Original Article

The relationship of neonatal serum vitamin B_{12} status with birth weight

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Earlier studies have shown a relationship between maternal vitamin B_{12} status and birth weight. This study extends those findings directly in terms of neonatal vitamin B_{12} status and birth weight. One hundred and twelve women were followed from the first trimester of pregnancy and maternal blood was obtained in all three trimesters along with cord blood at birth of their neonates. The maternal and cord serum vitamin B_{12} concentrations were examined in relation to birth weight. There was a significant correlation between vitamin B_{12} concentration in maternal antenatal serum during each of the trimesters of pregnancy and cord serum (all $P<0.01$). Neonates that were born with lower birth weights (categories of < 2500 g and 2500-2999 g) had significantly lower mean cord serum vitamin B_{12} concentrations when compared to those who were ≥ 3000 g ($P = 0.02$ and $P = 0.05$ respectively). A similar, however, non significant trend was observed for antenatal vitamin B_{12} concentrations at first and third trimesters. Cord serum vitamin B_{12} concentrations were significantly correlated with birth weight, up to 40 weeks of pregnancy (r=0.28, P=0.01) but not beyond that (≥ 40 weeks gestation). Vitamin B_{12} status in the mother was related to neonatal vitamin B_{12} status as measured by cord serum vitamin B_{12} concentration. In addition, low neonatal vitamin B_{12} concentrations were adversely associated with low birth weights.

Key Words: neonatal vitamin B_{12}, birth weight, India

Introduction

The prevention of low birth weight (LBW; <2500g), which affects nearly 30% of infants born in India, is a public health priority. Adverse outcomes for mothers and infants during pregnancy have been largely attributed to widespread maternal malnutrition. Previous studies have suggested that maternal status of micronutrients may influence the risk of LBW[1], and multiple micronutrient supplementation to antenatal women, at the level of once or twice the recommended daily allowance, has been shown to increase birth weight by approximately 100g.[2-4] In a prospective observational study, recently carried out in Bangalore, India, we demonstrated a significant relationship between low maternal vitamin B_{12} status and an increased risk of intra-uterine growth retardation (IUGR) after adjusting for potential confounding factors such as maternal weight, weight gain, age, education and parity.[5] In that study, we also demonstrated that vitamin B_{12} intake was significantly correlated to the antenatal serum vitamin B_{12} concentrations, implicating poor vitamin B_{12} intake as a possible cause of low vitamin B_{12} status. Vitamin B_{12} intake in this study population was mainly from consumption of fish, egg, milk and minimally from red meat. Other reports from Brazil[6] and India[7] have also demonstrated low maternal vitamin B_{12} status in pregnancy. In the general Indian population, low vitamin B_{12} intakes have been recorded in men and women living in urban slums[8] and low vitamin B_{12} status has been shown in middle class men and women, some of whom were non-vegetarians reporting intakes of egg, poultry and lamb >2 times a week.[9] Low cobalamin status has also been demonstrated in Asian Indians living in the USA, due primarily to low dietary intake; interestingly, homocysteine concentration did not always reflect a low cobalamin status.[10] Given the relationship between maternal vitamin B_{12} intake and B_{12} status, and between status and birth outcome[5], it is of interest to confirm that these relationships also extend to more direct measures of vitamin B_{12} status in the neonate,

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such as in the cord serum at birth, in addition to documenting the relationship and magnitude of difference between the maternal and cord serum concentrations of vitamin B_{12}. In particular, the relationship between neonatal serum vitamin B_{12} status at birth and birth weight has not been documented. Therefore, we investigated neonatal vitamin B_{12} status at birth using measures of cord serum, its association with maternal status and its direct effect on birth size in an urban hospital-based study, where the mothers came from differing socio-economic strata and had heterogeneous dietary intakes.

Subjects and Methods

Study design

The study was a prospective cohort study conducted at St. John's Medical College Hospital, Bangalore, India, from November 2001 to August 2003. This 1200 bed tertiary hospital draws patients of diverse socioeconomic status, from urban slums to high income residential areas. Pregnant volunteers were enrolled in early pregnancy (baseline) and followed up until delivery. Information on socio-demographic factors at baseline (approximately 12 weeks of gestation, 12.9 ± 3.3 weeks) and on maternal anthropometry, dietary intake, and blood at baseline, 2nd trimester of pregnancy (approximately 24 weeks of gestation, 24.1± 2.0 weeks) and 3rd trimester of pregnancy (approximately 34 weeks of gestation, 33.9 ± 1.2 weeks) and cord blood collected from the placental side of the cut umbilical cord, at delivery, were collected. The Institutional Ethical Review Board at St. John's Medical College approved all study procedures, and written informed consent was obtained from each study subject at enrolment.

Study population

All pregnant women aged 17-40 years who were below 20 weeks of gestation, and registered for antenatal screening at the Department of Obstetrics and Gynecology at St. John's Medical College Hospital were invited to participate in the study. Every effort was made to recruit women as early in their pregnancy to carry out baseline measurements at 12 weeks of gestation. Women with multiple pregnancies, those with a clinical diagnosis of chronic illness such as diabetes mellitus, hypertension, heart disease and thyroid disease, those who tested positive for hepatitis B (HbSAg), HIV or syphilis (VDRL) infections or who anticipated moving out of the city before delivery were excluded. Four hundred and seventy eight women consented to be part of the study and were recruited. Of them, 410 (85.8%) completed the study with a known pregnancy outcome. In a sub-sample of 185 women, in whom blood collections were available for at least two trimesters of pregnancy, micronutrient concentrations of vitamin B_{12} were measured from serum samples obtained at all three trimesters of pregnancy and from cord serum at delivery. Cord blood was obtained in 112 cases.

Sociodemographic and anthropometric information

At the baseline visit, trained research assistants interviewed the study subjects to obtain information on age, obstetric history, family composition and socioeconomic status. Gestational age (in weeks) was calculated from the reported first day of the last menstrual period (LMP). Subsequent ultrasonographic measurements done within 2 weeks of the initial visit and again closer to the time of delivery were used to confirm gestational age calculated by LMP. A digital balance (Soehnle, Germany) was used to record the weights of all mothers to the nearest 100 g. Measurements of height were made using a stadiometer to the nearest 1 cm. Maternal body mass index (BMI) was calculated using weight and height at baseline (kg/m^2). None of the women were smokers.

Serum vitamin measurement

Blood samples drawn from all subjects after an overnight fast by venipuncture using trained personnel or collected at birth from the placental side of the cord, were collected in plain vacutainers (Beckton Dickinson, New Jersey, USA). Serum vitamin B_{12} was determined using a kit employed on an Automated Chemiluminescence System ACS:180 (Bayer Diagnostics, Tarrytown, USA). The intra batch CV assessed by using multiple determinations of pooled human serum with a vitamin B_{12} concentration of 348 pmol/L (n = 20) was 2.6% and inter batch CV (n=20) done over a period of 3 weeks (n=15) was 3.4%.

Birth data

Infants were weighed to the nearest 10 g on a standard beam scale balance immediately after birth. LBW was defined as birth weight <2500g (WHO, 1995). Preterm delivery was defined as delivery before 37 weeks of gestation. Of the 410 women who had a known pregnancy outcome, there were 26 spontaneous abortions, 7 still births, 30 premature deliveries and 347 births at full term.

Statistical analysis

All analyses were done with the SPSS program (version 11.5, SPSS, Chicago, IL). Only cases who delivered a full-term infant and in whom cord vitamin B_{12} concentration was also available (n=112) are included in this analysis. Results are presented as mean ± SD. Mean values were compared by the one way analysis of variance with post-hoc tests (LSD). Correlations between cord serum vitamin B_{12} and birth weight was assessed using Pearson's correlation coefficient. Two sided P values <0.05 were considered statistically significant. Women who delivered full term live babies and in whom cord blood was not collected had similar serum vitamin B_{12} concentrations (pg/ml) when compared with those used in this analysis at the 1st, 2nd and 3rd trimesters of pregnancy; 255 ± 125 (n=22), 202 ± 55 (n=27) and 206 ± 74 (n=28) vs 229 ± 81 (n=89), 208 ± 57 (n=100) and 197 ± 54 (n=106) respectively. Mean serum vitamin B_{12} concentrations in mothers who had fetal losses and preterm babies were not significantly different from the group of mothers used in the main analysis of this report.

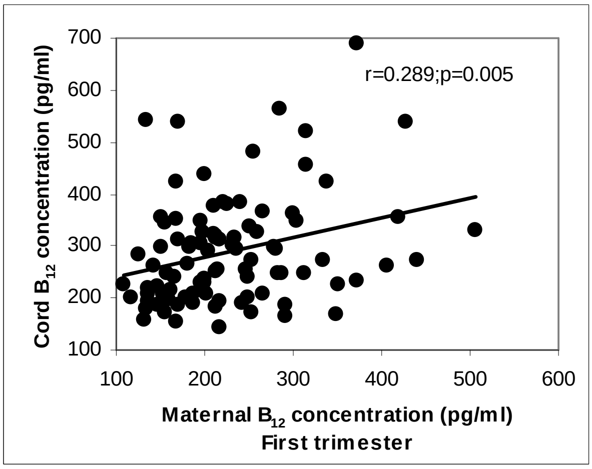
Results

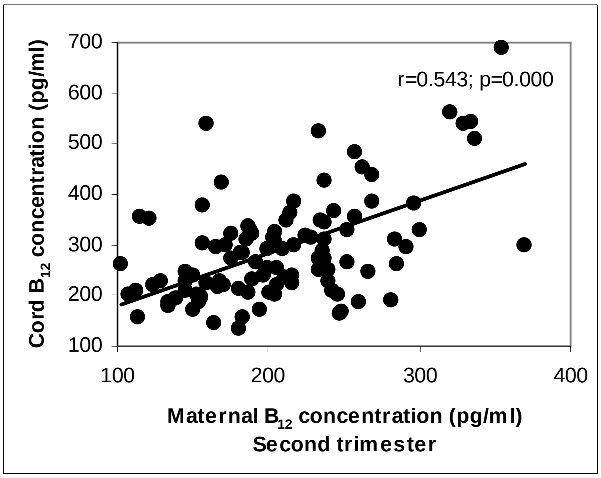
Demographic characteristics of the study population are listed in Table 1. Approximately 40% of the mothers were educated up to high school and the remaining 60 % had either a post-high school diploma or at least a university degree. Primiparous women made up 64% of the study cohort. Approximately 20% of the women had a

Table 1. Maternal baseline characteristics (n=112)

Parameter	Value
Age (y)	24.2 ± 4.0
Parity[1]	
0	72 (64.3)
1-2	38 (33.9)
>3	2 (1.8)
Educational level[1]	
Up to high school	44 (39.3)
Diploma	33 (29.5)
University degree & above	35 (31.3)
Anthropometry	
Weight (kg)	53.1 ± 11.0
Height (m)	1.54 ± 0.06
BMI (kg/m^2)	22.2 ± 4.13

Mean ± SD; N (%).





BMI less than 18.5 kg/m^2 at enrolment. Mean birth weight was 2.90 ± 0.39 kg; 18% of the newborns had low birth weights (<2.5 kg). Concentrations of vitamin B_{12} in the newborns and their mothers during the 3 trimesters of pregnancy are presented in Figure 1. Neonatal concentrations were about 27% higher than in maternal samples measured at all times during pregnancy. There was a significant correlation between vitamin B_{12} concentration in maternal antenatal serum during each of the trimesters of pregnancy and cord serum (Fig. 1); a strong relationship was observed for the 2nd and 3rd trimesters [r=0.54 (P=0.000) and r=0·56 (P=0.000) respectively]. The relationship between neonatal serum B_{12} levels and birth weight was assessed initially by a group-wise analysis which showed that significant differences existed in cord serum vitamin B_{12} concentrations between groups of infants, based on birth weight (Table 2).

Maternal serum vitamin B_{12} concentrations at each trimester increased with increasing birth weight. However, these increases in maternal serum B_{12} were significant only during the 2nd trimester; here maternal serum vitamin B_{12} values were significantly higher in the ≥3000 g birth weight group as compared to the LBW (<2500g) group (Table 2). We extended the analysis of the

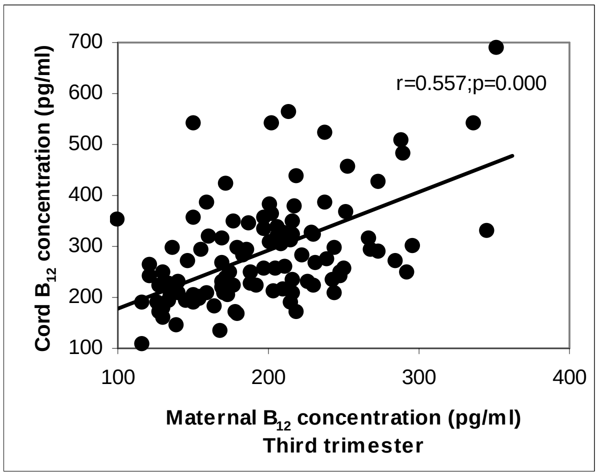


Figure 1. X-axis in the different panels represents maternal serum vitamin B_{12} status. Upper Left Panel : First trimester, Lower Left Panel: Second trimester, Upper Right Panel: Third trimester. Correlation values (r and P value) given in each panel for respective trimester.

Table 2. Neonatal (cord) and maternal (first, second and trimester) serum vitamin B_{12} status (pg/ml) in relation to birth size

Period	Birth weight			ANOVA (P value)	Post –hoc group comparisons (P value)		
	Group 1 <2500 g	Group 2 2500-2999 g	Group 3 >3000 g		Group 1 vs. Group 2	Group 1 vs. Group 3	Group 2 vs. Group 3
Neonate	264 ± 85† (n=20)	268 ± 93‡ (n=45)	320 ± 127 (n=47)	0.038	0.893	0.022	0.054
Mother 1st trimester	211 ± 88 (n=16)	231 ± 78 (n=39)	234 ± 78 (n=39)	0.611	0.395	0.886	0.337
Mother 2nd trimester	188 ± 45† (n=19)	208 ± 56 (n=43)	221 ± 62 (n=44)	0.106	0.208	0.280	0.036
Mother 3rd trimester	186 ± 52 (n=19)	191 ± 45 (n=44)	211 ± 61 (n=42)	0.120	0.725	0.091	0.084

Group 1: < 2500 g; Group 2: 2500-2999 g; Group 3: > 3000 g; †Significant difference by one-way ANOVA between birth weight category <2500 g vs >3000 g. ‡Significant difference by one-way ANOVA between birth weight category 2500-2999 g vs ≥ 3000 g.

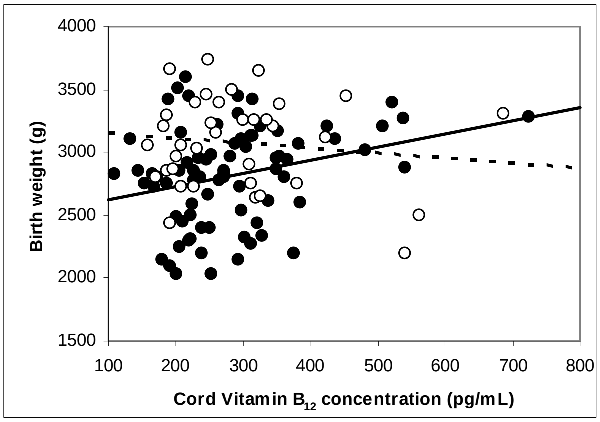


Figure 2. Figure shows a scatter plot of neonatal serum vitamin B_{12} status and birth weight. Solid line represents the relationship between the variables for babies with gestational age of 37-39 weeks (r=0.3, *P*=0.013). Dashed line represents the same relationship for babies with gestational age ≥ 40 weeks (r=0.1, *P* = 0.45).

relationship between neonatal serum B_{12} concentration and birth weight by evaluating whether there was a linear association between these variables (Fig. 2). When cord serum B_{12} concentrations were plotted against birth weight for all infants, there was no significant relationship. However, when cord serum B_{12} values were correlated with birth weights of infants born between 37-39 weeks of gestation, there was a significant correlation (r=0.28, *P*=0.01, n=76). In contrast, there was no relationship (r= -0.13, *P*=0.45, n=36) between cord serum B_{12} concentrations and birth weight when this was assessed in infants who were born at or after 40 weeks of gestation.

Discussion

The present study showed that vitamin B_{12} status in the mothers was correlated to neonatal vitamin B_{12} status, as measured by cord serum vitamin B_{12}, at all trimesters of pregnancy, similar to what has been shown before.[11,12] In general, both maternal and fetal vitamin B_{12} concentrations were lower than reported in western subjects[11]; this may be linked to their lower dietary vitamin B_{12} intake as has been suggested in ovo-lacto vegetarians and low-meat eaters[13] and our earlier report in vegetarian and non-vegetarian Indian pregnant women.[5] Cord serum vitamin B_{12} concentrations were linearly associated with birth weight, such that increasing concentrations were associated with increasing birth weight. In an earlier analysis using the same, but extended, dataset[5], we had demonstrated that a low maternal vitamin B_{12} concentration throughout pregnancy was independently associated with an increased risk of intrauterine growth retardation (IUGR), after controlling for confounding factors, in urban Indian women.

Furthermore, vitamin B_{12} status was significantly related to vitamin B_{12} intake at each of the 3 trimesters in these women. The association between vitamin B_{12} in the mother and neonate as early as in the first trimester suggests that it is important to enhance maternal B_{12} stores. This may need to be considered as early as the peri-conceptual period, although this would need to be tested prospectively. Previous studies on vitamin B_{12} status and its effect on birth weight have produced conflicting results. An earlier study reported negative correlations between birth weight and maternal vitamin B_{12} concentration at delivery in smokers in a group of western women.[14] More recently, Yajnik *et al.*,[7] reported no relationship between maternal plasma vitamin B_{12} concentration and offspring size in rural Indian women. The authors concluded that the lack of an association might have been due to an overall low vitamin B_{12} status. Another study conducted in the United Kingdom showed no relationship between maternal vitamin B_{12} concentrations in early pregnancy and birth weight[15]; the mean vitamin B_{12} status in this study was 324 $\pm$ 132 pg/ml, which was about one and a half times the value observed in the present study, suggesting that it would be difficult to demonstrate a nutrient effect in these women who were vitamin B_{12} replete. The reason the present study may have shown an association between vitamin B_{12} and birth size might be related to the relatively wide inter-quartile ranges of vitamin B_{12} status observed; 132-363 pg/ml across all trimesters of pregnancy compared to 118-203 pg/ml in the rural Indian study.[7]

Vitamin B_{12} deficiency has a role in elevating plasma homocysteine (Hcy) and lowering methyl donor levels in pregnancy and has been implicated in adverse pregnancy outcomes including low birth weight.[16] Methionine synthase is an enzyme which catalyzes the methylation of homocysteine to methionine using vitamin B_{12} as a cofactor and methyltetrahydrofolate as a substrate.[17] The formation of methionine through this pathway represents an important component of the one-carbon metabolism for synthesis of phospholipids, proteins, myelin, catecholamines, DNA and RNA. A deficiency of either vitamin B_{12} and/or folic acid is likely to affect this pathway resulting in an elevation of plasma Hcy with a relatively low methionine level. Low vitamin B_{12} concentrations in pregnant women and their babies are associated with low S-adenosyl methionine to S-adenosyl homocysteine ratios.[6] An earlier report on Indian subjects showed an association between higher plasma homocysteine (Hcy) concentrations and low birth weight, but could not demonstrate a relationship between vitamin B_{12} status and birth weight although there was a significant inverse relationship between vitamin B_{12} status and plasma homocysteine (Hcy) status.[7] From a speculative view-point, it might also be considered that the antenatal supplementation of folate, as is the norm, without vitamin B_{12} could aggravate the methyl folate trap,[18] and decrease the rate of neural growth and myelination in utero, leading to a diminished trophic effect on muscle growth and baby size. This is not unreasonable, as myelination has been shown to be retarded in a vitamin B_{12} deficient child[19] and clinical cobalamin deficiency with growth failure has been reported in 2 breast fed children of vegan mothers[20]; after treatment for cobalamin deficiency, both children showed marked improvement in cobalamin status and development. An association between low serum and amniotic fluid concentrations of B_{12} and neural-tube defects has also been reported.[21]

It is not clear why there was a significant association between birth weight and cord serum B_{12} of term infants with a gestational age of 37-39 weeks and not in infants who were delivered ≥ 40 weeks gestation in the present study. It is known that as pregnancy extends post term, the incidence of placental insufficiency and fetal post-maturity (dysmaturity) increases rapidly as a consequence of reduced respiratory and nutritive placental function.[22] Postmaturity is correlated with an increased incidence of placental lesions, fetal hypoxia-asphyxia, intrauterine growth retardation, increased perinatal death, and neonatal morbidity.[22] At a biochemical level, placental physiopathology in post term, post mature pregnancies is not well understood. However, it can be speculated that the relationship between blood nutrient concentrations and birth weight might be confounded by poor placental function in late term pregnancies.

In summary, the present study extends and confirms our earlier observations that there is a relationship between increasing antenatal vitamin B_{12} concentrations and birth weight in Indian babies. The low maternal vitamin B_{12} status translates into a low neonatal vitamin B_{12} status as evinced by cord serum vitamin B_{12} concentrations. The neonatal vitamin B_{12} status – birth weight relationship seems to operate up to a term gestation of 40 weeks. Beyond this age, there appears to be no relationship between neonatal vitamin B_{12} status and birth weight.

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新生兒血清維生素B_{12}狀況與出生體重的相關性

早期研究指出母親的維生素B_{12}營養狀況與嬰兒出生體重具相關性。本研究延伸先前的發現，針對新生兒維生素B_{12}營養狀況與出生體重。112名女性從懷孕第一期即開始追蹤，並且取得其三個孕期的血液及其新生兒出生時的臍帶血。評估母親及新生兒臍帶血中的血清維生素B_{12}濃度與出生體重的相關性。懷孕三個時期與臍帶的血清均與母親產前的血清維生素B_{12}濃度具有顯著相關(所有$P<0.01$)。新生兒出生時體重較輕者(分<2500公克及2500-2999 公克 兩類) 比起出 生時 體重≥3000公克者，其臍帶血清的維生素B_{12}平均濃度顯著較低(P值分別為0.02及0.05)。然而，產前第一孕期跟第三孕期之維生素B_{12}濃度雖有類似的趨勢，但是不顯著。懷孕週數40週以前，臍帶血清中維生素B_{12}濃度與出生體重達統計顯著相關(r=0.28，P=0.01)，但是之後就沒有此現象(懷孕週數≥40週)。母親維生素B_{12}的營養狀況與新生兒的維生素B_{12}的營養狀況(以臍帶血清中的維生素B_{12}濃度代表)相關。此外，低新生兒維生素B_{12}濃度與低出生體重呈相關負相關。

關鍵字：新生兒維生素B_{12}、出生體重、印度。