



# A Study of Relationship between Maternal Serum Vitamin D Level with Hydatidiform Mole

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## Research Article

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## Abstract

A hydatidiform mole (HM) is a gestational trophoblastic disease that originates from the placenta. The exact cause of it is still unknown. Failure in the early detection of the condition may expose women to a higher rate of severe complications including persistent gestational trophoblastic neoplasia. Vitamin D deficiency is common in women of reproductive age and its lower level is presumably related to abnormal implantation, uncharacteristic fetal growth patterns, adverse birth outcomes, and reproductive failure. The present study is designed to evaluate the association of maternal serum vitamin D level with hydatidiform mole. The knowledge of which expected to be used for the prevention of hydatidiform mole and its complications and correction of deficiency during pregnancy. This was a case-control study among purposively selected pregnant women attending the outpatient and inpatient department of Obstetrics and Gynaecology, Institute of Child and Mother Health, Matuail, Dhaka from January 2021 to December 2021. A total of 70 pregnant women between 18-45 years of age were included in this study in their first trimester (up to 13 weeks) of gestation. Among them, 35 diagnosed women with hydatidiform mole were considered as the cases and the rest of the 35 matched healthy pregnant women were selected as controls. After taking consent and matching eligibility criteria, data were collected from patients on variables of interest using the predesigned semi-structured questionnaire by interview, observation, relevant clinical examination and laboratory investigation of the participants. Their maternal serum vitamin D level was investigated. Descriptive analysis was done using Microsoft Excel 2010 and the analytic software SPSS v27.0, where required. The overall average maternal serum vitamin D levels were significantly low among the cases compared to controls ( $18.27 \pm 8.89$  vs.  $26.29 \pm 8.01$  ng/mL,  $P < 0.001$ ). The difference in serum vitamin D levels between partial and complete moles was not significant ( $p > 0.05$ ). Maternal serum vitamin D deficiency and insufficiency were noted more in the cases 45.7% and 31.4% respectively, while 57.1% of the controls had

sufficient levels of vitamin D level ( $P=0.010$ ). Considering maternal serum vitamin D level of 30 ng/mL as a cut-off value, odd's ratio calculation showed HM was 4.5 times more likely in women with low maternal serum vitamin D level ( $<30$ ) than those with  $\geq 30$  ng/dL ( $OR=4.50$ ,  $CI_{95\%}=1.599-12.664$ ;  $P=0.003$ ). In conclusion, a low level of maternal serum vitamin D level was found associated with hydatidiform mole.

**Keywords:** Pregnancy; Maternal Serum; Vitamin D Level; Women

**Abbreviations:** HM: Hydatidiform Mole; hCG: Human Chorionic Gonadotropin; PHM: Partial HM; CHM: Complete HM; ICMH: Institute of Child and Mother Health; SD: Standard Deviation; GTN: Gestational Trophoblastic Neoplasia; VDD: Vitamin D Deficiency.

## Introduction

Hydatiform mole (HM), also known as a molar pregnancy or mole, is referred to as an abnormal pregnancy characterized by varying degrees of trophoblastic proliferation (both cytotrophoblast and syncytiotrophoblast) and vesicular swelling of placental villi associated with an absent or an abnormal fetus/embryo [1]. Morphologically hydatidiform moles arise from a transformation of the inner embryonic cell mass prior to differentiation into embryonic tissue. Without normal differentiation into the embryonic endoderm and ectoderm, the inner cell mass produces extraembryonic mesoderm and molar vesicles leading to the hydatidiform mole [2]. Most cases of molar pregnancy are diagnosed in the first trimester around 8 to 14 weeks by ultrasound, where the mass of placental tissues often have grape-like appearance containing many small fluid-filled sacks (cysts) [3]. The conceptus in molar pregnancies is almost always non-viable and following diagnosis, molar tissue is evacuated from the uterus by surgical curettage and the patient is followed up with serial serum human chorionic gonadotropin (hCG) estimations [4]. Epidemiologic studies have reported wide regional variations in the incidence of hydatidiform mole. Estimates from studies conducted in North America, Australia, New Zealand and Europe have shown the incidence of the hydatidiform mole to range from 0.57–1.1 per 1000 pregnancies, whereas studies in Southeast Asia and Japan have suggested an incidence as high as 2.0 per 1000 pregnancies [1]. This discrepancy in the incidence of HM worldwide could be attributed to methodological differences or the lack of centralized databases or it could be linked to genetic, socioeconomic and nutritional factors [1]. In the United States, hydatidiform moles are observed in approximately 1 in 600 therapeutic abortions and 1 in 1,000–1,200 pregnancies [5]. In the Middle East, the incidence of molar pregnancy is estimated at 1 in 160 pregnancies [6]. The incidence in India is one in 400; 80% of the cases are uncomplicated and 20% are associated with an extensive list

of perioperative complications, some of which may be of a critical nature [7]. On the evaluation of molar pregnancy in a prospective study in Bangladesh, the incidence of molar pregnancy was reported 5.3 per 1,000 deliveries (1 in 188 deliveries) [8]. HM comprises two distinct entities, partial HM (PHM) and complete HM (CHM), based on clinical, morphological and genetic characteristics [9]. In complete moles, the genetic material is solely derived from the father with the maternal genetic component lost either late in oocyte development or at the time of conception [10]. CHM often presents with vaginal bleeding. Most result from fertilization of an ovum devoid of maternal genetic material by a single sperm that duplicates (monospermy; approximately 85%) but a subset is due to fertilization by two sperm (dispermy) [11]. Early CHMs are characterized by a redundant bulbous villous growth pattern, hypercellular myxoid villous stroma, a labyrinthine network of villous stromal canalicular vascular structures, karyorrhectic debris within stroma, and at least focal trophoblastic hyperplasia on villi and the undersurface of the chorionic plate [12]. Vitamin D is a prohormone derivative from cholesterol. It is obtained either through photosynthesis in the skin with exposure to ultraviolet B radiation or through dietary sources. Major dietary sources of Vitamin D include oily fish, fortified margarines and some breakfast cereals, while smaller amounts are present in red meat and egg yolk, although these contribute only small amounts compared to endogenous synthesis [13]. Components of vitamin D synthesis are expressed in the ovary, decidua, endometrium and placenta. An inadequate vitamin D level has been associated with recurrent implantation failure and pregnancy loss and is associated with pregnancy-related disorders [14]. In early pregnancy, trophoblasts produce in response to vitamin D, and some investigators have demonstrated that vitamin D influences local anti-inflammatory responses and induces decidualization for successful pregnancy [15]. Only few studies have been conducted on role of vitamin D in women with gestational trophoblastic neoplasia and there is no such study yet in Bangladesh. Hasanzadeh M, et al. [16] observed that 25 (OH) vitamin D serum level is significantly lower in women with GTN than normal pregnant women [16]. Therefore, this study aimed to analyze the association of serum level of vitamin D with hydatidiform mole to better understand the potential role of Vitamin D in the pathogenesis of HM among

the Bangladeshi women.

## Materials and Methods

### Study Design

This study was a case-control study.

### Place of Study

The study was carried out in the Department of Obstetrics and Gynaecology, Institute of Child and Mother Health (ICMH), Matuail, Dhaka, Bangladesh.

### Period of Study

The duration of study was 12 months (From January 2021 to December 2021).

### Study Population

The study population included women at their first trimester of gestation attending in the outdoor and indoor of the Department of Obstetrics and Gynaecology of ICMH, Matuail, Dhaka. They were divided into two groups-

**Case:** Women with hydatidiform mole at their first trimester (age – 18 to 45 years).

**Control:** Healthy pregnant women without hydatidiform mole at their first trimester (age – 18 to 45 years).

### Sample Size Determination:

- Total calculated sample size,  $n = 50$  (in each group)
- Due to time limitation and resource constrains, a total number of 70 patients were selected for the study fulfilling the selection criteria.
- Therefore, total sample size was 70 (cases = 35, controls = 35).
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### Selection Criteria

#### Inclusion Criteria for Cases:

- Women at their first trimester of pregnancy with hydatidiform mole (confirmed by ultrasonography and raised  $\beta$ -hCG level)

#### Inclusion Criteria for Controls:

- Age matched healthy women in their first trimester of pregnancy with single viable fetus diagnosed by ultrasonography who gave consent.

#### Exclusion Criteria:

- Women who were taking vitamin D or calcium supplementation three months prior to pregnancy.
- Women diagnosed with chronic renal disease, liver disease, thyroid disorder, and any other malignant

conditions.

- Women who were taking anticonvulsant, glucocorticoid, anti-cancer, antiretroviral drugs.

### Data Collection Technique

Subjects were selected purposively according to availability of patients. Detailed history and clinical information were obtained by a preformed semi-structured questionnaire. Questionnaires were given to women including age, occupation, educational qualification, monthly family income, family history, place of residence, as well as gynecological and obstetrical history (gravida, para) were recorded.

### Study Procedure

After obtaining approval of Institutional Review Board, this case control study was conducted in ICMH, Matuail, Dhaka, during January 2021 to December 2021. In this period (after approval of protocol), the purpose and procedure of the study were discussed with the pregnant women and informed written consent was taken from those who agreed to participate in the study. A total of 70 participants aged 18-45 years were selected non-randomly fulfilling the inclusion and exclusion criteria for the study. 35 cases were enrolled as women with hydatidiform mole as per operational definition while the rest of 35 healthy pregnant women was considered the controls. The respondents were in their first trimester of pregnancy matched for age and gestational age. For each subject, separate data collection sheet was prepared. Socio-demographic, gravida, and presenting symptoms related data were collected from the patients using the pretested semi-structured questionnaire. Participants' vital signs and measurements of laboratory variables were recorded in a checklist. With maintaining all the aseptic precautions 5 ml of venous blood were collected from the ante-cubital vein using a sterile needle and syringe for estimation of serum vitamin D level. The needle was detached from the nozzle and transferred blood immediately into a red top tube with a gentle push to avoid hemolysis and the sample was allowed to clot, which was then transported from ICMH to biochemistry laboratory of IBN SINA diagnostic center, Doyagonj, Dhaka and then centrifuged at 4400 rpm for 10-15 minutes, and the serum was separated for biochemical assay on the day of collection. The separated serum was collected in eppendorf tube labeled appropriately for biochemical assay. The serum was assayed immediately or was stored at 20°C when the analysis was delayed, to avoid loss of bioactivity and contamination. Serum vitamin D level was then measured with the fully automatic Atellica IM 25 OH Vitamin D Total assay. Data were expressed as distribution of percentage and by mean  $\pm$  standard deviation (SD). For statistical analyses, chi square, Unpaired Student's t test, and Fisher's exact tests were

done. For demonstration of association odd's ratio analysis were used. The data was analyzed using Microsoft Excel 2010 and latest version of SPSS (v27.0) software, where required.

### Statistical Analysis

Statistical analyses were carried out by using computer based statistical software, SPSS 27.0 version (SPSS Inc, Chicago, IL, USA). Results were shown as table and expressed

as frequency & percentage for qualitative data and mean  $\pm$  SD for quantitative data and compared by Chi- square test or Fisher's Exact test for qualitative variables and Unpaired Student's t test for quantitative variables where was applicable. Serum vitamin D level was categorized based on the cut off value as normal ( $\geq 30$ ) and low ( $< 30$ ). Odds ratio (at 95%CI) was calculated to see the association of maternal serum vitamin D level with hydatidiform mole. A 'p' value  $\leq 0.05$  was considered as statistically significant (Tables 1-5).

### Results

Socio-Demographic Characteristics	Case n (%)	Control n (%)	Total n (%)	P-value
Age (years)				
Mean $\pm$ SD	25.4 $\pm$ 4.96	25.5 $\pm$ 3.73		0.957a
Education				
Illiterate	3 (8.6)	2 (5.7)	5 (7.1)	
Primary	13 (37.1)	15 (42.9)	28 (40.0)	0.805b
SSC/equivalent	12 (34.3)	9 (25.7)	21 (30.0)	
HSC & above	7 (20.0)	9 (25.7)	16 (22.9)	
Occupation				
Home maker	22 (62.9)	27 (77.1)	49 (70.0)	0.250b
Student	5 (14.3)	1 (2.9)	6 (8.6)	
Service holder	8 (22.9)	7 (20.0)	15 (21.4)	
Monthly household income				
Lower class ( $\leq 7,378$ Tk.)	4 (11.4)	2 (5.7)	6 (8.6)	0.789b
Lower middle class (7,379-28,810 Tk.)	29 (82.9)	30 (85.7)	59 (84.3)	
Upper middle class (28,811-89280 Tk)	2 (5.7)	3 (8.6)	5 (7.1)	

<sup>a</sup>Unpaired t test was done to measure the level of significance. <sup>b</sup>Fisher's exact.

**Table 1:** Distribution of the respondents according to socio-demographic characteristics by group (case = 35, control = 35).

A total of 35 cases and 35 controls were selected for the study. For this study purpose respondent's age were matched according to selection criteria and there was no statistically

significant difference in between the case and control groups regarding education, occupation and monthly family income ( $p > 0.05$ ) (Table 2).

BMI (kg/m <sup>2</sup> )	Group		Total n (%)	P-value
	Case n (%)	Control n (%)		
Underweight ( $< 18.5$ )	0 (0.0)	1 (2.9)	1 (1.4)	
Normal (18.5 – 24.9)	30 (85.7)	27 (77.1)	57 (81.4)	0.540 <sup>b</sup>
Overweight (25.0 - 29.9)	5 (14.3)	7 (20.0)	12 (17.1)	
Mean $\pm$ SD	24.49 $\pm$ 1.60	24.45 $\pm$ 2.21		0.921 <sup>a</sup>

<sup>a</sup>Unpaired t test was done to measure the level of significance. <sup>b</sup>Fisher's exact.

**Table 2:** Distribution of the study subjects according to BMI by group (case = 35, control = 35).

There was no significant difference in mean ( $\pm$ SD) body mass index of both case and control groups of patients ( $p=0.921$ ), and majority of the patients belonged to normal

weight group (85.7% in cases and 77.1% in controls) (Table 3).

Parameter	Case (Mean±SD)	Control (Mean±SD)	p value
Serum vitamin D level (ng/ml)	18.27 ± 8.89	26.29 ± 8.01	<0.001a
Minimum – Maximum	6.9 – 32.8	8.0 – 36.0	

<sup>a</sup>Unpaired t test was done to measure the level of significance.

**Table 3:** Distribution of mean (±SD) serum vitamin D level by group (case = 35, control = 35).

(Table 3) demonstrated the overall distribution of maternal vitamin D level by group, where the mean (±SD) vitamin D level among the cases were 18.27±8.89 ng/ml (range:

6.9 – 32.8 ng/ml) and in controls were 26.29±8.05 ng/ml (range: 8.0 – 35.0), which was statistically highly significant (p<0.001).

Parameter	Partial Mole (n=2) (Mean±SD)	Complete Mole (n=33) (Mean±SD)	p value
Serum vitamin D (ng/ml)	20.50 ± 0.71	18.13 ± 9.15	0.166 a
Minimum – Maximum	20.0 – 21.0	6.98 – 32.80	

<sup>a</sup>Unpaired t-test was done to measure the level of significance.

**Table 4:** Distribution of study subjects according to the type of hydatidiform mole and mean (±SD) of vitamin D level (case = 35).

Among the 35 cases, 33(94.3%) had complete hydatidiform mole whereas 2(5.7%) had partial hydatidiform mole. The mean (±SD) differences of serum vitamin D level

between the types of HM were statistically not significant (p=0.166).

Serum vitamin D level (ng/ml)	Groups		p- value	OR (95% CI)
	Case n (%)	Control n (%)		
Low (deficient/insufficient, <30)	27 (77.1)	15 (42.9)	0.003 <sup>c</sup>	4.5 (1.599-12.664)
Normal (sufficient, ≥30)	8 (22.9)	20 (57.1)		

<sup>c</sup>Chi-square (χ<sup>2</sup>) test was done to measure the level of significance.

**Table 5:** Odds ratios (OR) and 95% confidence intervals (CI) for hydatidiform mole according to serum vitamin D level in pregnancy (case = 35, control = 35).

There was significant difference in regards of deficient vitamin D level in between case and control groups (p=0.003) and the respondents with insufficient/deficient level <30 ng/ml had 4.50 times more chance to develop hydatidiform mole compared to that of the respondent with normal/sufficient vitamin D level (≥30 ng/ml) (OR=4.50; 95% CI = 1.599-12.664).

## Discussion

This case-control study was conducted to compare the serum vitamin D level in women with hydatidiform mole and normal pregnant women without hydatidiform mole, as a biochemical marker for risk estimation and evaluate any association between serum vitamin D level and hydatidiform mole. Seventy women between 18-45 years of age in their first trimester (up to 13 weeks) of gestation attending the inpatient and outpatient department of Department of Obstetrics and Gynaecology, Institute of Child and Mother Health (ICMH) were included in this study. Among them, 35 diagnosed women with hydatidiform moles were considered

as the cases, and the rest of the 35 normal pregnant women without hydatidiform moles were selected as the controls.

On evaluating the respondents' socio-demographic characteristics in the present study, ages were matched according to selection criteria where the mean (±SD) distribution among the cases and control groups was found almost similar (25.4±4.96 and 25.5±3.73 years respectively, p=0.957). Early marriage and higher birth rate are probably responsible for such distribution. 37.1% of case and 42.9% of the control patients were educated up to the primary level. Most of the participants were housewives (case: 62.9% and control: 77.1%), followed by service holder (case: 22.9% and control: 20.0%). Most of the study participants belonged from lower middle class social status with an average monthly family income of 7,379-28,810 Tk. only (case: 82.9%, vs. control: 85.7%). None of these socio-demographic characteristics in the study was found statistically significant (p>0.05). My findings were similar to Mulisya O, et al. [17], where the mean age at presentation was 27.90±7.1 years, majority of the participants were married with a low



socioeconomic status and had attained a primary level of education. Nahar S, et al. [18] observed 64% patients were between 20-29 years of age and only 10% were above 40 years mean age of the patients. Anyanwu M, et al. [19] also could not find an association between hydatidiform mole and age, ethnicity and occupation in Gambian women. The current study observed that the mean ( $\pm$ SD) BMI was nearly similar in both the cases and controls,  $24.49 \pm 1.60$  and  $24.45 \pm 2.21$  kg/m<sup>2</sup> respectively with p value 0.921. Majority (81.4%) of the respondents BMI was found within normal range. Only 2.9% respondents of control group had BMI <18.5 kg/m<sup>2</sup>. Maestá I, et al. [20] reported body mass index (BMI) has not affected the risk of progression to gestational trophoblastic neoplasia (GTN) or the efficacy of chemotherapy. Ringrose JS, et al. [21] also confirmed that there was a negative correlation between BMI and 25(OH) D ( $r = -0.202$ ,  $p = 0.002$ ). In contrast, Sinha K, et al. [22] found hyperthyroidism was common in patients with molar pregnancy and low BMI with a statistical significance ( $p = 0.005$ ) when compared with normal and high BMI patients. Their result revealed serum level of D were significantly lower in the CHM group (0.02 mmol/l) when compared with the single viable pregnancy (0.03 mmol/l) and non-pregnant (0.03 mmol/l) groups ( $p < 0.001$ ). In a longitudinal study Toko EN, et al. [23] evaluated maternal Vitamin D status and adverse pregnancy outcomes, including premature birth, stillbirth, normal delivery, molar pregnancy, and infant anthropometric variables. They documented insufficient plasma 25(OH)D (<75 nmol/L) in 50.8% and deficient (<50 nmol/L) in 20.6% of the cases. Hamilton SA, et al. [24] showed 48% vitamin D deficiency (VDD); an additional 37% insufficient in a diverse group of women presenting for obstetrical care. Lee JM, et al. [25] measured plasma 25-hydroxyvitamin D in 40 healthy mother-infant pairs. Although a majority of mothers received a daily prenatal multivitamin vitamin D deficiency (<30 nmol/L), was detected in 50% of mothers and 65% of their newborn infants. El-Zayadi AA, et al. [26] assessed the role of vitamin D deficiency and early pregnancy loss and showed that the mean value of 25(OH)D was significantly lower among miscarriage group ( $21.0 \pm 8.5$  ng/mL) than control group ( $26.5 \pm 8.3$  ng/mL) as  $p = 0.005$ . And the majority of miscarriage group (42.5%) had 25(OH) D deficiency while 40.0% and 17.5% of cases had insufficiency and sufficiency which was significantly different than control group ( $p = 0.049$ ). 25(OH)D  $\leq 24.5$  ng/mL was a significant factor that increased the likelihood of first-trimester miscarriage with sensitivity 80%. Hasanzadeh M, et al. [16] investigated serum vitamin D level for comparison of levels in women with gestational trophoblastic neoplasia and healthy women. They found pathologic diagnosis in 83.33% (25 patients) was complete hydatidiform mole and in 16.67% (5 patients) was partial

hydatidiform mole. 25(OH) vitamin D serum level in 73.3% of GTN patients and 2.1% of normal pregnant women was lower than 10 ng/ml and among all participants, only 6.3% of pregnant patients had 25(OH) vitamin D serum level higher than 30 ng/ml. 25(OH) vitamin D serum level between complete and partial hydatidiform mole groups had no significant difference ( $P = 0.384$ ). Therefore, in the current study, all the findings showed the association of low vitamin D levels among women with hydatidiform mole. So, screening for serum vitamin D level in preconceptions and early pregnancy might be considered as a part of the routine antenatal check-up.

## Conclusion

The findings of this study suggest that low maternal serum vitamin D level is significantly associated with an elevated risk for hydatidiform mole. Therefore, this study concludes that low level of serum vitamin D can be considered an important biomarker responsible for the development of hydatidiform mole.

## Limitations

This study had some limitations as well-

- The study was conducted in a single hospital. So, the study population might not represent the whole community.
- Sample size was not adequate.
- The sample was taken purposively. So, there may be a chance of bias that can influence the results.
- Other factors related to vitamin D absorption and molar pregnancy were not evaluated in this study.
- Sun exposure time and clothing patterns of the patients were not evaluated in this study.
- Limited resources and facilities.

Therefore, the study findings cannot be generalized to the entire population.

## Recommendations

In the light of the findings of the present study and discussion, therefore, it is recommended:

- To undertake further prospective study with a larger sample size to find out the validity of the findings of the present study.
- Other risk factors of hydatidiform mole should be evaluated.
- Multi-centric studies may be done.
- RCT is needed to prove that sun exposure and dietary supplementation of vitamin D can prevent hydatidiform mole.

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