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

By

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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.

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Approval

The thesis titled “A Review on Association of Mothers’ Single Nucleotide Polymorphism (BsmI) of Vitamin D Receptor Gene with Risk of Preterm Birth and Low Birth Weight” submitted by Hasan Shahriyer Tonmoy (19146019), 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

This study does not involve any animal or human trial.

Abstract

Preterm birth and low birth weight are linked to increased neonatal morbidity and mortality and can harm a child's health and development. An expanding corpus of research confirms that a number of genetic and immunological variables contribute to premature delivery and low birth weight. Vitamin D can have substantial impact on pregnancy and birth outcomes by influencing calcium balance, immunity, and cell proliferation. Its deficiency in pregnant women can lead to adverse results. The vitamin D receptor (VDR) is crucial to the endocrine system, regulating gene expression alongside encoding the VDR protein. This review explored the impact of the maternal vitamin D receptor gene's single nucleotide polymorphism, BsmI on VDR activity and their associations with preterm delivery and birth weight. The findings of this review revealed a correlation between the VDR gene polymorphism BsmI and preterm birth, whereas, no connection was observed for low birth weight.

Keywords: pregnancy; vitamin D; vitamin D receptor; BsmI polymorphism; gestational duration; preterm birth; birth weight.

Dedication

This work is dedicated to my parents, whose unrelenting encouragement and assistance have been the propelling force behind my academic trajectory. Their trust in me and my abilities has inspired me to pursue my passions and chase my dreams. This research paper is a humble demonstration of my appreciation for their affection, guidance, and sacrifices.

Acknowledgement

I want to start by expressing my sincere appreciation to Allah Ta'ala for giving me the fortitude, insight, and direction necessary to complete this paper.

I am thankful to the Almighty for granting me the good fortune of having a kindhearted and supportive personality like Dr. Raushanara Akter (Professor of the School of Pharmacy, Brac University) as my project supervisor. I would like to extend my sincere appreciation to her for her invaluable direction, mentoring, and unwavering support during this transformative journey. Her commitment and expertise have significantly shaped my understanding and approach to research. I would also like to thank Professor Dr. Eva Rahman Kabir (Dean of the School of Pharmacy, Brac University) and Professor Dr. Hasina Yasmin (Program Director and Assistant Dean of the School of Pharmacy, Brac University) for allowing to work on this project along with their constant support and guidance throughout the process.

My profound gratitude goes out to all of my teachers, who have influenced me to follow my aspirations and taught me a lot of valuable things. In addition, it is essential to express gratitude for my colleagues and acquaintances, whose unshakable presence has served as a continual wellspring of motivation and assistance.

Last but not least, I would want to convey my utmost appreciation to my parents, whose unflinching presence and unwavering support have always accompanied me throughout my many pursuits. Their encouragement, sacrifices, and love have made this journey possible.

The project's successful completion would not have been feasible without the irreplaceable support and guidance provided by each of these people. I express my enduring gratitude for their significant contributions.

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List of Acronyms

7DHC	7-dehydrocholesterol
25(OH)D	25-hydroxyvitamin D
APR	Acute-phase Response
BPD	Bronchopulmonary Dysplasia
BV	Bacterial Vaginosis
CAMP	cathelicidin
CRP	C-reactive protein
DBP	D Binding Protein
DV	Daily Value
EC	Endocrine Society
eNOS	Endothelial Nitric Oxide Synthase
FGF23	Fibroblast Growth Factor 23
FTN	Full-term Newborns
GDM	Gestational diabetes mellitus
GMCSF-2	Granulocyte Macrophage Colony Stimulating Factor-2
HCG	Human Chorionic Gonadotropin
HGVS	Human Genome Variation Society
IOM	Institute of Medicine

IU	International Unit
IVH	Intraventricular Hemorrhage
LPS	Lipopolysaccharides
NEC	Necrotizing Enterocolitis
NF-κB	Nuclear Factor-kappa B
OR	Odds Ratio
PPROM	Premature Rupture of Membranes
PTB	Preterm Birth
PTH	Parathyroid Hormone
PTN	Preterm Neonates
LBW	Low Birth Weight
RDA	Recommended Dietary Allowance
RDS	Respiratory Distress Syndrome
RXR	Retinoid X Receptor
SGA	Small for Gestational Age
SNP	Single Nucleotide Polymorphism
SNV	Single Nucleotide Variation
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus

TLR4	Toll-like Receptor 4
TNF	Tumor Necrosis Factor
UVB	Ultraviolet B
VDBP	Vitamin D Binding Protein
VDD	Vitamin D Deficiency
VDR	Vitamin D Receptor

Chapter 1: Introduction

1.1 An Overview on Preterm Birth and Low Birth Weight

Despite revolutionary advancements in healthcare technology, unintended pregnancy outcomes still pose significant challenges to the public's health (Chiavaroli et al., 2016; Goldenberg et al., 2008; Lawn et al., 2011). Preterm birth (PTB), which is characterized as birth prior to the 37th week of pregnancy, remains the leading reason for death in newborns and the secondary leading cause in under-five children (Blencowe et al., 2012; WHO, 1970). Preterm birth has immediate effects within the first month of life and lasting consequences for infants, families, and the community. Global Burden of Disease studies reveal that preterm birth contributes to 3.1% of lifelong disabilities, surpassing the combined impact of HIV and malaria (Howson et al., 2013; Murray et al., 2012). Premature birth exposes infants to risks like low blood sugar, sepsis, jaundice, respiratory issues, and long-term neurocognitive deficits, posing significant medical, social, and economic challenges (Goldenberg et al., 2008; Hall & Greenberg, 2016; S. W. Wen et al., 2004). In addition to PTB, low birth weight (LBW), labelled as a neonate weighing below 2500g, is a prevalent cause of both immediate and later childhood illness and perinatal death. Low-birth-weight babies have up to 40 times greater mortality rates and are more likely to have long-term problems (Goldenberg & Culhane, 2007). The exact causes of PTB and LBW remain complex and multifactorial, involving genetics, stress, inflammation, infections, environmental or occupational factors, along with pregnant women's nutritional status (Crider et al., 2005; Hendler et al., 2005; Kramer et al., 2009; Lawson et al., 2009; Michalowicz et al., 2009; Scholl, 2005; Tamura et al., 1992). Nowadays, a substantial amount of research is being undertaken how vitamin D metabolism affects pregnancy, specifically preterm birth (Møller et al., 2013; Qin et al., 2016).

1.2 Prevalence of Preterm Birth and Low Birth Weight

Despite consistent efforts in antenatal care, preterm birth persists as a significant global health problem. The estimated worldwide preterm birth rate is 11.1%, leading to about 15 million preterm babies in 2010 across 184 countries (Blencowe et al., 2012; Tielsch, 2015). This prevalence varies among regions, with Africa and South Asia contributing 60% of preterm births. Developed countries also grapple with this issue, showing a prevalence of roughly 6-7%, while the United States has the highest rate at 10% (Sheikh et al., 2016). Detailed data on countries with noteworthy preterm birth counts and rates is available in Figure 1 and.2.

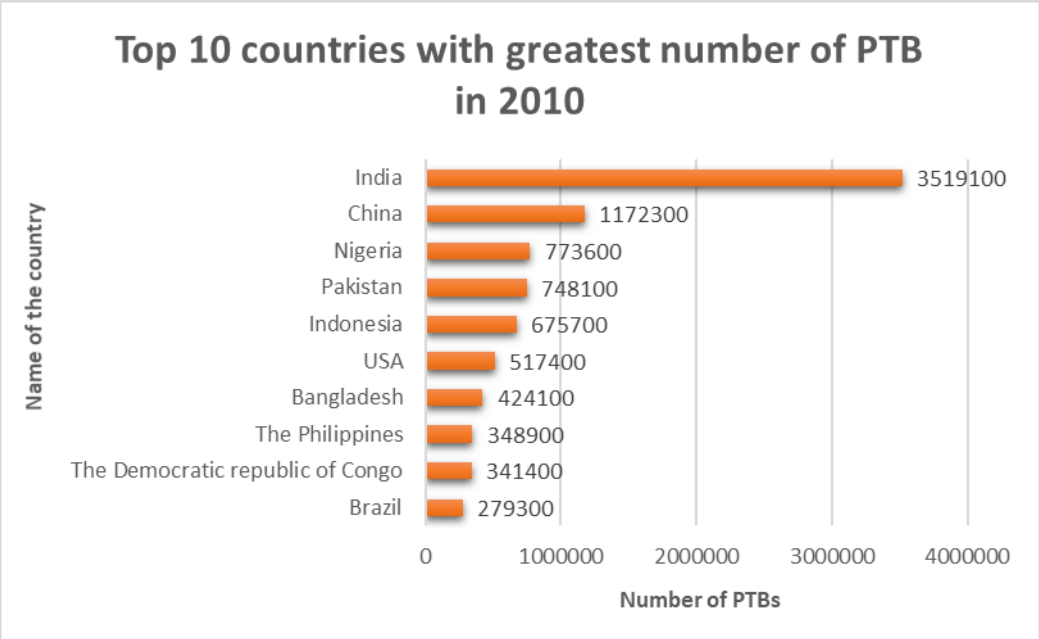

Figure 1: The 10 countries with the highest total number of PTBs in 2010 (Blencowe et al., 2012)

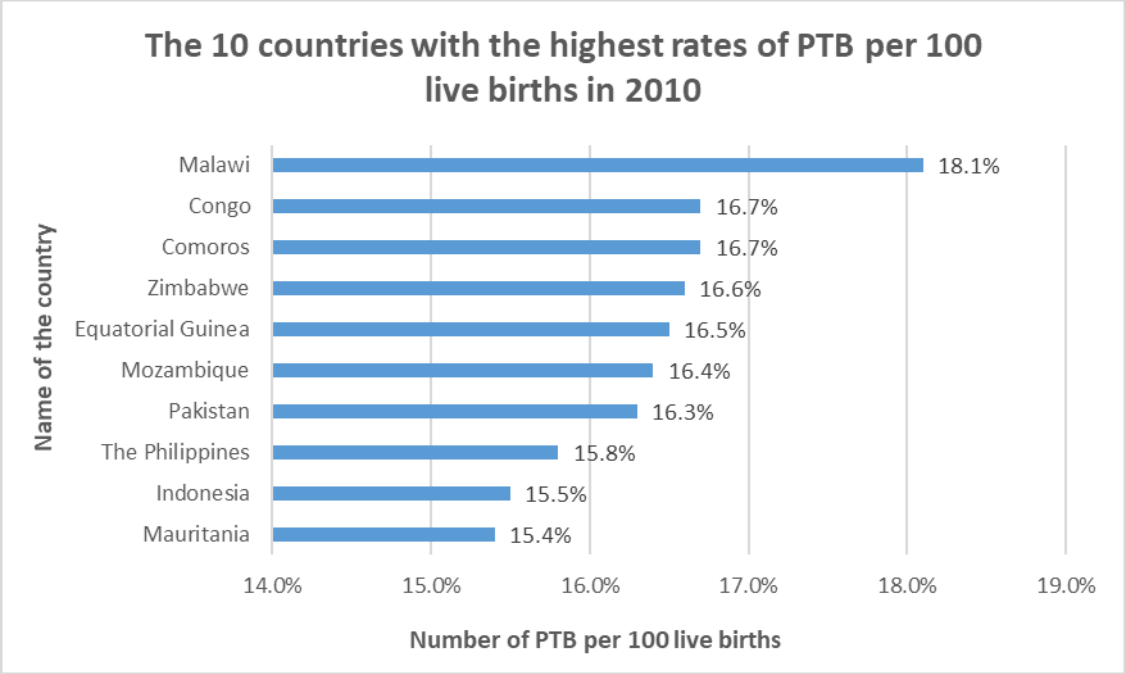

Figure 2: Top 10 countries with the greatest PTB per 100 live births rates in 2010 (Blencowe et al., 2012)

Approximately 32 million babies are born yearly with low birth weight (LBW) or small-for-gestational-age (SGA), mostly, 96.5%, in developing nations (Black, 2015). Racial disparities are apparent, with a 13.8% LBW rate for non-Hispanic Black (NHB) women in 2007 versus 7.2% for non-NHW women (Martin et al., 2001). Bangladesh shows a low birth weight prevalence of 23% to 60% (Yasmin et al., 2001).

1.3 Vitamin D and its Biological Functions

The fat-soluble prohormone group, vitamin D, was initially identified in cod liver oils for its anti-rachitic properties in the early 1900s (Zhang & Naughton, 2010). This hormone, with a history spanning 750 million years, has been generated by a range of organisms. Sunlight exposure triggers its synthesis in plants, animals, phytoplankton, and zooplankton (Holick, 2003). Vitamin D has two primary precursors: plant-based vitamin D_2 (Ergocalciferol) and skin-produced vitamin D_3 (Cholecalciferol) in response to ultraviolet B (UVB) radiation exposure (Holick, 2003; Zhang & Naughton, 2010).

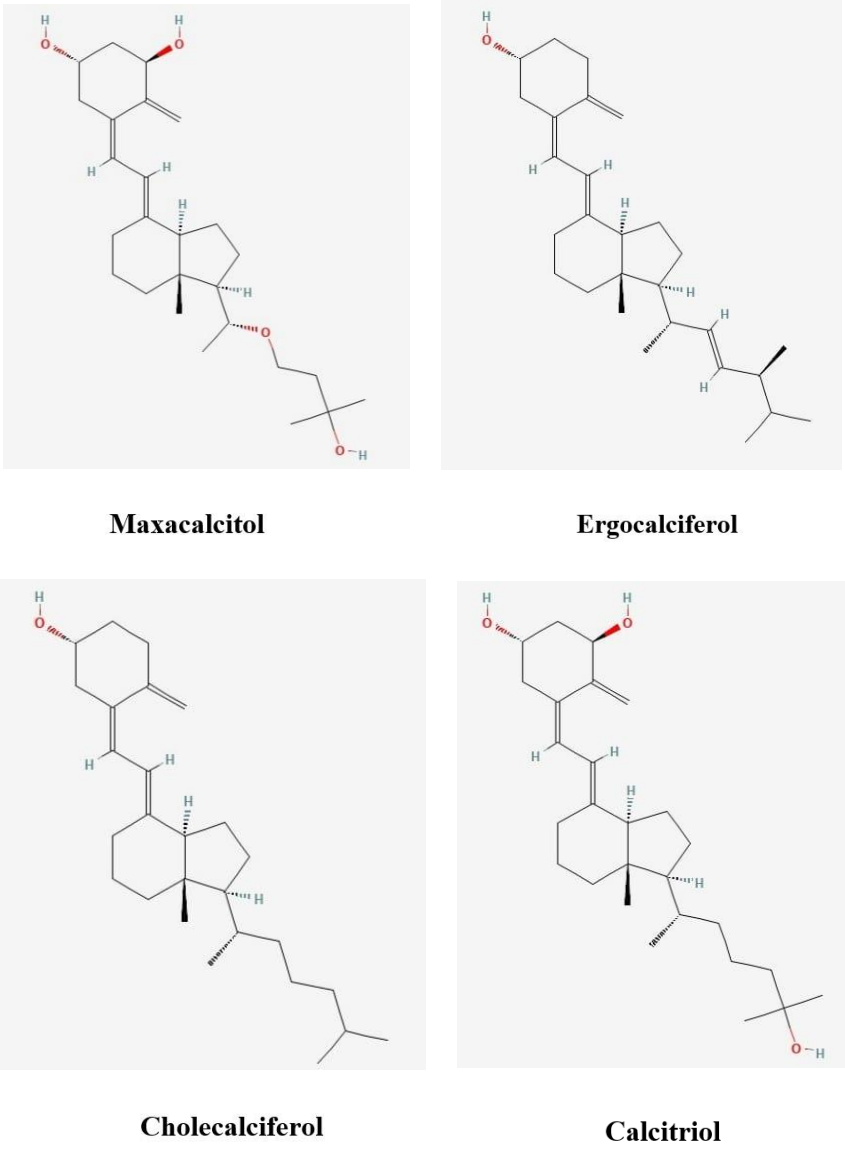

Figure 3: Structures of vitamin D analogues (PubChem, 2019, 2023b, 2023c, 2023a)

The vitamin D hormone is critical for sustaining proper plasma calcium levels, preventing conditions like rickets and osteomalacia. It achieves this through 3 key mechanisms:

• Firstly, it stimulates calcium absorption proteins in the intestines (Underwood & DeLuca, 1984).

• Calcium deficiency triggers the production of Receptor activator of nuclear factor kappa-B ligand (RANKL) by osteoblasts, consequently promoting the development of osteoclasts and

loss of bone mass through parathyroid hormone (PTH) and vitamin D (Garabedian et al., 1972; GARABEDIAN et al., 1974; Suda et al., 2003).

• Additionally, it assists in the final 1% calcium reabsorption in the renal tubule, working with PTH (Yamamoto et al., 1984).

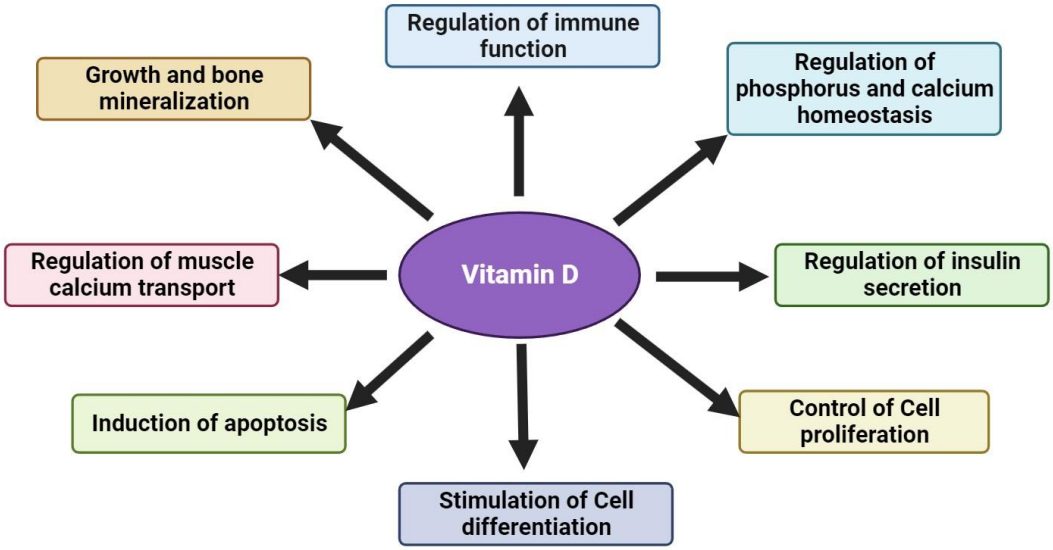

Figure 4: Biological functions of vitamin D (Layana et al., 2017; Scientific Image and Illustration Software, 2023)

Calcium absorption and increasing uptake by enterocytes rely heavily on PTH along with the vitamin D hormone. Stable plasma calcium levels trigger PTH secretion, enhancing vitamin D hormone release, which mobilizes bone calcium and is influenced by the parathyroid gland's calcium sensing (Brenza & DeLuca, 2000; Brown et al., 1993; Tanaka & DeLuca, 1984). This dynamic process improves calcium absorption, bone mobilization, and kidney reabsorption. Excess calcium prompts the C cells of thyroid gland to produce calcitonin, an inhibitor of bone calcium release (JONES et al., 1998), stimulating renal 1α-hydroxylase and generating non-calcemic vitamin D. The vitamin D system prioritizes normal serum calcium via dietary sources (Shinki et al., 1999). In calcium deficiency, it intensifies bone mobilization, kidney

reabsorption, and may contribute to osteoporosis. The vitamin D hormone primarily supports skeletal mineralization, not direct bone anabolism (DeLuca, 2004).

Vitamin D expands its functions beyond bone by aiding the promyelocytes differentiate into monocytes, the progenitors of giant osteoclasts. Through the RANKL system, this essential process helps vitamin D trigger osteoclast formation. Upon differentiation into a functioning cell line, cell growth remarkably halts, and this mechanism is unrelated to calcium or phosphorus (Suda et al., 2003).

Parathyroid gland's vitamin D receptor is crucial for renal osteodystrophy treatment using vitamin D hormone and analogs. It regulates gene production and inhibits cell growth, aiding parathyroid health in healthy individuals and dialysis patients (Darwish & DeLuca, 1999; DeLuca, 2004; JONES et al., 1998; Slatopolsky et al., 2003).

Vitamin D modulates the renin-angiotensin system (RAS), reducing hypertension as well as heart disease risk (Akter et al., 2022; Wu-Wong et al., 2007).

Vitamin D positively impacts pancreatic beta cell function. Experiments on deficient mice showed reduced insulin secretion, improved by vitamin D supplementation. Vitamin D also guards beta cells from cytokine-induced apoptosis (Bornstedt et al., 2019; Gysemans et al., 2005; Wolden-Kirk et al., 2014).

Regarding immunology, Hypovitaminosis D impacts T cell-mediated immunity, while excess suppresses immune functions. Immune-mediated illnesses including multiple sclerosis, type 1 diabetes, and systemic lupus are being researched (Cantorna et al., 1998; Lemire et al., 1992; Zella & DeLuca, 2003). Vitamin D therapy reduces inflammation, improves immunity (Griffin et al., 2001), and aids transplant rejection reduction (Hullett et al., 1998). More investigation is required to comprehend vitamin D analogs' mechanisms against autoimmune conditions.

1.4 Sources of Vitamin D

Vitamin D, a vital fat-soluble nutrient which functions as a hormone, comprises vitamin D_2 (Ergocalciferol) from plants and fungi, including Mushrooms with UV exposure, and vitamin D_3 (cholecalciferol), naturally present in foods like fatty fish and egg yolks. It's additionally added to fortified foods and supplements in many countries (J. Liu, 2012).

Table 1: Common Dietary Sources of Vitamin D (Uriu-Adams et al., 2013)

Food	IUs/serving	% DV
1 tablespoon of cod liver oil	1360	340
3 ounces cooked swordfish	566	142
3 ounces cooked salmon (sockeye)	447	112
3 ounces canned tuna in water	154	39
1 cup vitamin D-fortified orange juice	137	34
1 cup vitamin D-fortified nonfat, reduced fat, and whole milk	115-124	29-31
Yoghurt fortified with 20% of the DV for vitamin D, 6 oz.	80	20
1 tablespoon fortified margarine	60	15
2 sardines, canned in oil, drained	46	12
3 ounces cooked beef liver	42	11
1 big egg (the yolk contains vitamin D)	41	10
10% DV of vitamin D added to 0.75–1 cups of ready-to-eat cereal	40	10
1 ounce Swiss cheese	6	2

Table 1 presents vitamin D content in different dietary sources, including unfortified Western diets offering about 100 IU or 2.5 mg/day of vitamin D (Institue of Medicine, 1997). US retail milk and infant formulas are often fortified with varying levels, and traditional multivitamins contain 200-400 IU (5-10 mg) of vitamin D, with higher doses emerging (Hathcock et al., 2007; Patterson et al., 2010).

Outdoor workers' sun exposure can elevate serum 25(OH)D similar to oral doses of 2800-5000 IU (70-125 mg) per day. Sunlight converts 7-dehydrocholesterol to provitamin D, more available in the past. Certain professions have 25(OH)D levels around 122 nmol/L, while healthy sunbathers reach over 200 nmol/L (Barger-Lux & Heaney, 2002). However, levels decrease to 74 nmol/L (40% reduction) in winter, indicating intense sun exposure doesn't guarantee higher winter concentrations (Vieth, 1999).

1.5 Synthesis and Metabolism of Vitamin D

Vitamin D is distinct based on its availability from food sources and skin synthesis. Vitamin D_3 is produced by ultraviolet B radiation acting on 7-dehydrocholesterol (7DHC), enabling its acquisition through diet and skin (Provitamin D_3). The precursor, provitamin D_3, transforms to vitamin D_3 via heat isomerization in the skin, also converting to inert forms or reverting to 7DHC (MacLaughlin et al., 1982; Webb, 2006). Vitamin D gets into the bloodstream through a binding protein (WEBB et al., 1989). Figure 5 depicts the synthesis and metabolism of cutaneous vitamin D.

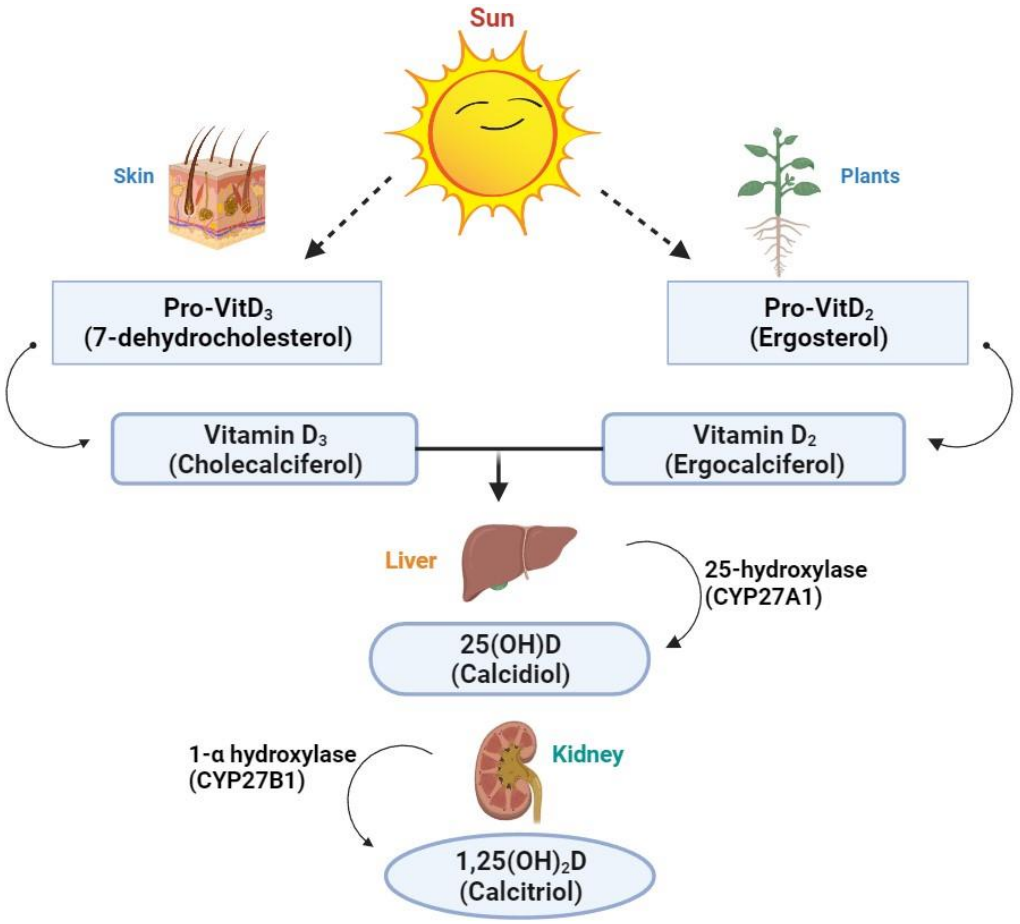

Figure 5: Cutaneous Vitamin D synthesis and Metabolism (Scientific Image and Illustration Software, 2023; Vuolo et al., 2012)

In the kidney, 1α,25(OH)$_2$D (calcitriol), the active hormone, results from the conversion of vitamin D_3 by 1-α-hydroxylase (CYP27B1). Before this, the liver's enzyme 25-hydroxylase (CYP2R1) converts it to 25-hydroxyvitamin D (25(OH)D) (Uriu-Adams et al., 2013).

1.6 Vitamin D Deficiency and its Complications

Vitamin D deficiency's definition is debated. Experts generally see levels below 50 nmol/L (20 ng/mL) as deficient, 51–74 nmol/L as insufficient, above 30 ng/mL as sufficient, and exceeding 375 nmol/L as toxic (150 ng/mL) (Chapuy et al., 1996; Dawson-Hughes et al., 2005; Holick, 2007; Holick et al., 2005; Malabanan et al., 1998; Thomas et al., 1998). Deficiency can have

both musculoskeletal and non-skeletal consequences (Heaney et al., 2003; Holick, 2007; Vieth, 1999).

Musculoskeletal Consequences

Inadequate vitamin D levels can result in rickets among children, accompanied by related signs, symptoms, and growth complications. In adults, insufficient vitamin D can exacerbate conditions like osteopenia and osteoporosis, increasing the likelihood of fractures (Bakhtiyarova et al., 2006; Chapuy et al., 1996; Holick, 2007; Huldschinsky, 1919; Nesby-O'Dell et al., 2002). Long-standing evidence associates musculoskeletal weakness with a lack of this nutrient, resulting in muscle weakness, body instability, and a heightened risk of falling (Bischoff-Ferrari, Dietrich, et al., 2004; Broe et al., 2007; Simpson et al., 1985; Visser et al., 2003). Insufficiency of vitamin D in adults may cause issues in bone mineralization, resulting in osteomalacia characterized by thickened osteoid layers on bones, potentially contributing to osteoporosis, both of which can elevate the likelihood of fractures, especially fractures in the hip (Lips, 2001). The interaction between PTH and serum 25(OH)D levels was explored in older adults, revealing that adequate 25(OH)D stabilizes status of PTH and that vitamin D supplements enhance bone mineral density, an effect subjected to the genotype of the vitamin D receptor (Lips, 2001).

Non-skeletal Consequences

Due to decreased synthesis of vitamin D_3, living in higher latitudes in the US is linked to an elevated incidence of common malignancies like prostate, colon, and breast cancer (Holick & Chen, 2008), with adults having below 50 nmol/L 25(OH)D status experiencing 30–50% enhanced likelihood of these cancers (Ahonen et al., 2000; Garland et al., 2006; Giovannucci et al., 2006; Grant, 2002; Grant & Garland, 2006).

Higher latitudes are additionally linked to elevated risks of multiple sclerosis, type 1 diabetes, and hypertension (Embry et al., 2000; Ponsonby et al., 2002; Rostand, 1997; Stene et al., 2000). Children with vitamin D intake of 2000 IU daily in their first year have a 78% lower type 1 diabetes risk, likewise women consuming over 400 IU of vitamin D daily possess a 40% lower chance of rheumatoid arthritis and multiple sclerosis (Hyppönen et al., 2001; Munger et al., 2004).

Moreover, higher latitudes and hypovitaminosis D elevate the likelihood of developing schizophrenia (McGrath, 2002) and depression (Gloth et al., 1999), while extreme vitamin D deficiency in African Americans raises tuberculosis risk and severity (Chan, 2000).

1.7 Rationale of the Study

The study investigates the link between maternal vitamin D Receptor gene's single nucleotide polymorphism, BsmI and the incidence of preterm birth and low birth weight. VDR BsmI SNPs impact vitamin D receptor protein and vitamin D metabolism, influencing bone wellness, immune function, and cellular growth. These SNPs reflect individual responses to vitamin D and disease susceptibility. The VDR gene is vital for fetal development and can potentially serve as a genetic predictor for assessing the risk adverse pregnancy outcomes. This review examines vitamin D's impact on pregnancy outcomes, extensively explores the correlation between BsmI SNP within the VDR gene and preterm birth & low birth weight, identifies additional genetic predictors, proposes prevention strategies, and provides future research recommendations.

1.8 Aim and Objectives of the Study

Aim

The study aims to examine the link between mothers' single nucleotide polymorphism of the vitamin D receptor gene (BsmI) and the risk of preterm birth and low birth weight among neonates.

Objectives

Specific objectives of the study are to:

• Demonstrate the need for mothers' vitamin D level for optimal pregnancy outcomes.

• Examine if maternal vitamin D intake, sun exposure, and age impact the relationship between mothers' VDR SNPs (specifically BsmI) and preterm birth & low birth weight.

• Examine the biological mechanisms underlying the association between maternal VDR SNPs, particularly BsmI and PTB & LBW, including changes in gene expression and protein function.

Chapter 2: Methodology

This review is based on credible scholarly articles from reputable sources. Relevant search terms and keywords were identified, including "pregnancy," "vitamin D," "vitamin D receptor," "BsmI polymorphism," "gestational duration," "preterm birth," and "birth weight." Multiple databases, such as PubMed, Google Scholar, Elsevier, ScienceDirect, and Wiley Online Library, were searched using advanced options to narrow results. Keywords were combined for better relevance, and reference lists were checked for additional sources. Initially, around 300 articles were found, with irrelevant ones excluded after title and abstract screening. Over 100 articles were extensively studied, notes were taken, and essential data were highlighted. Proper citations in "APA 7th Edition" style were ensured throughout the paper, with all sources well organized for easy access during writing. The gathered information was critically analyzed and used to compose the project paper.

Chapter 3: Vitamin D and Pregnancy

3.1 Significance of Vitamin D for Maternal and Child Health

Insufficient vitamin D levels at several life phases, including conception, fetal development, childhood, and adulthood, raise concerns about potential impacts. The diet of expectant and lactating mothers can affect fetal and newborn growth, potentially leading to lasting consequences like physical changes and health issues including type 2 diabetes, heart disease, obesity, and hypertension (Momentti et al., 2018). Adequate levels of this vitamin are imperative to both fetal and maternal well-being, especially for proper bone growth, dental health, and overall development during pregnancy (Fiscaletti et al., 2017).

Expectant mothers with ample vitamin D levels and increased calcium transfer to the fetus support proper bone development, reducing the risk of low blood calcium in newborns and the chances of both innate and developmental rickets in children. Mother's 25(OH)D may cross the placenta, potentially transmitting vitamin D deficiency (VDD) onto the fetus and newborn, with both immediate and prolonged effects (Fiscaletti et al., 2017).

In the course of pregnancy, calcitriol, the vitamin D's active form, substantially rises throughout the first trimester and doubles by the third. Beyond its role in providing fetal calcium, this rise is vital for immune adjustments essential for a healthy pregnancy. Vitamin D influences dendritic cell maturation and T-cell response balance, favoring Th2 dominance to prevent fetal rejection. This shift toward Th2 dominance critically supports a healthy pregnancy (Hayes et al., 2003; Raghupathy, 2001; Spilianakis et al., 2005).

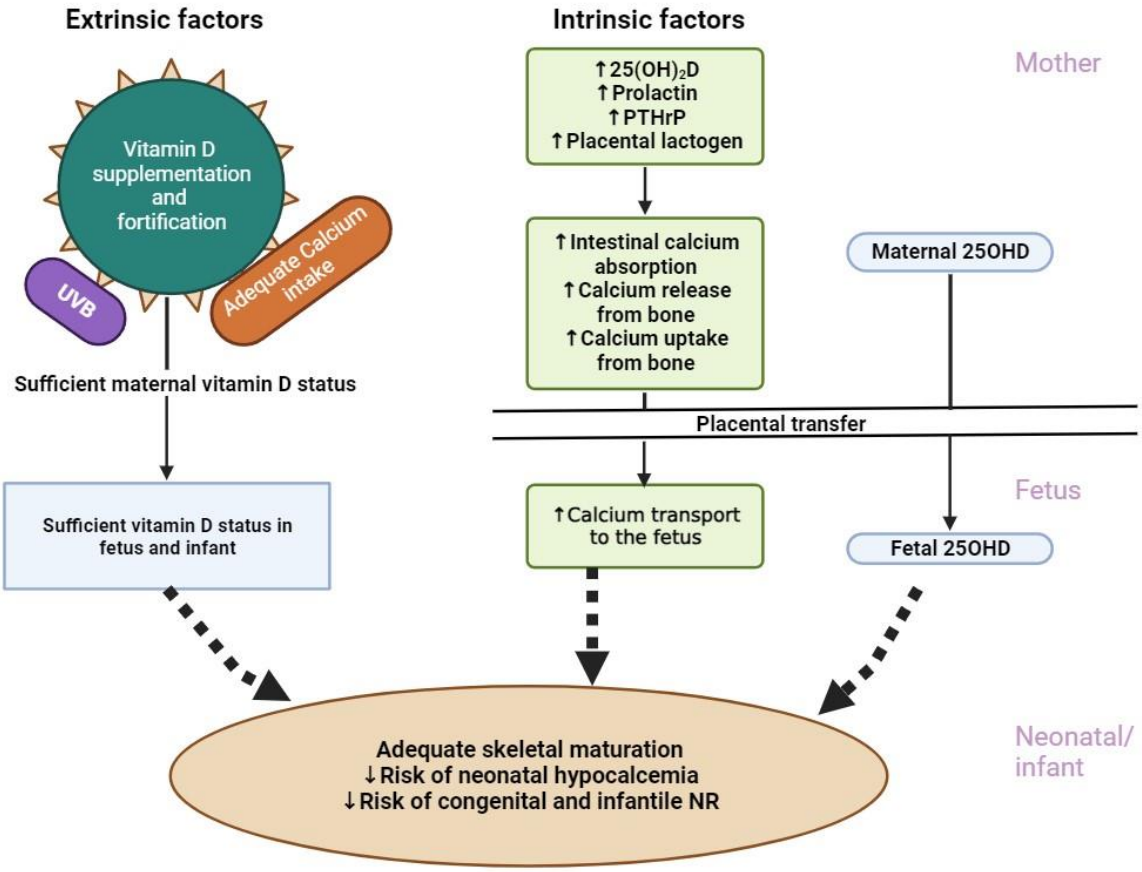

Figure 6: Schematic depiction of pregnancy factors and physiological alterations that promote optimal bone health in offspring (Fiscaletti et al., 2017; Scientific Image and Illustration Software, 2023)

Overall, vitamin D is essential for immune regulation during pregnancy, contributing to the maintenance of a healthy pregnancy and possibly protecting against pregnancy-related disorders such as preeclampsia. Nonetheless, further study is necessary to fully understand the mechanisms and determine the ideal vitamin D levels or supplementation for pregnant women (Evans et al., 2004).

3.2 Vitamin D Requirements for Pregnant Women

Pregnant women don't get enough vitamin D from the recommended 200 IU (5 g) per day, as specified by the Institute of Medicine, is 200 IU (5 g). In order to fulfill the nutritional requirements, it is recommended that pregnant women include a supplement comprising 1,000 IU of vitamin D with their prenatal nutrient containing 400 IU, resulting in a daily intake ranging from 1,500 to 2,000 IU. The maximum safe dosage may be extended up to 10,000 IU/day (Food and Nutrition Board Institute of Medicine, 1997; Holick et al., 2011).

3.3 Prevalence of Vitamin D Deficiency among Pregnant Women

Despite prenatal nutrient recommendations, alarmingly high rates of vimanin D shortage are seen during conception: 4% to 60% in mothers and 3% to 86% in newborns across countries (Palacios & Gonzalez, 2014; Prentice, 2008). In a recent North West England study, 27% of expectant mothers had insufficient vitamin D levels (50 nmol/L), which increased to 48% after delivery. In addition, 7% were deficient in vitamin D (25 nmol/L), and 11% remained deficient postpartum. 24% of four-month-old infants had unsatisfactory (25-50 nmol/L) vitamin D status (Emmerson et al., 2018). A UK study on pregnant teenagers raised concerns as 30% had below 25 nmol/L 25(OH)D readings (Baker et al., 2009). 84% of expecting women in India showed vitamin D concentrations below 22.5 ng/mL (Sachan et al., 2005). A rural Bangladesh research showed 47.2% had insufficient amount (30–50 nmol/L) of vitamin D, while 17.3% were deficient (less than 30.0 nmol/L) (Ahmed et al., 2021).

3.4 Unfavorable Pregnancy Outcomes linked to Vitamin D deficiency

Inadequate vitamin D levels throughout conception remain a rising concern globally. Studies report deficiencies in 30–80% of expectant females (Ginde et al., 2010). Low vitamin D levels result in undesirable consequences like gestational diabetes, pre-eclampsia, and preterm birth

(Aghajafari et al., 2013; J. Wen et al., 2017). It affects fetal size, bone formation, and neonatal health (Eckhardt et al., 2015; Miliku et al., 2016).

Fetal Repercussions

The fetus relies on maternal vitamin D and calcium stores, raising deficiency concerns (Walsh et al., 2013). Deficiency of vitamin D in newborns (cord blood at 11 ng/mL) occurs in 46% of supplemented mothers' babies (Basile et al., 2007). Maternal hypovitaminosis D is correlated with adverse neonatal outcomes, including small-for-gestational-age births, premature delivery, impaired tooth and bone growth, and higher infection risk (Karras et al., 2014).

Short for Gestational Age and Low Birth Weight

Burris and colleagues discovered that inadequate (below 10 ng/mL) 25(OH)D serum status tripled the incidence65 of Short for Gestational Age (SGA) in the second trimester in one research finding (Burris et al., 2012). Another research involving more than 3,000 pregnancies discovered that low serum 25(OH)D at 13 weeks was connected to low weight at birth and increased SGA risk (Leffelaar et al., 2010). Adequate vitamin D (>15 ng/mL) prior to 26 weeks is related to a higher weight at birth and reduced SGA risk (Gernand et al., 2013). Despite mixed results, a 2013 meta-analysis confirmed the connection of low vitamin D with SGA prevalence (Aghajafari et al., 2013).

Bone Health

Gestational deficiency of vitamin D can affect long-term bone development and mineralization in childhood, since vitamin D is linked to fetal femoral growth (Ioannou et al., 2012; Morley et al., 2006; Walsh et al., 2013; Weiler et al., 2005). While several researches show shorter

long bones in babies of mothers with hypovitaminosis D (Morley et al., 2006), others contradict this (Gale et al., 2008; Weiler et al., 2005), prompting further research (Lawlor et al., 2013).

Respiratory Illness

Newborns are more likely to get respiratory syncytial virus infection and other respiratory illnesses if their mothers have vitamin D insufficiency (Belderbos et al., 2011; Camargo et al., 2011). Recurrent wheezing risk might be lower in kids with higher cord blood vitamin D (Camargo et al., 2007, 2011). The link to asthma remains unclear (Camargo et al., 2011; Gale et al., 2008), warranting more investigation.

Type 1 Diabetes

Children of moms with vitamin D insufficiency are potentially in threat of acquiring type 1 diabetes. A nested case-control research revealed a twofold greater chance in the offspring of pregnant women with inadequate vitamin D (Sorensen et al., 2012), while certain Finnish research showed no differences (Miettinen et al., 2012).

Atopic Symptoms

Atopic symptoms, including eczema and food-related allergies, might have a correlation with the mother's vitamin D level (Gale et al., 2008; Weisse et al., 2013). However, a study of 231 newborns over the span of their first year found that vitamin D levels below 20 ng per mill in cord blood corresponded to an increased prevalence of eczema (Jones et al., 2012).

Psychomotor development and neurological disease

Higher vitamin D levels corresponded with superior cognitive and psychomotor growth at 14 months in a Spanish sample (Morales et al., 2012), suggesting its role in pregnancy. Limited

sunlight exposure during birth month linked to multiple sclerosis risk (Torkildsen et al., 2012), while maternal milk intake and proper vitamin D could lower child multiple sclerosis risk (Mirzaei et al., 2011)

Maternal Repercussions

Pre-eclampsia

Low vitamin D has been attributed to an elevated prevalence of pregnancy issues, including pre-eclampsia. Studies associate pre-eclampsia with low vitamin D, especially in high-risk groups (Azar et al., 2011; Fernandez-Alonso et al., 2012; Powe et al., 2010; Shand et al., 2010). While a 2013 meta-analysis hints at a link, more research is needed for clarity, especially in high-risk women (Aghajafari et al., 2013).

Type 2 Diabetes

Gestational diabetes mellitus (GDM) is caused, or at least exacerbated, by a lack of vitamin D, which disrupts glucose regulation during conception (Aghajafari et al., 2013; Senti et al., 2012). Early in pregnancy, hypovitaminosis D enhance GDM risk, without regard for age, race, or weight. Higher vitamin D status lowers maternal hyperglycemia risk, notably for smokers (Tomedi et al., 2013), suggesting improved levels might reduce GDM risk.

Cesarean delivery

Research on vitamin D and caesarean delivery varies. Some studies suggest low vitamin D could raise caesarean likelihood, while some dispute this impact. Clarifying this connection is vital due to caesarean-related complications (Merewood et al., 2009; Scholl et al., 2012).

Depression

Initial findings hint at a relationship between low early pregnancy vitamin D and higher postpartum depression (Brandenbarg et al., 2012). African-American women show a similar association (Cassidy-Bushrow et al., 2012). Establishing causality is complex due to timing. More research is required to understand depression's possible link to vitamin D deficiency.

Chapter 4: Pathophysiology of Preterm Birth and Low Birth Weight

Approximately 70% of preterm births are spontaneous, with 45% due to early labor, while 25–30% from preterm premature rupture of membranes (PPROM). Additionally, roughly 30% result from obstetricians inducing early delivery due to an unfavorable uterine environment (Goldenberg et al., 2008). Genetic influences significantly impact maternal and fetal genomes and pregnancy duration. Recent studies encompass factors like the in utero environment, familial context, mother's genetics (13-25%), fetal genetic variation (11–35%), collectively shaping pregnancy duration (York et al., 2014). Exploring pregnancy complications, especially preterm birth (PTB), reveals disruptions in maternal immune responses, including the escalation of infection-related cytokines triggering premature labor, akin to preterm labor (Romero et al., 2006). The intricate interplay of fetal genotype effects and maternal genotype-influenced in utero environment further complicates our understanding (Alkhuriji et al., 2013; Crider et al., 2005; Grisaru-Granovsky et al., 2007; Rai, 2014; Siddesh et al., 2014). Given these complexities, it's clear our grasp of preterm birth mechanisms is limited, underscoring the need for intensified research and effective preventive strategies.

4.1 Risk Factors for Preterm Birth

Preterm birth (PTB) risk is heightened by numerous factors, as examined extensively in various reports (Alleman, 2014; Anum et al., 2009; Goldenberg et al., 2008; Richard E Behrman, 2007), with Figure 7 illustrating key risk factor categories (Sheikh et al., 2016).

Behavior & Socio-demographics

This category includes maternal demographic risk variables like socioeconomic position, age, race, marital status, and education, along with behavior such as consuming tobacco, alcohol, or drugs that increase susceptibility. Additional risk factors comprise vitamin D, folic acid, iron deficiencies, low prenatal weight, obesity, anxiety, depression, stressful work environments, and abuse, all implicated in PTB. Recent reviews delve into behavioral and sociodemographic aspects (Sheikh et al., 2016).

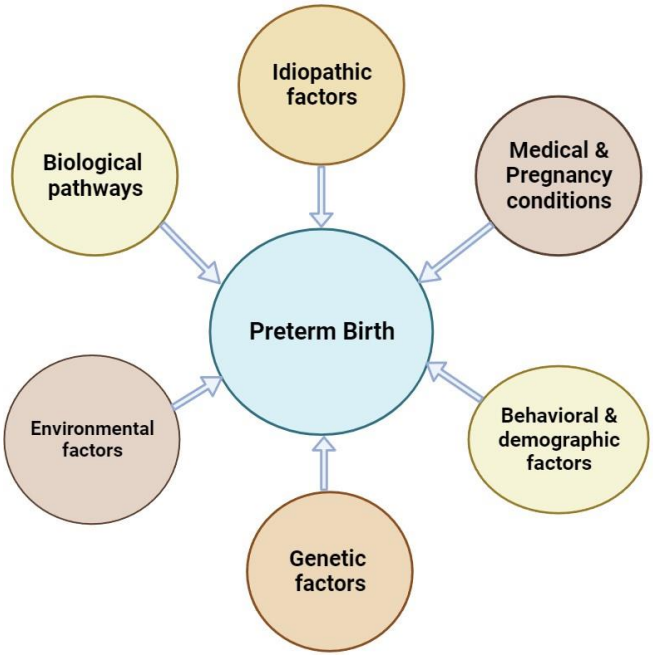

Figure 7: Risk factors associated with preterm birth (Scientific Image and Illustration Software, 2023; Sheikh et al., 2016)

Medical & Pregnancy Conditions

Factors such as multiple pregnancies, prior PTB history, short interpregnancy intervals, uterine distension, vaginal bleeding, hypertension, diabetes, thyroid disorders, cervical conditions, and uterine over-distension further heighten PTB risk, with medical and pregnancy conditions thoroughly explored in recent reviews (Sheikh et al., 2016).

Genetic Influence

Genetic factors significantly influence PTB, accounting for 25% to 40% of cases, as indicated by familial aggregation, genetic correlations, twin studies, and SNP-based investigations (Sheikh et al., 2016).

Environment

Additionally, environmental pollutants like Bisphenol A, air pollution, agricultural factors, and electronic waste contribute to PTB, which is under ongoing investigation (Richard E Behrman, 2007; Sheikh et al., 2016).

Biological Pathways

Biological pathways, including infections, inflammation, adrenal activation, decidua defects, uterine distension, and microbial infections, play critical roles in PTB, offering insights into its complexities (Sheikh et al., 2016).

In total, PTB, being a complex condition, stems from diverse factors, with about half having identifiable causes and the rest remaining idiopathic (Sheikh et al., 2016).

4.2 Complications of Preterm Birth

Premature delivery carries significant consequences, including higher newborn mortality, increased infection susceptibility, and greater risks of future health problems like neurodevelopmental, cardio-metabolic, and inflammatory disorders in premature infants (Arpino et al., 2010; Goedicke-Fritz et al., 2017; Markopoulou et al., 2019; Moster et al., 2008; Sonnenschein-van der Voort et al., 2014).. Inadequate bone mass worsens these effects, leading to post-birth growth issues (Finken et al., 2016) and frequent intensive care stays, driving

healthcare costs to over $26 billion in the US and contributing to about 35% of infant deaths (IOM, 2007). Even late preterm births (34–36 weeks) show raised mortality risks up to age 36 due to various health concerns (Crump et al., 2011).

Despite better survival rates, concerns remain about learning, psychological challenges, and adulthood issues. Decreasing gestational age is linked to more medical and social problems in adulthood, posing unique challenges in motor skills, cognition, behavior, psychology, and social functioning during early education for very premature births (Bhutta et al., 2002; Hack et al., 2005; Hille et al., 2001; Litt et al., 2005; Marlow et al., 2005; Saigal et al., 2003). Recent studies link premature toddlers to autism spectrum disorder (Limperopoulos et al., 2008). Earlier research also suggests lower academic performance and reduced likelihood of parenthood among very preterm individuals, perpetuating a cycle of health challenges that extends to women born prematurely, who face higher preterm birth risks (Swamy et al., 2008).

4.3 Risk Factors for Low Birth Weight

A research performed by Yadav and colleagues, investigated variables that may lead to low birth weight (LBW) in 258 mothers, with 80% from rural areas. It found that the majority of LBW infants were born to moms aged 19 to 30, while normal birth weight babies had mothers aged 20 to 29, consistent with similar research in developing countries (Karim et al., 2011; Nahar et al., 1998).

Residence didn't significantly impact birth weight, implying equal access to maternal and child health services. Illiteracy was prevalent (61% of mothers), with 26% having LBW babies; educated mothers had lower LBW rates (15%), possibly due to greater health awareness. Household head education influenced birth weight, but parental education didn't. Religion and birth weight were not significantly linked (Yadav et al., 2011). Higher family income is correlated with fewer LBW cases (Yadav et al., 2011).

The birth-to-conception interval had minimal impact, indicating nutrition as a more influential factor. Previous pregnancy history (abortion, stillbirth, and neonatal death) had no significant link to birth weight (Yadav et al., 2011), aligning with prior studies (Khatun & Rahman, 1970).

4.4 Complications of Low Birth Weight

Babies born with very low weight have an 85% chance of surviving hospitalization, while premature birth carries a 2-5% risk of medical complications leading to death within 2 years (Fanaroff et al., 2007). Table 2 outlines major short and long-term issues tied to low birth weight (Eichenwald & Stark, 2008).

Table 2: Major Complications in Infants with Extremely Low Birth Weight (Eichenwald & Stark, 2008)

Affected Organ or System	**Acute/Immediate Problems**	**Long-Term Problems**
Pulmonary	Neonatal apnea, bronchopulmonary dysplasia, RDS, air leak	Reactive pulmonary illness, asthma, BPD
Gastrointestinal	food intolerance, necrotizing enterocolitis, growth failure, hyperbilirubinemia	Short bowel syndrome, cholestasis, growth failure
Central nervous system	Periventricular white-matter degeneration, intraventricular haemorrhage, hydrocephalus	hearing loss, hydrocephalus, cerebral shrinkage, neurodevelopmental delay
Immunologic	Immune deficits, perinatal and hospital-acquired infections	Bronchitis, respiratory syncytial virus infection

Ophthalmologic	Premature retinopathy	Myopia, strabismus, retinal detachment, blindness
Cardiovascular	pulmonary hypertension, patent ductus arteriosus, hypotension	pulmonary hypertension, adult-onset hypertension
Renal	Acid-base disturbances, electrolyte and water imbalances	Adulthood hypertension
Hematologic	Iatrogenic anemia, the requirement for frequent transfusions, preterm anemia	N/A
Endocrine	Hypoglycemia, momentary low thyroxine levels, a lack of cortisol	Impaired control of blood sugar, elevated insulin resistance

Chapter 5: Vitamin D Receptor Gene Polymorphisms

5.1 Vitamin D Receptor and its Location

A pivotal steroid hormone receptor, the vitamin D receptor (VDR), often called the calcitriol receptor, oversees diverse biological effects attributed to vitamin D. Encoded by the VDR gene (gene Identifier: 7421 and Molecular Identification Number: 601769), it actively manages gene transcription, mediating vitamin D's impact (Whitfield et al., 1995), including nuclear transcription factor activity prompted by ligands (Kato, 2000). Calcitriol, the primary ligand, notably binds to VDR in the nucleus (Knabl et al., 2017).

Recent research highlights elevated VDR gene expression across various cell types, including the immune system, thymus, type-II alveolar cells, osteoblasts, chondrocytes, skin epithelium, and placental components like villous trophoblasts, decidua, and placental vessel smooth muscle cells (Barrera et al., 2008; Knabl et al., 2017; Pike & Meyer, 2012; Pospechova et al., 2009; Shahbazi et al., 2011). However, a distinct pattern emerges, with fewer vitamin D receptors present in erythrocytes, fully developed striated muscle cells, and differentiated cerebral cortex neural cells (Bischoff-Ferrari, Borchers, et al., 2004).

5.2 How does Vitamin D Receptor Work?

Compelling evidence strongly highlights the significant repercussions of vitamin D level imbalances on human wellness, leading to diseases (Zhang & Naughton, 2010). The vitamin D receptor in the nucleus plays an integral part in how the body reacts to this nutrient. Vitamin D’s active form, calcitriol, attaches to the blood’s vitamin D binding protein (VDBP). It then works with VDR in the cytoplasm of cells to form a molecular ensemble. Accompanied by the retinoic acid X receptor (RXR), the combination departs for the nucleus, forming a heterodimer (Barsony & Prufer, 2002; Bikle, 2014). Together, they enable gene transcription relying on vitamin D, which governs a significant portion of the human genome (3–10%), particularly in

mineral metabolism. This regulatory mechanism extends to metabolic pathways and is intertwined with embryological and immunological responses (Nair & Maseeh, 2012; Rosen et al., 2012; Zhu et al., 2013)..

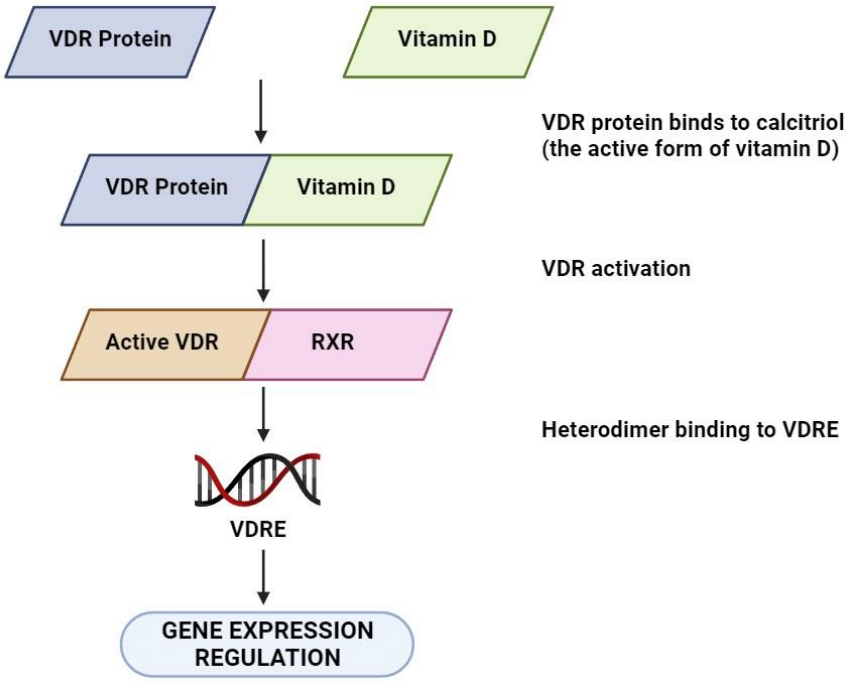

Figure 8: VDR protein's function in regulating gene expression (Agliardi et al., 2023; Scientific Image and Illustration Software, 2023)

5.3 Signaling by VDRs during Preterm Birth

In their research, scientists have found significant links between maternal vitamin D levels and placenta's defense against infectious microbes via toll-like receptors (Evans et al., 2006; N. Liu et al., 2009). Vitamin D stimulates cathelicidin production in decidua and cytotrophoblasts, crucially countering bacterial infections. Insufficient vitamin D limits toll-like receptor activation in systemic macrophages, decreasing cathelicidin levels and compromising microbial defense (Hewison, 2011; N. Q. Liu & Hewison, 2012). Moreover, vitamin D's active form, calcitriol, suppresses key immune response cytokines (IL-6, TNF-α, & GMCSF-2).

During pregnancy, myometrial smooth muscle cells and tissue display heightened inflammatory responses to lipopolysaccharides (LPS) and IL-1, which are associated with premature birth in mouse models (Helmer et al., 2002; Sehringer et al., 2000). An important discovery is that vitamin D inhibits protein production induced by LPS and IL-1 in UtSM cells, reducing levels of inflammation-associated contractility proteins (Buhimschi et al., 2003; Romero et al., 1991; Thota et al., 2013). This finding underscores the significance of mitigating premature birth risk and highlights vitamin D's protective role in regulating placental and uterine responses to infections and inflammation (N. Q. Liu et al., 2011).

5.4 Gene Polymorphism and their Types

The concept of genetic polymorphism pertains to the inheritance of an attribute that is controlled by a solitary genetic locus containing 2 alleles, where the allele with the lower prevalence has an abundance of 1% or above. It includes random processes or exogenous influences like viruses or radiation causing DNA sequence changes in individuals, groups, or populations. Mutations are DNA sequence differences linked to diseases. External perturbations are termed "mutations," not "polymorphisms," even if they create polymorphisms. Mutations in nucleotides cause polymorphisms, which are inherited from parents (Ismail & Essawi, 2012).

It's important to note that polymorphisms in genes come in a variety of forms:

- Tandem repeat polymorphisms
- Copy-number variations
- Single Nucleotide polymorphism

5.5 Single Nucleotide Polymorphism of VDR Genes

Located on chromosome 12 (12q13-14) over 75 kilobases, the VDR gene has nine exons (Suksawatamnuay et al., 2020) and allelic variations akin to other receptor genes on the same chromosome (Taymans et al., 1999). Extensive research has honed in on the genetic polymorphism of VDR, notably BsmI (rs1544410), ApaI (rs797532), TaqI (rs731236), and FokI (rs2228570), in relation to clinical outcomes (Agliardi et al., 2023). Figure 5.1 visually represents VDR activation and associated polymorphisms.

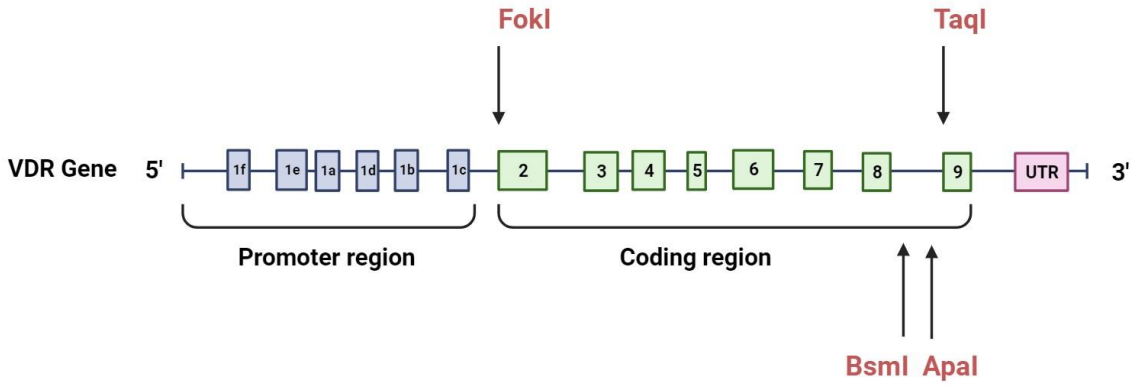

Figure 9: Common SNPs of the VDR gene (Agliardi et al., 2023; Scientific Image and Illustration Software, 2023)

The exact mechanisms behind genetic variations within the VDR gene impacting observed traits in association studies are uncertain. Specific SNP locations, like TaqI at exon-9; FokI at exon-2; ApaI and BsmI at intron-8, are of interest. Such SNPs involve distinct nucleotide changes, such as A to G for TaqI, G to A for FokI, G to A for BsmI, and A to C for ApaI (Kosik et al., 2020). TaqI alters protein function, while BsmI and ApaI change mRNA stability and expression, impacting VDR synthesis, vitamin D levels, calcium balance, and non-classical functions (Swamy et al., 2011).

5.6 VDR BsmI Gene Polymorphism

The VDR BsmI gene polymorphism (rs1544410), found within an intron between exons 8 and 9, is believed to impact the translational activity of VDR and the stability of its mRNA. because of significant linkage disequilibrium with a polyadenosine microsatellite repeat in the 3' untranslated region (Mangin et al., 2014; Mory et al., 2009), frequently co-occurring with the A allele (ApaI) and the T allele (TaqI). This relationship is linked to enhanced serum $1,25(OH)_2D_3$ levels (Marco et al., 1999; Morrison et al., 1994), while some studies indicate a link between the B allele and reduced VDR activity (Morrison et al., 1994; Uitterlinden et al., 2004), suggesting a negative feedback mechanism where the VDR ligand causes CYP27B1 inhibition, limiting excessive $1,25(OH)_2D_3$ production (Takeyama et al., 1997). This interaction may protect heterozygous individuals by maintaining intermediate $1,25(OH)_2D_3$ concentration in the serum and activity of VDR (Carless et al., 2008). According to recent studies, the VDR gene polymorphism BsmI is linked to enhanced intestinal calcium absorption in children & women (Ames et al., 1999; Gennari et al., 1997), and heightened renal phosphate absorption in men, shedding insight on its influence on calcium and phosphate metabolism (Ferrari et al., 1999).

5.7 VDR Gene Polymorphisms and Adverse Pregnancy outcomes

The vitamin D Receptor gene variations have been linked to a range of health conditions, including metabolic disorders, immune challenges, and different cancers (Valdivielso & Fernandez, 2006). These variations have prompted investigations into their potential roles in predicting complications during pregnancy and impacting the health of both mothers and newborns (Baczyńska-Strzecha & Kalinka, 2016; Barchitta et al., 2018; Randis, 2008).

Regarding neonatal repercussions, premature infants are vulnerable to conditions like respiratory distress syndrome (RDS) due to their underdeveloped lungs (Course &

Chakraborty, 2020). Vitamin D has shown potential for reducing RDS risk, particularly at elevated levels (Ataseven et al., 2014). Genetic variations within the VDR gene, such as the TaqI polymorphism, appear to be correlated with an elevated RDS risk (Ustun et al., 2020). Similarly, intraventricular hemorrhage (IVH), which involves genetic and environmental factors, might be influenced by VDR gene variations affecting vascular endothelial cell function (Ni et al., 2014; Szpecht et al., 2017). The likelihood of bronchopulmonary dysplasia (BPD), a condition tied to insufficient lung maturation, has been linked to the VDR gene polymorphism ApaI (Kosik et al., 2020). Additionally, the Toll-like receptor 4 (TLR4), involved in NEC development, is influenced by the VDR gene polymorphism ApaI, indicating a potential role for this vitamin in TLR4 signaling (Kosik et al., 2020).

Maternal repercussions include pre-eclampsia, where VDR gene polymorphisms like BsmI and FokI have been connected to hypertension beyond pregnancy (Bodnar et al., 2007). The FokI polymorphism, for instance, may lower hypertension risk through its effect on plasma renin activity (Vaidya et al., 2011). Gestational Diabetes Mellitus (GDM), influenced by genetic along with environmental factors, has ties to VDR gene variations, potentially predisposing people to type-1 and type-2 diabetes (Motohashi et al., 2003; Tizaoui et al., 2014). Certain variants like BsmIBB, BsmIBb, and TaqItt predispose to T1DM (Sahin et al., 2017), while VDR FokI, TaqI, and ApaI SNPs show associations with GDM in diverse populations (Aslani et al., 2011; Rahmannezhad et al., 2016). A possible osteoporosis risk, particularly in postmenopausal women, has been explored in relation to VDR gene haplotypes, with varying effects observed in different cell lines (Gennari et al., 1997).

Chapter 6: Findings on Association of Single Nucleotide VDR Gene Polymorphism BsmI with Preterm Birth & Low Birth Weight

6.1 Interrelation between VDR BsmI SNP & Preterm Birth

Manzon and colleagues studied ApaI, TaqI, FokI and BsmI polymorphisms among a population residing in Israel to determine their impacts on preterm delivery. The research found substantial differences between preterm deliveries and controls, notably in mothers' FokI and TaqI VDR alleles. Interestingly, the maternal FokI variation had an OR of 3.317%, suggesting a higher risk of preterm delivery. ApaI, TaqI, and BsmI genetic variants did not significantly affect preterm birth, with odds ratios of 0.41, 0.232, and 1.13, respectively (Manzon et al., 2014).

In another study, Baczyńska-Strzecha and her colleague examined 100 preterm and 99 full-term Polish moms in 2016. Researchers found three genetic variations in participants: ApaI, TaqI, and Bsm1. The research found no substantial genetic variation differences between preterm and full-term groups, despite these variances. Intriguingly, the preterm cohort displayed a higher frequency of BsmI/BB-ApaI/aa-TaqI/tt & BsmI/bb-ApaI/AA-TaqI/TT variants. Conversely, the preterm delivery incidence was also lowered by two genotype combinations: BsmI/BB-ApaI/Aa-TaqI/tt & BsmI/Bb-ApaI/AA-TaqI/Tt. This shows that certain genetic differences may raise the chance of preterm birth, while others may reduce it (Baczyńska-Strzecha & Kalinka, 2016).

Rosenfeld and his colleagues found a substantial correlation among maternal BsmI polymorphism and likelihood of PTB in a separate investigation, comprising 146 Israeli-Jewish preterm and 229 full-term women. Remarkably, the research found a negative connection between maternal BsmI polymorphism A allele count and PTB risk. Even after controlling for other covariates, this link remained strong, indicating that a greater A allele count continuously

lowered PTB risk. The research also found that mothers with spontaneous miscarriages had a higher PTB risk, especially if their babies had non-mutated (homozygous BB or bb) BsmI gene variations rather than the mutated (heterozygous Bb) genotype. These data show that the maternal BsmI polymorphism may affect PTB risk in women who have had previous instances of miscarriage (Rosenfeld et al., 2017).

In their initial 2018 Mamma and Bambino Cohort research, Barchitta and colleagues found no association between the VDR BsmI SNP and preterm birth. Integrating their data with Rosenfeld and Baczyńska-Strzecha's findings and using the Q-test and I^2-test for heterogeneity evaluation, they found no significant differences. However, their meta-analysis of many genetic models found a negative correlation between mothers' BsmI polymorphism and premature birth. The recessive variant of the rs1544410 (BsmI) gene (AA vs. GG + AG) was linked to a lower incidence of PTB, suggesting a protective effect. The dominating model (AA+AG vs. GG) didn't show a meaningful correlation. The meta-analysis confirms that BsmI protects against preterm birth, with the extent varying by genetic model (Baczyńska-Strzecha & Kalinka, 2016; Barchitta et al., 2018; Rosenfeld et al., 2017).

Dutra accompanied by his colleagues found numerous interesting results in another study of 40 moms with preterm neonates (PTNs) as cases and 92 moms with full-term newborns (FTN) as controls. The maternal BsmI/CT single nucleotide variation (SNV) was more prevalent in the FTN group than in the PTN group, indicating a genetic composition linked to a lower chance of preterm delivery. Conversely, the BsmI/TT genotype elevated preterm birth risk by 2.36 times when paired with a 25 (OH)D deficit. This shows that the TT genotype and low vitamin D levels increase preterm birth risk. Preterm newborns had more BsmI/TT genotypes, whereas FTN neonates had more CT genotypes of the BsmI SNV (Dutra et al., 2020). Another case-control study conducted in the same year in Slovenia didn't reveal any substantial association for VDR BsmI SNP with preterm birth (Gašparović Krpina et al., 2020)

A study Wang and colleagues at Zhoushan Maternal and Child Health Hospital, China, Wang et al. investigated the link between genetic variation BsmI (rs1544410) and gestational week from August 2011 to May 2018. However, their findings showed an absence of correlation between BsmI and the gestational week, indicating limited impact on gestation length (Wang et al., 2021).

Table 3: Studies on VDR gene variations and preterm birth risk

Population Origin	**Participants**	**VDR SNPs**	**Findings**	**Reference**
Israel (Jewish)	33 Caucasian moms with PTNs (between 24 and 35 weeks), and 98 with FTNs	TaqI **BsmI** ApaI FokI	Preterm mothers were more likely to have the FokI/C gene. However, no link was seen between the BsmI genotype and preterm birth.	(Manzon et al., 2014)
Poland	100 Caucasian moms with PTNs (22-36.6 weeks) and 99 moms with FTNs	TaqI **BsmI** ApaI	Despite no differences in individual genotype frequencies, preterm birth mothers were more likely to carry the genotypic combinations: BsmI/BB-ApaI/aa-TaqI/tt & BsmI/bb-ApaI/AA-TaqI/TT	(Baczyńska-Strzecha & Kalinka, 2016)
Israel (Jewish)	146 white moms with their PTNs (at	TaqI **BsmI**	The genotype ApaI/AA appeared to be linked to an	(Rosenfeld et al., 2017)

	24–36 weeks), 229 women with their FTNs.	ApaI FokI	elevated preterm birth incidence. If their neonates received the non-mutated BsmI gene variant (BB or bb), mothers who had natural miscarriages were more likely to deliver prematurely.	
Italy	17 moms & their PTNs (< 37 weeks gestation), 187 moms & their FTNs	**BsmI** ApaI FokI TaqI	FokI polymorphism genotypes enhanced preterm birth risk in mothers. However, recessive BsmI (AA vs. GG + AG) reduced preterm birth risk.	(Barchitta et al., 2018)
Slovenia	118 spontaneously induced PTB following natural conception cases and 119 term singleton controls	ApaI TaqI **BsmI** FokI Cdx2	No association for BsmI SNP was discovered.	(Gašparović Krpina et al., 2020)
Brazil (Southeast)	40 moms and their PTNs (between 23 and 32 weeks), and 92 moms with FTNs	**BsmI** ApaI FokI TaqI	Prematurity risk was increased by the BsmI/TT as well as ApaI/AA genotypes, irrespective of Insufficiency in vitamin D.	(Dutra et al., 2020)

China	A total of 3465 pregnant women, with 202 of them being PTB	**BsmI**	No substantial association between BsmI and gestational week was discovered	(Wang et al., 2021)

6.2 Interrelation between VDR BsmI SNP & Low Birth Weight

Limited research has addressed genetic factors affecting birth outcomes related to vitamin D metabolism and overlooked 'maternal' VDR gene variations in newborn birth weight. However, potential ethnicity-specific responses to maternal VDR gene polymorphisms regarding birth weight hint at the need for further investigation. This emphasizes the necessity of comprehensively understanding how genetics and vitamin D contribute to birth outcomes across diverse ethnic groups (Swamy et al., 2011).

Lorentzon and colleagues found a connection between the VDR BsmI SNP & birth height, implying its influence on fetal bone development. In contrast, birth weight showed no significant correlation (Lorentzon et al., 2000). Within a primarily Caucasian cohort, insufficient maternal serum 25(OH)D status was linked to reduced birth weight in higher-functioning VDR FokI genotypes. However, no noteworthy correlation emerged between the BsmI SNP and birth weight (Morley et al., 2009).

Silvano and his team explored SGA neonates who didn't grow much after birth among prepubertal children. Intriguingly, no significant variations were detected in BsmI genotype distributions across diverse birth weight categories (Silvano et al., 2011). Similarly, A meta-analysis conducted on data from the "Mamma & Bambino" Cohort failed to reveal substantial variations in gestational length or birth weight among different BsmI genotypes (Barchitta et al., 2018).

Based on findings from a recent case-control research, it was shown that the FokI/TT variant of VDR exhibited an association with reduced birth weight in newborns of European descent who had spontaneous preterm birth (SPTB). There were no observed associations between VDR BsmI SNP and any further medical characteristics of SPTB mothers and their babies (Gašparović Krpina et al., 2020).

Ultimately, available evidence suggests that BsmI genotypes may not substantially impact newborn weight.

6.3 Limitations of the Findings

Conflicting VDR polymorphism research arises from variable study factors, notably sample sizes impacting reliability and generalization. Small studies, like Baczyska-Strzecha's, hold limited relevance (Baczyńska-Strzecha & Kalinka, 2016). Ethnicity profoundly affects SNV distribution, particularly in mixed populations such as Asians and Caucasians, resulting in distinct VDR polymorphism prevalence and associations (Manzon et al., 2014). Racial origins contribute to inconsistent findings (Dutra et al., 2020). Unmeasured variables, like maternal practices and vitamin D levels, might influence associations (Barchitta et al., 2018). Genetic naming variations and analysis methods further complicate interpretation (den Dunnen et al., 2016). Recognizing ethnicity, unmeasured variables, and genetic nomenclature is vital for accurate VDR polymorphism research interpretation. Addressing these complexities in future studies is essential (den Dunnen et al., 2016; Dutra et al., 2020).

Chapter 7: Conclusion and Future Recommendations

Conclusion

Both preterm birth and low birth weight are serious worldwide healthcare concerns with complex causes. Maternal vitamin D deficiency is shown to cause preterm birth, and the VDR gene, responsible for the encoding of vitamin D receptor, takes part in regulating the levels of this vitamin through genetic variations (SNPs). Several researches have delved into the correlation between VDR BsmI SNP and the likelihood of preterm birth, with some providing evidence for the association while others failing to reach a conclusive outcome. However, almost no evidence of a BsmI SNP connection with low birth weight has yet been reported. In essence, the current findings are inconclusive, highlighting the need for more research to comprehensively comprehend how VDR gene SNPs relate to adverse pregnancy outcomes. The mother's health, lifestyle, surroundings, infections, race, ethnicity, and smoking all influence birth weight and the premature birth risk. Additionally, the variation in a particular gene is not the only genetic component that influences adverse pregnancy outcomes. Nonetheless, ensuring sufficient vitamin D intake and closely monitoring pregnant women and fetuses are essential for achieving optimal outcomes.

Future Recommendations

Future research recommendations for this subject include:

• Increasing sample sizes for stronger statistical power by studying larger populations;

• Including diverse ethnic groups to grasp VDR polymorphisms' impact on PTB and LBW;

• Analyzing functional aspects of VDR polymorphisms for their link to PTB and LBW;

• Considering maternal stress, nutrition, and pollutant exposure in future studies to better • understand PTB and LBW risk;

• Conducting longitudinal studies to observe PTB and LBW progression while factoring in genetics and the environment; and

• Exploring epigenetic changes for a deeper understanding of VDR polymorphisms' connection to PTB and LBW.

Health organizations and governments should increase awareness of PTB and LBW risks, targeting pregnant women and the public through educational campaigns, materials, and community outreach. Pregnant women should prioritize a healthy lifestyle, infection prevention, sufficient vitamin D intake, monitoring, safe supplementation, and healthcare provider guidance.

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