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Original Research Article

The effect of the maternal vitamin D level on the risk of spontaneous pregnancy loss in the first trimester

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ABSTRACT

Background: Pregnancy loss in the first trimester is one of the most disappointing matters for a mother. But spontaneous pregnancy loss in the first trimester is the most common negative outcome of pregnancy. It's estimated that about 10% of known pregnancies are lost in the first trimester whereas fewer than 4% of pregnancies miscarry in the second trimester. Aim of current study was to assess the effect of the maternal vitamin D level on the risk of spontaneous pregnancy loss in the first trimester.
Methods: It was a case-control study conducted in the department of obstetrics and gynecology, Sir Salimullah medical college Mitford hospital, Dhaka, Bangladesh during the period of September 2018 to August 2019. A total of 100 patients were included in this study. Statistical analyses of the results were obtained by using window-based computer software devised with SPSS version 22.0.
Results: In analyzing the association of serum vitamin D status with first-trimester pregnancy state it was observed that more than half (52.0%) patients had severe deficiency (<10 ng/ml) in the case group and 14 (28.0%) patients in the control group. In total 24 (48.0%) patients had deficiency (10-20 ng/ml) in case and 35 (70.0%) in control group. Only 1 (2.0%) patient had insufficiency (21-29 ng/ml) in control group. The difference was statistically significant ($p<0.05$) between the two groups.
Conclusions: Maternal serum vitamin D deficiency was significantly associated with early spontaneous pregnancy loss in the first trimester.

Keywords: First trimester, Miscarriage, Serum vitamin D, Gestational age

INTRODUCTION

Spontaneous pregnancy loss in the first trimester is the most common negative outcome of pregnancy. It's estimated that about 10% of known pregnancies are lost in the first trimester whereas fewer than 4% of pregnancies miscarry in the second trimester. Low vitamin D concentrations in pregnancy are widespread worldwide and the effects of vitamin D deficiency in pregnancy have been associated with some adverse pregnancy outcomes. Low levels of vitamin D are common in pregnant women and have been shown in several epidemiological studies worldwide. Vitamin D deficiency is implicated in immune cell regulation at the feto-maternal interface and is associated with pre-

eclampsia, gestational diabetes, bacterial vaginosis compromised intrauterine growth. The association between deficient vitamin D status and pregnancy loss is less well defined. A history of failed clinical pregnancies may predispose to increased pregnancy loss, decreased serum vitamin D levels among child-bearing-aged women. There are limited studies done to identify the "association of maternal serum vitamin D deficiency with early spontaneous pregnancy loss in the first trimester" in Bangladesh. It has been estimated that almost one billion people in the world suffer from vitamin D deficiency or insufficiency.[1] In South Asia, 80% of the apparently healthy population is vitamin D deficient (<20 ng/ml) and up to 40% is severely deficient (<9 ng/ml).[2] In developing countries, the prevalence of hypovitaminosis D ranges between 30-90%. In North India, 96% of neonates, 91% of healthy school girls, 78% of healthy hospital staff, and 84% of pregnant were found to have hypovitaminosis D.[2] In Bangladesh hypovitaminosis D is common in women regardless of age, lifestyle, and clothing with much higher prevalence in low-income lactating women.[3] In a normal pregnancy, circulating maternal concentrations or 1,25(OH)2D are elevated from the first trimester, there is a progressive increase during gestation, and by the third trimester 1,25(OH)2D is increased over two-fold compared with a post-partum level on non-pregnant controls. Local production of 1,25(OH)2D may be especially important for the increase in the earlier stages of pregnancy, as 1-alpha hydroxilase activity in the desidual and placenta has been observed to be the highest during the first two trimesters. This local activation of vitamin D suggested to influence implantation, partly through the immunomodulation effects 1,25(OH)2D and partly by the regulation of target genes associated with implantation. Effects on implementation could explain the early rising 1,25(OH)2D levels since the demand to meet the increased calcium requirement for mineralization of the fetal skeleton should only increase requirement later in pregnancy.[4] Vitamin D3 also plays a major role in controlling cell proliferation and maturation and in modulating an immune response in both innate and adaptive forms.[5] Vitamin D metabolic pathway involves multiple enzymatic reactions. Vitamin D is metabolized in the liver to the form 25(OH)D, which is used to determine a patient's vitamin D status; 25(OH)D is metabolized in the kidneys by 25-hydroxyvitamin D-1 alpha-hydroxylase (CYP27B1) to its active form, 1,25-(OH)2D.[6] The increased synthesis of 1,25(OH)2D is linked to higher CYP27B1 activity in the maternal kidneys, placental trophoblasts, and deciduas.[7] To date, little is known regarding the determinants of the levels of CYP27B1 in serum, nor a possible association between the level of the enzymes in early pregnancy loss has been explored. A lot of epidemiological published literature refers to the global occurrence of vitamin D deficiency and insufficiency.[8] In a study they recorded the vitamin D deficiency incidence (a serum level of <20 ng/ml) in women during reproductive age to be 31%. Reports from the "National health and nutrition examination surveys" described that the problem is variable between racial and ethnic categories, "with non-Hispanic blacks possessing a higher rate of vitamin D deficiency and" insufficiency when compared to white ethnic groups.[9] These results were supported "by Forrest and Stuhldreher, who registered" that blacks had the highest incidence of Vitamin D insufficiency (82.1%) and then followed by Hispanics (69.2%).[10] In spite of its global prevalence, wide geographical screening for vitamin insufficiency has not been adopted because of the expensive serum assays. For that reason, screening has been carried out only for groups at great risk for vitamin D deficiency.[11] Recently, a great deal of attention has been focused on vitamin status during pregnancy. Evidence about the role of vitamin D in human reproduction has been proved by a number of researchers.[12] Globally, vitamin D deficiency is a frequent problem among women at the age of childbearing.[13]

General objectives

General objective of the study was to assess the effect of the maternal vitamin D level on the risk of spontaneous pregnancy loss in the first trimester.

Specific objectives

Specific objectives of the study were to collect the socio-demographic information of the participants, to collect information regarding sunlight exposure and the clothing style of the participants, to collect information regarding the dietary habits of the participants and to dig out the association of serum vitamin D status with first-trimester pregnancy.

METHODS

Presented study was a case-control study conducted in the department of obstetrics and gynecology, Sir Salimullah medical college Mitford hospital, Dhaka, Bangladesh during the period September 2018 to August 2019. A total of 100 patients were included in this study. Among them, 50 pregnant women having early spontaneous pregnancy loss in the first trimester (documented by ultrasonography as missed or incomplete abortion) was considered as a case (group I). Age, gestational age, and BMI matched another 50 women in their early live pregnancy (documented by ultrasonography) was served as control (group II). A purposive sampling method was used in this study. According to the inclusion criteria of this study women having regular menstrual cycles, 21-35 years of age, BMI within the range of 18.5-29.9 kg/m^2 were included. Besides these, cases were pregnant women with early spontaneous pregnancy loss. Gestational age and BMI matched pregnant women with early live pregnancy comprised the control subjects. On the other hand, according to the exclusion criteria of this study pregnant women using vitamin D or hormone at least 3 months prior to enrolment or with multiple pregnancies, autoimmune disorders, chromosomal

abnormalities, thyroid dysfunction, diabetes mellitus, renal dysfunction, and malignancy were excluded. Age of the patient, occupation, education, locality or area of residence, socio-economic condition, and personal behavior were considered as demographic variables of this study. Gestational age and number of pregnancy loss were the obstetric variables. Anthropometric variables were height (M), weight (Kg) and BMI (Kg/m^2). Serum vitamin D level 25(OH)D (ng/ml) was considered as a biochemical variable. The gestational age was calculated from the last menstruation period (LMP) and ultrasonography. All the subjects attending and out-patient department of obstetrics and gynecology, Sir Salimullah medical college Mitford hospital, Dhaka, Bangladesh during the study period and who fulfilled the inclusion criteria were enrolled in the study. A physical examination of all the participants was done. The demographic and obstetrics information was collected in a pre-structured datasheet. The body weight of the participants was measured barefooted. The average weight (0.5 kg) of the clothes was later deducted from the dignified weight. The measurement of weight was done after the bladder has been emptied and before a meal. The heights of the subjects were measured barefooted in the standing position with meter scales. Body mass index was determined by measuring weight (kg) divided by height square (meter). The blood sample was collected for measurement of 25(OH)D levels. Vitamin D, in the form of 25(OH)D estimation was carried out by a chemiluminescent microparticle immunoassay using the ARCHITECT in the laboratory of the biochemistry department of BSMMU. Vitamin D levels were defined as 'severe deficiency: <10 ng/ml', 'deficiency: 10-20 ng/ml', 'insufficiency: 21-29 ng/ml', and 'sufficiency: ≥30 ng/ml. Statistical analyses of the results were obtained by using window-based computer software devised with SPSS version 22.0.

RESULTS

In current study in both the case and control groups, the highest numbers of participants were from the 21-25 years' age group which was 80% in group I and 68% in group II. The mean age was 22.88±1.88 years in group I and 23.96±3.56 years in group II. Two third (66.0%) of patients had primary education in group I and 29 (58.0%) in group II. The majority of patients were housewives and belonged to rural areas in both groups. The majority of the patients had normal BMI in both groups. The mean BMI was 22.26±1.52 kg/m2 in group I and 22.35±1.4 kg/m2 in group II. None of the demographic parameters were statistically significant. It was also observed that all (100.0%) patients belonged to lower middle income in group I and group II. The difference was statistically not significant (p>0.05) between the two groups. Besides these, it was found that the majority (86.0%) of patients in group I and 41(82.0%) patients in group II had sunlight exposure for <1/2 hour.

Table 1: Socio-demographic status of participants (n=100).

Characteristics	Group I (N=50)		Group II (N=50)		P value
	Frequency	%	Frequency	%	
Age (years)					
21-25	40	80.0	34	68.0	0.080
26-30	9	18.0	13	26.0	
31-35	1	2.0	3	6.0	
Mean±SD	22.88±1.88		23.96±3.56		0.061
Range (min-max)	20-33		20-35		
Education					
No education	9	18.0	11	22.0	0.712
Primary	33	66.0	29	58.0	
Secondary	8	16.0	10	20.0	
Occupation					
Housewife	31	62.0	21	42.0	0.086
Service	6	12.0	4	8.0	
Domestic worker	13	26.0	24	48.0	
Daily labor	0	0.0	1	2.0	
Area of residence					
Urban	10	20.0	12	24.0	0.629
Rural	40	80.0	38	76.0	
Family income status (per month)					
Lower	0	0.0	0.0	0.0	-
Lower-middle	50	100.0	50.0	100.0	
Upper-middle	0	0.0	0.0	0.0	

The majority (90.0%) of the patients wore a veil in group I and 44 (88.0%) in group II. The difference was statistically not significant (p>0.05) between the two groups. In current study 12(24.0%) patients used to consume milk 4 times a week in group I and 16 (32.0%) in group II. Eight (16.0%) patients had egg consumption per day in a group I and 6 (12.0%) in group II.

Table 2: Sunlight exposure and clothing style of participants (n=100).

Parameters	Group I (N=50)		Group II (N=50)		P value
	Freq.	%	Freq.	%	
Sunlight exposure in hours/day					
<1/2	43	86.0	41	82.0	0.585
1/2-1	7	14.0	9	18.0	
>1	0	0.0	0	0.0	
Clothing style					
With veil	45	90.0	44	88.0	0.749
Without veil	5	10.0	6	12.0	

Table 3: Distribution of dietary habits regarding vitamin D containing food (n=100).

Dietary habits	Group I (N=50)		Group II (N=50)		P value
	Freq.	%	Freq.	%	
Milk consumption 4 times a week					
Yes	12	24.0	16	32.0	0.373
No	38	76.0	34	68.0	
Egg consumption per day					
Yes	8	16.0	6	12.0	0.564
No	42	84.0	44	88.0	
Small fish intake per day					
Yes	44	88.0	46	92.0	0.505
No	6	12.0	4	8.0	

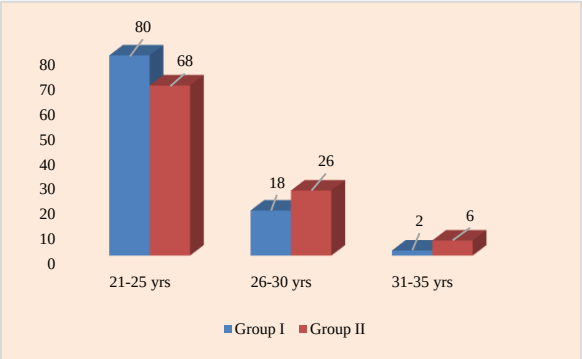

Figure 1: Group wise patient's age distribution.

The majority (88.0%) patients had small fish intake per day in group I and 46 (92.0%) in group II. The difference was statistically not significant (p>0.05) between the two groups. It was observed that more than half (52.0%) patients had severe deficiency (<10 ng/ml) in group I and 14 (28.0%) patients in group II. 24 (48.0%) patients had deficiency (10-20 ng/ml) in group I and 35 (70.0%) in group II. Only 1 (2.0%) patient had insufficiency (21-29 ng/ml) in group II. None of the patients had sufficient serum vitamin D levels. It was observed that the mean vitamin D level was 9.98±2.56 ng/ml in group I and 11.51±2.96 ng/ml in group II. The difference was statistically significant (p<0.05) between the two groups. In analyzing the association of serum vitamin D status with first-trimester pregnancy state it was observed that more than half (52.0%) patients had severe deficiency (<10 ng/ml) in the case group and 14 (28.0%) patients in the control group. In total 24 (48.0%) patients had deficiency (10-20 ng/ml) in case and 35 (70.0%) in control group. Only 1 (2.0%) patient had insufficiency (21-29 ng/ml) in control group. The difference was statistically significant (p<0.05) between the two groups.

Table 4: Distribution of the study subjects according to vitamin D level in ng/ml (n=100).

Vitamin D levels	Group I (N=50)		Group II (N=50)	
	Freq.	%	Freq.	%
Severe deficiency (<10)	26	52.0	14	28.0
Deficiency (10-20)	24	48.0	35	70.0
Insufficiency (21-29)	0	0.0	1	2.0
Sufficiency (30)	0	0.0	0	0.0

Table 5: Comparison of serum vitamin D level between the patients group (n=100).

Vitamin D level (ng/ml)	Group I (N=50)	Group II (N=50)	P value
Mean±SD	9.98±2.56	11.51±2.96	<0.01
Range	6.7-14.5	8.8-21.7	

Table 6: Association of serum vitamin D status with first trimester pregnancy state (n=100).

Vitamin D levels	Group I (N=50)		Group II (N=50)		P value
	Freq.	%	Freq.	%	
Severe deficiency	26	52	14	28	<0.05
Deficiency	24	48	35	70	
Insufficiency	0	0	1	2	
Sufficiency	0	0	0	0	

DISCUSSION

In current present study, it was observed that the majority of the patients had normal BMI in both groups. The mean BMI was 22.26±1.52 kg/m2 in group I and 22.35±1.4 kg/m2 in group II. The difference was statistically not significant (p>0.05) between the two groups. In a study by Ghaedi et al it was found that 66.7% of those with SPL and 58.3% of the women with RPL had normal BMI.[15] In another study, Andersen et al observed that the

maternal BMI was 23.26 kg/m2 21.01-27 kg/m^2 in group I and 23.38 kg/m^2 varied from 21.26-26.18 kg/m^2 in group II, which is similar to the present study.[16-18] In current study, it was observed that 52.0% patients had severe deficiency (<10 ng/ml) and 48.0% in deficiency (10-20 ng/ml). The mean vitamin D level was 9.98±2.56 ng/ml varied from 6.7-14.5 ng/ml. Shareif et al found the mean vitamin D level was 11.5±3.1 ng/ml in women with a history of pregnancy loss, which is comparable with the present study.[17]

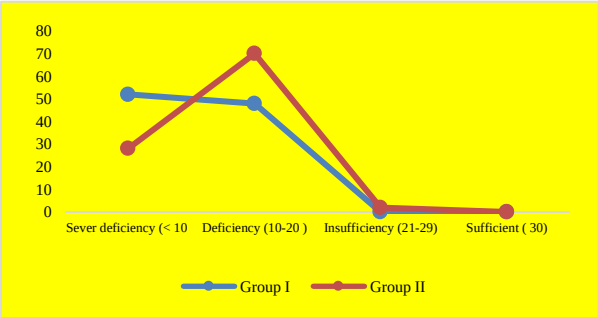

Figure 2: Group wise patient's vitamin D status.

Kuhr et al observed 25.6% of patients had a deficiency and 74.4% had insufficiency.[18] Kota et al observed that 41.4% had women with pregnancy loss were vitamin D deficient.[19] In current study, it was observed that the mean vitamin D level was 9.98±2.56 ng/ml in group I and 11.01±2.96 ng/ml in group II. The difference was statistically significant (p<0.05) between the two groups. Similarly, Li et al also found that serum vitamin D level was significantly decreased in pregnancy loss (42.49±11.17 µg/l) when compared to the control group (50.57±3.18 mg/l) suggesting that an altered localized maternal vitamin D state may influence pregnancy outcome.[20] In current study, it was observed that 52.0% of patients had severe deficiency <10 ng/ml in group I and 28.0% of patients in group II. 48.0% of patients had deficiency 10-20 ng/ml in group I and 70.0% in group II. Only 2.0% of patients had insufficiency 21-29 ng/ml in group II. The difference was statistically significant (p<0.05) between the two groups. Adequate vitamin D concentrations were essential during pregnancy. Vitamin D deficiency in the mother could be vertically transmitted to the fetus. The risk of pregnancy loss in pregnant women with a low concentration of vitamin D is 1.71 with 95% CI: 1.2–2.4. It means that vitamin D deficiency was associated with PL in the first-trimester of pregnancy. Kuhr et al observed 25.6% of patients had a deficiency and 74.4% had insufficiency in women with recurrent pregnancy loss.[18] In another study by Kota et al observed that 41.4% had women with pregnancy loss were vitamin D deficient. On the other hand, Moller et al studies did not find an association between vitamin D deficiency and the clinical outcome of miscarriage in the first-trimester pregnancy.[19,21] This discrepancy may be explained not only by methodological differences but also by differences in this study population relative to other published studies, including the difference in maternal age and gestational age of specimen collection.

Limitations

Limitations of the current study were; it was a single-centered short lengthen study with a small sample size. So, the findings of this study might not reflect the precise scenario of the whole country. Samples were taken by the purposive method in which questions of personal biases might arise. Confounding variables for vitamin D deficiency could not be excluded.

CONCLUSION

Serum vitamin D deficiency is evident in almost all the study participants but it is significantly lower in pregnant women with early spontaneous pregnancy loss in the first trimester than in control. For getting more reliable information we would like to recommend conducting more studies in several places with larger sample size. We can consider serum vitamin D as a screening test in the pre-conceptional period and intervention programs for raising vitamin D levels in those women can be carried out in order to prevent vitamin D deficiency linked to pregnancy loss in the first trimester.

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