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Research Article

Association of Neural Tube Defects with Maternal and Neonatal Serum Vitamin B_{12} Level in Bangladesh: A Multicenter Case Control Study

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Abstract

Background: Neural tube defects (NTDs), a congenital deformity of the central nervous system attributed to multifactorial etiology including nutritional factors e.g. folic acid deficiency. Some studies suggested deficiency of vitamin B_{12} may be another factor behind NTDs due to its intimate metabolic pathway with folic acid. This study aimed to identify the association of NTDs with maternal and neonatal serum vitamin B12 level.

Methods: This case-control study was conducted from January 2014 to June 2015 in three tertiary level hospitals at Dhaka, Bangladesh. 32 cases (neonate with NTDs-mother pair) were selected from Bangabandhu Sheikh Mujib Medical University (BSMMU) Hospital (18), Dhaka Medical College Hospital (8) and Sir Salimullah Medical College and Mitford hospital (6). 40 age and sex matched controls were selected from BSMMU. A baseline assessment of the mothers on age, parity, education, residence, antenatal checkup, method of delivery and socio-economic status was taken. Vitamin B_{12} was estimated from the venous blood sample of the mother and newborn within 7 days after delivery. We considered < 200 pg/ml of vitamin B_{12} as 'deficiency', 200 - 300 pg/ml as 'marginal deficiency' and > 300 pg/ml as 'normal'. Quantitative data were expressed as mean ± SD and qualitative data were expressed as proportion. Chi-square test and student's unpaired t-test was used for comparison of categorical and continuous variables respectively. Pearson correlation was used to determine the correlation between continuous variables.

Result: Mothers with low socio-economic status ($p = 0.004$) and irregular antenatal checkup ($p = 0.029$) were significantly higher among the cases. Serum vitamin B_{12} level of mother ($p < 0.01$) and newborn ($p < 0.01$) were significantly lower among the cases. Vitamin B12 deficient newborn were significantly higher among the cases (50% vs. 25%). Maternal and neonatal serum vitamin B12 levels were positively correlated with both case (Pearson R = 0.517) and control (Pearson R = 0.627) groups.

Conclusion: This study finding suggests that both maternal and neonatal low serum vitamin B12 level is associated with NTDs. Vitamin B_{12} supplementation along with folic acid may be considered for to-be-mothers to prevent NTDs.

Keywords: *Bangladesh; Neural Tube Defects; Newborn; Tertiary Care Centers; Vitamin B_{12}*

Abbreviations

NTDs: Neural Tube Defects; BSMMU: Bangabandhu Sheikh Mujib Medical University; DMCH: Dhaka Medical College Hospital; SSMCH: Sir Salimullah Medical College and Mitford Hospital

Background

Being one of the common birth defects worldwide [1], 0.3 million babies are born with neural tube defects (NTDs) worldwide every year, resulting in approximately 0.088 million deaths and 8.6 million disability-adjusted life years [2]. NTDs ranging from anencephaly causing death of the fetus to spina bifida occulta causing partial paralysis of the neonate develop during the first month of pregnancy due to non- or incomplete closure of neural tube [3]. The etiology of NTDs is the additive involvement of several risk factors including genetic, environmental and nutritional factors [1]. From a preventive point of view, maternal nutritional risk factors provide a battling front. Maternal folate deficiency has been widely regarded as an important risk factor to increase the vulnerability to NTDs in the fetus and up to 75% NTDs incidence has been reduced by folic acid supplementation to to-be-mothers [1,4,5]. Several studies suggested that deficiency of other nutrients may have potential role in development of NTDs. Due to its close link to folate metabolism and as infant store and cord blood concentration of vitamin B_{12} is linked to maternal serum vitamin B_{12} level pre-pregnant and pregnant state, vitamin B_{12} is perceived to be an important determinant of NTDs [6-9]. One study reported that 42% of the pregnant mothers in Bangladesh are vitamin B_{12} deficient [10]. Regarding NTDs, although a nationwide population-based data is unavailable, using available surveillance data, the reported prevalence in Bangladesh is 4.7 per 1000 live birth [11]. Despite the high prevalence of vitamin B_{12} deficient mothers and almost twice of the global average prevalence of NTDs, no data is available in Bangladesh to distinguish the relationship of NTDs with maternal and newborn serum vitamin B_{12} level. Therefore, this hospital based multi-center study was aimed to identify the association of NTDs with maternal and neonatal serum vitamin B_{12} level.

Materials and Methods

Study site and population: This case-control study was conducted from January 2014 to June 2015 in three tertiary level hospitals at Dhaka, Bangladesh: Bangabandhu Sheikh Mujib Medical University (BSMMU) Hospital, Dhaka Medical College Hospital (DMCH) and Sir Salimullah Medical College and Mitford Hospital (SSMCH). 32 cases (mother- neonate with NTDs pairs) were selected from the neonatal intensive care unit of BSMMU (18), DMCH (8) and SSMCH (6). 40 postnatal age and sex matched controls with diagnosis other than NTDs were selected from BSMMU. Mothers who took vitamin B_{12} or B-Complex supplementation during pregnancy period, had history of diabetes mellitus, took anticonvulsant or antifolate drugs and/or had radiation exposure during the first trimester of pregnancy were excluded from the study (Figure 1).

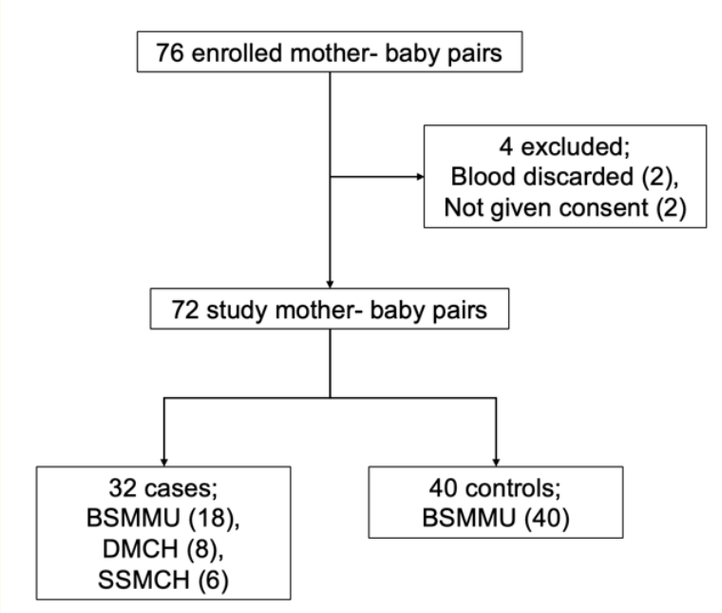

Figure 1: *Study profile. BSMMU = Bangabandhu Sheikh Mujib Medical University Hospital; DMCH = Dhaka Medical College Hospital; SSMCH = Sir Salimullah Medical College and Mitford Hospital.*

Laboratory method: We draw 2 - 3 ml of venous blood for vitamin B_{12} estimation from the mother and newborn by venipuncture within 7 days after delivery and collected them in a capped polypropylene tube labeled with allocated number to reduce bias and transferred them to the department of biochemistry, BSMMU with standard procedure. Serum was separated by centrifugation (4000 rpm for 5 minutes), and hemolyzed sample was discarded. Serum vitamin B_{12} level was calculated using the Chemiluminescent Microparticle Immunoassay on Architect 2000 analyzer. We considered < 200 pg/ml of vitamin B_{12} as 'deficiency', 200 - 300 pg/ml as 'marginal deficiency' and >300 pg/ml as 'normal' [12].

Statistical analysis: We analyzed the data using the SPSS version 20.0 of SPSS Inc., Chicago, IL. Quantitative data was expressed as mean ± SD and qualitative data was expressed as proportion. We used Chi-square test and student's unpaired t-test for comparison of categorical and continuous variables respectively. Pearson correlation was used to determine the correlation between continuous variables. *p* value of < 0.05 was considered statistically significant.

Results

Among different types of NTDs observed among the study subjects, meningomyelocele (63%) was the most common followed by encephalocele (15%) and meningocele (9%) (Figure 2).

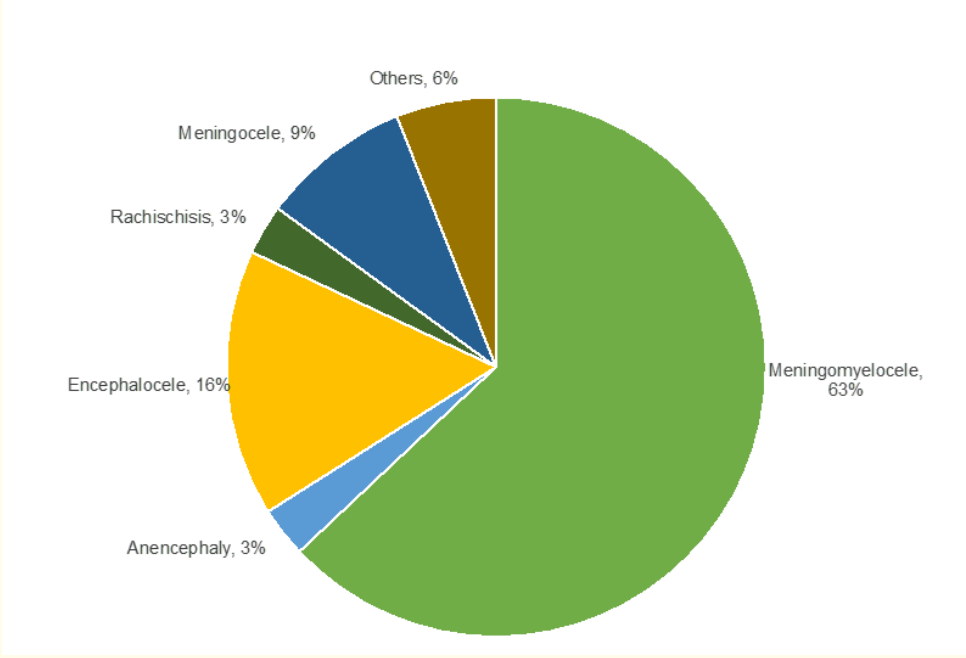

Figure 2: *Different types of neural tube defects observed among cases (n = 32).*

Comparison on baseline characteristics of the mothers showed that lower socio-economic status and irregular antenatal checkup were significantly high among the case compared to the control. However, we observed no significant difference among age of mother, maternal parity, delivery of neonate by normal delivery, high socio-economic status, education and rural residence between case and control (Table 1).

Baseline characteristics if mothers	Case (n = 32)	Control (n = 40)	p value
Age of mother in years (mean ± SD)	26.08 ± 5.66	25.73 ± 4.36	0.086
Parity of mother (mean ± SD)	1.87 ± 1.8	1.77 ± 0.88	0.127
Normal vaginal delivery of the neonate	13 (41)	7 (18)	0.055
Socio-economic status[a]			
Low	12 (38)	3 (8)	0.004
Middle	13 (41)	20 (50)	1
High	7 (21)	17 (42)	0.111
Education			
Illiterate	5 (16)	0	1
≥ 10 years	11 (34)	10 (25)	0.542
< 10 years	16 (50)	30 (75)	0.051
Rural residence	15 (47)	21 (53)	0.812
Irregular antenatal checkup	15 (47)	8 (20)	0.029

Table 1: *Baseline characteristics of mother between case and control group.*
[a]Socio-economic status was categorized arbitrarily based on family income per month: low (< BDT 10000), middle (BDT 10000 - 20000), high (> BDT 20000).

We found that serum vitamin B_{12} level of the mother and the newborn were significantly lower among the cases than the controls. No significant difference was observed between maternal deficiency and marginal deficiency of vitamin B_{12} between cases and controls. Vitamin B_{12} deficiency of newborn were significantly high among the cases than the controls; however, there was no significant association with marginal deficiency of vitamin B_{12} between newborn of two groups (Table 2).

Characteristics	Case (n = 32)	Control (n = 40)	p value
Serum vitamin B_{12} (pg/ml) of mother (mean ± SD)	202.06 ± 51.68	276.25 ± 89.02	< 0.01
Serum vitamin B_{12} (pg/ml) of newborn (mean ± SD)	238.09 ± 64.37	373.22 ± 145.43	< 0.01
Differential level of serum vitamin B_{12} (pg/ml) of mother, n (%)			
Normal (> 300 pg/ml)	3 (9)	18 (45)	1
Marginal deficiency (200 - 300 pg/ml)	13 (41)	12 (30)	0.48
Deficiency (< 200 pg/ml)	16 (50)	10 (25)	0.05
Differential level of serum vitamin B_{12} (pg/ml) of newborn, n (%)			
Normal (> 300 pg/ml)	4 (12)	23 (58)	1
Marginal deficiency (200 - 300 pg/ml)	20 (63)	15 (37)	0.06
Deficiency (< 200 pg/ml)	8 (25)	2 (5)	0.03

Table 2: *Serum vitamin B_{12} level of the mother and newborn between case and control groups.*

In both case and control group, we observed statistically significant positive correlation between maternal and neonatal serum vitamin B_{12} levels (Figure 3).

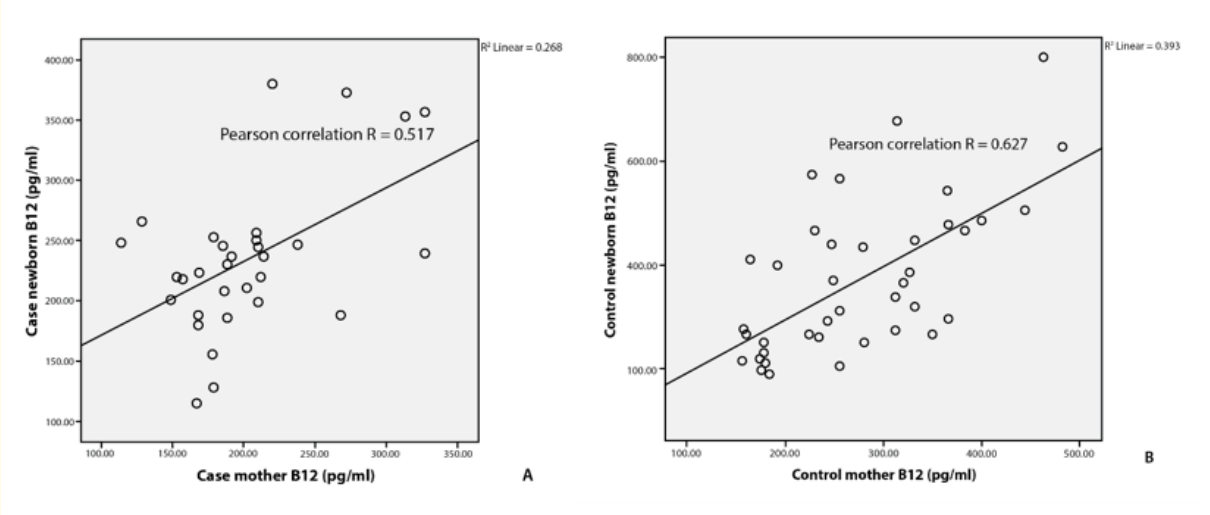

Figure 3: *Correlation of serum vitamin B12 between mother and newborn. A. Case; B. Control.*

Discussion

We have observed that the mean maternal serum B_{12} level of the case mothers is lower than the control mothers. Moreover, 50% of the case mothers are vitamin B_{12} deficient, which is only 25% in case of control mothers. Maternal vitamin B_{12} deficiency has been widely reported in low- and middle-income countries as well as in Bangladesh [10,13,14]. It is well documented that the deficiency of folate is an important risk factor for NTDs, although the mechanism by which folate causes NTDs is unknown [1]. The intimate linkage of vitamin B_{12} with folate is due its cofactor activity for the enzyme methionine synthase, which uses 5-methyltetrahydrofolate as a carbon donor. Thereby, deficiency of vitamin B_{12} can disrupt the intracellular folate pathway [15]. Due to this closely linked metabolism, it has been discussed that cellular uptake and utilization of folate cofactors can be augmented by vitamin B_{12} supplementation, which in turn can prevent NTDs. Moreover, it has also been argued that food fortification with combined folic acid and vitamin B_{12} may yield prevent NTDs better than folic acid alone as vitamin B_{12} might have a self-determining role in this case [16]. Fetal and newborn vitamin B_{12} status is thought to be determined by the maternal vitamin B_{12} status during pregnancy [9]. Vitamin B_{12}, facilitated by transcobalamin, is transported across the placenta, although very little is known about this pathway from the maternal to the fetal circulation. Further, the placenta can regulate fetal B_{12} uptake and reduced transcobalamin synthesis which causes vitamin B_{12} deficiency to the neonate [17]. We have found that NTDs affected newborns had a lower level of serum vitamin B_{12} level compared to the unaffected newborns and affected newborns have a higher percentage of either deficiency or marginal deficiency of vitamin B_{12}. A positive correlation was also revealed between the mother and newborn of both groups, that is the lower the mother's serum vitamin B_{12}, the lower was the baby's serum vitamin B_{12} and vice versa which has been documented elsewhere [7]. This also emphasize the discussion of vitamin B_{12} supplementation to the to-be-mothers. In our study, NTDs mother are mostly from low socioeconomic status. Possible explanations of low level in these populations were due to low animal source food intake, religious believe, malabsorption in developing countries for their poor socio-economic condition [18,19]. We also observed d a higher rate of history of irregular antenatal check-up among the case mothers which might be due to their financial burden. Worldwide meningomyelocele and encephalocele are the two most common birth defect among the NTDs [20,21] which is also our findings.

Strength and Limitations

Strength of this study its being case-control in nature. We have taken at least one age and sex matched control in this multicenter study. However, sample of the study was small and causes of NTDs were not considered in the study.

Conclusion

This study finding suggests that both maternal and neonatal low serum vitamin B_{12} level is associated with NTDs. Further study with large sample size would yield a more acceptable finding in this regard. Vitamin B_{12} supplementation along with folic acid should be considered for to be mothers to prevent NTDs. Large multicenter randomized control trial may be carried out to establish whether periconceptional vitamin B_{12} supplementation decreases NTDs.

Ethics Approval and Consent to Participate

Ethical approval was taken from institutional review board of BSMMU. Written informed consent was taken from the mother.

Availability of Data and Material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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This self-funded research study was Fakhrul Amin's (first author) Doctor of Medicine (MD) thesis.

Authors' Contributions

FA, AFMP, MS coined the idea and designed the study; FA. AM, SKD, MKHS, FJBR collected the data; FA and AM analyzed and interpret the data; FA SKD wrote the first draft of the manuscript; all authors reviewed, revised, and approved the final version of the manuscript to be published.

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