EPDS outcome and an apparent protective effect of breastfeeding for 6 months.[25] The relationship between breastfeeding and postpartum depression may be multifactorial, as previously described, and not necessarily of linear causality, for example, there may be a greater tendency for women who are depressed and have feelings of low self-esteem to choose not to breastfeed. It may also reflect the choice of some women taking antidepressants not to breastfeed due to concerns about the effect of antidepressant therapy on the baby.

Strengths and weaknesses of the study

The strengths of this study are that, as demonstrated by Inskip *et al*,[17] the SWS is broadly representative of women of reproductive age in England and Wales. Our sample size is the largest to date examining the relationship between nutrient variables and postpartum depressive symptoms. The study has good power to detect an effect, with a *post hoc* power calculation indicating that we had >99% power to detect a reduction of 10% in red-cell folate concentration in those who scored $\geq$13 on EPDS, and 88% power to detect a 6% reduction.

A further strength is that red-cell folate concentration is a more accurate reflection of overall folate status over time than serum folate or dietary intake data.[18] Measurements of red-cell folate concentration before and during pregnancy have not been examined previously in relation to incident postpartum low mood, and this longitudinal data enabled a more direct examination of possible causality. Cross-sectional assessments of folate status and depression have shown stronger relationships than longitudinal findings, indicating a possible reverse causation effect.

To date, no study has examined folate status before conception and during pregnancy in relation to depressive symptoms postpartum. Our study has addressed this within the general population and so a major strength is that it provides findings that inform our understanding of risk factors for postnatal depression that can be generalised.

The main limitation of this study is that the EPDS is a screening tool for postpartum depression, limiting the extent to which it can be applied as evidence, although there is a correlation between the EPDS and longer diagnostic assessments.[21] The way in which questions were phrased in the SWS may introduce an element of recall bias because women were asked about the worst 2 weeks rather than the last 2 weeks, and may also therefore represent postpartum 'blues' as well as postnatal depression; this may have contributed to a higher prevalence of those scoring $\geq$13 on the EPDS, compared with an estimated population prevalence of 10–15%.[1]

Another limitation is the length of time elapsing between measurement of red-cell folate during pregnancy and screening for postpartum depression, which was on average 1 year. It is likely that because of physiological changes between early pregnancy and the postpartum period, early pregnancy red-cell folate may not be closely related to postpartum red-cell folate. Nevertheless, we considered it worthwhile examining folate status and nutritional intake at this time in relation to postpartum depression given that early pregnancy is a vulnerable time nutritionally due to factors such as poor maternal diet because of sickness/hyperemesis gravidarum. This vulnerability may be counteracted by the routine use of 400 μg folic acid supplementation in the first trimester. Future research could involve measuring red-cell folate during the puerperium or early postpartum period and subsequent symptoms of postpartum depression in case a true causal relationship has been missed in this study due to the length of time between serum folate measurement and screening for depression. Also there may be a role for the use of a direct homocysteine assay as a marker of functional folate/B-vitamin deficiency.

Conclusions

Owing to the small numbers of women in our sample with very low folate status compared with the population, we cannot exclude a true effect of clinical folate deficiency on the development of postpartum depressive symptoms. However, given that our sample is broadly representative of women aged 20–34 years in the UK, we suggest that low folate status in early pregnancy is unlikely to be a clinically significant problem in the general population with respect to postpartum depression.

It is interesting to note that anxiety or depression indicated by the GHQ at baseline predicted postpartum depressive symptoms independent of a prior history of mental illness. In current practice, a woman's previous mental health history is taken into account when adopting a case-finding approach to identifying women at risk of postpartum depression. However, a case may be made for clinicians to make careful assessment of the mental state of women planning a pregnancy to identify those at higher risk.

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ETHICAL APPROVAL

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CONFLICTS OF INTEREST

None.

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