A Review on Association of Mothers' Vitamin D Deficiency and Single Nucleotide Polymorphism of Vitamin D Receptor Gene (ApaI) with Risk of Preterm Birth and Low Birth Weight

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

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Approval

The project titled “A Review on Association of Mothers’ Vitamin D Deficiency and Single Nucleotide Polymorphism of Vitamin D Receptor Gene (ApaI) with Risk of Preterm Birth and Low Birth Weight” submitted by Tinni Dutta (18346088) of Summer 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on September 2023.

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Ethics Statement

The study does not involve any kind of animal or human trial.

Abstract

Preterm birth and low birth weight are significant public health concerns associated with adverse neonatal outcomes and long-term health implications. Preterm birth is the leading cause of death in infants under the age of one year and vitamin D deficiency during pregnancy is linked to preterm birth and low birth weight. There is a very significant link between vitamin D deficiency and adverse pregnancy outcomes. For fetal growth and development, pregnant women must have a sufficient nutritional vitamin D level. Various genetic factors have been implicated in the susceptibility to these conditions, and the maternal Vitamin D Receptor (VDR) gene polymorphism- ApaI, has emerged as a potential candidate. This review aims to provide a discussion of the existing literature on the association between mothers' vitamin D deficiency and single nucleotide polymorphisms (SNPs-ApaI) of the VDR gene and the risk of preterm birth and low birth weight.

Keywords: Preterm birth; low birth weight; vitamin D receptor; single nucleotide polymorphisms (SNPs);public health; adverse outcomes.

Dedication

I dedicate this work to my beloved parents who believed in me.

Acknowledgement

First, I am grateful to almighty for giving me all the opportunities, sound health, and dedication to complete my project work. I feel grateful to the almighty for having a supportive and kindhearted personality like my supervisor Dr. Raushanara Akter (Professor of the School of Pharmacy of BRAC University). Without her constant support, motivation, and monitoring the work could not be done. Whenever I faced any problem without hesitation, I asked her for help and ma'am helped me without seeing the time.

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List of Acronyms

PTB	Preterm birth
LBW	Low birth weight
SGA	Small-for-gestational-age
VDBP	Vitamin D binding protein
VDD	Vitamin D deficiency
VDR	Vitamin D receptor
SNP	Single nucleotide polymorphism
SNV	Single nucleotide variant
WHO	World health organization
IUGR	Intrauterine growth restriction
PPROM	Pre-labor premature rupture of membranes
SPTB	Spontaneous preterm birth
NR	Nutritional rickets
GWG	Gestational weight gain
VDREs	Vitamin D response elements
RCTs	Randomized Controlled Trials
PTN	Preterm neonates
VitD	Vitamin D

Chapter 1: Introduction

1.1 An overview on Preterm Birth & Low Birth weight

Preterm birth (PTB) is the main cause of neonatal mortality and the 2nd most prevalent reason of death below five years old children. Preterm delivery complications are the primary cause of infant mortality, accounting for thirty-five percent of the world's annual deaths which is 3.1 million and the 2nd main cause of death among infants below the age of five after pneumonia (Lawn JE D. R., 2013). Preterm birth, also known as PTB, A woman is considered to have preterm birth (PTB) if she gives birth to her baby earlier than 37 weeks of her pregnancy (Liu & al, 2012). PTB is divided into two broad categories: (1) Spontaneous preterm birth (SPTB) and (2) Provider-initiated preterm birth (Harrison, 2015). In spite of advances in medical technology, unfavorable pregnancy consequences are the major concern for the people health (Chiavaroli, et al., 2016). The primary risk issues for preterm birth include women age, a short inter-pregnancy gap, multiple pregnancies, drug usage, smoking, infections or insufficient gestational weight gain (Pino, et al., 2017). Women are more likely to acquire PTB due to a number of factors, including demographics like ethnicity, immunological processes including infection and inflammation, inherited factors with a mother's history of PTB, nutritional deficiencies, and immunological processes (Knight, 2015). Despite the fact that SPTB involves several components, immunological and genetic factors conduct a crucial part in SPTB initiation. Spontaneous pre-term delivery is a complex process caused by the combination of elements that causes the uterus to shift from a resting state to active contractions and labor earlier than the thirty-seven week of pregnancy (P, 2005). Different gestational ages, social and environmental circumstances, as well as potential reasons, can all play a role in the events that causes spontaneous pre-term delivery. In up to half of all cases, it cannot be detected in any way. A strong risk factor is a history of premature birth in the mother, which is most likely

caused by the interaction of multiple risk factors, including genetic, epigenetic, and environmental variables (Plunkett J, 2008). Morbidity is still an ongoing concern despite the fact that clinical developments have significantly reduced the mortality rate of premature babies. It is unknown if preterm infants will reach developmental milestones at the same pace as term-born children. Many preterm newborns appear to act and have distinct developmental trajectories that set them apart from term children as they grow, even among those without congenital problems. According to several studies, preterm newborns have the potential to achieve weight and height catch-up throughout the initial two years of their lives (Euser, de Wit, Finken, Rijken, & Wit, 2008). Additionally, it is linked to a higher risk of death when comparable to the risk of preterm delivery in females delivered at the same gestational age (Kent AL, 2012). According to the World Health Organization (WHO) estimations of preterm birth rates, there were 14.9 million preterm births worldwide in 2010, out of a total of 135 million live births. This corresponds to an 11.1% preterm birth rate (Blencowe H C. S., 2012). It is estimated that over 60% of preterm births take place in sub-Saharan Africa and South Asia, regions where around 9.1 million infants (12.8% of total births) are projected to be born prematurely annually. Africa and Asia collectively exhibit a higher absolute count of preterm babies compared to the combined total of all other continents as a direct result of their high levels of fertility and high rates of births in comparison to those found in other regions of the world. The prevalence of PTB varies by ethnicity.

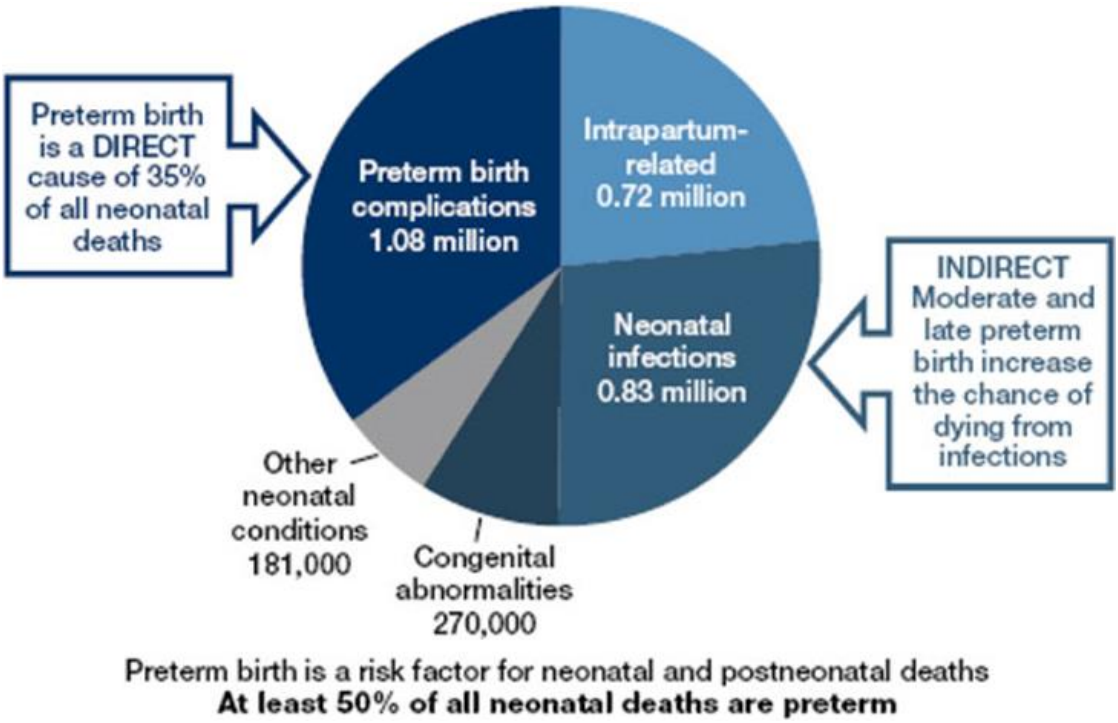

Figure 1: 3.1 million neonatal fatal incidents in 193 countries in 2010 (Lawn JE D. R., 2013)

Black women have a PTB rate of 16.3%, whereas Native American women have a rate of 13%, Hispanic women have a rate of 11.3%, and Asian and Indian women have a rate of 10% (Howson CP, 2012). The impact of ethnicity has long been debated in preterm birth, but evidence is available. The influence of ethnicity is being extensively examined in many population-based studies going back to the 1970s (Kent AL, 2012). While previous research has linked this particular variance to economic status and daily lifestyle, a more recent study suggests that genetic factors may also play a role. For instance, Black African babies are more likely to be born early than white newborns (Patel RR, 2004). However, Black African babies are born from a specific gestational age have less shortness of breath (Patel RR, 2004) neonatal mortality (Farrell PM, 1976) and are at a lower risk of requiring special care than babies of Caucasian ethnicity (P:, 2005). The prevalence and underlying causes of provider-initiated preterm birth vary widely. A recent American study was shown that more than half of all premature births that were started by healthcare providers and took place between 34 and 36 weeks of pregnancy were carried out for non-clinical reasons. This highlights the importance

of further understanding the factors contributing to provider-initiated preterm births and the need for appropriate medical indications in order to prevent unnecessary interventions (Gyamfi -Bannerman C, 2011). According to the most recent figures provided by the World Health Organization (WHO) regarding global rates of preterm births, out of the 135 million live births that took place around the world in 2010, 14.9 million babies were delivered prematurely, which indicates a preterm birth rate of 11.1 (Blencowe H C. S., 2012). These regions predict an annual occurrence of 9.1 million premature deliveries, which accounts for 12.8% of all newborns. Two of these areas have a high total number of premature births because they have high fertility rates and a disproportionately large number of newborns in comparison to the rest of the globe. As a result, these two regions have a high infant mortality rate. The average proportion was highest in countries with low income (11.8%), followed by countries with low-middle income (11.3%), and it was lowest in countries with high income (9.4%) and high-middle income (9.3%). On the other hand, a relatively high prevalence of premature birth can be seen in many nations with high incomes, and these births contribute significantly to the mortality and diseases that affect newborns. Annually, the United States witnesses the birth of about 500,000 infants that are delivered prematurely, accounting for 42 percent of the total number of preterm births that take place in high-income countries. The countries of Southeast and South Asia have the highest rate for each Millennium Development Goal area, with an estimated 13.4% of the population being born prematurely (Figure1). In high-income countries, more than 60% of infants born at less than 28 weeks of gestation surroundings in the year 1990, and approximately two-thirds of these children grew up without any form of handicap (Mohangoo AD, 2011). It is estimated that there were 15 million premature births in 2010, of which more than one million died as a direct result of complications during the first month of life, and many more died as a result of the indirect effects of their premature delivery, and millions more experienced lifelong impairments. The majority of preterm births occur in low-

income countries, particularly those in South Asia. Premature birth, however, is a significant worldwide health concern with a significant burden that is present also in nations with high revenues. For instance, approximately one out of eight babies are born prematurely in the United States. Preterm birth rates are high in both the most prosperous and poorest countries, yet there are some regions where preterm infant survival rates are significantly different. In areas with high incomes, half of the infants delivered at 24 weeks may survive, but in low-income areas, 50% of newborns born at 32 weeks of pregnancy still die from the absence of fundamental healthcare (Lawn JE D. R., 2013). In addition, it is projected that 20 million infants around the world are born with little birth weight, often known as LBW, which is defined less in weight than 2500 grams at birth. It is important to emphasize that almost all, nearly 95%, of these low birth-weight newborns are born in countries that are still considered to be developing. The prevalence of LBW is particularly high in South-Central Asia as well as in Africa. LBW is primarily attributed to two main factors: preterm birth, which refers to babies born before reaching 37 weeks of gestation, and intrauterine growth restriction (IUGR), a state where the baby fails to grow adequately inside the womb. It is crucial to be aware of that both preterm birth and IUGR significantly increase the likelihood of severe health complications and even mortality among newborns. Among the various risk factors contributing to LBW, maternal nutritional status emerges as one of the most crucial factors to consider (Imdad A, 2013).

1.2 A Global Perspective of Vitamin D for Health

Over a period of more than 500 million years, the rays of the sun contribute to the synthesis of vitamin D on this planet. In the 1600s, as the industrial era swept over Europe's northern regions, buildings were constructed, which caused children to suffer from the bone-deforming disease rickets. Rickets, a disease that has been linked to vitamin D deficiency, was initially described in clinical terms for the first time in 1651 by Glisson. He discussed kids who had

rickets, also referred to as the Morbus Anglorum at the period since of its prevalence in England. Sniadecki presented the first explanation for the potential link between Northern European industry and rickets. In 1822, he claimed that adolescents in Warsaw's inner city suffered from rickets due to limiting exposure to the sun. In clinical studies, he found that infants living in rural regions outside of Warsaw did not have rickets, but infants who were born in Warsaw were seriously affected by the condition. Based on these findings, he hypothesized that infants staying in remote areas outside of Warsaw had no rickets (Sniadecki, 1939). The early 20th century marked the discovery of the connection between rickets and a lack of sunlight, and around 1920, accounts of rickets being treated by sunlight began to circulate (Holick, 2011). At the beginning of the 20th century, it was believed that more than between 80 and 90% of children residing in the northern parts of Europe and the northeast region of the United States exhibited symptoms of rickets (MF., 2006). Additionally, in 1931, the federal government of the United States formed an agency with the mission of encouraging moderate sun exposure in infants and toddlers to minimize the chance of rickets and improve the overall health of their bones (Hess AF, 1921). The federal government of the United States formed an agency with the mission of encouraging moderate sun exposure in infants and toddlers in order to decrease the incidence of rickets and improve the overall condition of their bones (Hess AF, 1921). Lack of vitamin D has been identified as a global epidemic that can have a variety of negative effects on the health of individuals (Hossein-nezhad A, 2012). Deficiency in vitD is linked to an increase chance of developing diabetes, especially type 1 diabetes, heart disease, certain kinds of cancer, cognitive decline, depression, pregnancy-related complications, autoimmune diseases, allergies, and even depression in those who have a weak immune system (MF, 2012). On the other hand, having low levels of vitD in pregnancy can increase a person's risk of developing mental illness, diabetes, and MS later in life through

having an influence on particular target organs, such as the immune system, as well as epigenetic variables (Lucas RM, 2008).

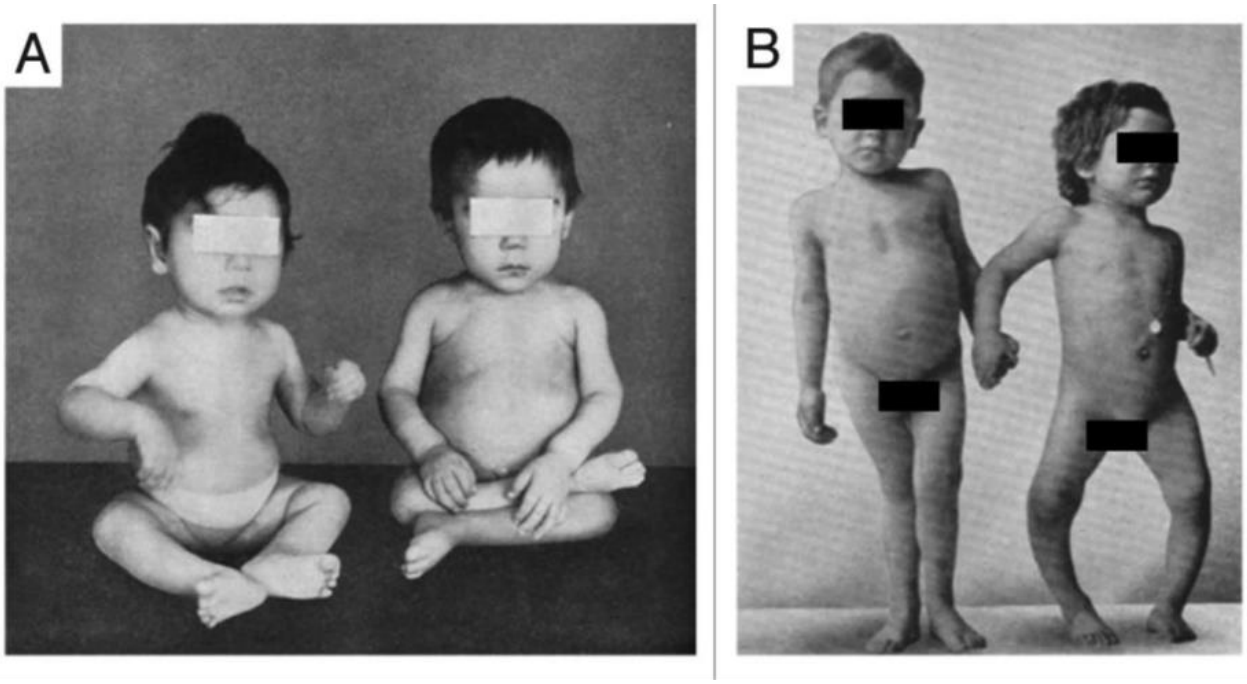

Figure 2. Skeletal deformities observed in children with rickets in 1930 (MF., 2006)

A sufficient intake of vitD is necessary for healthy bone development. Children and women who are pregnant are particularly susceptible to vitamin D deficiency (VDD), and some studies have connected VDD to negative health effects in both circumstances (K, 2003). Following a discussion of the onset and treatment of nutritional rickets, it was suggested people to take vitamin D supplements and that foods be fortified with vitamin D with the help of government support (MF, 2010). Despite tremendous improvements over the past century, a number of risk factors for symptomatic VDD still exist. The mother's nutritional status has a significant impact on how well a child develops in terms of nutrition. Prenatal gene expression is altered by a mother's diet, which may make women more susceptible to conditions like diabetes mellitus and hypertension (Sherzay N, 2016). In human populations, genetic polymorphisms can raise the chance of acquiring disorders that change how the body responds to nutrition metabolically.

The absorption of dietary vitamin D depends primarily on the small intestine. In the kidney and GI tract, mineral homeostasis is regulated by vitamin D. It has an impact on 10% of the human genome and has a role in development as well as growth. The wellness of both the mother and the unborn child depends on maintaining vitamin D homeostasis throughout pregnancy. The various unfavorable maternal outcomes (Dror DK, 2010) and including low birth weights seen in (Reichetzeder C, 2014) expectant mothers linked to inadequate vitamin D. Previous studies shown that both African-Americans and Caucasians had an increased risk of PTB when a pregnant woman has low vitamin D levels. Since 1, 25-dihydroxyvitamin D (calcitriol) deficiency may be another risk factor for pregnancy and labor difficulties but further research is required. Vitamin D has biological effects through attaching to the vitamin D receptor (VDR) located in bones, kidneys, small intestine, and nerve cells and mediates gene expression (Valdivielso JM, 2006). Collaboration between academics, government, and industry, as well as countries of varied latitudes, is critical for identifying long-term solutions to the global problem of vitamin D insufficiency (A P. , 2008).

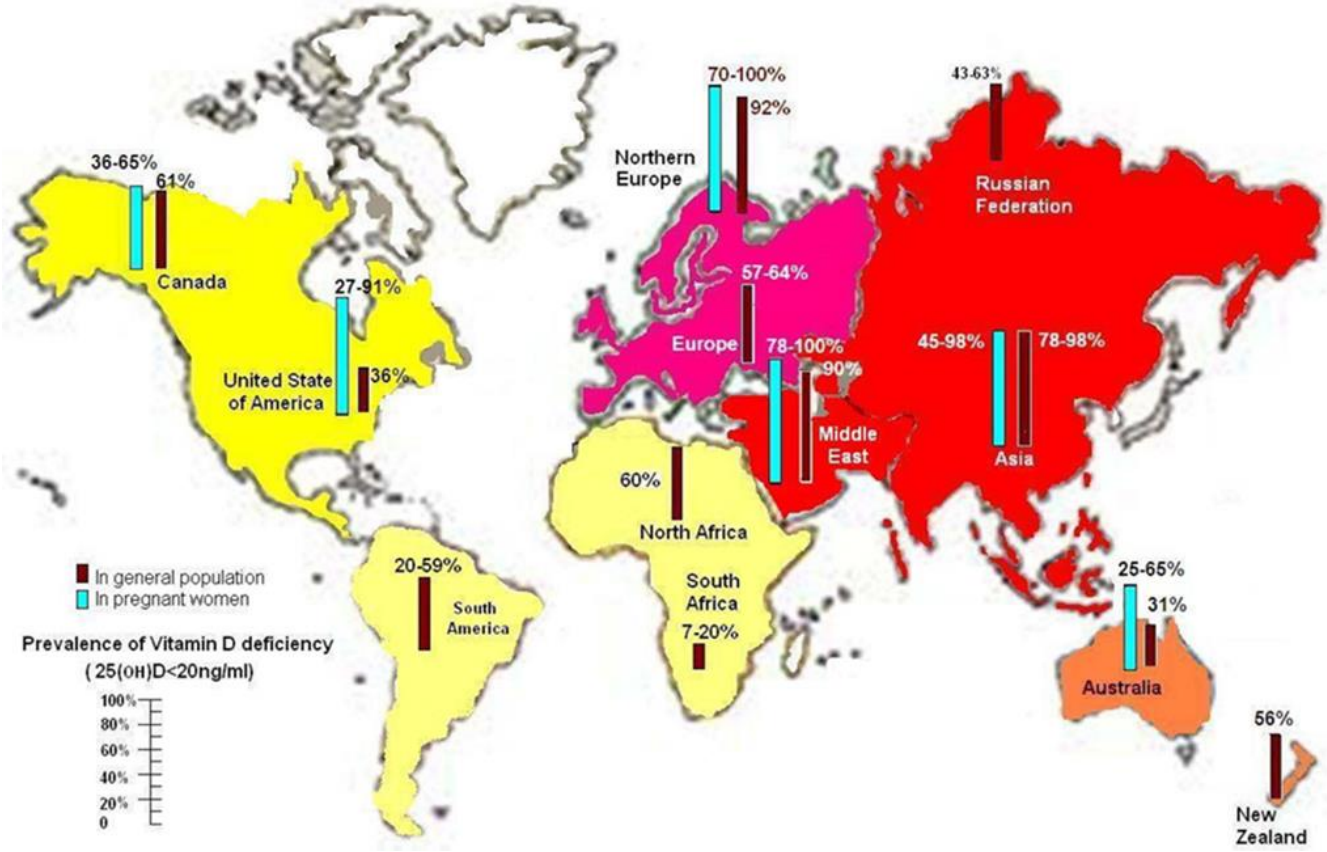

Figure 3: Vitamin D insufficiency affects pregnant women and the general population globally (A P. , 2008)

1.3 Vitamin D metabolism and Biological Function

The lack of vitamin D is acknowledged as a serious public health issue, especially huge percentages of the population in most nations generally do not fulfill the dietary requirements for vitamin D established by the Vitamin D Dietary Guidelines (Cashman, 2018). A number of disorders, including extra-skeletal diseases including cancer, autoimmune, cardiovascular, and metabolic issues, as well as neurological and autoimmune diseases have been linked to low level of vitD, according to several observational studies (Mulligan ML, 2009). Ergocalciferol, sometimes referred to as vitamin D2, is synthesized by the process of irradiation of plants, plant products, or dietary sources. On the other hand, cholecalciferol, usually known as vitamin D3, is endogenously generated in the skin upon exposure to ultraviolet (UV) radiation or sunshine.

The liver is responsible for the conversion of vitamin D3 to 25-hydroxyvitamin D3 (25(OH) D), which then undergoes conversion to 1, 25-dihydroxyvitamin D3 (1, 25(OH) 2D) in the kidney. This active form of vitamin D3 plays a crucial role in enhancing calcium absorption within the gastrointestinal system. The active component of 1, 25(OH) 2D interacts to the vitamin D receptor once it enters the cell. In the cells of the intestinal tract, (1, 25(OH) 2D) has the well-known influence on the active calcium transport. Calcium is able to enter the cell because of the proteins that are found in the membrane. The skin produces 7-DHC, which sunlight converts to vitamin D3. The 7-DHC molecule is present in every layer of human skin (MF, 2012). The skin synthesizes pre-vitamin D3, which can undergo two different processes for conversion. Firstly, it can be transformed into lumisterol, tachysterol, and 7-DHC by exposure to light. Alternatively, pre-vitamin D3 can be turned into vitamin D3 through a heat-induced process involving membrane-enhanced isomerization. Both of these pathways lead to the same end result: vitamin D3. Vitamin D3 synthesized in the epidermis needs to undergo additional processing in order to become active. The liver mostly performs the first stage, 25-hydroxylation, but it also occurs in other tissues. The most common type of vitamin D in circulation is 25(OH) D. The biological impacts of 1,25-dihydroxyvitamin D (1,25(OH)2D) are facilitated by its interaction with the vitamin D receptor (VDR), which in turn modulates the transcriptional activity of numerous downstream genes. During pregnancy, there are several aspects of vitamin D biosynthesis that play an important part in the physiology of the developing baby. In comparison to women who were not pregnant, amount of 1,25(OH) 2D increased dramatically, with a twofold increase in the first trimester of pregnancy, a subsequent two to threefold increase throughout pregnancy, and a rapid decline following delivery (Bikle, Malmstroem, & Schwartz, 2017). There are still large knowledge gaps regarding the regulation of serum 1, 25(OH) 2D concentrations in pregnancy. This is due to the fact that PTH concentrations are lower in pregnant women compared to non-pregnant women (Møller, et al.,

2013). When it comes to the regulation of serum 1, 25(OH) 2D levels during pregnancy, it's possible that other hormones, like PTH-related peptides, also play a part. Additional support for the hypothesis that the synthesis of 1, 25(OH) 2D is dependent upon substrate availability or impacted by serum 25(OH) D concentrations during pregnancy can be observed by the observation that pregnant women exhibit elevated amounts of 1, 25(OH) 2D and 25(OH) D in their bloodstream compared to non-pregnant women (Yap C, 2014). Furthermore, the formation of 1, 25(OH) 2D occurs locally at the tissue level by the placenta. Nevertheless, the placenta's synthesis of 1, 25(OH) 2D does not make a substantial contribution to the circulating blood levels of 1, 25(OH) 2D. Several observational studies have reported a raise in DBP levels in pregnancy, with maximum blood DBP concentrations roughly 40-50% higher than in non-pregnant women around the beginning of the third quarter and progressively declining during the duration of the pregnancy. The observed elevation in DBP levels has been identified as a significant factor linked to a higher likelihood of premature labor and the delivery of infants with low birth weight (Karras, Koufakis, Fakhoury, & Kotsa, 2018). The mother's vitamin D level is crucial to the development of the unborn child throughout pregnancy, there is an extremely significant association between the concentrations of 25(OH) D in the cord blood of the mother and the fetus. While 25-hydroxyvitamin D (25(OH) D) is capable of passing the placenta, the synthesis of 1, 25-dihydroxyvitamin D (1, 25(OH) 2D) occurs inside the renal system of the growing child (Møller, et al., 2013).

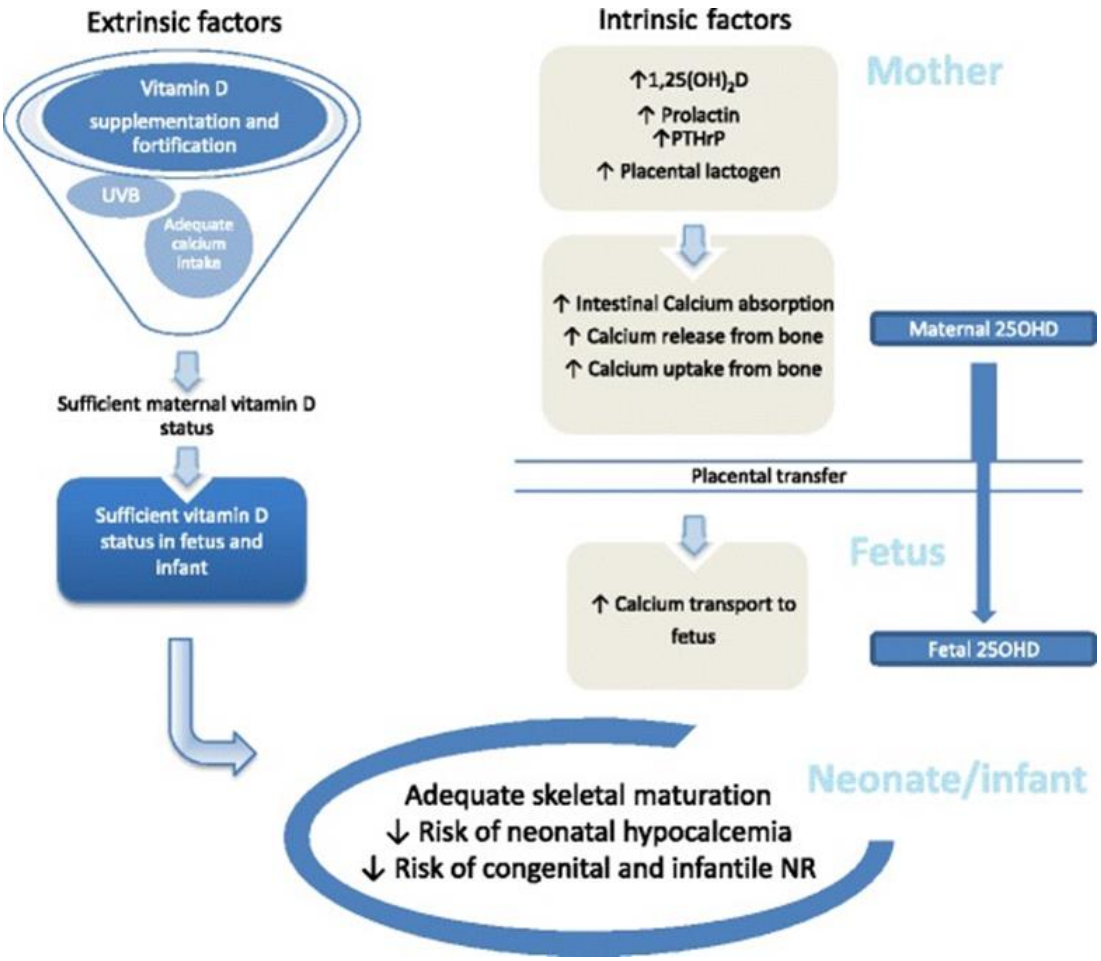

Figure 4: Schematic representation of maternal factors and physiological changes during pregnancy (Aghajafari F, 2013)

In average, when compared with the amounts of 25(OH) D found in the mother's serum, the concentrations of 25(OH) D found in the cord blood range from 50 to 80 percent **(**O'Callaghan, et al., 2018**)**. This demonstrates how crucial it is for expecting mothers to have the right amount of vitamin D through supplements. Pregnancy and nursing are two scenarios that necessitate for an optimum vitamin D status to prevent disruptions in bone and mineral metabolism. From a physiological perspective, it is essential for preserving the balance of calcium (a mineral) and bone (Kovacs, 2014). Within the cytosol, the VDR protein can be shown to possess both ligand binding and DNA binding domains. The exposure of the Vitamin D receptor gene in the placenta affects the activity of multiple genes, including those that are essential for implantation, fetal development, and bone formation.

Endometrial skeletal mineralization and growth during pregnancy can be affected by a woman's vitamin D status (Manzon L A. G., 2014). Vitamin D's downstream biological activity can also be affected by polymorphisms in the VDR gene, which can have an effect on the exposure and activity of the gene itself (Gao L, 2010). There are several polymorphism areas found in the VDR gene. The restriction enzymes found BsmI, TaqI, ApaI, and FokI polymorphisms near the 3' terminal of the VDR gene. The polymorphisms are related to Type 1 diabetes mellitus (Moran JM, 2015) polycystic ovary syndrome, (Al-Moubarak S, 2013). As a result, genetic disparities in prematurity in relation to VDR gene polymorphism must be explored. The purpose of this study is to investigate the genetic factors that contribute to the risk of PTB & LBW, specifically focusing on the VDR gene polymorphism.

1.4: The Role of Vitamin D in Pregnancy

Pregnancy is a period characterized by rapid transformations, encompassing alterations in physical dimensions, physiological processes, and the assumption of additional responsibilities. A woman is responsible for both her own health and well-being as well as the health and development of her unborn child during this time in her life (Daly S, 1997). The results of a recent study in South Carolina, USA, with approximately 494 women of various racial and ethnic origins who had completed the Block Food Frequency questionnaire, where the average daily diet only contained 200 IU/day of vitamin D (Hollis BW, 2011). In contrast, after getting 10-15 minutes of total body exposure to sunlight, the body produces 10,000–15,000 IU of vitamin D throughout the course of a 24-hour period (Matsuoka LY, 1990). Numerous epidemiological studies have found connections between vitamin D deficiency and alterations in the health of individuals. Conversely, there exists a correlation between elevated levels of 25-hydroxyvitamin D (25(OH) D) in the bloodstream and enhanced glucose regulation as well as better pancreatic beta-cell functionality (Chiu K, 2004), rheumatoid

arthritis, systemic lupus erythematous and type 1 and type 2 diabetes (Kimball SM, 2007). However, there has been increasing evidence from laboratory research that vitamin D, which functions as a pre-hormone, is crucial for immune system maintenance (Liu PT, 2006).

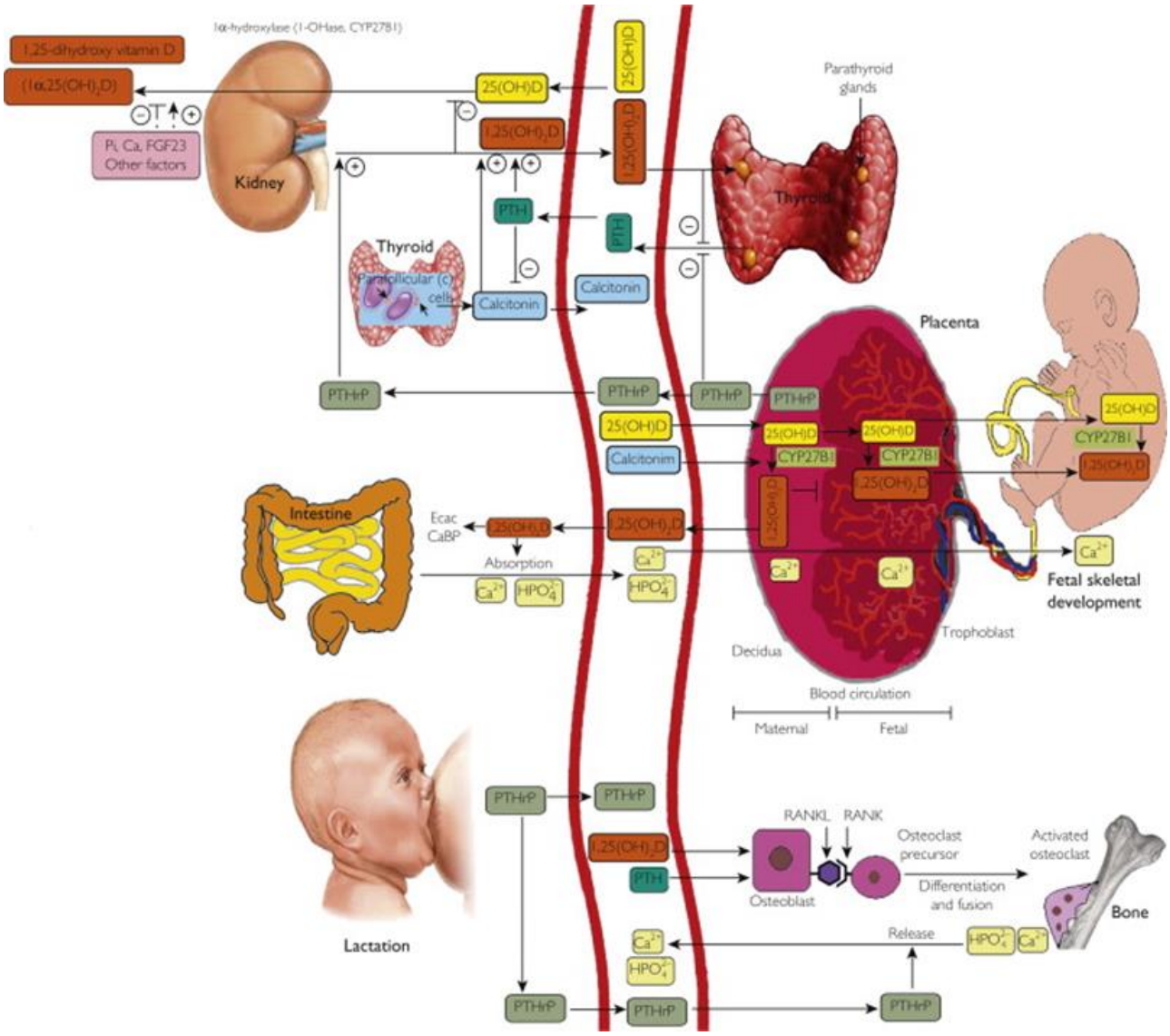

Figure 6: Vitamin D circulation in pregnancy (Kalra P, 2012)

In order to facilitate optimal fetal skeletal development, dental enamel formation, and potentially overall fetal growth and development, it is imperative for pregnant women to maintain adequate levels of nutritional vitamin D (Brooke OG, 1980). There was an association between the levels of vitamin D ingested during pregnancy and the growth characteristics of newborn newborns when they were compared to the maternal intakes of milk and vitamin D throughout pregnancy. The study found a positive correlation between maternal vitamin D intake during pregnancy and birth weight. Specifically, for every additional 40 IU of vitamin D intake, there was an associated increase in birth weight of 11 grams (Mannion C, 2006).

1.5 Synthesis of Vitamin D

Upon exposure to sunshine, the 7-dehydrocholesterol present in the skin undergoes a process of absorption of ultraviolet B rays, leading to its conversion into pre-vitamin D3, which undergoes isomerization, producing two primary photoproducts known as lumisterol3 and tachysterol3.The primary form of vitamin D that is found in circulation is known as 25-hydroxyvitamin D. The liver and kidneys manufacture 1, 25-dihydroxyvitamin D in a process that proceeds from this type. The form that is biologically active of vitamin D is known as 1, 25-dihydroxy vitamin D. Vitamin D receptors are widely distributed throughout many cells and organs inside the human body, and a considerable number of these cells and organs possess the ability to produce 1, 25-dihydroxy vitamin D. Proteins, DNA, RNA, and 7-dehydrocholesterol absorb solar energy through the skin when exposed to sunshine. The epidermis absorbs the majority of these UVB rays. As a result, the skin produces vitamin D3. Because of this, vitamin D3 is constantly available in the skin after sun exposure even if it is immediately washed with soap and water (MF, 2012).

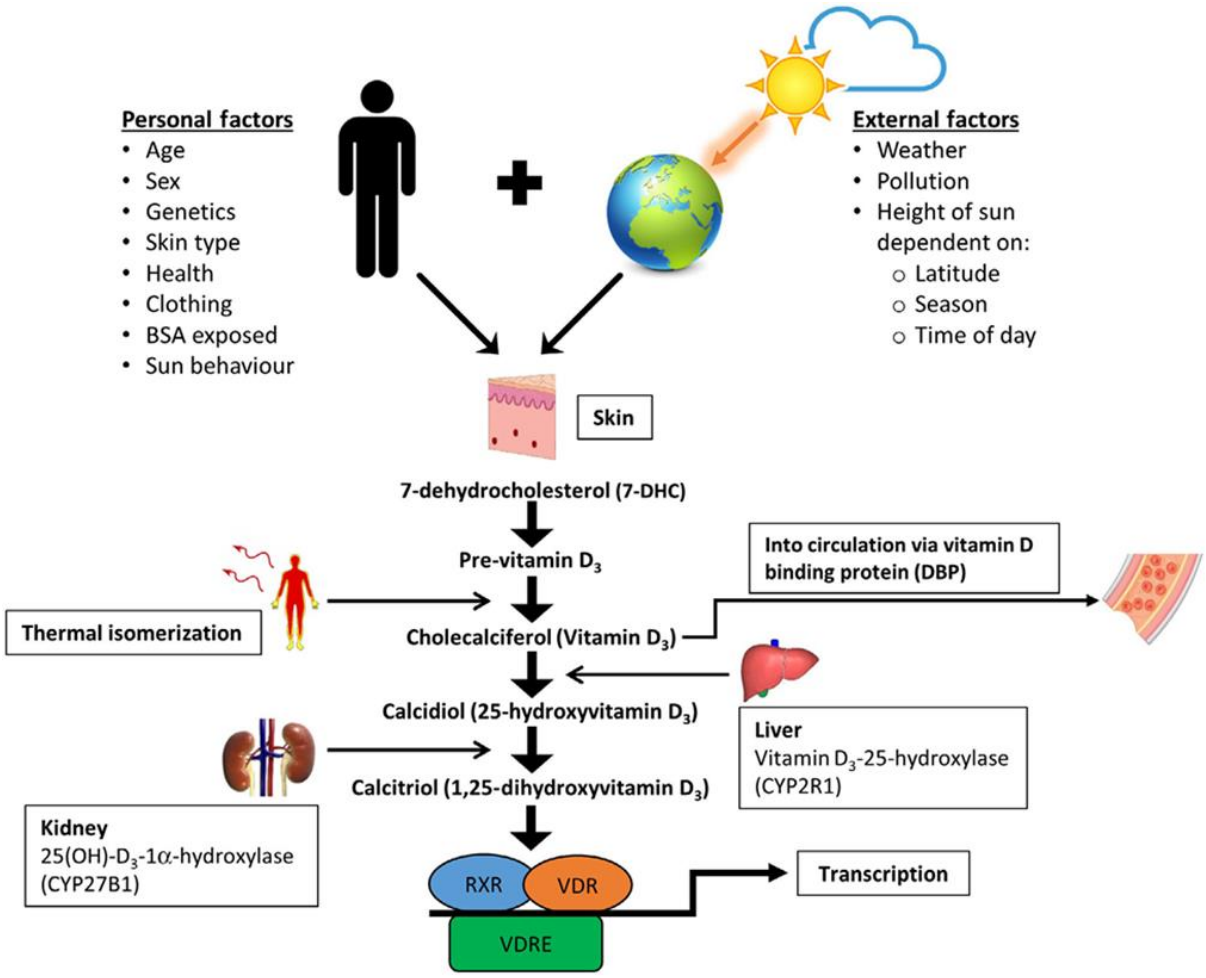

Figure 7: Synthesis of Vitamin D (Holick, 2011)

1.6 Rational of the Study

Observational research from around the world continues to show that many populations, especially pregnant women, have high incidence of vitamin D inadequacy. It is crucial to acknowledge that pregnant women and the unborn baby both are increasing vulnerability to vitamin D insufficiency and researchers should pay particular attention to this population. This study elucidates the physiological importance of vitD during pregnancy. Additionally, it investigates the correlation between the vitamin D levels in expectant mothers and negative pregnancy outcomes. Furthermore, there are genetic variables that may alter status of vitD level in both mother and newborn. Finally, to evaluate the current study on the potential negative impact of vitamin D deficiency on maternal and fetal adverse outcomes such as pregnancy-related diabetes, preeclampsia, and LBW in addition to premature birth.

1.7 Aim and Objectives of the Study

Aim

This review is aimed to identify the prevalence of vitamin D deficiency during pregnancy as well as its connection to VDR polymorphism, including infant preterm birth and low birth weight, both of which can put neonatal at an elevated risk of morbidity and mortality.

Objectives of the study are:

- To discuss the impact of D deficiency on unfavorable pregnancy outcomes such as PTB & LBW
- To delineate how single nucleotide variations in the VDR might lead to unfavorable pregnancy outcomes.
- To discover whether VDR polymorphisms are linked to the prevalence of PTB.

Chapter 2

Methodology

This review has been written using the most recent research and articles found in the electronic databases PubMed and Google Scholar. For the purpose of writing this review paper, more than 30 articles have been reviewed. Research is currently being done to determine how vitamin D insufficiency and variations in the vitamin D receptor gene (VDR) affect unfavorable outcomes such as PTB and LBW. SNPs in the VDR, which account for 63 of the gene's polymorphisms and five of which have undergone extensive research, may be responsible for the link between vitamin D status and PTB. The currently available evidence suggests the potential existence of an association between specific single nucleotide polymorphisms (SNPs) and PTB; nevertheless, the findings are inconclusive.

Chapter 3

Vitamin D deficiency and risk of Preterm birth & Low birth weight

3.1 Vitamin D Effects on Maternal and Neonatal Health

Body's immune system, bone mineralization, calcium balance, cell growth, and disease prevention all depend on the vitD level. Recent study has emphasized vitD has impacts on implantation, cytokine synthesis, and the immune response to infection in the placenta (Shin, Choi, Longtine, & Nelson, 2012). In order to keep up with the growing demand for calcium that the fetus has as it is growing and developing, enough amount of vitD in the mother's system is required. There is a positive correlation between the administration of vitD to mothers and the increased circulation of 25-hydroxyvitamin D levels, as well as higher birth weight and birth length. In contrast to the initial trimester, pregnant individuals who refrained from consuming vitamin D supplements had a reduction in circulating 25-hydroxyvitamin D levels throughout the last trimester (Hashemipour, et al., 2013). Inadequate maternal circulation 25-hydroxyvitamin D levels in expecting mothers may be risky to both moms and newborns, according to a number of observational studies. Lower 25-hydroxyvitaminD levels are associated with repeated miscarriage, hypertension, and diabetes during pregnancy, uterine infections, preterm birth, SGA infants, and poor child health. Over one billion children and adults worldwide suffer from vitD inadequacy. It is impossible to overstate the dangers of a vitamin D deficiency. Numerous acute and chronic conditions, including preeclampsia, childhood dental decay, periodontal disease, autoimmune disease, infections, heart disease, deadly malignancies, type 2 diabetes, and neurological issues have been linked to vitD deficiency. There is mounting evidence that VDD during pregnancy is linked to serious clinical consequences, such as obstetric difficulties, premature delivery, and negative effects on the skeleton, system of immunity, and pulmonary system in offspring (Curtis, Moon, Harvey, &

Cooper, 2018). Throughout pregnancy, the fetus is totally reliant on the maternal vitD levels, which also regulate placental function. Several observational studies have indicated that mother vitamin D insufficiency may influence various outcomes for both the mother and the newborn, including preeclampsia, gestational diabetes, PTB, LBW, and SGA (Holick, 2011).

3.2 Maternal Vitamin D Deficiency and Adverse Pregnancy Outcomes

Pregnancy and delivery problems account for at least eighteen percent of the worldwide burden of disease in women of reproductive age, making them the major cause of disability and death in these nations. Each year, a staggering number of over 50 million women face challenges related to their maternal health, alongside the issue of maternal mortality. Additionally, each year, there are close to 8 million cases of stillbirth and fatalities in neonates. 2 In underdeveloped nations, major vitamin D insufficiency and maternal difficulties typically inflict a rapid economic burden on their families (Bener, Al-Hamaq, & Saleh, 2013). There is a clear correlation between inadequate levels of vitamin D and a number of potentially negative pregnancy outcomes, thus explaining why it is common to experience a lack of vitamin D when pregnant in many parts of the world (Mulligan ML, 2009). To maintain a healthy state throughout life, both vitD and calcium are essential. VitD insufficiency is particularly prevalent in children and pregnant women. Numerous studies have connected VDD to poor health outcomes in both kids and expectant mothers (Golden NH, 2014). Numerous adverse newborn complications including premature birth, impairment to the formation of the baby's bones and teeth, and an elevated risk of infections link to low maternal vitamin D levels. Maternal hypovitaminosis D is referred to as 25-hydroxy vitamin D levels in the mother dropping below 20 ng/ml or 50 nmol/l, link to higher risk of adverse neonatal outcomes in a growing number of observational research studies (Aghajafari F, 2013). Because the mother gives the fetus the 30 g of calcium it requires for proper bone growth, both the uptake of calcium in the intestines and bone calcium reabsorption is increased (Bishop N, 2012). Maternal VDD before or during

pregnancy can have serious consequences for fetuses and infants. It is said that between 60 and 80% of pregnant women compared to ethnic minority groups who live in temperate areas have a VDD level below 25 nmol/L (A P. , 2008). The mother's vitamin D status reflects the developing baby and newborn. Umbilical cord 25OHD levels were found to have significant linear associations with maternal 25OHD plasma levels, with cord levels being below mother levels, suggesting the presence of a placental diffusion barrier (CS, 2008). Therefore, the mother's VDD state can be carried on to the fetus and child, and depending upon how severe it is, it may have both short-term and long-term effects. This condition is frequently connected with unfavorable consequences for both the mother and the baby.

3.2.1 Maternal Outcomes

Pre-eclampsia:

Pre-eclampsia is more prevalent in women with VDD and is characterized by gestational hypertension as well as proteinuria after 20 weeks of pregnancy. According to two recent systematic analyses, data analysis revealed that compared to women taking no medicine, those women taking daily vitamin D intake and calcium had higher 25hydroxyvitaminD levels and a decreased incidence of pre-eclampsia from five RCTs with about 1300 women which include a Cochrane review (Agarwal S, 2016). In two RCTs, the pre-eclampsia risk ratio (RR) for vitamin D intake in pregnancy was 0.52 (95% CI 0.25-1.05) compared to a placebo effect or no treatment (Sablok A B. A., 2015). It's fundamental to understand that both of these RCTs' supplements varied; for example, Asemi et al.'s trial used daily 400 IU of cholecalciferol (Asemi Z, 2013) but in Sablok et al.'s study, a singular administration of 60,000 IU, dual administrations of 120,000 IU, or quadruple administrations of 120,000 IU were employed (Sablok A B. A., 2015). The addition of calcium resulted in a substantial reduction in the incidence of pre-eclampsia. The incidence of pre-eclampsia was significantly lower among

women who were administered vitamin D and calcium supplements compared to those who did not get such supplementation (De-Regil LM, 2016).

Gestational Diabetes Mellitus (GDM):

The available data regarding the association between maternal vitamin D deficiency (VDD) and the heightened risk of gestational diabetes mellitus (GDM) exhibit inconsistencies. Severe VDD, defined as a value of 12.5 nmol/L in two cross-sectional investigations was considerably greater in women with GDM (Bener A, 2013). The initiation of high-dose vitamin D (5000 IU daily) in the second trimester of gestation did not result in the normalization of glucose levels during the oral glucose tolerance test. However, it demonstrated a significantly greater efficacy in preventing neonatal vitamin D deficiency compared to low-dose vitamin D (400 IU daily). These findings were derived from a randomized controlled trial that investigated the impact of vitamin D administration on maternal glucose metabolism during the period of pregnancy (Yap C, 2014).

3.2.2 Infant outcomes:

Congenital Rickets and Hypocalcaemia Complications:

Rickets that appear within the first month of birth are a sign of congenital rickets, (Munns CF S. N., 2016) which has been linked to VDD during pregnancy (Glorieux FH, 2012). Infants may have tetany, hypocalcemic convulsions, elevated intracranial pressure, and other neurological issues. Poor maternal vitamin D status is associated with negative infant outcomes, such as increased blood alkaline phosphatase (Kalra P, 2012), greater fontanelle size at birth and neonatal hypocalcemia, according to evidence from interventional and observational research (Delvin EE, 1986).

Premature Infants:

VDD risk rises with prematurity. Approximately 15 million infants are delivered prematurely on an annual basis across the globe (Blencowe H C. S., 2012). Premature neonates' exhibit limited mineral reserves due to the predominant accumulation of skeletal calcium and phosphorus during the final trimester of gestation. Moreover, they are also born during a phase of rapid development which includes a quick accumulation of bone minerals (Bishop N, 2012). Poor early intake, recurrent illness, protracted immobilization, and drugs that affect bone mineral homeostasis, such as steroids and diuretics, make it more difficult to accumulate minerals

Anthropometry:

Regarding a potential effect of maternal vitamin D intake throughout pregnancy on birth anthropometry, there is insufficient and inconsistent information (Munns CF S. N., 2016). A RCT carried out in Bangladesh discovered that babies delivered to moms who got vitD fortification thirty-five thousands IU/week in their last trimester showed improved early postnatal linear development in comparison to babies born to mothers who received a placebo. To comprehend the connection between maternal vitD supplementation and newborn anthropometry, further study is required (Roth DE, 2013). The differences in baby anthropometry data suggest that supplementing vitamin D-deficient pregnant mothers may be especially significant in developing countries.

3.3 Risk Factors Associated with Preterm Birth

Table 1: Risk Factors Associated with Types of Preterm Birth (Blencowe H C. S., 2012)

Types	Risk Factors	Examples	Interventions
Spontaneous Preterm birth:	Age at pregnancy and pregnancy pacing	Teenage pregnancy, Immature maternal age, or short inter-pregnancy interval	Encourage family planning to start in youth and to continue between pregnancies as part of preconception care
	Multiple pregnancy	Twin and higher-order pregnancy rates rising with assisted conception	Introducing and maintaining the most effective policies for assisted reproduction
	Infection	Urinary tract infections, malaria, HIV, syphilis.	Pregnancy-related infections become the focus of sexual health programs focused on prevention and treatment.
	Manner of living	Smoking, excess physical activity, alcohol consumption	All women of reproductive age are addressed as part of behavioral and community initiatives, and pregnant women are the focus of prenatal counselling with early pregnancy problems diagnosis and treatment.
Provider-initiated preterm birth	Obstetric indications for medical induction or cesarean delivery pregnancy indication	Prior classical cesarean section, Placenta Accrete	Programmers and policies to lessen the use of caesarean delivery or labor induction when it is not medically necessary
	Other- Not recommended by a doctor	There exists an overlap between indicated provider-initiated preterm birth and the risk variables associated with spontaneous preterm delivery.	

Table 2: Long-term Impact of Preterm Birth on Survivors (Blencowe H C. S., 2012)

Long-term Outcomes	**Impacts**	**Examples:**
Specific physical effects	Blurred vision	• Increased hypermetropia and myopia • Blindness or high myopia after retinopathy
	Chronic lung disease of prematurity	• From reduced exercise tolerance to requirement for home oxygen
	Long-term heart disease	• Reduced lung function • Increased rates of asthma • Increased blood pressure
Family, economic and social effects	• Effects on health services and families	• Risk of preterm birth in offspring
Neuro - developmental/ Behavioral effects	• Mild impairments in executive functioning • The individual has a range of developmental delays, varying from moderate to global in nature.	

Chapter 4

Association of VDR Single Nucleotide Polymorphism with Preterm Birth and Low Birth weight

Calcitriol is also known as active vitamin D3 maintains the equilibrium of calcium and phosphate among other things. The most popular vitamin D supplement, cholecalciferol, may transform the precursor to the active ingredient of calcitriol by the function of the liver and tissues. Similar to other steroid hormones, calcitriol affects the exposure of its target genes via interacting to the receptor VDR. In fact, VDR expression occurs concurrently in conventional target tissues such bone, kidney, and gut where hormones are controlled. VDR is also involve in bone mineralization, calcium resorption, and phosphate resorption, among other non-classical target tissues. For instance, it acts as an immuno-modulator in immune cells and in the reproductive, endocrine, muscular, brain, skin, and liver systems as well (Verstuyf, Carmeliet, Bouillon, & Mathieu, 2010). The extensive diversity of genes regulated by the vitamin D receptor (VDR), along with the unique functions of vitamin D in different tissues. Research has revealed a correlation between preterm birth and insufficient levels of vitamin D. On a global scale, the average prevalence of insufficient vitamin D levels during the gestational period is 87.0% and 29.8%, respectively. VitD insufficiency linked to an increased risk of pregnancy related diabetes, preeclampsia, fetal growth limitation, and preterm birth in pregnancy (Aghajafari F, 2013). The nuclear receptor known as the vitamin D receptor (VDR) controls the function of vitamin D with high affinity by acting as a ligand-activated gene transcription factor. In several human tissues, including the placenta, muscle, osteoblasts, and chondrocytes, the VDR gene, which is found on chromosome 12q12-14, is highly expressed. A heterodimer formed by the nuclear retinoid X receptor (RXR) and the ligand-bound VDR binds cofactors to control gene transcription by recognizing VDRE in the promoter regions of

vitamin D target genes. The active component of vitamin D, has been found to affect bone metabolism and mineral homeostasis (AW & Minireview, 2006). Vitamin D receptors are found in the placenta. This demonstrates that locally synthesized 1, 25[OH] 2D3 may affect fetal-placental development and function via controlling cell proliferation and differentiation (Viganò, et al.). The vitamin D receptor (VDR) is an essential component of the vitamin D system that affects bone mineral homeostasis, chemical detoxification, cancer prevention, and the mammalian hair cycle. Serious issues with gene activation caused by polymorphism in the VDR gene can impact calcium metabolism (JC., 2017), cell proliferation, and immunological function. ApaI, BsmI, FokI, and TaqI are the most extensively researched single nucleotide variations (SNVs) in relation to clinical outcomes of the VDR gene (Barchitta M M. A., 2018). In regards to the link between VDR gene variations and premature birth, studies have yielded results that are opposing to one another (Pasco JA, 2008).

Chapter 5

Summary of Findings on Association of Single Nucleotide VDR Gene Polymorphisms with Preterm Birth & Birth Weight

Table 3 Connection of VDR gene Polymorphism with the risk of preterm birth (Barchitta M M. A., 2018)

Origin of Population	Groups	Outcomes	References
Israel (Jewish)	33 Caucasian mothers had Preterm neonates (24–35 weeks gestation) 98 mothers and their Full-term neonates	In mothers who gave birth prematurely, the FokI/C allele frequency was noticeably greater.	Manzon et al. 2013 (Manzon L A. G., 2014)
China	57 mothers had Preterm neonates 84 mothers had Full-term neonates	The FokI/FF genotype has been linked to an increased risk of preterm delivery.	Cai et al. 2016 (Cai W, 2016)
Brazil (Northeast)	104mothers had Preterm neonates 85 mothers who had Full-term neonates	Preterm birth risk was increased by the FokI/T allele.	Javorski et al. (2018) (Javorski N, 2018)
Italy	17 mothers and their Preterm neonates 187 mothers and their Full-term neonates	Mothers' FokI polymorphism genotype was linked to a higher risk of preterm delivery.	(Barchitta M M. A., 2018)

5.1 Interrelation of Single Nucleotide VDR Gene Polymorphism (ApaI) with Preterm Birth

Table 4 Association of VDR Polymorphism (ApaI) with Preterm Birth (Rosenfeld T, 2017)

Origin of Population	Groups	Outcomes	References
Poland	100 Caucasian mothers had Preterm neonates 99 mothers who had Full-term neonates	In mothers who gave birth prematurely, the genotype combinations BsmI/BB-ApaI/AA-TaqI/TT and BsmI/BB-ApaI/TT were more common.	Baczyńska-Strzecha et al. (2016) (Baczyńska-Strzecha M, 2017)
Brazil (Southeast)	40 mothers and their Preterm neonates (23–32 weeks gestation) 92 mothers and their Full-term neonates	The preterm risk was raised by the BsmI/TT and ApaI/AA genotypes.	Dutra et al. 2020 (Letícia Veríssimo Dutra, 2020)
Israel (Jewish)	146 Caucasian mothers and their Preterm neonates (24–36 weeks gestation) 229 mothers and their Full-term neonates	Preterm delivery was linked to an increased risk of the ApaI/AA genotype.	Rosenfeld et al. (2017) (Rosenfeld T, 2017)

A study conducted by Baczyńska-Strzecha and his collogues (Baczyńska-Strzecha M, 2017) examined a group of hundred Polish preterm mothers and ninety-nine full-term mothers. The researchers found no significant differences in the types of individual genotypes. However,

they did observe that the combinations of BsmI/bb-ApaI/AA-TaqI/TT and BsmI/BB-ApaI/aa-TaqI/tt - genotypes were remarkably more common in the premature birth group. On the other hand, the combinations of BsmI/Bb-ApaI/AA-TaqI/Tt and BsmI/BB- ApaI/Aa-TaqI/tt-genotypes were associated with a reduced danger of premature birth. Rosenfeld et al. discovered that the CC homozygous genotype of the ApaI single nucleotide variable (SNV) was connected to premature delivery in a separate study involving one hundred forty-six Israeli-Jewish women and their premature children, as well as two hundred twenty-nine other women and their full-term newborns. In the present study, AA genotype of the ApaI SNVs, were significantly more frequent in the PTN mothers. With regard to the relationship between 25(OH) D levels and the genotypes of the gene VDR variants, the PTN mothers with the AG genotype of the TaqI, the AA genotype of the ApaI, and the AG genotype of the FokI SNVs had significantly lower 25(OH) D levels. Mothers with the TT variant genotype of the BsmI and the AA genotype of the ApaI SNVs with 25(OH) D deficiency had an increased risk of preterm birth, whereas the carriers of the GG genotype of the TaqI SNV had a lower risk. Furthermore, in 2011, Swamy and associates evaluated the impact of 38 VDR polymorphisms on a number of birth outcomes in a prospective trial involving 615 pregnant women. They demonstrated, in short, that birth weight was strongly related with 8 of the 38 SNPs examined—including ApaI—in black women but not in white women (Swamy, Garrett, Miranda, & Ashley-Koch, 2011).

5.2 Interrelation of Single Nucleotide VDR Gene Polymorphism (ApaI) with Low birth weight

The observation of a Brazilian cohort evaluation conducted by Marcos Pereira-Santos and his collogues' (Marcos Pereira-Santos, 2019) stated that the offspring of women with heterozygous alleles for the ApaI single nucleotide polymorphism (GA) were observed to have a reduced birth weight compared to other individuals. Furthermore, in a comprehensive prospective study conducted by Swamy and colleagues, 615 pregnant women were registered to investigate the impact of 38 VDR polymorphisms on various birth outcomes. One noteworthy finding from the study was that among the 38 SNPs examined, including ApaI, eight of them demonstrated a significant influence on birth weight, but only in black women and not in white women. As a result, the Authors came to the conclusion that the strength of this association may be influenced by ethnicity, which could potentially contribute to the observed racial disparities in various pregnancy outcomes.

Chapter 6

Conclusion

Finally, to conclude, a group of women at risk for PTB and LBW was analyzed for the impact of vitamin D deficiency and VDR polymorphism (ApaI). The presence of VDR gene polymorphisms provides an explanation for the observed differences in VitD levels and their association with the susceptibility to premature birth. The presence of genotypes of the ApaI/AA single nucleotide variants (SNVs), either independently or in combination with vitamin D insufficiency, exhibited a greater susceptibility to premature birth. There exists a correlation between insufficient levels of Vitamin D and a higher susceptibility to pregnancy-related diabetes, preeclampsia, fetal growth limitation, and preterm birth during pregnancy. This review shows that low levels of vitamin D and VDR gene polymorphism (ApaI) are linked to adverse pregnancy outcomes such as LBW and PTB.

Chapter 7

Future Recommendations

The connection between vitamin D insufficiency and the single nucleotide polymorphism of VDR (ApaI) with PTB and LBW has only been the subject of a small number of research studies. Vitamin D levels vary around the globe and among different ethnic groups that are influenced by environmental and genetic variables. So, researchers should focus more on this area of study.

- Taking quick and accurate measurements whenever clinical and psychological signs of premature birth or low birth weight is observed. For instance, seeking medical advice, determining the serum vitamin D levels, and taking vitamin D supplements as needed.
- Informing the general public about the serious effects of vitamin D deficiency.
- Suggest people to provide sufficient amount of vitamin D level during pregnancy.

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