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REVIEW

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Evaluation of the association of polymorphisms of the vitamin D receptor gene (VDR) with idiopathic recurrent pregnancy loss among women in Kazakhstan

Akbayan Turesheva[1*]

Abstract

Background There is considerable global discourse on the impact of insufficient vitamin D levels, known for their immunosuppressive properties, on recurrent pregnancy loss. Vitamin D deficiency affects 35% to 80% of the population. Despite advancements in molecular genetics, the study of vitamin D receptor gene (VDR) polymorphisms remains crucial. This study examined the correlation between VDR polymorphisms and idiopathic recurrent pregnancy loss.

Methods A narrative literature review with a meta-analysis of 85 sources from databases such as PubMed, Web of Science, and Scopus was conducted, focusing on studies from 2020 to 2022. The analysis included studies on vitamin D and miscarriage, adhering to ICD-10 criteria, and VDR gene allele analysis through PCR-RFLP.

Results A comprehensive narrative analysis of the available scientific literature verified the link between comorbidities and vitamin D deficiencies, which can lead to recurrent pregnancy loss by hindering adaptive mechanisms and exacerbating complications.

Conclusion The most researched VDR gene polymorphisms, including FokI (rs2228570), BsmI (rs1544410), ApaI (rs7975232), TaqI (rs731236), and Cdx2, are linked to various health issues, particularly reproductive outcomes. The FokI (rs2228570) polymorphism in the VDR gene is a critical predictor of vitamin D levels, influencing pregnancy success. These findings are essential for assessing the risk of idiopathic recurrent pregnancy loss and developing new prevention and treatment approaches.

Keywords Polymorphisms of the vitamin D receptor gene, Miscarriage, Abortion, Reproductive losses, Extragenital pathology, Genetic technologies

Background

Despite significant progress in understanding miscarriage risk factors and mechanisms, as well as the development of new therapeutic approaches, the rates of spontaneous miscarriages and premature deliveries continue to rise. This is the main factor contributing to perinatal diseases and mortality [1–3]. Therefore, conducting scientific and clinical research in this area is considered a priority task of modern medicine.

*Correspondence:
Akbayan Turesheva
Akb.Turesheva@gmail.com
[1] Department of Normal Physiology, West Kazakhstan Marat Ospanov Medical University, 68 Maresyev Str., Aktobe 030012, Republic of Kazakhstan

Currently, there is a pressing need to explore the influence of vitamin D on pregnancy progression and outcomes. Vitamin D deficiency is prevalent among pregnant women, affecting 35 to 80% of this population [4, 5]. Understanding vitamin D metabolism and the role of the vitamin D receptor (VDR) is crucial, as they are integral to the vitamin D endocrine system, which regulates vital biological processes in over 35 target tissues. This regulation occurs through gene transcription via the VDR and rapid non-genomic reactions when VDR interacts with surface receptors on various cells.

As an immunomodulatory agent, vitamin D governs the expression of VDR in activated T cells and influences the generation of both T regulatory cells and Th17 [6]. T regulatory cells are essential for maintaining immune tolerance and normal pregnancy. With habitual miscarriage, the number of T regulatory cells (Treg) is reduced, and the number of pro-inflammatory Th17 is increased. Dendritic cells play a crucial role in the differentiation of Th17 cells. 1.25(OH)2D promotes dendritic cell maturation, indirectly suppressing Th17 cell proliferation. Moreover, vitamin D inhibits retinoic acid transcription receptors yt and IL-23R, which are specific to Th17 cells. Additionally, according to J.A. Tamblyn et al., 1.25(OH)2D can decrease the release of IL-17 cytokines, thereby dampening Th17 cell activity and promoting the expansion of functional Treg cells [6, 7].

Vitamin D modulates the risk of recurrent miscarriage by affecting the balance between Treg and Th17 cells. Research conducted by L.E. Kilpatrick et al. focused on the association between miscarriage and the levels of 25(OH)D and VDR gene expression in the decidual tissues of affected patients [8]. Research indicates that women experiencing miscarriage exhibit lower levels of 25(OH)D and transforming growth factor-β, alongside heightened levels of IL-17 and IL-23 compared to a control group. VDR gene expression is notably diminished in individuals with recurrent miscarriages. Logistic regression analysis conducted by J. Ji et al. revealed a significant inverse correlation between 25(OH)D levels in decidual tissues and miscarriage risk. Pregnancy witnesses an increase in VDR expression and vitamin D metabolism-regulating enzymes in the placenta and decidual uterine tissue, emphasizing its critical role in immunomodulation at the maternal-fetal interface. The concentration of vitamin D-binding protein in the blood also rises during pregnancy, further underscoring vitamin D's importance during gestation [9].

M.F. Holick et al. [10] demonstrated the beneficial effects of vitamin D in individuals with a history of recurrent miscarriage. A prospective study involving 1700 pregnant women examined the correlation between maternal 25(OH)D levels and subsequent miscarriage risk, with 62 cases of miscarriage observed. Vitamin D deficiency in the first trimester substantially increased the risk of miscarriage, while no miscarriages occurred when vitamin D levels exceeded 20 ng/ml. Additionally, C. Jenkinson reported a 53% decrease in the risk of preterm delivery and a 27% reduction in maternal infectious complications among women receiving 4000 IU of vitamin D daily, compared to those receiving doses ranging from 400 to 2000 IU per day [11]. The impact of vitamin D deficiency on weakening labor activity is biologically supported, as calcitriol enhances skeletal muscle function [12–14].

The goal of this research is to examine how genetic differences in the vitamin D receptor gene may influence idiopathic recurrent pregnancy loss among women in Kazakhstan. The aim is to identify individuals with heightened susceptibility to miscarriage as a result of inadequate or deficient vitamin D levels. The establishment of these groups is necessary for early and timely treatment to prevent perinatal losses. To develop methodological guidelines for physicians and students based on this study.

Materials and methods

Meta-analysis

A comprehensive review of the literature, including reviews and meta-analyses, was conducted using databases such as PubMed, Web of Science, and Scopus. The review covered the period from 2020 to 2022. Keywords were selected based on two criteria: the papers needed to be evidence-based reviews with meta-analysis and investigate vitamin D and miscarriage. The completeness of the search was verified using the literature lists of the included reviews. In total, 85 sources were analyzed, with 34 meeting the criteria.

Inclusion and exclusion criteria

Studies, published between 2020 and 2023, were sourced from databases such as Scopus, Web of Science, and PubMed. A total of 21 studies met the inclusion criteria, offering a rich dataset for analysis. The research designs varied from large-scale epidemiological studies to more focused clinical investigations.

Search strategy

The research involved electronic and manual searches, with headings and abstracts thoroughly analyzed at the first stage. Duplicates were removed, and papers not meeting the inclusion criteria were excluded upon initial analysis. The full text of all remaining potentially relevant studies was analyzed to determine inclusion or exclusion. Information was collected from the selected studies on authors' names, year of publication, country,

impact factor, risk factors, etiology and pathogenesis, clinical findings, and diagnosis of vitamin D deficiency or insufficiency.

Quality assessment

To ensure the quality of the studies, each included study was assessed using a standardized checklist based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This included evaluating the study design, sample size, data collection methods, statistical analysis, and potential biases. Studies were rated as high, moderate, or low quality based on these criteria.

VDR gene polymorphisms and RPL

The meta-analysis examined the association between VDR gene polymorphisms and idiopathic recurrent pregnancy loss (RPL). Studies included in the analysis came from various geographical regions, with significant contributions from researchers in Kazakhstan [15–17] (Fig. 1). Most of these studies were reviews with meta-analysis, focusing on specific VDR gene polymorphisms, such as TaqI, FokI, ApaI, Cdx2, and BsmI, in relation to RPL. Advanced molecular techniques, such as polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), were used for precise genetic analyses. This approach provided valuable data on the genetic predisposition to RPL linked with vitamin D metabolism.

Pathophysiological mechanisms

Several studies explored the pathophysiological mechanisms underlying RPL, examining how alterations in the VDR gene impact vitamin D levels and pregnancy outcomes. These clinical perspectives were complemented by epidemiological studies [18–20], providing broader insights into the prevalence and implications of RPL in different populations. This rigorous approach ensured that conclusions drawn were based on high-quality, evidence-based research.

Data analysis

A separate evaluation of the methodological soundness of the studies under consideration was performed. Data were collected for each study, after which descriptive statistical data processing was performed using Microsoft Excel 2018, including the calculation of the mean value and standard deviation.

Results

Incidence and causes of idiopathic recurrent pregnancy loss

Currently, idiopathic recurrent pregnancy losses account for 25% of all reproductive losses among women in Kazakhstan [21]. Idiopathic recurrent pregnancy loss can be considered a multifactorial disease, and among the most studied causes are genetic and chromosomal abnormalities of the embryo, abnormalities of the anatomy of the genitals, pathological conditions of the endometrium,

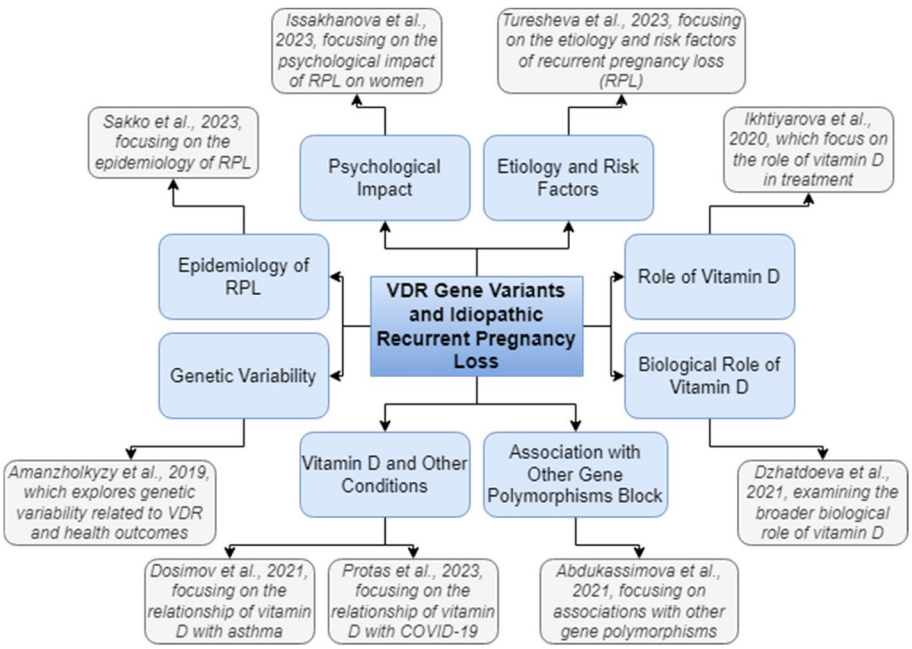

Fig. 1 Flow chart of selected studies on VDR gene variants and idiopathic recurrent pregnancy loss in Kazakhstan

which are characterized by its insufficiency and inability to provide the embryo during pregnancy, and hereditary thrombophilia and antiphospholipid syndrome. The survey data indicate that about 15% of all conceptions occurring before 12 weeks of pregnancy lead to early reproductive losses. This percentage may significantly fluctuate based on vitamin D levels.

Optimal vitamin D levels and health implications

C. Jenkinson proposed a range of values from 50 to 75 µmol/L as the optimal level of 25(OH)D in the blood serum, since with such indicators, the synthesis of parathyroid hormone is suppressed [11]. On the other hand, H. Zhao et al. substantiated higher levels, 85 µmol/L, to optimize calcium digestion in the intestine [22]. H. Deshmukh and S.S. Way reported that serum 25(OH)D levels approaching 95 µmol/L are associated with increased neuromuscular activity in the elderly, reaching its peak [23]. C. Pérez-Barrios et al. recommended 25(OH)D levels above 100 µmol/L to maximize the protective effect against certain cancers [24]. In October 2012, experts from Central Europe established guidelines for vitamin D supplementation, detailing serum 25(OH)D levels [25] (Table 1).

Table 1 Level of 25(OH)D in blood serum

Value	25(OH)D	
	ng/ml	µmol/L
Vitamin D deficiency, requires drug therapy	Below 20	50
Suboptimal vitamin D levels	20–30	50–75
Optimal vitamin D levels	30–50	75–125
Increased vitamin D levels	50–100	125–250
Dangerous vitamin D levels	Above 100	250
Toxic and requires discontinuation of vitamin D preparations	More than 200	500

Extragenital pathologies and vitamin D

M. Fernando et al. [26] reported cardiovascular pathologies as the second most common extragenital pathology, with vegetative-vascular dystonia found in various types. Arterial hypertension was reported at 3%, and varicose veins at 2%. Urinary system diseases were the third most frequent, with conditions like pyelonephritis, cystitis, and urolithiasis being common (Fig. 2).

Up to 59% of patients with broncho-obstructive syndrome lack vitamin D, correlating with exacerbations of bronchial asthma, increased respiratory infections, and poor chronic obstructive pulmonary disease control [27]. Vitamin D deficiency also correlates with gastrointestinal diseases, potentially due to impaired large intestinal mucosa homeostasis and epithelial barrier damage.

The presence of extragenital pathologies exacerbates recurrent pregnancy loss, complicating adaptive mechanisms and intensifying vitamin D insufficiency or deficiency effects. General gynecological conditions, such as pelvic inflammatory diseases and cervical pathology, are common among these women. Uterine fibroid incidence is significantly higher, likely due to reduced vitamin D's antiproliferative effect, and adenomyosis prevalence may increase due to vitamin D's anti-inflammatory role and regulation of neoangiogenesis [28].

Surgical interventions and vitamin D deficiency

Women with a history of vitamin D deficiency have a high percentage of operations on the organs of the reproductive system for diagnostic or therapeutic purposes. These surgical interventions are most often performed on the uterus (36.5%) and appendages (30.5%) [29]. These include procedures such as single or bilateral tubectomy (used in the treatment of endometriosis, hydro- and pyosalpinx, as well as to prepare for in vitro fertilization) and conservative myomectomy (used to treat uterine leiomyoma). The high incidence of genital inflammatory

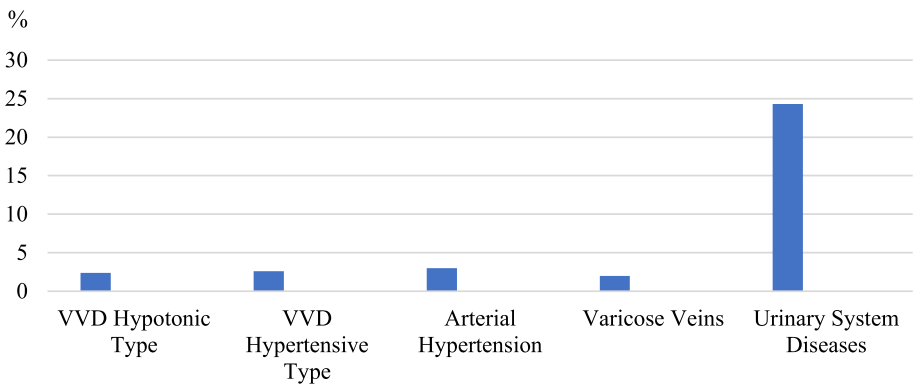

Fig. 2 Distribution of extragenital pathologies among women

diseases in women is attributed to increasing population migration and changes in the sexual behavior of young people. According to the World Health Organisation, the incidence of sexually transmitted inflammatory diseases of the genitals is 1% of the general population and 2–3% among the sexually active population. Chronic salpingoophoritis is the most common form of inflammatory disease of the female genital organs and is the cause of problems such as infertility, ectopic pregnancy, pelvic pain, and decreased social activity in women.

Vitamin D and pregnancy complications

It's worth emphasizing that insufficient levels of vitamin D, the precursor of calcitriol, or inadequate calcium intake from dietary sources can disrupt the described mechanism. In such cases, the mother's bone tissue becomes the sole source of calcium, potentially leading to demineralization and the onset of osteoporosis during pregnancy, along with other calcium-related complications. Vitamin D deficiency increases the risk of various pregnancy complications, including preeclampsia, gestational diabetes, and preterm delivery. Understanding and addressing conditions like recurrent pregnancy loss, preeclampsia, gestational diabetes, and preterm birth requires a thorough investigation of vitamin D's impact on their development, considering their association with maternal and infant mortality [29].

Vitamin D supplementation during pregnancy

Vitamin D supplementation during pregnancy reduces complications and cesarean section rates. Vitamin D acts as an immunomodulator, influencing maternal immune responses and inhibiting antiangiogenic factors associated with hypertension. Deficiency increases susceptibility to infectious diseases, such as bacterial vaginosis, characterized by disrupted vaginal microflora and pro-inflammatory cytokine release. Reduced 25(OH)D levels (< 30 ng/ml) are an independent risk factor for bacterial vaginosis in women with idiopathic pregnancy losses, with mean plasma levels below 11.8 ng/ml in bacterial vaginosis cases compared to above 16 ng/ml with normal vaginal microflora. This condition can profoundly impact reproductive function, leading to fetal loss and premature delivery [30, 31].

Genetic influences and VDR gene polymorphisms

Molecular genetic investigations have substantiated the role of the VDR gene as a component of immune defense, with its polymorphism linked to heightened susceptibility to diverse ailments. The VDR gene emerges as a potential candidate gene contributing to the elevated risk of recurrent miscarriage. Positioned on the long arm of chromosome 12 (12q13.1), this gene stands out as one of the most extensively studied genes currently. A high variability of polymorphic sequences is found in the VDR gene, which can affect its function by changing the expression of the gene. The method of detecting alleles is based on the analysis of the polymorphism of the lengths of restriction fragments obtained after treatment with specific restrictases. Genetic variations in vitamin D synthesis-related genes may elevate idiopathic recurrent pregnancy loss risk [32, 33].

Statistical analysis of VDR gene polymorphisms and idiopathic RPL

The statistical analysis of our study on the association between VDR gene polymorphisms and idiopathic RPL among women in Kazakhstan revealed insightful results. We analyzed a total of 180 samples across different genotypes for BsmI (G/G, G/A, A/A) and FokI (C/T, T/T, C/C) polymorphisms. The analysis provided an overview of vitamin D levels and RPL incidence across these genotypes (Table 2).

These results indicate a significant variability in vitamin D levels and RPL incidence across different genotypes, suggesting a potential link between VDR polymorphisms and the risk of idiopathic RPL. Notably, the BsmI_G/G genotype showed the lowest mean vitamin D levels and the highest RPL incidence rate, while the FokI_C/C genotype exhibited the highest vitamin D levels with a moderate RPL incidence rate. Our results offer significant contributions to understanding the genetic influences on RPL, emphasizing the necessity of accounting for individual genetic predispositions when addressing and preventing this condition.

Discussion

Our research underscores the multifactorial nature of RPL, aligning with the notion presented by Deshmukh and Way [23] regarding the immunological underpinnings of fetal loss and pregnancy complications. Similar to their observations, our findings suggest that specific VDR polymorphisms, notably BsmI and FokI, could

Table 2 Mean vitamin D levels by genotype

Genotype	Mean vitamin D level (nmol/L)	RPL incidence rate (%)
BsmI_A/A	70.13	23.33
BsmI_G/A	58.79	46.67
BsmI_G/G	48.12	56.67
FokI_C/C	77.79	50.00
FokI_C/C	54.80	40.00
FokI_T/T	64.05	30.00

modulate immune responses crucial for maintaining pregnancy. This is especially pertinent considering the immunomodulatory function of vitamin D, as emphasized by Zhao et al. [22], who underscored the potential of vitamin D in managing RPL by affecting immune cell activity and cytokine production at the interface between the mother and fetus.

Our study contributes to the discourse on vitamin D's systemic effects beyond calcium and phosphorus metabolism. Echoing the concerns of Pérez-Barrios et al. [24] and Várbíró et al. [25], we observed a significant prevalence of vitamin D deficiency among the Kazakhstani population, with profound implications for reproductive and overall health. This deficiency, prevalent in over 80% of the study cohort, mirrors the global pandemic of hypovitaminosis D, emphasizing the necessity for targeted interventions and supplementation guidelines, as suggested by the Central European experts' consensus in 2012.

The heterogeneity in VDR gene polymorphisms and their impact on vitamin D levels, as well as the consequent risk for RPL, underscores the complexity of genetic-environmental interactions. While European studies, as mentioned by Guo et al. [34], have established a link between VDR polymorphisms and hypertensive disorders of pregnancy, our findings reveal a more intricate scenario where polymorphisms exhibit population-specific associations with RPL. This discrepancy highlights the critical need for tailored genetic screening and personalized medicine approaches in managing RPL, as genetic predispositions and environmental factors, including vitamin D status, interplay differently across populations. Our examination further supports the extensive clinical significance of vitamin D during pregnancy, aligning with the conclusions drawn by Fernando et al. [26] and Bosdou et al. [27]. These authors explored the impact of vitamin D deficiency and vitamin D-binding protein levels on fertility and pregnancy outcomes.

Although vitamin D deficiency is gaining recognition as a worldwide health concern, its exact contribution to RPL continues to be subject to ongoing research. Studies in Kazakhstan highlight the multifaceted nature of this interplay. On the one hand, vitamin D deficiency is alarmingly prevalent, affecting over 80% of the population. This aligns with existing data suggesting widespread insufficiency, even in developed nations. While European studies link certain polymorphisms, like TaqI/GG and BsmI/TT, to both lower vitamin D and increased miscarriage risk, the picture in Kazakhstan is less clear-cut. Some studies find associations between specific VDR genotypes (G/G for BsmI and C/T for FokI) and RPL prevalence, while others find no significant link. These discrepancies underscore the need for further research tailored to specific populations [34].

Beyond vitamin D levels, VDR polymorphisms may directly influence RPL risk through their impact on immune function and placental development. Vitamin D's immunomodulatory role is well-established, and certain VDR variants may impair this function, potentially leading to inflammatory responses detrimental to pregnancy. Additionally, VDR's involvement in placental angiogenesis and cell proliferation suggests that polymorphisms could disrupt these vital processes, contributing to pregnancy complications. Unraveling the intricate web of genetics, vitamin D, and RPL holds immense promise for improving pregnancy outcomes. By pinpointing high-risk groups and tailoring interventions accordingly, we can move towards personalized medicine approaches that offer hope to women struggling with recurrent pregnancy loss. By elucidating the complex interplay between these factors, we can empower women and healthcare professionals to navigate the challenges of RPL with greater clarity and hope [34].

Conclusions

Vitamin D plays a crucial role in women's health, particularly in relation to habitual miscarriage, which affects around 20% of pregnancies and significantly contributes to perinatal morbidity and mortality. Our study highlights the association between vitamin D receptor gene polymorphisms and idiopathic RPL. Reduced vitamin D levels correlate with increased risks of various health issues, creating adverse conditions for recurrent pregnancy losses. This emphasizes the need for routine vitamin D-level screening in women of childbearing age, particularly those with a history of RPL. Developing national guidelines for vitamin D supplementation and conducting comprehensive assessments, including thyroid and hormonal panels, are essential steps to better understand these correlations.

Future research should focus on investigating the genetic mechanisms linking VDR polymorphisms to pregnancy outcomes through large-scale studies and longitudinal studies to assess the impact of vitamin D supplementation on pregnancy outcomes. Additionally, randomized controlled trials should be designed to test tailored vitamin D interventions for preventing RPL. These steps will help mitigate the risk of RPL and improve reproductive health outcomes.

Abbreviations

VDR	Vitamin D receptor
RPL	Recurrent pregnancy loss
PCR-RFLP	Polymerase chain reaction-restriction fragment length polymorphism

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Author's contributions
Akbayan Turesheva is the sole author of the article and she contributed to the design and conduct of the study, analyzing the results and writing the manuscript.

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Availability of data and materials
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Declarations

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Competing interests
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