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Review Article

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Association of Maternal Serum Vitamin D Level with Hydatidiform Mole-A Systemic Review

Ferdous Jahan Binte Rashid[1*], Syeda Nazia Akhter[2], Rehana Pervin[3], Fakhrul Amin Badal[4], Abida Sultana[5], Kaberi Das[6] and Noushin Zahan Avee[7]

[1]*Assistant Surgeon, Department of Obstetrics and Gynecology, Sheikh Hasina Medical College, Tangail, Bangladesh*

[2]*Professor, Department of Obstetrics and Gynecology, ICMH, Dhaka, Bangladesh*

[3]*Assistant Professor, Department of Obstetrics and Gynecology, Sheikh Hasina Medical College Hospital, Tangail, Bangladesh*

[4]*Assistant Professor, Department of Neonatology, Shaheed Ziaur Rahman Medical College, Bogura, Bangladesh*

[5]*Medical Officer, Department of Obstetrics and Gynecology, Upazila Health Complex, Sakhipur, Tangail, Bangladesh*

[6]*Medical Officer, Department of Obstetrics and Gynecology, ICMH, Matuail, Dhaka, Bangladesh*

[7]*Assistant Surgeon, Department of Obstetrics and Gynecology, Sheikh Hasina Medical College Hospital, Tangail, Bangladesh*

[*]Corresponding author

Ferdous Jahan Binte Rashid, Assistant Surgeon, Department of Obstetrics and Gynecology, Sheikh Hasina Medical College, Tangail, Bangladesh.

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ABSTRACT

Hydatidiform mole is an abnormal type of pregnancy, in which a potentially anomalous ovum is abnormally fertilized resulting in a subsequently non-viable conceptus becoming an enlarged growth in the uterus with dangerous complications. These moles can occur as either complete or partial, each with its own unique features. Like other risk factor, nutritional risk factors are associated with increased likelihood of development of HM. Low dietary intake of carotene, inadequate protein and animal fats are thought to be associated with increased risk of HM. Vitamin D is a steroid hormone with receptors found throughout the body including ovary, uterus, and placenta and has natural immunomodulator with anti-inflammatory properties. At the ovarian level, vitamin D has been shown to enhance ovulation. In the human syncytiotrophoblast, vitamin D and its components act together to enhance the expressions of human chorionic gonadotropin (hCG), human placental lactogen, estrogen and progesterone. Furthermore, vitamin D co-regulates cell proliferation, differentiation and apoptosis in numerous tissues and $1,25(OH)_2D_3$ also inhibits angiogenesis and metastasis. Deficiency of vitamin D may lead to increased ROS and decreased antioxidative defense systems that could lead to oxidative injury in patients with HM. In the human syncytiotrophoblast, vitamin D and its components act together to enhance the expressions of human chorionic gonadotropin (hCG), human placental lactogen, estrogen and progesterone. Furthermore, vitamin D co-regulates cell proliferation, differentiation and apoptosis in numerous tissues and $1,25(OH)_2D_3$ also inhibits angiogenesis and metastasis. Deficiency of vitamin D may lead to increased ROS and decreased antioxidative defense systems that could lead to oxidative injury in patients with HM. Studies showed there is significant association of low vitamin D level and obstetric complications like early pregnancy loss, premature rupture of membrane, fetal growth restriction and also many extra-skeletal diseases like ovary and colon cancer. In developing countries like-Bangladesh, vitamin D deficiency is much more common and starting in early life and persisting across the life span due to limited exposure to sunlight and low consumption of animal sources food. Therefore, this study was intended to determine the association of vitamin D and hydatidiform mole in a Bangladeshi woman, which may help in deciding about vitamin D supplementation as a preventive measure of hydatidiform mole.

Keywords: Hydatidiform Mole (HM), Maternal Serum Vitamin D Level

Introduction

Vitamin D has become increasingly recognized as a pluripotent regulator of biological functions above and beyond its classical effects on bone and calcium homeostasis [1]. Vitamin D receptor (VDR) and the functionally active form of its ligand, $1,25\text{-}(OH)_2D_2$, have been implicated in female reproduction function and myeloid leukemia cell differentiation [2]. This is necessary for embryo implantation and fertilization, as well as hematopoietic development. Vitamin D modulates reproductive processes in female; its nuclear receptor has been identified in the uterus, oviduct, ovary, placenta, and fetal membranes [3]. The placenta is one of the first extra-renal tissues shown to be capable of synthesizing $1,25(OH)_2D_3$, with CYP27B1 activity detectable in both maternal decidua and fetal trophoblast. Human uterine endometrial cells and decidual cells synthesize $1,25\text{-}(OH)_2D_3$ [4]. 1-Hydroxylase and VDR expression increase in first- and second trimester placenta and decidua compared with nonpregnant endometrium. Patients with vitamin D deficiency have an inherited defect in the gene for 1-

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hydroxylase, are unable to convert 25(OH)D_3 to 1,25-$(OH)_2D_3$ and defective decidualization. 1,25-$(OH)_2D_3$, its synthetic enzymes and receptor are all present at the fetal-maternal interface. 1,25-$(OH)_2D_3$ has a physiological role in endometrial cell differentiation into decidual cells, a crucial step in the process of blastocyst implantation [5]. The precise function of placental synthesis of 1,25$(OH)_2D_3$ remains unclear but is likely to involve localized tissue-specific responses with both decidua and trophoblast also expressing the vitamin D receptor (VDR) for 1,25$(OH)_2D_3$ [6]. In developing countries like-Bangladesh, vitamin D deficiency is much more common and starting in early life and persisting across the life span due to low exposure to sunlight and low consumption of animal sources food [7]. Vitamin D deficiency is very common in pregnant women [5]. There was scarcity of study to establish relationship of vitamin D and Hydatidiform mole. The prevalence of hydatidiform mole was higher among all entities of gestational trophoblastic disease [8]. By analyzing the association of serum level of vitamin D with hydatidiform mole of such patients is essential for early detection of malignant trophoblastic tumors and to reduce mortality rate. Supplementation with vitamins D may be suggested as a strategy for the prevention of CHM and its progression to GTN. The findings of this study in Bangladeshi women might help in deciding about vitamin D supplementation as a preventive measure of Hydatidiform mole.

Serum Vitamin D Level with Hydatidiform Mole

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 [9]. Dietary vitamin D is absorbed in upper part of the small intestine and enters circulation through thoracic duct in the chylomicron fraction, after which it associates with a α-globulin fraction in the blood [10]. It is then transported to the liver and hydroxylated to 25-hydroxyvitamin D [25(OH)D_3]. Additional hydroxylation of 25(OH)D occurs in the kidney and yields a wide variety of vitamin D metabolites, including 1,25-dihydroxy vitamin D [1,25$(OH)_2D_3$] [11]. Directly post-coitus, the seminal fluid induces a pro-inflammatory immune response, activating neutrophils and macrophages, as well as cytokine and chemokine pathways [12,13]. This response contributes to the endometrial remodeling necessary for implantation. It has been suggested that the maternal immune system acts as a quality control for semen. Less immunogenic seminal fluid leads to impaired endometrial receptivity [12]. Induced by the reaction to paternal semen, maternal Th cells that are regulated by regulatory T (Treg) cells are involved in building immune tolerance towards paternal antigens [14]. Sufficient transforming growth factor (TGF)-β quantity in the seminal fluid supports the adequate Treg activation [12]. In the oviduct sperm cells binding to the epithelium, stimulate an anti-inflammatory response by upregulating TGF-β and interleukin (IL)-10 and thereby supporting spermatocyte passage and oocyte fertilization [13]. Effector functions of Tregs are promoted by 1,25$(OH)_2D_3$ which have immuno-suppressant functions and are of critical importance to the establishment of pregnancy [15].

Maternal age and a history of GTD have been established as strong risk factors for hydatidiform mole and choriocarcinoma and major etiological hypotheses, including parental age, AB0 blood groups, history of GTD, reproductive factors, oral contraceptive use and other environmental factors. There is limited information on other possible etiological risk factors for GTD, such as smoking habits, alcohol consumption, diet, socioeconomic status and herbicide exposure. Other risk factors include diets low in protein, folic acid, vitamin deficiencies especially vitamin D and carotene [16]. Nutritional deficiencies in these elements are potential risk factors for CHM [17]. Decreased consumption of carotenoids as well as lower serum levels of vitamins A, D, and E and folate have been reported in HM [18].

Moreover, vitamin D can be able to exert protective effects against ROS and nitric oxide and may prevent oxidative damages. This vitamin regulates the gamma- glutamyl transpeptidase (g-GT) expression, which contributes to reduced glutathione (GSH) synthesis. GSH is essential to glutathione peroxidase (GPX) activity, which participates of the cellular enzymatic antioxidant defense system. Vitamin D can also increase glucose-6-phosphate dehydrogenase (G6PD), glutamate-cysteine ligase (CGL) and glutathione reductase activity, increasing GSH formation. Indirectly this vitamin acts in antioxidants synthesis by regulating Klotho and Nrf2 (Nuclear factor erythroid 2-related factor 2) expression, which are important to ROS signaling pathway function. Vitamin D, acting with Klotho and Nfr2, regulates antioxidant systems expression, which could prevent oxidative stress [19]. Additionally, homogenous distribution of vitamin D and VDR expression in syncytiotrophoblasts, cytotrophoblasts and chorion villus stroma both in the missed abortion group and the induced abortion group was reported [20].

Vitamin D Level

Vitamin D insufficiency affects almost 50% of the population worldwide [1,15]. An estimated 1 billion people worldwide, across all ethnicities and age groups, have a vitamin D deficiency (VDD) [12,16]. This pandemic of hypovitaminosis D can mainly be attributed to lifestyle and environmental factors that reduce exposure to sunlight, which is required for Ultraviolet-B (UVB)-induced vitamin D production in the skin. Black people absorb more UVB in the melanin of their skin than do white people and, therefore, require more sun exposure to produce the same amount of vitamin D [18]. The high prevalence of vitamin D insufficiency is a particularly important public health issue because hypovitaminosis D is an independent risk factor for total mortality in the general population [19]. Emerging research supports the possible role of vitamin D against cancer, heart disease, fractures and falls, autoimmune diseases, influenza, type-2 diabetes, and depression. The major source of vitamin D for children and adults is exposure to natural sunlight [1,14-16]. Thus, the major cause of VDD is inadequate exposure to sunlight [2,20]. Wearing a sunscreen with a sun protection factor of 30 reduces vitamin D synthesis in the skin by more than 95% [18]. People with a naturally dark skin tone have natural sun protection and require at least three to five times longer exposure to make the same amount of vitamin D as a person with a white skin tone [13,15]. There is an inverse association of serum 25(OH)D and body mass index (BMI) greater than 30 kg/m^2, and thus, obesity is associated with VDD [19].

Hydatidiform Mole

Hydatidiform mole is an abnormal condition of the placenta where there are partly degenerative and partly proliferative changes of young chorionic villi. These results in formation of clusters of small cysts of varying sizes. Because of the superficial resemblance of hydatid cyst, it is named as hydatidiform mole. Histologically, the disease is characterized by (i) hydropic degeneration and swelling of the villous stroma, (ii) absence of villous blood vessels and (iii) proliferation of both the trophoblastic epithelia to a varying degree. Irrespective of trophoblastic cell proliferation, it is the preservation of a villous structure that determines the benign nature of the trophoblastic disease [21].

Complete Mole

A complete hydatidiform mole resembles bunches of grapelike vesicles, pearly white in color and translucent, containing watery fluid. The vesicles vary in size from a few millimeters up to 2-3 cm in diameter and are attached to the main stalk by thin pedicles. A few hemorrhagic areas are seen in between the bunches. The fetus, amniotic sac and the placenta are conspicuously absent. The size of the mole depends on the duration of pregnancy and degeneration. Karyotype is 46,XX; 46,XY [21].

Partial Mole

A partial mole resembles the placenta but contains a few vesicles on its maternal surface. A fetus is identifiable in this case. In a partial mole, some or most of the villi appear normal. The fetus most often shows gross malformation, fetal growth restriction and in utero death. Very few live babies are born through a partial mole. The fetal blood vessels are seen on ultrasound scan. Karyotype is 69XXY; 69XXX [21].

Vitamin D-level

Vitamin D (also referred to as calciferol) is a fat-soluble vitamin, the functions of which are not limited to skeletal health benefits and may extend to the aid of insulin secretion and insulin sensitivity.

Reference values of serum vitamin D levels are as follows [10]
Low/inadequate level:
Deficient: ≤20 ng/ml Insufficient: 20-29 ng/ml
Adequate/normal level: ≥30 ng/ml

Blood Sample Collection and Measurement of Serum Vitamin D Level

A 5 ml brachial blood sample was obtained from each subject of both groups by venipuncture and collected in a capped polypropylene tube was labeled with the allocated number. Serum was separated at room temperature or by centrifugation (4000 rpm for 5 minutes), and hemolyzed sample was discarded. Specimens were stored for up to 28 days at 2-8°C after the date of collection. Serum vitamin D level was estimated in the Biochemistry laboratory at IBN SINA diagnostic center, Doyagonj, Dhaka with proper procedure. The level of serum vitamin D was expressed in ng/ml. Cut off value of vitamin D range from 30-<100ng/ml was sufficient level, deficiency was <20 ng/ml, insufficient was 20-<30 ng/ml and more than100ng/ml were toxic level.

Safety Precautions

As the study was ran in COVID-19 pandemic situation, all the procedures were performed after wearing PPE (personal protective equipment). Gloves, lab coat and safety glasses were worn when handling all human blood products and tissues. Disposable materials were placed in a biohazard bag. Non-disposable material at the end of working day were disinfected. Washing hands thoroughly was done after removal of personal protective devices used in handling instruments and specimens.

Conclusion

In summary, evaluations carried out in the present study indicate an inverse significant association between maternal VD level and chance of having low-weight infant. Therefore, this study concludes that low level of serum vitamin D can be considered an important biomarker responsible for the development of hydatidiform mole. It was concluded to be a relationship between plasma folate and homocysteine levels and HM. As previously stated, vitamin D receptors are located in the placenta, and as the vitamin D level is important for the placenta development in early pregnancy, the serum 25 OH-D vitamin levels were compared in this study between CHM patients and control subjects.

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