ASSOCIATION OF MOTHERS' VITAMIN D RECEPTOR'S TAQI GENE WITH RISK OF PRETERM BIRTH AND BIRTH WEIGHT: A REVIEW

By

TASNIM ISLAM NIZHUM

19146014

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
Brac University
May 2023

Declaration

It is hereby declared that

1. The thesis submitted is my/our 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/We have acknowledged all main sources of help.

_____

Student's Full Name & Signature:

Approval

The thesis titled "Association of Mothers' Single Nucleotide Polymorphisms of TaqI with Risk of Preterm Birth and Birth Weight: A review" submitted by Tasnim Islam Nizhum of Spring, 2023 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.).

Supervised By: _____

Dr. Sharmind Neelotpol
Professor,
School of Pharmacy
BRAC University

Approved By:

Program Director: _____

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean,
School of Pharmacy
BRAC University

Dean: _____

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
BRAC University

Ethics Statement

This study does not include any animals or human trails.

Abstract

TaqI is a single nucleotide polymorphism (SNP) located in the exon 9 of the vitamin D receptor (VDR) gene of the immune system-related cells and tissues of placenta with paracrine effect. Recent research has concentrated on the potential contribution of VDR gene variations, the SNP TaqI, BsmI and ApaI, to the development of conditions like different cancers, autoimmune diseases, preterm delivery, low-birth-weight preeclampsia, and infection susceptibility. These genetic variations might impact the stability and effectiveness of translation and transcription in VDR gene. A single base shift (T to C) in codon 352, at the 3' end of the gene, is the TaqI single nucleotide polymorphism. However, there is lack of information to explain the relation of mother's SNPs on fetal outcome, requiring more attention from researchers to develop beneficial approaches. Therefore, this review was aimed to evaluate the association of mothers' SNP of TaqI with risk of preterm birth and birth weight.

Keywords: SNPs, Polymorphism, TaqI, Vitamin D receptor, Preterm birth, Birth weight

Acknowledgement

I want to start by thanking the Almighty, who keeps my life progressing, for all of His strength, compassion, and direction along the way. I would not have been able to carry out this research without His blessings.

Then, I would like to acknowledge and convey my earnest gratitude to my honorable teacher & supervisor, Dr, Sharmind Neelotpol, Professor, School of Pharmacy, BRAC University, for helping and guiding me with the topic of **"*Association of Mothers' Single Nucleotide Polymorphisms of TaqI with Risk of Preterm Birth and Birth Weight: A Review*"** and for her instructive guidance, empathetic interaction, constant advice, valuable remarks & direct supervision which have brought this study to its fulfillment. She contributed to each phase of the study as well starting from the title selection and protocol development until the fulfillment of my research.

I would also like to express my gratefulness to all the professors and faculty members of the **School of Pharmacy, BRAC University** for their continuous support.

At last, I thankfully recall the co-operation of my fellow classmates and friends. Last but not the least, I am in indebted to my parents and family for their co-operation and support during the whole study period.

Table of Contents

List of Tables

List of Figures

List of Acronyms

ANC- Antenatal care

BMI- Body mass index

CVD- Cardiovascular disease

DBP- Vitamin D-binding protein

IUGR- Intrauterine growth restriction

LBW- Low Birth weight

NCDs- Non-communicable diseases

PCR- Polymerase chain reaction

PTB- Preterm birth

RFLP- Restriction Fragments Length Polymorphism

SGA- Small for gestational age

SNP- Single nucleotide variants

Th2- T helper 2 lymphocytes

TNF- Tumor necrosis factor

VDD- Vitamin D deficiency

VDR- Vitamin D receptor

Vit D- Vitamin D

WHO- World Health Organization

Chapter 1

Introduction

Despite advancements in healthcare, adverse pregnancy outcomes remain a significant public health issue. Preterm birth (PTB) is a significant problem, as it is the major reason of death among newborns and the reason of death that ranks second among children under the age of five. The World Health Organization (WHO) depicts that more than 15 million infants, or over 10% of all babies, are born prematurely each year (Barchitta et al. 2018). Several risk factors of PTB have already been identified. Genetic susceptibility plays a significant role in affecting the environment within the intrauterine, duration of pregnancy, and growth of fetus. Genetic variations found in both fetuses and mothers have been identified as contributing factors to this effect (York et al., 2014). The largest risk factors for subsequent PTB are personal and family history of PTB, therefore, the research is concentrated on identifying variances in genes that could be potential candidates. Researchers are currently conducting extensive findings on the significant role of vitamin D metabolism during pregnancy, with a particular focus on its potential link to preterm birth. Cholecalciferol, also referred to as vitamin D3, is one of the two forms of Vitamin D produced in the skin through exposure to sunlight to ultraviolet light. It is a precursor to hormones and a fat-soluble vitamin. It is widely known that vitamin D is important for calcium and phosphorus metabolism, but it has also been found to play a role in other biological processes, such as immunomodulation at the feto-maternal interface. Research has shown that there may be a connection between the level of Vitamin D and premature birth of neonates, which could be influenced by SNPs in the VDR. According to (Gunter, 2023), a single nucleotide polymorphism is a change or alteration in the DNA sequence of an organism's genome at only one base position situated in the DNA which pertains to

both non-coding regions of the genome and genes.. The VDR gene has been found to have 63 polymorphisms, and out of those, five have been extensively studied: Cdx2, FokI and BsmI, ApaI, and TaqI in the promoter, second coding exon, and 3' untranslated regions respectively. It's interesting to note that there may be a connection between the levels of vitamin D and PTB which could be influenced by these SNPs in the VDR (Krpina et al. 2020; Rosenfeld et al. 2017; Javorski et al., 2018). Also, it is important to identify the primary genetic risk factors for adverse pregnancy outcomes, as they account for approximately one-third of the risk.

Previous studies have looked at specific genetic variations in the vitamin D receptor (VDR) to determine the potential impact on reducing pregnancy complications and improving neonatal health. Results have shown that certain maternal VDR polymorphisms can lead to the development of hypovitaminosis D and other outcomes, with either protective or negative effects (Karras et al., 2021). Research has found that certain variations in the VDR gene can lead to lower birth weight and smaller skin folds in newborns, as well as a higher risk of small-for-gestational-age infants in both black and white mothers. There is also a gender-specific pattern of genetic variations in placental vitamin D metabolism that can affect birth weight. In a recent analysis of data, it was discovered that specific patterns of VDR gene variations can impact birth weight and other neonatal outcomes. Additionally, maternal genetic differences in the GC gene, which encodes the vitamin-D binding protein, can affect the correlation between maternal and cord-blood concentrations of 25(OH)D and birth weight (Barchitta et al. 2018; Chung et al. 2017; Workalemahu et al., 2017). To date, one of the most explored VDR polymorphisms is rs731236 (TaqI). There is a modification in TaqI where a one nucleotide changes from A to G within exons 9. Various studies have shown that TaqI SNPs do not alter the protein structure of VDR, but they may affect the efficiency and

stability of the mRNA translation process. Many research studies have also linked polymorphisms in the VDR gene with a variety of human diseases and an increased risk of neonatal complications, including respiratory distress syndrome (RDS), intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, and retinopathy of prematurity (Imani et al., 2020; Kosik et al., 2020). TaqI is one of the most extensively sought single nucleotide variations (SNVs) including ApaI, BsmI, FokI of the VDR gene in relation to clinical outcomes. It has been studied that individuals with the CC genotype variation within the TaqI polymorphism have a 5.22 times higher risk of developing RDS. Additionally, preterm infants with RDS were found to have a 3.26 times higher likelihood of having the TaqI CT genotype variation. (Kosik et al., 2020). On the other hand, studies have also showed limited connection between PTB and VDR (TaqI) polymorphisms. The VDR gene TaqI polymorphism was found in the non-coding region, and had no impact on the ultimate protein of concern. Hence, the research did not identify any significant findings in the distribution pattern of the TaqI genotype/allele (Patel et al., 2017).

Vitamin D has a positive impact on immune function, neuroprotection and cardiac function due to the widespread distribution of (VDR) in almost every tissue. One of the most extensively researched single nucleotide polymorphisms (SNPs) associated with various diseases and outcomes is the Taq1 of the gene. Currently, the evidence linking VDR polymorphisms to negative pregnancy outcomes is not strong or conclusive. There is a lot of variation in the findings across different studies, which makes it difficult to draw definitive conclusions. With inconclusive, controversial and inconsistent findings of different studies, this review is performed to weigh the association of Mothers' Single Nucleotide Polymorphisms of TaqI with Risk of Preterm Birth and Birth Weight

1.1 Aim of study

The aim of this review is assessing the relationship of mother's single nucleotide polymorphism in the TaqI gene with the risk of PTB and LBW.

1.2 Objectives

- Assessing the relationship within the mother's vitamin D levels and single nucleotide polymorphism of the TaqI gene
- To evaluate the risk of PTB due to alteration of SNP of the TaqI
- To find out the measurements to deduce the chance of LBW in neonates as a result of alteration of single nucleotide polymorphism of the TaqI gene

Chapter 2

Methodology

This study was conducted by reviewing PubMed, Elsevier, ResearchGate, for relevant literature, searching for relevant information with keywords ‘pregnancy', ‘preterm birth’, ‘low birth weight’, ‘vitamin D’, ‘vitamin D receptor’, ‘single nucleotide polymorphism’ in accordance to articles relevant to the research. The review paper discusses the association of Vitamin D receptor gene TaqI single nucleotide polymorphism on low maternal vitamin D levels and its contribution in causing preterm birth and low birth weight in neonates. The information for these articles was obtained manually. Additionally, sources were cited using the Mendeley software.

Chapter 3

Result and Discussion

Preterm birth (PTB) with LBW is one of the major reasons of the death of newborn babies globally (Samuel et al., 2019). Almost 35% of neonatal deaths occur due to preterm birth whereas LBW contributes to 40–60% of newborn mortality. The genetic implications on preterm birth and LBW in understanding the impact of environmental factors can be challenging. For instance, a mother's diet during pregnancy can affect genetic expression and elevated the chance of having various disorders, such as diabetes and hypertension, in the individual. (Sangkaew et al., 2018). In the human population, genetic polymorphism may raise the chance of diseases that alter the metabolic response to diet. About 10% of the human DNA is modulated by dietary vitamin D, which also plays a role in developmental processes. Prematurity and low birth weight that may result from the mother's vitamin D deficiency during pregnancy are just two potential health outcomes that occurs due to vitamin D homeostasis during pregnancy (Patel et al., 2017). The VDR gene has different versions called single nucleotide polymorphisms (SNPs). These variations have been associated with various physical and medical traits in certain groups of people, especially during pregnancy. The most studied VDR SNPs are FokI, BsmI, ApaI, and TaqI, identified as rs10735810, rs1544410, rs7975232, and rs731236, respectively. (Rosenfeld et al., 2017).

3.1 Preterm birth: Definition, etiology and risk factors

Preterm birth (PTB) refers to the delivery before 37th week of pregnancy. Prematurity is the leading factor behind the mortality of children under the age of 5. Preterm babies may experience both immediate and long-term health complications, which can affect various systems such as the immune system, cardiovascular system and many others.

Additionally, issues such as growth and development may arise. (Oliveira et al., 2016; Blencowe et al., 2013). PTB may be caused by various risk factors such as an unhealthy lifestyle, mental stress, pregnancy at a younger or older age, and malnutrition (Bilge et al., 2015). It is depicted that a deficiency in vitamin D controls the levels in body inflammatory factors that trigger an increase in uterine contraction hormones like prostaglandin, resulting in preterm birth (Yang et al., 2016).

3.2 Pathophysiology of preterm birth resulting from vitamin D deficiency

Vitamin D deficiency during pregnancy is frequent around the world. Professional bodies have recommended a daily vitamin D intake of 400 IU foe every infant in order to address the widespread concern about childhood vitamin D deficiency. (Lian et al., 2021). Vitamin D's effect on the innate immune reaction is most likely the main process underlying its ability to avoid preterm birth. Immune cells like macrophages and dendritic cells have vitamin D detectors that allow them to recognize microbe-derived molecules. These immune cells generate antimicrobial peptides after becoming activated. The perinatal infections linked to preterm delivery may be prevented due to this antimicrobial pathway. Additionally, 1,25-dihydroxyvitamin D has been demonstrated to have a suppressive impact on a number of cytokines linked to inflammation (interferons, interleukin 6, and tumor necrosis factor [TNF]). The method by which deficiency of vitamin D in mothers is linked to elevated risk for PTB is believed to be this steroid hormone's involvement in a number of other immunomodulatory effects (Yang et al., 2016; Woo, Giurgescu and Wagner 2019).

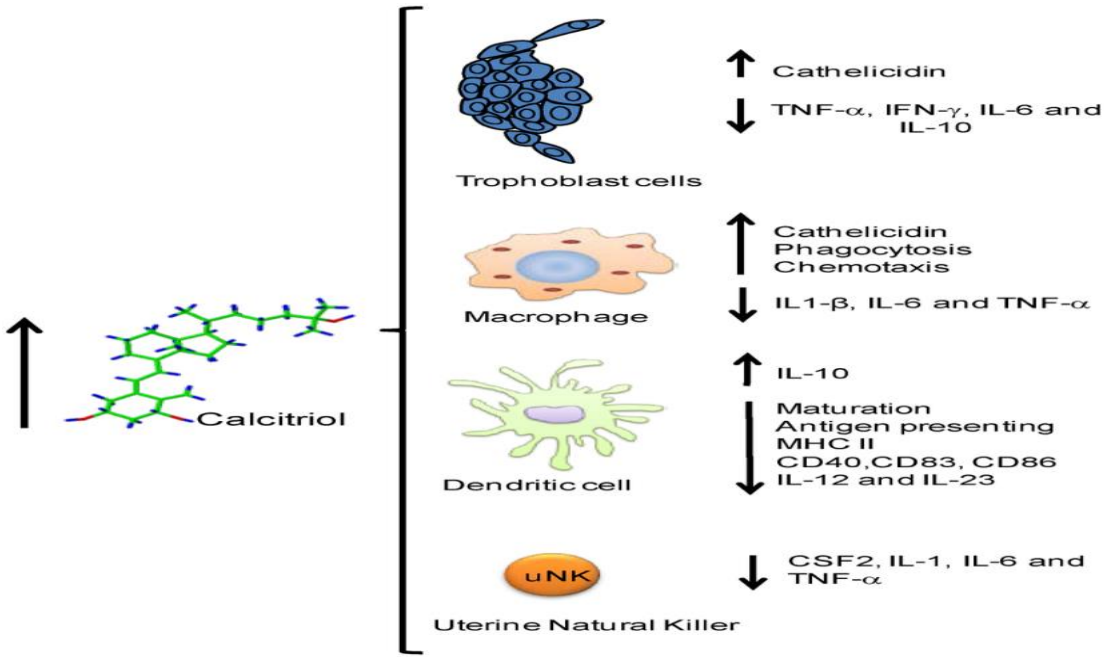

Figure-1: Calcitriol's Impact on the Immune System in Pregnancy (Barrera et al., 2015).

Figure 1 indicates that calcitriol has an impact on the immune system in pregnant women. It plays a role in regulating various aspects of the immune system in both immune cells for instance macrophages, dendritic cells and non-immune cells (like trophoblasts) at both the systemic and fetoplacental levels. This leads to changes that promote a Th2 profile, which is associated with a successful pregnancy.

3.3 Low birth weight: Definition, etiology and risk factors

Low birth weight can result from restricted development in the womb or premature birth, and can have negative impacts on health such as increased risk of development of infants, including high rates of infant mortality, stunted growth, and impaired cognitive development and chronic non-communicable diseases later in life. The World Health Organization defines low birth weight as less than 2500 grams at birth. (5.5 pounds) (World Health Organization 2022). Globally, it is estimated that 20% of all births result in low LBW, which equates to over 20 million births each year. Developing

countries have a higher incidence of LBW at 7%, which is more than double the rate of developed countries. Southern Asia is the region with the highest number of LBW newborns, accounting for almost half of all cases worldwide. The weight of newborns in Bangladesh is influenced by a variety of factors, including biological and demographic factors. Factors such as the mother's education, wealth index, antenatal care (ANC) visits, delivery place, and mode of delivery, as well as the mother's height, weight, body mass index (BMI), age, and parity, were all significantly associated with low birth weight. (Khan et al., 2018; Pollob, et al., 2022).

3.4 Pathophysiology of low birth weight resulting from vitamin D deficiency

Low birth weight is believed to result from intrauterine growth restriction (IUGR) and premature delivery, but the specific cause of low birth weight remains unclear. IUGR occurs when there is not enough blood flow and nourishment from the mother to the fetus, which affects the baby's physical measurements. Babies with IUGR show signs of malnutrition at birth. As Preterm delivery is caused by extra-uterine infection, trauma, illness, IUGR, fetal infection, and anomalies, growth retardation as a consequence of preterm birth leads to LBW (Basel and Singh, 2020). Vitamin D (vit D) is important for fetal development as it interacts with the parathyroid hormone and helps keep up with Ca2+ homeostasis. Research has found that low levels of vit D during and after pregnancy can have a negative impact on bone mineralization and may increase the likelihood of small for gestational age (SGA) births. Furthermore, the deficiency of vitamin D in pregnant women that occur during colder months can result in SGA births more frequently. (Khalessi et al., 2015).

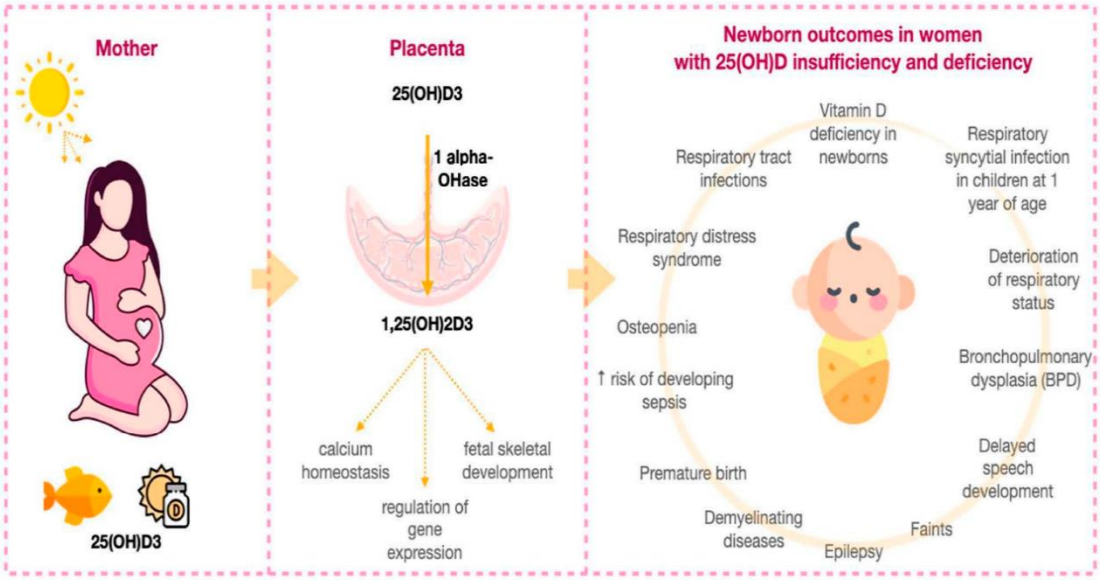

Figure-2: Effect of maternal 25(OH)D insufficiency and deficiency on neonates (Karpova et al., 2022).

Figure 2 shows that low levels of 25(OH)D in women who are can lead to numerous health complications, not only for the mother but also for the newborn. These complications include a higher risk of neonatal health issues such as premature birth, small for gestational age babies, low birth weight, limited head growth, and reduced length and weight of the fetus in the third trimester. Additionally, babies may have a lower Apgar score at 1 and 5 minutes after birth, and are more susceptible to respiratory syncytial infections and respiratory problems like BPD. Low levels of 25(OH)D during pregnancy have also been linked to asthma and wheezing.

3.5 Single nucleotide vitamin D receptor polymorphisms

The active vitamin D metabolite, 1,25-dihydroxyvitamin D (1,25-dihydroxycholecalciferol or $1,25(OH)_2D_3$), selectively binds to a specific vitamin D receptor (VDR) (Morrison et al., 1994). The vitamin D receptor controls the transcription of genes that play a role in the metabolism of calcium, proliferation and differentiation of cells, and T-cell regulated immune responses. Additionally, vitamin

D receptors are present in pancreatic β cells (Johnson et al., 2004), It is important to note that maintaining normal insulin levels in response to glucose levels is crucial for glucose tolerance. (Bilge et al., 2015; Ishida and Norman, 1988; Zaki et al., 2017). The VDR gene plays a key role in how vitamin D affects our bodies. If there are any impairments or reduced functionality due to genetic changes, it can affect how vitamin D is distributed and used throughout the body. This can impact the overall balance of vitamin D in our circulation and its metabolite activity.

The VDR gene was analyzed using Restriction Fragments Length Polymorphism assays to identify four significant polymorphisms. One of these polymorphisms, located in intron 8 and detected by the Apa-1 restriction enzyme (rs7975232), results in a change from T (variant "A") to G (variant "a").(Faraco et al. 2010). There are two genetic variations that have been identified. The first one is called Bsm-1 polymorphism (rs1544410) and is located in intron 8. This variation causes a change from A to G, resulting in two variants: "b" and "B". The second variation is called Taq-1 (rs731236) polymorphism and is observed in exon 9. This variation results in a silent mutation in codon 352 and changes T to "t" and C to "T".(Morrison et al., 1994). The transition of Fok-1 (rs2228570) in exon 2 leads to the production of two variants of VDR protein, one with 427 amino acids (f (T)) and the other with 424 amino acids (F (C)). In certain cell types, the F variant is more active than the other variant. (Cieślińska et al., 2018).

3.6 Association of single nucleotide polymorphism of TaqI with Vitamin D deficiency resulting in PTB and LBW

During pregnancy, there is a threat of deficiency of vitamin D and shortage resulting from low concentration of vitamin D in blood, have been linked in studies to preterm.

Vitamin D3, also known as cholecalciferol, is naturally produced in the skin when it is exposed to ultraviolet B rays from sunlight. Additionally, it can also be obtained from certain foods such as fatty fish and plants which consists of cholecalciferol and ergocalciferol respectively(Christakos et al., 2015; Bouillon et al., 2008; Wang et al., 2017). In order to become active, both vitamin D2 and vitamin D3 must go through two hydroxylation reactions: the first occurs in the liver where 25-hydroxylase creates 25(OH) D (the circulating form), and the second occurs in the kidneys by 1α-hydroxylase where 1,25(OH)2D is produced (the metabolically active form) (Fleet, 2017).

25(OH) D Vitamin D levels should be over 30 ng/mL to be considered acceptable; under 20 ng/mL to be considered inadequate. During pregnancy, having insufficient vitamin D levels can increase the likelihood of pregnancy complications such as diabetes during pregnancy, hypertension, limitation in the growth of fetus, bacterial vaginosis due to bacteria, c-sections, as well as preterm. Globally, the mean for gestational insufficiency is 87.0%, while deficiency of Vitamin D is 29.8%. (Pfotenhauer et al., 2017; Aghajafari et al., 2013).

The VDR gene with the Gene ID 7421; MIM 601769 encodes the vitamin D receptor (VDR), located on chromosome 12q13.11. This receptor is responsible for most of the biological effects associated with vitamin D. It belongs to the family of steroid hormone receptors and regulates effects in vitamin D by controlling gene transcription of various kinds (Whitfield et al., 1995). Important errors in the activation of genes which impact metabolism of calcium, cell growth, and immunological role can result from changes in the VDR gene. TaqI is one of the most extensively researched single nucleotide

variations (SNVs) including ApaI, BsmI, FokI of the VDR gene in relation to clinical outcomes.(Dutra et al., 2020; Bouillon et al., 2008)

As a precursor to hormones, vitamin D has been linked to a number of metabolic conditions, including obesity, diabetes, cardiovascular disease (CVD) risk factors, and inflammatory diseases. Most affected groups include children as well as women, despite the fact that the general populace was found to have declined levels of vitamin D. Vitamin D receptors of type Nuclear, found in many organs, allow vitamin D to regulate gene transcription. The impacts of VDR have been linked to the pathogenesis of obesity. According to (Zaki et al., 2017), there are noticeable variations between obese and control cases in the VDR gene polymorphism, where, females who possess the alleles Tt or tt for TaqI have noticeably low serum 25(OH) D, high HOMA-IR, and blood pressure when compared to those with the common homozygous alleles AA, FF, TT for the VDR. In (Patel et al., 2017) researchers looked into whether the VDR gene polymorphism could be a factor in making West Indian women who were pregnant more susceptible to prematurity. The study found that women with PTB had lower levels of 25 (OH) D in their blood compared to the control group. This confirms that a lack of vitamin D can increase the risk of premature birth. The difference in levels was statistically significant ($p<0.05$). The study found that women with a history of preterm birth have different variations of the VDR TaqI polymorphism gene compared to control subjects. Specifically, 48.61% had the TT genotype, 43.06% had the Tt genotype, and 8.33% had the tt genotype, whereas the control group had 52.17%, 39.13%, and 8.7%, respectively. There was no significant difference ($p=0.73$) observed between the PTB group and control group in terms of the frequency of T alleles 70.14% vs. 71.71% and t alleles 29.86% vs 28.26% of VDR TaqI polymorphism.(Patel et al.,

2017). Similar results were generated in (Karras et al. 2020) where groups of maternal Vitamin D status were defined using a 50 nmol/l threshold. The percentage of mothers with 25(OH)D ≥50 nmol/l was 64%, while it was 36% in those with less than 50 nmol/l.. Regardless of the Vitamin D threshold used, there were no variations detected in the distribution of genotype of the additional polymorphisms ApaI, TaqI, BsmI, FokI within the various maternal groups, there are differing levels of Vitamin D status. (Karras et al., 2020)**.** The amount of vitamin D present in a mother is directly linked to the amount found in her fetus. Not having enough vitamin D has been linked to a higher chance of certain childhood illnesses. During pregnancy, the level of albumin decreases and the production of vitamin D-binding protein in the liver increases. As a result, there is a change in the way the mother's body processes vitamin D. This reduces the amount of free vitamin D available and leads to an increase in the 25(OH) D conversion to 1, 25(OH)2D3 using the placenta. The placenta is the main site for this conversion outside of the kidneys because of the ascended activity of 1α-hydroxylase.(Smith et al. 2019). Additionally, when a baby is born prematurely, of vitamin D transfer to fetus may be affected. Therefore, researchers have conducted studies to examine the levels of vitamin D in the bloodstream of pregnant women. (Qin et al., 2016; von Websky et al.. 2018). According to (Dutra et al., 2019), mothers who gave birth prematurely and have the AG genotype, AA genotype, AG genotype TaqI, ApaI, FokI SNV respectively, had lower levels of 25(OH) D compared to full term mothers. Likewise, premature infants carrying the GG genotype (FokI SNV) had lower levels of 25(OH) D compared to full term babies. (Tayel et al.) also studied the genotype of VDR and its association with vitamin D estimation where VDR polymorphism at rs731236 TaqI CC and CT genotypes and C allele frequencies were predominant in cases however they were not significantly different versus healthy control either in mothers group with vitamin D

deficiency (Tayel et al., 2018). Table 1 has shown the association between single nucleotide polymorphism of TaqI with Vitamin D deficiency in different studies (Table 1).

Table-1: Association between single neucleotide polymorphism of TaqI with Vitamin D deficiency resulting in preterm and low birth weight.

Authors	Gene	Genotype	Ethnicity	Total cases of Vitamin D deficiency	Controlled group (Vitamin D sufficiency)	Allele	Genotyping Method	p value
Dutra et al., 2020 (Dutra et al. 2019)	TaqI/A > G	AA AG GG	Mixed	-	-	Allele A Allele G	TaqMan Assay	0.165 0.016
Patel et al., 2017 (Patel et al. 2017)	rs731236	TT Tt tt	Mixed	25.74±4.56 22.34±9.34 23.45±8.63	-	Allele T Allele t	PCR-RFLP	ref 0.27 0.42
Zaki et al., 2017(Zaki et al. 2017)	TaqI	TT Tt Tt T t	Mixed	57.7% 39.8% 10.4% 69.5% 59.8%	7-3.8% 18.1% 8.32% 82.9% 17.1%	Allele T Allele t	PCR-RFLP	0.3
Karras et al., 2020 (Karras et al. 2020)	TaqI	TT Tt tt	Mixed	14 (31) 23 (51) 8 (18)	11 (44) 10 (40) 4 (16)	Allele T Allele t	PCR-RFLP	0.6
Tayel et al., 2018	TaqI	C/C T/C T/T	Mixed	-	-	Allele T Allele C	TaqMan Assay	0.818

Currently, screening women who are pregnant and have a risk of vitamin D deficiency may benefit from taking daily doses of vitamin D supplements ranging from 600 to 1000 IU are advised by some nations and international scientific groups. More research, according to the WHO, is required before vitamin D supplementation in amounts higher

than 200 units per day is advised. It is significant to note that mother's deficiency of vitamin D is associated to a number of other pregnancy and neonatal complications, including an increased risk of diabetes mellitus with the mother, preterm birth, low birth weight as well as potential non genetic impacts on fetus (Woo et al., 2019).

3.9 Association of single nucleotide polymorphism of TaqI Premature birth

The link between vitamin D levels and PTB might be influenced by specific genetic variations in the vitamin D receptor gene, known as single nucleotide polymorphisms . There are 63 variations in the VDR gene, but only five have been studied thoroughly including Cdx2, FokI, BsmI, ApaI, and TaqI in the promotion, second coding exon and 3' untranslated region respectively. Based on the evidence available, there may be a link between specific Single nucleotide polymorphisms and preterm birth. However, the results are conflicting. (Krpina et al., 2020).

Previous studies suggest that there is no significant link between VDR variants and the risk of having prematurity. (Table 2).

Table-2: Some studies on the association of single nucleotide polymorphism of TaqI and premature birth

Authors	Gene	Genotype	Ethnicity	Total cases of preterm birth	Controlled group number	Allele	Genotyping Method	p value
Baczyńska-Strzecha et al., 2016 (Baczyńska-strzecha and Kalinka 2016)	rs731236	TT Tt tt	Caucasian	45 (45%) 41 (41%) 14 (14%)	37 (37%) 49 (49%) 13 (13%)	Allele T Allele t	TaqMan Assay	0.4668
Rosenfeld et al., 2017 (Rosenfeld et al. 2017)	rs10735810,	TT tt Tt	Mixed	39.7% 15.5% 44.8%	40.8% 14.1% 45.1%	-	RFLP	0.944
Dutra et al., 2020 (Dutra et al. 2019)	TaqI/A > G	AA AG GG	Mixed	19 (47.5%) 18 (45%) 3 (7.5%)	25 (27.2%) 46 (50%) 21 (22.8%)	Allele A Allele G	TaqMan Assay	0.072
Manzon et al., 2014 (Manzon et al. 2014)	rs10735810	T > C	Jewish/Arab	11.5%	33.9%	Allele T Allele C	RLFP	0.032
Patel et al., 2017 (Patel et al. 2017)	rs731236	TT Tt tt	Mixed	35 (48.61%) 31 (43.06%) 06(8.33%)	72 (52.17%) 54 (39.13%) 12 (8.7)	Allele T Allele t	PCR-RFLP	0.59 0.96

Studies that have linked certain variations in the VDR gene with an increased likelihood of preterm birth were listed in Table 2. (Manzon et al. 2014) The study examined 33 Jewish Israeli mothers of Caucasian descent and their premature babies (born between

24-35 weeks gestation) as well as 98 other mothers and their full-term newborns. The T allele of TaqI SNV is less common in preterm mothers, but no correlation was found between genotypes and preterm/full-term birth (Manzon et al., 2014). Furthermore, (Baczyńska-Strzecha et al., 2016) 100 mothers of preterm babies and 99 mothers of full-term babies were studied from Poland. The frequencies of individual genotypes were similar between the two groups. However, we observed that certain genotype combinations, such as BsmI/bb-ApaI/AA-TaqI/TT and BsmI/BB-ApaI/aa-TaqI/tt, were more common in the preterm group. On the other hand, the BsmI/Bb-ApaI/AA-TaqI/Tt and BsmI/BB-ApaI/Aa-TaqI/tt combinations were associated with a lower risk of preterm birth (Baczyńska-strzecha and Kalinka, 2016). In contrast, (Rosenfeld et al., 2017) study consisted of 146 Israeli women who were Jewish and their premature newborns, as well as 229 FTNs of other type, discovered that the TaqI SNV genotype was not linked to premature birth (with a p-value greater than 0.05). (Rosenfeld et al., 2017).

In another study by (Dutra et al) mothers of preterm neonates were found to have a higher occurrence of the AAG (TaqI/A- ApaI/A-FokI/G) and GCA (TaqI/G-ApaI/C-FokI/A) haplotypes. On the other hand, mothers of full-term neonates had a higher frequency of the GG genotype of TaqI, CT genotype of BsmI SNVs, and GCG (TaqI/G-ApaI/C-FokI/G) haplotype. Certain gene genotypes, such as AG FokI and certain ApaI genotypes, are linked with lower levels of 25(OH) D. Mothers with AA ApaI and TT BsmI genotypes are at higher risk of preterm birth with 25(OH) D deficiency, while carriers of GG TaqI have lower risk. (Dutra et al., 2019).

The variants that were studied were identified using a validated and reliable method called qPCR with TaqMan probes. This discovery suggests that there could be a link between the marker locus and the likelihood of premature birth.

3.10 Association of single nucleotide polymorphism of TaqI with LBW

A sensitive measure of the population's general health is the baby's birth weight. Cognitive deficits, motor delays, cerebral palsy, as well as other behavioral and psychological issues are risks for LBW infants. Additionally, it is a predictor of future neonatal deaths, child malnutrition, and cardiovascular disease risks in adulthood in addition to being an indirect sign of maternal health (Arnold, Hoy and Wang, 2016; Thapa et al., 2022; Baas et al., 2021). Newborn birth weight can be influenced by social and environmental factors, but genetics have the greatest impact. Researchers have also found a link between vitamin D and pregnancy end results (Liu and Hewison, 2012). Most people are aware that vitamin D is important for human bone development, but during pregnancy it serves many other purposes, including aiding in implantation, supporting a healthy pregnancy, facilitating fetal growth by delivering calcium, promoting the production of placental hormones, and reducing inflammation.(Liu and Hewison, 2012). Moreover, VDR plays a role in the various effects of vitamin D, and when its expression in the placenta is reduced, it can contribute to complications during pregnancy (Murthi et al., 2016). The presence of VDR in the human placenta suggests that vitamin D may affect the development, growth, and cell differentiation of the fetus and placenta, as well as signaling between the mother and fetus (Krpina et al., 2020).

The impact of VDR SNPs on VDR protein function and signaling is not yet fully understood, but certain variations can alter the levels of vitamin D in the bloodstream and its effectiveness in the body (McGrath et al., 2010) Studies show that the vitamin

D receptor genotype has an impact on the ideal vitamin D level and can lower the risk of negative perinatal results. On the other hand (Krpina et al. 2018) found that newborn birth weight was impacted by the FokI TT genotype, but there was no variation in the occurrence of FokI genotypes/alleles among patients and controls. Likewise, indicated that the presence of the mother's FokI T allele significantly raised the likelihood of SPTB, with odds ratios of 3.32 and 7.49 (Manzon et al., 2014) and (Javorski et al., 2018). In a previous study that examined the link between Vitamin D receptor polymorphism and birth weight among the newborns, it was discovered that the FokI A allele was connected to lower birth weight. This finding contradicts the results of Kepina. (Barchitta et al., 2018). Additionally, other researchers have observed an intriguing impact of fetal VDR genotype on anthropometric measurements at birth in pregnant women with lower levels of vitamin D. Morley et al. discovered that variations in the VDR gene of infants influenced the influence of vitamin D insufficiency in mothers on the size of their newborns at birth (Morley et al., 2009). Infants who have homozygous FokI major allele or are heterozygotes may have lower newborn birth weight if they have low levels of vitamin D.

Furthermore, (Javorski et al., 2018) discovered a notable variation in Cdx2 genetic variations between the maternal group with SPTB and the control group. Additionally, I recognized a correlation between this genetic variation and the birth weight of newborns. It's worth mentioning that children who had ApaI heterozygotes had a lower birth weight. (Pereira-santos et al., 2019). In non-Hispanic black women, there is a correlation between certain SNPs in the maternal Vitamin D receptor gene and a decrease in newborn birth weight (Swamy et al., 2011). Differences in population, participant selection, and sample size could explain the varying results in the five SNPs

studies. None of these findings showed any relation between TaqI-SNP and low birth weight among pregnant mothers.

Chapter 4

Conclusion

Despite extensive study, the genetic factors that contribute to unexpected birth without a known cause before the due date is still poorly understood. Determining potential mechanisms and genetic factors responsible causing spontaneous idiopathic preterm birth allows for the identification of targets for diagnostic and therapeutic interventions. Our findings imply that single and multiple variants in the VDR gene, especially TaqI polymorphism in the mother can be linked to preterm births of fetus. The TaqI polymorphism has been reported to influence susceptibility to some diseases such as diabetes mellitus. Studies also suggests, Vitamin D receptor TaqI polymorphism might comprise within the predisposition to respiratory distress syndrome (RDS) in neonates born prematurely. Therefore, this genetic changes suggestively can be used as a diagnostic tool to foretell pre-term deliveries along with other factors, particularly for women who have had prior miscarriages. Since vitamin D levels can be changed by diet, this creates a potential treatment pathway to influence results. Future research is necessary to determine whether nutritional therapies can provide a potential solution for the genetic preside position. In order to confirm the link between genotype and preterm birth risk, we require larger, multi-center studies due to the complexity of gene-gene and gene-environment interactions. Additionally, we need to analyze a higher number of vitamin D receptor polymorphisms and their combinations.

Limitation of the study

The major shortcoming of our findings were there only few studies done regarding VDR polymorphisms and PTB risk. These studies investigated the relationship between various racial groups and people of different ethnicity in medium to large populations., therefore this review cannot be particular for a single group of population. However, we cannot perform a meta-analysis of the association between VDR polymorphisms and the measurements of a newborn's body dimensions due to inconsistent reported outcomes. Moreover, a few findings studied the impact of genetic polymorphism of Vitamin D with birth weight and most of them remain controversial.

In future studies, it would be beneficial to gather more data on other body measurements. Additionally, it's important to consider the impact of unmeasured factors like sun exposure, mother's habits, and levels of vitamin D in the blood. Vitamin D levels from supplements as well as fortified foods were not measured or calculated in these findings; therefore, there is no accurate way to measure vitamin D intake was investigated due to informal investigation, lack of consistency and the use of non-specific questions. In addition, some studies have revealed no connection between PTB and VDR (TaqI) polymorphisms. The TaqI polymorphism of the VDR gene is found in the non-coding region, and it has no impact on ultimate protein. The distribution pattern of TaqI genotype and allele was not produce any notable findings in several research (Patel and Sodagar 2017).

Another possible weakness confined in our findings is that not all the studies performed examination of TaqI SNP from the maternal gene specifically. Previous research has indicated that the maternal genotype is the primary factor that impacts subsequent preterm birth (PTB). It is important to note that our findings may be limited by multiple

comparisons and the potential for false positive results, underscoring the need for further confirmation of our conclusions regarding specific genetic polymorphisms.

Future Research Plan

The interactions between the mother and fetus at a molecular and biological level are still not fully understood. While there are many social and environmental factors that can affect a newborn's birth weight, genetics has the greatest impact. Such research may ultimately help in building bridges between the genetic predisposition pregnancy outcome such as preterm birth, low birth weight and level of maternal vitamin D. This research suggest that it may be important to examine the association between maternal 25-(OH)D status and birth size in the context of infant VDR genotype. However, when conducting future studies on low birth weight, it is important to take into account environmental factors such as diet and nutrition.

Similarly, future studies should investigate the effects of other genetic variations in vitamin D metabolism genes, including DHCR7, CYP2R1, CYP24A1, and GC. These variables can influence vitamin D status, but unmeasured factors may limit our conclusions on the association with neonatal measures and low birth weight risk. Additional research, including observational studies and clinical trials, is needed to develop effective preventive strategies.

Lastly, more studies are needed to understand the relationship between genotype and preterm birth risk. Analyzing more VDR polymorphisms and their combinations is crucial due to the complexity of gene-gene and gene and environment interactions. Discrepancies in health outcomes may be due to variations in genetics, ethnicity, and race are notable factors and latitude of habitance. Population-specific studies are necessary.

Chapter 5

Reference

Aghajafari, F., Nagulesapillai, T., Ronksley, P. E., Tough, S. C., O'Beirne, M., & Rabi, D. M. (2013). Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. Bmj, 346.

Arnold, L., Hoy, W., & Wang, Z. (2016). Low birthweight increases risk for cardiovascular disease hospitalisations in a remote Indigenous Australian community–a prospective cohort study. *Australian and New Zealand Journal of Public Health*, *40*(S1), S102-S106.

Baas, E. M., Romijn, M., van der Pal, S. M., Vrijlandt, E. J., Rotteveel, J., & Finken, M. J. (2021). No association between glucocorticoid receptor polymorphisms and long-term respiratory outcome after very preterm birth. *Endocrine*, *73*(1), 226-229.

Baczyńska-Strzecha, M., & Kalinka, J. (2016). Influence of Apa1 (rs7975232), Taq1 (rs731236) and Bsm1 (rs154410) polymorphisms of vitamin D receptor on preterm birth risk in the Polish population. *Ginekologia Polska*, *87*(11), 763-768.

Barchitta, M., Maugeri, A., La Rosa, M. C., Magnano San Lio, R., Favara, G., Panella, M., ... & Agodi, A. (2018). Single nucleotide polymorphisms in vitamin D receptor gene affect birth weight and the risk of preterm birth: Results from the "mamma & bambino" cohort and a meta-analysis. *Nutrients*, *10*(9), 1172.

Barrera, D., Díaz, L., Noyola-Martínez, N., & Halhali, A. (2015). Vitamin D and inflammatory cytokines in healthy and preeclamptic pregnancies. *Nutrients*, *7*(8), 6465-6490.

Bilge, U., Unalacak, M., Unluoglu, I., Ipek, M., Celer, O., & Akalm, A. (2015). Relationship between 1, 25-dihydroxy Vitamin D levels and homeostatic model

assessment insulin resistance values in obese subjects. *Nigerian journal of clinical practice*, *18*(3), 377-380.

Blencowe, H., Cousens, S., Chou, D., Oestergaard, M., Say, L., Moller, A. B., ... & Lawn, J. (2013). Born too soon: the global epidemiology of 15 million preterm births. *Reproductive health*, *10*(1), 1-14.

Bouillon, R., Carmeliet, G., Verlinden, L., Van Etten, E., Verstuyf, A., Luderer, H. F., ... & Demay, M. (2008). Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocrine reviews*, *29*(6), 726-776.

Christakos, S., Dhawan, P., Verstuyf, A., Verlinden, L., & Carmeliet, G. (2016). Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. *Physiological reviews*, *96*(1), 365-408.

Cieślińska, A., Kostyra, E., Fiedorowicz, E., Snarska, J., Kordulewska, N., Kiper, K., & Savelkoul, H. F. (2018). Single nucleotide polymorphisms in the vitamin D receptor gene (VDR) may have an impact on acute pancreatitis (AP) development: A prospective study in populations of AP patients and alcohol-abuse controls. *International journal of molecular sciences*, *19*(7), 1919.

Dutra, L. V., Affonso-Kaufman, F. A., Cafeo, F. R., Kassai, M. S., Barbosa, C. P., Santos Figueiredo, F. W., ... & Bianco, B. (2020). Association between vitamin D plasma concentrations and VDR gene variants and the risk of premature birth. *BMC Pregnancy and Childbirth*, *20*(1), 1-11.

Dutra, L. V., Affonso-Kaufman, F. A., Cafeo, F. R., Kassai, M. S., Barbosa, C. P., Santos Figueiredo, F. W., ... & Bianco, B. (2020). Association between vitamin D plasma concentrations and VDR gene variants and the risk of premature birth. *BMC Pregnancy and Childbirth*, *20*(1), 1-11.

Fleet, J. C. (2017). The role of vitamin D in the endocrinology controlling calcium

homeostasis. *Molecular and cellular endocrinology*, *453*, 36-45.

KC, A., Basel, P. L., & Singh, S. (2020). Low birth weight and its associated risk factors: Health facility-based case-control study. *PloS one*, *15*(6), e0234907.

Ishida, H., & Norman, A. W. (1988). Demonstration of a high affinity receptor for 1, 25-dihydroxyvitamin D3 in rat pancreas. *Molecular and cellular endocrinology*, *60*(2-3), 109-117.

Javorski, N., Lima, C. A. D., Silva, L. V. C., Crovella, S., & de Azêvedo Silva, J. (2018). Vitamin D receptor (VDR) polymorphisms are associated to spontaneous preterm birth and maternal aspects. *Gene*, *642*, 58-63.

Johnson, J. D., Kuang, S., Misler, S., & Polonsky, K. S. (2004). Ryanodine receptors in human pancreatic β cells: localization and effects on insulin secretion. *The FASEB journal*, *18*(7), 878-880.

Karpova, N., Dmitrenko, O., Arshinova, E., & Nurbekov, M. (2022). Influence of 25 (OH) D Blood Concentration and Supplementation during Pregnancy on Preeclampsia Development and Neonatal Outcomes. *International Journal of Molecular Sciences*, *23*(21), 12935.

Karras, S. N., Koufakis, T., Antonopoulou, V., Goulis, D. G., Alaylıoğlu, M., Dursun, E., ... & Kotsa, K. (2020). Vitamin D receptor FokI polymorphism is a determinant of both maternal and neonatal vitamin D concentrations at birth. *The Journal of Steroid Biochemistry and Molecular Biology*, *199*, 105568.

Khalessi, N., Kalani, M., Araghi, M., & Farahani, Z. (2015). The relationship between maternal vitamin D deficiency and low birth weight neonates. *Journal of family & reproductive health*, *9*(3), 113.

Khan, J. R., Islam, M., Awan, N., & Muurlink, O. (2018). Analysis of low birth weight and its co-variants in Bangladesh based on a sub-sample from nationally representative

survey. *BMC pediatrics*, *18*(1), 1-9.

Gašparović Krpina, M., Barišić, A., Peterlin, A., Tul, N., Ostojić, S., Pereza, N., & Peterlin, B. (2020). Vitamin D receptor polymorphisms in spontaneous preterm birth: a case-control study. *Croatian medical journal*, *61*(4), 338-345.

Lian, R. H., Qi, P. A., Yuan, T., Yan, P. J., Qiu, W. W., Wei, Y., ... & Yi, B. (2021). Systematic review and meta-analysis of vitamin D deficiency in different pregnancy on preterm birth: Deficiency in middle pregnancy might be at risk. *Medicine*, *100*(24).

Manzon, L., Altarescu, G., Tevet, A., Schimmel, M. S., Elstein, D., Samueloff, A., & Grisaru-Granovsky, S. (2014). Vitamin D receptor polymorphism FokI is associated with spontaneous idiopathic preterm birth in an Israeli population. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *177*, 84-88.

McGrath, J. J., Saha, S., Burne, T. H., & Eyles, D. W. (2010). A systematic review of the association between common single nucleotide polymorphisms and 25-hydroxyvitamin D concentrations. *The Journal of steroid biochemistry and molecular biology*, *121*(1-2), 471-477.

Morley, R., Carlin, J. B., Pasco, J. A., Wark, J. D., & Ponsonby, A. L. (2009). Maternal 25-hydroxyvitamin D concentration and offspring birth size: effect modification by infant VDR genotype. *European journal of clinical nutrition*, *63*(6), 802-804.

Morrison, N. A., Qi, J. C., Tokita, A., Kelly, P. J., Crofts, L., Nguyen, T. V., ... & Eisman, J. A. (1994). Prediction of bone density from vitamin D receptor alleles. *Nature*, *367*(6460), 284-287.

Murthi, P., Yong, H. E., Ngyuen, T. P., Ellery, S., Singh, H., Rahman, R., ... & Ebeling, P. R. (2016). Role of the placental vitamin D receptor in modulating feto-placental growth in fetal growth restriction and preeclampsia-affected pregnancies. *Frontiers in physiology*, *7*, 43.

Oliveira, L. L. D., Gonçalves, A. D. C., Costa, J. S. D. D., & Bonilha, A. L. D. L. (2016). Maternal and neonatal factors related to prematurity. *Revista da Escola de Enfermagem da USP*, *50*, 382-389.

Patel, H. V., Patel, N. H., & Sodagar, N. R. (2017). Vitamin d receptor (VDR) gene polymorphism and maternal vitamin d deficiency in indian women with preterm birth (PTB). *Asian J Pharm Clin Res*, *10*(9), 219-23.

Pereira-Santos, M., Carvalho, G. Q., Louro, I. D., Dos Santos, D. B., & Oliveira, A. M. (2019). Polymorphism in the vitamin D receptor gene is associated with maternal vitamin D concentration and neonatal outcomes: A Brazilian cohort study. *American Journal of Human Biology*, *31*(4), e23250.

Pfotenhauer, K. M., & Shubrook, J. H. (2017). Vitamin D deficiency, its role in health and disease, and current supplementation recommendations. *Journal of Osteopathic Medicine*, *117*(5), 301-305.

Islam Pollob, S. A., Abedin, M. M., Islam, M. T., Islam, M. M., & Maniruzzaman, M. (2022). Predicting risks of low birth weight in Bangladesh with machine learning. *PloS one*, *17*(5), e0267190.

Qin, L.L., Lu, F.G., Yang, S.H., Xu, H.L. & Luo, B.A., 2016. Does maternal Vitamin D deficiency increase the risk of preterm birth: A meta-analysis of observational studies. *Nutrients*, 8(5).

Rosenfeld, T., Salem, H., Altarescu, G., Grisaru-Granovsky, S., Tevet, A. & Birk, R., 2017. Maternal–fetal vitamin D receptor polymorphisms significantly associated with preterm birth. *Archives of Gynecology and Obstetrics*, 296(2), 215–222.

Samuel, T.M., Sakwinska, O., Makinen, K., Burdge, G.C., Godfrey, K.M. & Silva-Zolezzi, I., 2019. Preterm birth: A narrative review of the current evidence on nutritional and bioactive solutions for risk reduction. *Nutrients*, 11(8), 1–26.

Sangkaew, B., Nuinoon, M. & Jeenduang, N., 2018. Association of vitamin D receptor gene polymorphisms with serum 25 (OH) D levels and metabolic syndrome in Thai population. *Gene*, 659(March), 59–66.

Smith, C.J., Jasper, E.A., Baer, R.J., Breheny, P.J., Paynter, R.A., Bao, W., et al., 2019. Genetic Risk Scores for Maternal Lipid Levels and Their Association with Preterm Birth. (August), 641–650.

Swamy, G.K., Garrett, M.E., Miranda, M.L. & Allison, E.A.-K., 2011. Maternal Vitamin D Receptor Genetic Variation Contributes to Infant Birthweight among Black Mothers. *Am J Med Genet A.*, 155(6), 1267–1271.

Tayel, S.I., Soliman, S.E. & Elsayed, H.M., 2018. Vitamin D deficiency and vitamin D receptor variants in mothers and their neonates are risk factors for neonatal sepsis. *Steroids*, 134, 37–42.

Thapa, P., Poudyal, A., Poudel, R., Upadhyaya, D.P., Timalsina, A., Bhandari, R., et al., 2022. Prevalence of low birth weight and its associated factors: Hospital based cross sectional study in Nepal. *PLOS Global Public Health*, 2(11), e0001220.

Walani, S.R., 2020. Global burden of preterm birth. *International Journal of Gynecology and Obstetrics*, 150(1), 31–33.

Wang, H., Chen, W., Li, D., Yin, X., Zhang, X., Olsen, N., et al., 2017. Vitamin D and Chronic Diseases. *Aging and disease*, 8(3), 346.

von Websky, K., Hasan, A.A., Reichetzeder, C., Tsuprykov, O. & Hocher, B., 2018. Impact of vitamin D on pregnancy-related disorders and on offspring outcome. *Journal of Steroid Biochemistry and Molecular Biology*, 180, 51–64.

Whitfield, G.K., Hsieh, J.C., Nakajima, S., MacDonald, P.N., Thompson, P.D., Jurutka, P.W., et al., 1995. A highly conserved region in the hormone-binding domain of the human vitamin D receptor contains residues vital for heterodimerization with retinoid

X receptor and for transcriptional activation. *Molecular Endocrinology*, 9(9), 1166–1179.

Woo, J., Giurgescu, C., & Wagner, C. L. (2019). Evidence of an association between vitamin D deficiency and preterm birth and preeclampsia: a critical review. *Journal of midwifery & women's health*, *64*(5), 613-629.

World Health Organization, 2022. *Low birth weight*. Available at: https://bit.ly/3SCYDqR/, (Last accessed 01 December 2022)

World Health Organization, 2022. *Preterm and low birth weight infants*. Newborn Health-WHO. Available at: https://bit.ly/3KM2P5L/, (Last accessed 01 December 2022)

Yang, L., Pan, S., Zhou, Y., Wang, X., Qin, A., Huang, Y., & Sun, S. (2016). The correlation between serum vitamin D deficiency and preterm birth. *Medical science monitor: international medical journal of experimental and clinical research*, *22*, 4401.

Zaki, M., Kamal, S., Basha, W. A., Youness, E., Ezzat, W., El-Bassyouni, H., & Amr, K. (2017). Association of vitamin D receptor gene polymorphism (VDR) with vitamin D deficiency, metabolic and inflammatory markers in Egyptian obese women. *Genes & diseases*, *4*(3), 176-182.

Nizhum_Taq1

ORIGINALITY REPORT

17%	13%	15%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	bmcpregnancychildbirth.biomedcentral.com Internet Source	4%
2	www.ncbi.nlm.nih.gov Internet Source	1%
3	www.researchgate.net Internet Source	1%
4	Diptika Tiwari, Saswati Sanyal Choudhury, Anjuma Begum, Tina Nath, Sujoy Bose. "Maternal Vitamin D receptor gene variant genotype and its influence on preterm birth, low birth weight, and fetal death. A case-control study from Northeast India", Gene Reports, 2022 Publication	1%
5	innovareacademics.in Internet Source	1%
6	mdpi.com Internet Source	1%
7	Safaa I. Tayel, Shimaa E. Soliman, Hanan M. Elsayed. "Vitamin D Deficiency and Vitamin D	1%

Receptor Variants in Mothers and Their Neonates Are Risk Factors for Neonatal Sepsis", Steroids, 2018
Publication

8	"Vitamin D and the Lung", Springer Science and Business Media LLC, 2012 Publication	1 %
9	Lecanda, F.. "Impaired intramembranous bone formation in connexin43 null mice", Bone, 199811 Publication	<1 %
10	Moushira Zaki, Sanaa Kamal, Walaa A. Basha, Eman Youness, Wafaa Ezzat, Hala El-Bassyouni, Khalda Amr. "Association of vitamin D receptor gene polymorphism (VDR) with vitamin D deficiency, metabolic and inflammatory markers in Egyptian obese women", Genes & Diseases, 2017 Publication	<1 %
11	www.nature.com Internet Source	<1 %
12	Soo-Kyung Chun, Sangah Shin, Moon Young Kim, Hyojee Joung, Jayong Chung. "Effects of maternal genetic polymorphisms in vitamin D-binding protein and serum 25-hydroxyvitamin D concentration on infant birth weight", Nutrition, 2017 Publication	<1 %

13	Submitted to Anglo-American School of Moscow Student Paper	<1%
14	file.scirp.org Internet Source	<1%
15	www.em-consulte.com Internet Source	<1%
16	www.christchurchpharmacy.co.nz Internet Source	<1%
17	www.science.gov Internet Source	<1%
18	A UITTERLINDEN. "Genetic Vitamin D Receptor Polymorphisms and Risk of Disease", Vitamin D, 2005 Publication	<1%
19	mafiadoc.com Internet Source	<1%
20	Submitted to Hawler Medical University Student Paper	<1%
21	A Dawodu, C L Wagner. "Prevention of vitamin D deficiency in mothers and infants worldwide — a paradigm shift", Paediatrics and International Child Health, 2013 Publication	<1%
22	Samantha Kimball, Ghada El-Hajj Fuleihan, Reinhold Vieth. "Vitamin D: A Growing	<1%

Perspective", Critical Reviews in Clinical Laboratory Sciences, 2008
Publication

23	www.frontiersin.org Internet Source	<1 %
24	www.sgcard.org Internet Source	<1 %
25	acikerisim.baskent.edu.tr:8080 Internet Source	<1 %
26	Daniela Boleixa, Andreia Bettencourt, António Marinho, Ana Martins Silva et al. "Vitamin D", Elsevier BV, 2019 Publication	<1 %
27	Reza Ghiasvand, Ali Rashidian, Faezeh Abaj, Masoumeh Rafiee. "Genetic variations of vitamin D receptor and vitamin D supplementation interaction in relation to serum vitamin D and metabolic traits: a systematic review and meta-analysis", International Journal for Vitamin and Nutrition Research, 2022 Publication	<1 %
28	academic.oup.com Internet Source	<1 %
29	docksci.com Internet Source	<1 %

30	tau.amegroups.com Internet Source	<1 %
31	e-space.mmu.ac.uk Internet Source	<1 %
32	journals.plos.org Internet Source	<1 %
33	www.alexandrelevangelista.com.br Internet Source	<1 %
34	www.omicsdi.org Internet Source	<1 %
35	www.researchsquare.com Internet Source	<1 %
36	"Poster Presentation Abstracts", Osteoporosis International, 2006 Publication	<1 %
37	Rosnah Sutan, Mazlina Mohtar, Aimi Nazri Mahat, Azmi Mohd Tamil. "Determinant of Low Birth Weight Infants: A Matched Case Control Study", Open Journal of Preventive Medicine, 2014 Publication	<1 %
38	Vladimira Mondockova, Veronika Kovacova, Nina Zemanova, Martina Babikova et al. "Vitamin D Receptor Gene Polymorphisms Affect Osteoporosis-Related Traits and	<1 %

Response to Antiresorptive Therapy", Genes, 2023
Publication

39	Christopher S. Kovacs. "Fetus, Neonate and Infant", Vitamin D, 2011 Publication	<1 %
40	Cooper, James W., and Allison H. Burfield. "Assessment and management of chronic pain in the older adult", Journal of the American Pharmacists Association, 2010. Publication	<1 %
41	Michael W. Rich. "Fourth Pivotal Research in Cardiology in the Elderly (PRICE-IV) Symposium?Electrophysiology and Heart Rhythm Disorders in the Elderly: Mechanisms and Management", The American Journal of Geriatric Cardiology, 5/2007 Publication	<1 %
42	PERIANAYAGAM AROKIASAMY, ABHISHEK GAUTAM. "NEONATAL MORTALITY IN THE EMPOWERED ACTION GROUP STATES OF INDIA: TRENDS AND DETERMINANTS", Journal of Biosocial Science, 2008 Publication	<1 %

Exclude quotes	On	Exclude matches	< 4 words
Exclude bibliography	On		