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Maternal Calcium and Vitamin D Deficiency and Their Relation with Fetal Neural Tube Defects

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Abstract **Original Research Article**

Background: NTDs are major birth defects associated with significant fetal loss, mortality, morbidity, and healthcare costs. Although periconceptional folic acid supplementation has reduced their occurrence, NTDs remain a global concern. Recent studies have suggested a possible link between low maternal serum calcium and vitamin D levels and the development of NTDs. ***Objective:*** The objective of this prospective observational study was to investigate the relationship between maternal calcium and vitamin D deficiency during early pregnancy and the development of fetal neural tube defects (NTDs). ***Materials and Method:*** A total of 207 pregnant mothers in their first trimester were included in the study. Data on age, BMI, gestational age, and serum levels of total calcium and 25-hydroxyvitamin D were collected. Calcium deficiency was identified in 61 (29.5%) participants, while vitamin D deficiency was present in 139 (67%). Ultrasound scans between 18-22 weeks of gestation were conducted in 173 participants to search for fetal NTDs. ***Results:*** Among the study population, only 1 (0.6%) fetus was found to have an NTD on sonographic scan. The mother of this fetus exhibited both calcium and vitamin D deficiencies. However, statistical analysis did not reveal a significant relationship between maternal calcium and vitamin D deficiency and the development of fetal NTDs. ***Conclusion:*** Deficiency of calcium and vitamin D during early pregnancy does not appear to be associated with the development of fetal NTDs. Further research is needed to explore other potential risk factors for NTDs.

Keywords: NTDs, Calcium deficiency, Vitamin D deficiency.

INTRODUCTION

Neural tube defects (NTDs) are severe birth defects affecting the brain and spinal cord, resulting from the failure of the neural tube to close during early embryonic development. They are classified as open or closed, depending on the presence or absence of exposed neural tissue. Open NTDs, such as anencephaly and spina bifida cystica, involve abnormalities in the neural tube and its coverings with exposed neural tissue. Closed NTDs, including spina bifida occulta and tethered spinal cord, exhibit abnormal neural tube development but with intact overlying skin [1].

The worldwide incidence of NTDs is estimated to be approximately 1 per 1,000 live births, with significant geographic variations. For example, regions in China report an incidence of 1 in 100 live births, while Scandinavian countries report a much lower incidence of 1 in 5,000 live births [2]. In India, the reported incidence ranges from 0.5 to 11 per 1,000 births, and in Bangladesh, it is reported as 4.7 per 1,000 live births [3]. NTDs are associated with high rates of spontaneous abortions, medical terminations of pregnancies, and stillbirths [4]. In a study conducted at Bangabandhu Sheikh Mujib Medical University (BSMMU) Hospital in Bangladesh, NTDs accounted for 13.33% of all live and stillbirth anomalous deliveries [5].

The exact etiology of NTDs remains unknown, but they are believed to be multifactorial, with genetic and environmental factors playing a role [1]. Maternal low serum folate levels have been associated with an increased risk of NTDs, and periconceptional folic acid supplementation has shown to reduce the risk by more than 50% [6]. Other potential risk factors include maternal diabetes, oxidative stress, maternal hyperthermia, infections during early pregnancy, extreme maternal age, low serum vitamin B12 and zinc levels, and exposure to certain teratogens [7].

Calcium is an essential micronutrient involved in various physiological processes, including neural tube closure. Animal studies have shown that calcium ion influx within neural plate cells leads to cellular changes and folding of the neural plate during neural tube formation [8]. Vitamin D, a fat-soluble vitamin, plays a crucial role in calcium-phosphorus metabolism, bone mineralization, and other biological functions. Vitamin D deficiency has been associated with increased risk of various disorders [9]. Recent studies have suggested an association between low maternal serum calcium and vitamin D levels and the development of fetal NTDs [10].

Though periconceptional folic acid supplementation reduces the prevalence of NTDs, but still, it is one of the major congenital anomalies with high rate of fetal loss, neonatal mortality and lifelong disability. In all the previous studies regarding the association between fetal NTDs and maternal calcium and vitamin D, their levels were measured in second trimester after sonographic detection of fetal NTDs [10,18,19]. As neural tube closure occurs in early pregnancy, maternal calcium and vitamin D levels should be measured during this period to see the effect of their deficiency on development of fetal NTDs. As far as known, there is no previous study regarding exposure to outcome relationship between maternal calcium and vitamin D deficiency and development of fetal NTDs.

In this study, we aimed to investigate the relationship between maternal calcium and vitamin D deficiency during early pregnancy and the development of fetal NTDs. We measured maternal serum levels of calcium and vitamin D in the first trimester and compared them between cases with NTDs and healthy controls.

OBJECTIVES

General objective

- To observe the relationship of maternal calcium and Vitamin D deficiency in early pregnancy with fetal NTDs.

Specific objectives

- To measure maternal serum total calcium and 25(OH) vit-D in first trimester of pregnancy.
- To detect fetal NTD by second trimester ultrasonography.
- To observe the relationship between maternal calcium and 25(OH) vit-D deficiency and fetal NTDs.

METHODS AND MATERIALS

Study Design: This study was conducted as a prospective observational study.

Study Period: The data collection for this study took place from July 2017 to February 2019.

Study Locations: The study was carried out at Bangabandhu Sheikh Mujib Medical University and Dhaka Medical College Hospital, Bangladesh.

Study Population: The participants of this study were pregnant mothers in their first trimester who were attending the Obstetrics & Gynaecology OPD.

Sampling Technique: Purposive sampling technique was used to select the participants for the study.

Data Collection Procedure: Observational data sheet was filled through observation of serum levels of calcium and vitamin D in the first trimester and the presence or absence of fetal NTD during mid-gestation routine ultrasonography which had been done between 18 to 22 weeks. A serum total calcium level below 8.8mg/dl was referred to as calcium deficiency and a serum 25(OH) vit-D level below 18ng/ml was referred to as vitamin D deficiency.

Data Processing and Analysis: The collected data were processed and analyzed using SPSS vs 24.0 software. Descriptive statistics such as percentages and mean ± standard deviation (SD) were used to summarize the results. A significance level of $P<0.05$ was considered statistically significant. To compare the means between different groups, the unpaired t-test was employed. The chi-square test was used to analyze qualitative data.

Ethical consideration: Before the commencement of the study, the protocol of the following study was approved by the Ethical Review Committee (ERC) of Bangabandhu Sheikh Mujib Medical University. The respondents' informed consent was taken by describing the objectives and purpose of the study. They were also given the freedom to withdraw themselves from the study whenever they wanted and were ensured that the information obtained from them was kept confidential.

RESULT

Out of 207, calcium deficiency has been found in 61, that is 29.47% and calcium sufficiency was found in 146, which is 70.53% of total study population. Table 1 shows the mean, SD and range of age, BMI, gestational age during serum analysis, serum total calcium and serum 25(OH) Vit-D of all the 207-study population.

Table-1: Mean, SD and range of demographic and laboratory parameters of study population

Variable	Mean	SD	Range
Age (years)	26.8	3.9	20 - 36
BMI (kg/m^2)	22.51	3.17	17.4 – 30.1
Gestational age during serum analysis (weeks)	8.6	2.1	7 - 12
Calcium (mg/dl)	9.41	0.93	7.91 – 10.51
25(OH)D (ng/ml)	15.38	6.82	4.2 – 31.05

Table-2: Age distribution between vitamin D deficiency and sufficiency group

Age (years)	Vitamin D		*P* value
	Deficiency	Sufficiency	
< 30	111 (79.9%)	56 (82.4%)	
≥ 30	28 (20.1%)	12 (17.6%)	0.19
Total	139 (100%)	68 (100%)	
Mean ± SD	24.7 ± 3.82	25.3 ± 4.51	0.13

Table shows the age distribution between vitamin D deficiency and sufficiency group. Age of most of the study population is < 30 years in both groups. Chi square test found no significant difference among the age group. Unpaired 't' test also found no significant difference of mean (± SD) age between the two groups.

Thirty-four (16.42%) are dropped out among which 21 (61.76%) from calcium sufficiency and 13 (38.24%) from calcium deficiency group.

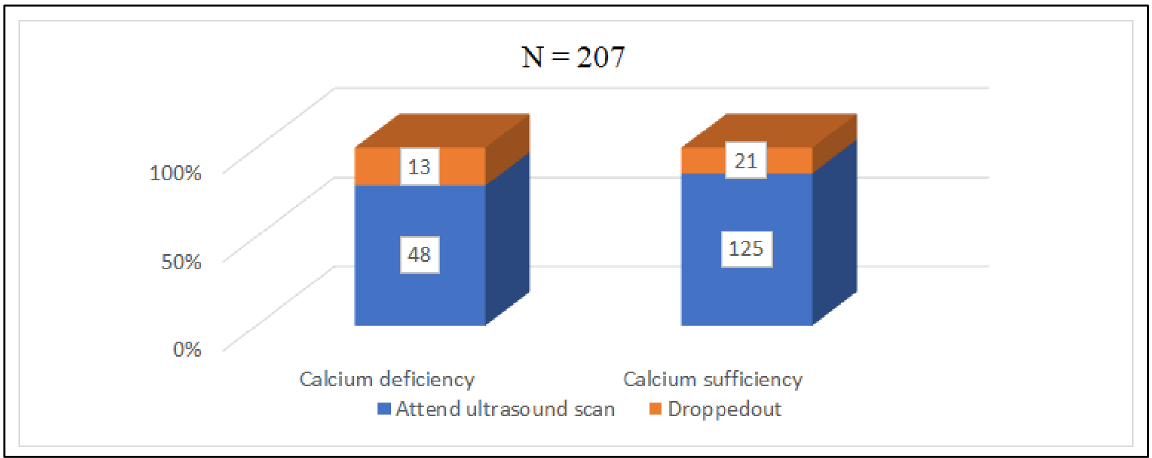

Figure 1: Distribution of dropped out cases among calcium deficiency and sufficiency group

173 pregnant mothers have been examined by ultrasonographic scan for the presence of fetal NTDs. Only 1 (0.58%) is found to have myelomeningocele and rest of them are free of any other type NTDs.

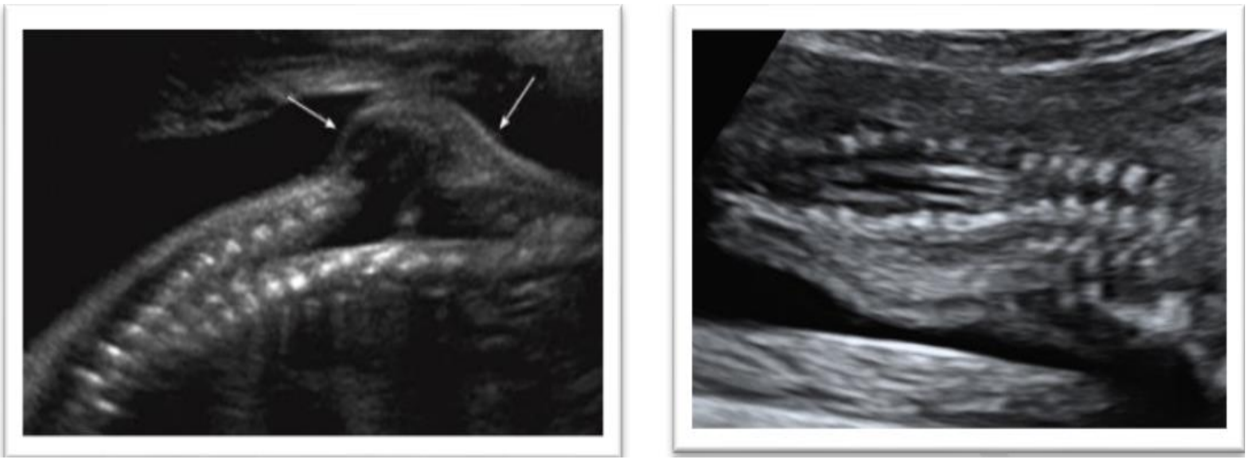

Figure 2: Fetal myelomeningocele on ultrasonography

Table-3: Presence of NTD in ultrasound scan among calcium deficiency with 25(OH) vit-D and sufficiency group

Findings of Ultrasound scan	Calcium		P value
	Deficiency	**Sufficiency**	
Presence of NTD	1 (2.1%)	0 (0%)	-
Absence of NTD	47 (97.9%)	125 (100%)	-
Total	48 (100%)	125 (100%)	1
	Vitamin D		
	Deficiency	**Sufficiency**	
Presence of NTD	1 (0.83%)	0 (0%)	-
Absence of NTD	120 (99.17%)	52 (100%)	-
Total	121 (100%)	52 (100%)	1

DISCUSSION

The etiology of NTDs is still unknown. Several studies have been done to search out risk factors of these devastating congenital malformations. The present study has been designed to observe the relationship between maternal calcium and 25(OH) vit-D deficiency and fetal NTDs.

In this study, mean age of the study population is 26.8 ± 3.9 years ranging from 20 – 36 years. The mean age is similar to that of Ates *et al*., [11]. who found it as 29.49 ± 4.9 years. But the age range is disimilar to the study of Bromage *et al*., [12, 13] as the range was 15 – 49 years and 17 – 50 years respectively in those studies. Mean BMI of the study population is 22.5 ± 3.2 kg/m2 as compared to 25.3 ± 4.5 kg/m2 found by Ates *et al.*, [11]. In the present study, serum calcium and vitamin D levels have been measured in first trimester of pregnancy which is also similar, but they only measured 25(OH) vit-D level [18]. On the contrary, measured only calcium level in third trimester of pregnancy and Bromage *et al*., [12] measured both calcium and 25(OH) vit-D levels in nonpregnant women. Mean serum calcium level of the present study is 9.41 ± 0.93 mg/dl which is comparable as the mean calcium of their study was 8.9 mg/dl and 8.7 ± 1.2 mg/dl respectively. In this study, mean 25(OH) vit-D level is 15.38 ± 6.82 ng/ml which is also comparable. Mean 25(OH) vit-D level was found 13 ± 9.4 ng/mL found mean 25(OH) vit-D levels as 16.72 ng/ml. The sample size of this study is also comparable to where it was 229. However, it was higher in the study. The study population was 631 Bangladeshi women and 900 Algerian women [13].

In this study, out of 207 study population, calcium deficiency was found in 61 which is about 29.5% of the study population. This proportion is larger than that of Gabby *et al.*, [4], who found only 16% calcium deficiency in first trimester of pregnancy. The higher proportion of calcium deficiency may be due to low dietery intake of calcium. Islam *et al.*, [14] stated that approximately 75% Bangladeshi women failed to consume recommended daily dietery calcium requirement.

25(OH) vit-D deficiency found to be very much common in women of reproductive age group. Another study found 25(OH) vit-D deficiency in 74.5% and 71.5% of Bangladeshi women of reproductive age. Another study found that 68% women had 25(OH) vit-D deficiency [5]. This study found more than 67% pregnant women had 25(OH) vit-D deficiency which is consistent with the study. But the study population of those study were nonpregnant women of reproductive age group. The high prevelance of 25(OH) vit-D may be due to less exposure to sunlight, covered dressing style and less dietery intake. Found 25(OH) vit-D deficiency in about 81% Turky pregnant women of first trimester which is slightly higher than that of the present study. Mean age of population among 25(OH) vit-D deficiency and sufficiency group is 24.7 ± 3.8 years and 25.3 ± 4.5 years respectively and the difference is not statistically significant (P >0.05). also found no significant age difference between 25(OH) vit-D deficiency and sufficiency group. Mean BMI of the 25(OH) vit-D deficiency group is 21.7 ± 3.6 kg/m2 and that of sufficiency group is 22.3 ± 4.2 kg/m2. The difference of mean BMI between 25(OH) vit-D deficiency and sufficiency group is not significant (P >0.05). But it is dissimilar to the study [16], who found significant difference of BMI between children with 25(OH) vit-D deficiency and normal 25(OH) vit-D level.

In this study, maternal serum calcium and 25(OH) vit-D levels were measured for research purpose but there is no data which support routine screening for these two nutrients in pregnant women in term of health benefit. The recommended dose of supplementation is 1.5 – 2.0 gm elemental calcium per day in pregnancy which should be started from 20 weeks of gestation until the end of pregnancy to prevent preeclampsia among the high-risk population [17], also recommended to advice pregnant mothers to expose to sunlight and to encourage receiving adequate nutrition to maintain adequate 25(OH) vit-D level. Daily dose of 200 IU 25(OH) vit-D supplementation is recommended for those with documented 25(OH) vit-D deficiency. As the present study was observational study, no intervention was taken by the investigator to the calcium and 25(OH) vit-D deficient study population rather all the study population have been advised to continue their regular antenatal checkup in Obstetrics and Gynaecology OPD.

During second trimester sonographic scan between 18 – 22 weeks of pregnancy, out of 207 study population, 34 (16.4%) are dropped out from the study. Among the drop out cases, 4 developed spontaneous abortion, 7 migrated to another region of the country and rest of them are not willing to come for sonographic scan as they are interest to continue their antenatal checkup in nearby health care center. So, 173 pregnant mothers have been scanned ultrasonographically for the presence of fetal NTDs. Among the drop out cases, 13 (38.2%) from calcium deficiency and 21 (61.8%) from calcium sufficiency group. Similarly, 18 (52.9%) from vitamin D deficiency and 16 (47.1%) from 25(OH) vit-D sufficiency group. So, 48 calcium deficient and 125 calcium sufficient mothers as so 121 and 52 25(OH) vit-D deficient and sufficient mothers respectively are undergone sonographic scan. Out of them, only 1 (0.6%) fetus found to have NTD which is myelomeningocele at the sacrococcygeal region. A large proportion of the study population was dropped out, so the condition of the neural tube of their fetuses was not known.

Age of the mother of the only NTD fetus is 30 years. She is not consanguineous, nondiabetic and there is no history of fever during periconceptional period. She is second gravida, no history of abortion and her first child is free from any type of NTDs. She started to take folic acid supplementation after being conceived at current issue. The levels of serum calcium and 25(OH) vit-D of the NTD mother are 8.13 mg/dl and 5.62 ng/ml respectively. She has both calcium and 25(OH) vit-D deficiency which is 2.1% and 0.83% among the deficiency population respectively. The relationship between maternal calcium as well as 25(OH) vit-D deficiency and fetal NTD is not statistically significant ($p > 0.05$).

Some recent studies have been conducted to find out the association of maternal calcium and 25(OH) vit-D levels with fetal NTDs. Daglar *et al.*, [10], showed that, unlike low maternal 25(OH) vit-D, low maternal calcium was associated with fetal NTDs. Nasri *et al.*, [18], found significant association between low maternal 25(OH) vit-D with fetal NTDs. Another study conducted by Sirinoglu *et al.*, [19], where low maternal 25(OH) vit-D was associated with fetal NTDs but low maternal calcium did not. So, all the relevant previous studies were not similarly conclusive about the association of low maternal calcium and 25(OH) vit-D with fetal NTDs and there is still area of argument. On the other hand, in all those studies maternal calcium and 25(OH) vit-D levels were measured in second trimester after sonographic detection of fetal NTDs and were compared them with healthy controls. The status of maternal calcium and 25(OH) vit-D in the early gestation was not known. As a result, it is difficult to state that whether their levels were normal or deficient during or around development of NTDs.

To resolve the dispute whether maternal calcium and 25(OH) vit-D deficiency is related or not to fetal NTDs, maternal serum calcium and 25(OH) vit-D levels have been measured during early pregnancy in this study and fetal NTDs are searched on mid gestation ultrasound scan between 18-22 weeks of gestation. But the present study has failed to find significant relation of maternal calcium and 25(OH) vit-D deficiency to fetal NTDs.

CONCLUSION

Neural tube defects are a group of major birth defects with significant fetal loss, neonatal and infant mortality and morbidity and substantial health care cost. Some recent studies were conducted to search out the association of low maternal calcium and 25(OH) vit-D levels with the development of fetal NTDs, but those were not equally conclusive. 25(OH) vit-D deficiency is much more common in early pregnancy. Calcium deficiency is not also uncommon. But this study found no significant relation of maternal calcium and 25(OH) vit-D deficiency with fetal NTDs.

LIMITATIONS OF THE STUDY

- Large proportion of the study population was dropped out during sonographic scan.
- The fetuses were not followed till birth due to time constrain.

RECOMMENDATION

- Further large study can be conducted with a minimum dropout.
- Large multicenter study may minimize dropout or even the study may be more strengthened.

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