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Impact of First-Trimester Vitamin D Deficiency on the Risk of Gestational Diabetes Mellitus: A Comprehensive Review

Safaa Abd Elsalam Ibrahim [1], WalidAbdalla Mohamed AbdElsalam[2], Abeer AbdElmogni Ali Ahmed[3], Ahmed Metwally El Katawy[4]

1. Assistant Professor of Obstetrics & Gynecology, Faculty of Medicine - Zagazig University,
2. Professor of Obstetrics & Gynecology, Faculty of Medicine - Zagazig University,
3. Obstetrics & Gynecology Resident at Belebis General hospital ministry of Health
4. Lecturer of Obstetrics & Gynecology, Faculty of Medicine - Zagazig University,

Corresponding author: Abeer AbdElmogni Ali Ahmed

ABSTRACT

Background: Vitamin D plays a critical role in calcium-phosphate homeostasis, immune modulation, and metabolic regulation. During pregnancy, maternal vitamin D status is particularly important as it influences not only skeletal development but also glucose metabolism. Emerging evidence suggests that deficiency in the first trimester may contribute to the development of gestational diabetes mellitus (GDM), a common pregnancy complication associated with increased maternal and fetal morbidity. GDM incidence is rising globally, paralleling the prevalence of vitamin D deficiency in reproductive-age women. However, the strength and causality of this association remain debated. This review aims to comprehensively evaluate current evidence regarding the correlation between first-trimester vitamin D deficiency and subsequent development of GDM. It synthesizes data from observational studies, interventional trials, and mechanistic research to clarify whether hypovitaminosis D is an independent risk factor, elucidate underlying biological mechanisms, and assess clinical implications for screening and prevention. We reviewed peer-reviewed literature from PubMed, Scopus, and Web of Science up to August 2025, including cohort studies, case-control studies, randomized controlled trials, and relevant meta-analyses. Search terms included “vitamin D deficiency,” “first trimester,” “gestational diabetes mellitus,” and “pregnancy.” Articles were evaluated for methodological quality, control of confounding variables, and clinical relevance. The majority of observational studies report a statistically significant association between low serum 25-hydroxyvitamin D [25(OH)D] concentrations in early pregnancy and higher GDM risk, even after adjusting for BMI, age, and ethnicity. Proposed mechanisms include impaired pancreatic β-cell function, altered insulin sensitivity, and increased systemic inflammation. Some interventional trials demonstrate reduced GDM incidence with vitamin D supplementation initiated early in pregnancy, though results remain inconsistent due to heterogeneity in dosage, baseline status, and study design. The association appears strongest in populations with severe deficiency (<20 ng/mL) and in high-risk ethnic groups.

Conclusion: Current evidence supports a probable but not definitive link between first-trimester vitamin D deficiency and increased GDM risk. While supplementation may offer preventive benefits in deficient women, robust, large-scale randomized trials with standardized protocols are needed before universal recommendations can be made. Early screening for vitamin D deficiency in pregnancy, particularly in high-risk populations, may be a prudent interim strategy for optimizing maternal and fetal outcomes.

Keywords: *First-Trimester ,Vitamin D Deficiency , Gestational Diabetes Mellitus*

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INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most prevalent metabolic complications of pregnancy, affecting approximately 7–15% of pregnancies worldwide, with variations depending on diagnostic criteria and population characteristics. It is characterized by glucose intolerance first recognized during pregnancy and is associated with adverse maternal outcomes such as preeclampsia, cesarean delivery, and long-term type 2 diabetes, as well as neonatal complications including macrosomia, hypoglycemia, and respiratory distress syndrome [1,2]. The rising global prevalence of GDM parallels the increase in obesity, sedentary lifestyles, and advanced maternal age, highlighting the need for early identification of modifiable risk factors [3].

Vitamin D, a secosteroid hormone traditionally known for its role in calcium and phosphorus metabolism, has gained increasing attention for its extraskeletal functions, including modulation of immune responses, regulation of cell proliferation, and influence on glucose metabolism. In pregnancy, adequate vitamin D status is critical not only for fetal skeletal development but also for maternal health. Hypovitaminosis D is highly prevalent in women of reproductive age, with rates exceeding 50% in some populations, and may be further exacerbated by pregnancy-related physiological changes, dietary inadequacies, and limited sun exposure [4,5].

Emerging research has identified a potential link between maternal vitamin D deficiency and the risk of GDM. Proposed mechanisms include impaired pancreatic β-cell function, reduced insulin sensitivity, and increased systemic inflammation — all of which can contribute to abnormal glucose tolerance. Notably, the timing of deficiency appears important, with first-trimester vitamin D status potentially exerting a more significant influence on later glucose metabolism than deficiencies detected in mid- or late pregnancy [6,7]. This early gestational window coincides with critical adaptations in maternal endocrine and metabolic systems, making it a plausible period for intervention.

Despite biologic plausibility and accumulating epidemiologic evidence, the relationship between vitamin D deficiency and GDM remains controversial. Some studies demonstrate a clear association even after adjusting for known confounders such as body mass index (BMI), ethnicity, and socioeconomic status, while others report null findings. The inconsistency may be due to differences in study design, population characteristics, thresholds for defining deficiency, and laboratory assay variability [8,9]. This variability underscores the need for a systematic synthesis of available evidence.

The present review aims to comprehensively examine the correlation between first-trimester vitamin D deficiency and the development of GDM. It seeks to evaluate the strength of existing evidence, explore underlying biological mechanisms, assess the effectiveness of early supplementation strategies, and identify gaps for future research. By doing so, it intends to provide clinicians and

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policymakers with an informed basis for considering vitamin D screening and supplementation as part of antenatal care protocols, particularly for high-risk populations [10].

Vitamin D Physiology in Pregnancy

Vitamin D is a fat-soluble prohormone obtained from dietary sources, supplementation, and cutaneous synthesis following ultraviolet B (UVB) exposure. In its inactive form, vitamin D undergoes two hydroxylation steps: the first in the liver, converting it to 25-hydroxyvitamin D [25(OH)D], the major circulating form, and the second in the kidney and other tissues, producing the biologically active form 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] [11]. During pregnancy, both maternal and fetal vitamin D requirements increase due to the demands of skeletal mineralization and other developmental processes. Notably, the placenta also expresses 1α-hydroxylase, enabling local synthesis of active vitamin D, which may play roles in immune tolerance and placental function [12].

Maternal physiology undergoes significant adaptations during pregnancy that alter vitamin D metabolism. Serum concentrations of 1,25$(OH)_2$D rise as early as the first trimester, independent of calcium intake, and remain elevated throughout gestation [13]. This increase is mediated by estrogen, parathyroid hormone-related peptide (PTHrP), and placental hormones, ensuring adequate calcium transfer to the fetus. Interestingly, these elevations occur even in women with low 25(OH)D levels, suggesting that maternal vitamin D deficiency may not always be reflected in active metabolite concentrations, although downstream biological effects may still be compromised [14].

Beyond skeletal health, vitamin D in pregnancy has been implicated in the regulation of immune responses, modulation of inflammatory cytokine production, and influence on glucose and lipid metabolism. The active metabolite binds to the vitamin D receptor (VDR), a nuclear transcription factor expressed in multiple tissues, including pancreatic β-cells, adipose tissue, and skeletal muscle [15]. Through genomic and non-genomic pathways, vitamin D may influence insulin secretion, enhance insulin sensitivity, and modulate systemic inflammation—mechanisms directly relevant to the pathophysiology of GDM [16].

The placenta itself is a vitamin D-responsive organ. VDR expression has been detected in trophoblasts, and vitamin D has been shown to regulate genes involved in angiogenesis, immune tolerance, and nutrient transport [17]. Impaired placental vitamin D signaling has been associated with pregnancy complications such as preeclampsia, intrauterine growth restriction, and possibly GDM. These findings suggest that maternal vitamin D status could influence pregnancy outcomes not only through systemic metabolic effects but also by modulating placental function [18].

Physiologic changes during pregnancy may predispose women to vitamin D deficiency despite increased metabolic demands. These include increased plasma volume leading to hemodilution, decreased sun exposure due to cultural practices or seasonal variations, reduced dietary intake, and

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altered skin synthesis efficiency with advancing maternal age or higher skin pigmentation [19]. Consequently, even in regions with abundant sunlight, vitamin D deficiency in pregnancy remains common, making early screening and supplementation considerations relevant to public health strategies [20].

Prevalence of Vitamin D Deficiency in Early Pregnancy

Vitamin D deficiency in early pregnancy is a widespread global health concern, with prevalence rates varying significantly by geographic location, season, ethnicity, and cultural practices. Estimates suggest that 20–90% of pregnant women have serum 25(OH)D concentrations below the generally accepted sufficiency threshold of 30 ng/mL (75 nmol/L), with the highest rates in Middle Eastern, South Asian, and African populations [21]. Even in high-income countries with food fortification programs, significant proportions of pregnant women remain deficient, especially during winter months and in those with limited sun exposure [22].

A large cross-sectional study in China involving over 10,000 pregnant women found that 76% had vitamin D insufficiency and 33% were severely deficient (<20 ng/mL) during the first trimester [23]. Similarly, research from the Middle East has documented deficiency rates exceeding 80% in early gestation, primarily due to clothing practices limiting UVB exposure, low dietary intake, and darker skin pigmentation reducing cutaneous synthesis [24]. In contrast, studies from Northern Europe demonstrate lower—but still substantial—rates of deficiency, indicating that latitude and seasonal variation alone cannot fully account for the global burden [25].

In many regions, dietary intake of vitamin D is inadequate to meet pregnancy requirements. Few natural food sources contain significant amounts, with oily fish, fortified dairy products, and supplements being the primary contributors. Surveys in the United States and Canada have found that pregnant women typically consume less than 200 IU/day from diet alone, well below the 600 IU/day recommended by the Institute of Medicine for pregnant women [26]. This gap is especially problematic in the first trimester when many women have not yet initiated prenatal vitamins, and nausea or dietary aversions may further reduce intake [27].

Socioeconomic status and lifestyle factors also influence vitamin D status in early pregnancy. Women with lower income, limited education, or restricted outdoor activity are more likely to present with deficiency [28]. Migrant populations from equatorial regions moving to higher latitudes may be at particular risk due to reduced UVB exposure, lack of dietary adaptation, and limited access to prenatal care [29]. These disparities highlight the importance of culturally tailored screening and supplementation strategies early in gestation.

Importantly, studies show that vitamin D deficiency detected in the first trimester tends to persist throughout pregnancy without targeted intervention. Unlike iron or folate supplementation, vitamin D

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screening is not universally incorporated into early antenatal visits in most countries. This missed opportunity for early correction may have implications for the prevention of metabolic disorders such as GDM, given that first-trimester status could influence later glucose tolerance [30].

Mechanisms Linking Vitamin D Deficiency to GDM

Vitamin D deficiency may influence glucose metabolism through effects on pancreatic β-cell function. The vitamin D receptor (VDR) is expressed in β-cells, and the active form 1,25-dihydroxyvitamin D regulates insulin gene transcription and modulates calcium flux, both critical for insulin secretion [31]. Experimental models show that vitamin D depletion impairs insulin synthesis and secretion, while repletion restores normal β-cell responsiveness [32]. These findings support a direct endocrine mechanism by which early pregnancy vitamin D deficiency could reduce β-cell reserve, increasing vulnerability to GDM in later trimesters.

Another proposed mechanism is the modulation of peripheral insulin sensitivity. Vitamin D enhances insulin receptor expression in target tissues and promotes translocation of glucose transporter type 4 (GLUT4) to the cell surface, facilitating glucose uptake [33]. Additionally, vitamin D may reduce lipotoxicity in adipose tissue, thereby improving insulin signaling pathways [34]. In pregnancy, when insulin resistance naturally increases, even a small impairment in these pathways may tip the balance toward hyperglycemia in women with pre-existing susceptibility.

Inflammation represents a third mechanistic link. Vitamin D has recognized immunomodulatory properties, suppressing pro-inflammatory cytokines such as TNF-α and interleukin-6 while enhancing anti-inflammatory mediators like interleukin-10 [35]. In GDM, elevated pro-inflammatory cytokines impair insulin receptor phosphorylation and disrupt downstream signaling cascades. Deficient vitamin D status could exacerbate this inflammatory milieu, contributing to both systemic insulin resistance and endothelial dysfunction [36].

The interplay between vitamin D and the renin-angiotensin system (RAS) also warrants attention. Vitamin D suppresses renin gene expression, and RAS overactivity has been associated with insulin resistance and β-cell apoptosis [37]. During pregnancy, excessive RAS activity can contribute to both metabolic and vascular complications. Vitamin D deficiency in early gestation may therefore indirectly elevate GDM risk by permitting unchecked RAS activation.

Finally, vitamin D's influence on placental function may mediate its relationship with GDM. Placental VDR activation regulates genes involved in nutrient transport, oxidative stress response, and angiogenesis [38]. Hypovitaminosis D in early pregnancy could impair placental glucose handling and vascular development, leading to altered maternal-fetal glucose exchange and increased fetal hyperinsulinemia. This concept is supported by studies linking low first-trimester vitamin D to higher cord blood insulin and C-peptide concentrations at birth [39].

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Pathophysiology of Gestational Diabetes Mellitus (GDM)

GDM develops when maternal pancreatic β-cells are unable to adequately compensate for the increased insulin resistance that occurs during pregnancy. Physiologically, insulin sensitivity declines progressively from early gestation, reaching its nadir in the third trimester [40]. This adaptation ensures a steady supply of glucose to the fetus but requires a compensatory increase in maternal insulin secretion. Failure of β-cell compensation leads to hyperglycemia, which is the hallmark of GDM [41]. Pregnancy-induced insulin resistance is largely mediated by placental hormones, including human placental lactogen (hPL), human placental growth hormone, progesterone, and cortisol [42]. These hormones antagonize insulin action, particularly in skeletal muscle and adipose tissue, resulting in reduced peripheral glucose uptake. This effect is compounded by increased maternal adiposity, which further impairs insulin signaling pathways. Chronic low-grade inflammation associated with pregnancy also contributes by inducing cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6, which disrupt insulin receptor signaling [43].

Genetic predisposition plays a substantial role in determining susceptibility to GDM. Variants in genes regulating β-cell function, insulin signaling, and glucose transport — such as TCF7L2, GCK, and IRS1 — have been linked to an increased risk [44]. Women with a family history of type 2 diabetes or previous GDM episodes exhibit impaired β-cell reserve even before pregnancy, making them more vulnerable to the metabolic stress of gestation. Additionally, environmental factors such as diet, sedentary lifestyle, and micronutrient deficiencies, including vitamin D deficiency, may act as modifiable contributors [45].

The hyperglycemic intrauterine environment has implications for both mother and child. In mothers, GDM increases the likelihood of preeclampsia, cesarean delivery, and progression to type 2 diabetes within 5–10 years postpartum [46]. For the fetus, chronic exposure to maternal hyperglycemia promotes excessive insulin production, leading to macrosomia, hypoglycemia after birth, and increased lifetime risk of obesity and metabolic syndrome [47]. These intergenerational effects highlight the importance of early detection and intervention.

Interestingly, recent studies suggest that metabolic disturbances leading to GDM may begin as early as the first trimester, long before glucose screening is typically performed at 24–28 weeks [48]. Subtle alterations in insulin sensitivity and β-cell function can be detected using fasting insulin, C-peptide, and homeostasis model assessment indices. This early onset of dysregulation provides a rationale for investigating early-pregnancy risk markers such as vitamin D status, which may influence the trajectory of maternal glucose metabolism throughout gestation [49].

Epidemiological Evidence & Observational Studies

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Several large-scale observational studies have examined the relationship between first-trimester vitamin D deficiency and subsequent GDM risk. A prospective cohort study in China involving over 3,000 pregnant women found that those with serum 25(OH)D levels below 20 ng/mL in the first trimester had a 1.8-fold increased risk of developing GDM, even after adjusting for BMI, maternal age, and season of blood sampling [50]. Similarly, a U.S. study of 1,200 ethnically diverse women reported that each 5 ng/mL decrease in early-pregnancy vitamin D was associated with a 12% increase in GDM risk [51]. These findings suggest that vitamin D status in early gestation may be an independent predictor of glucose intolerance later in pregnancy.

Meta-analyses further support this association. A 2019 systematic review pooling data from 26 studies involving more than 30,000 women concluded that vitamin D deficiency in early pregnancy was associated with a 45% higher odds of GDM [52]. The association remained significant after adjusting for traditional risk factors. Interestingly, the relationship appeared stronger in studies using stricter deficiency thresholds (<20 ng/mL) compared with those using insufficiency cut-offs (<30 ng/mL), suggesting a possible dose–response effect [53].

Not all observational studies have found consistent results, however. A cohort study in Sweden did not observe a significant association between first-trimester vitamin D levels and GDM after adjusting for maternal BMI and ethnicity [54]. Possible explanations include differences in population baseline vitamin D status, genetic variability in vitamin D metabolism, and methodological heterogeneity, such as timing of blood collection and assays used to measure 25(OH)D [55]. Such inconsistencies highlight the importance of standardized protocols for future research.

Ethnic disparities in the association between vitamin D status and GDM have also been observed. In a multi-ethnic Australian cohort, the association between low vitamin D and GDM was strongest among women of South Asian and Middle Eastern descent, populations already known to have high rates of both vitamin D deficiency and GDM [56]. This suggests that vitamin D may act synergistically with other genetic or environmental risk factors, amplifying overall susceptibility.

Seasonal variation adds another layer of complexity to interpreting observational data. Women whose first trimester occurred during winter months, when UVB exposure is minimal, tended to have lower vitamin D levels and higher GDM incidence [57]. While this pattern supports a potential causal link, it is also possible that seasonal differences in diet, physical activity, and infections could confound the observed association.

Finally, longitudinal studies tracking vitamin D status across pregnancy indicate that early gestational deficiency often persists into the second and third trimesters unless supplementation is initiated [58]. Given that metabolic changes predisposing to GDM may begin early in pregnancy, these findings

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reinforce the rationale for evaluating vitamin D status in the first trimester as a potential preventive strategy.

Interventional Trials on Vitamin D Supplementation and GDM Prevention

Randomized controlled trials (RCTs) have investigated whether vitamin D supplementation during pregnancy can reduce the incidence of GDM, with mixed results. One large RCT in Iran involving 700 pregnant women with first-trimester deficiency (<20 ng/mL) found that daily supplementation with 4,000 IU vitamin D from early pregnancy until delivery reduced GDM incidence by nearly 40% compared with placebo [59]. The protective effect remained significant after adjusting for BMI, maternal age, and baseline fasting glucose.

In contrast, a double-blind trial conducted in the United Kingdom, where baseline vitamin D deficiency was less severe, reported no significant difference in GDM rates between women receiving 1,000 IU/day from the first trimester and those given placebo [60]. Researchers hypothesized that the relatively low dose, higher baseline vitamin D levels, and smaller sample size may have limited the ability to detect a benefit. This highlights the potential importance of both dose and baseline status in determining the efficacy of supplementation.

Several trials have also examined combined supplementation approaches. In a Chinese study, pregnant women received either vitamin D alone, calcium alone, or a combination of both starting before 14 weeks of gestation. The combined group demonstrated the greatest improvement in insulin sensitivity and the lowest GDM incidence, suggesting synergistic effects between vitamin D and calcium on glucose metabolism [61]. This aligns with mechanistic evidence that both nutrients are involved in β-cell function and insulin secretion.

Timing of supplementation appears critical. Trials initiating vitamin D supplementation in the second trimester generally show smaller or nonsignificant effects on GDM prevention compared to those starting in early pregnancy [62]. Since early metabolic adaptations can influence later glucose tolerance, initiating supplementation before or during the first trimester may be necessary to achieve meaningful prevention.

Despite promising findings from some RCTs, meta-analyses indicate substantial heterogeneity in trial design, dosage, baseline deficiency rates, and diagnostic criteria for GDM [63]. These variations make it difficult to draw definitive conclusions about the preventive role of vitamin D. Current evidence suggests that supplementation is most likely to benefit women with severe deficiency, high baseline risk for GDM, and supplementation initiated early in pregnancy at sufficient doses.

Confounding Factors and Research Limitations

One of the major challenges in interpreting the association between vitamin D deficiency and GDM is the presence of multiple confounding variables. Body mass index (BMI) is a particularly strong

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confounder, as obesity is independently associated with both low vitamin D status and increased GDM risk [64]. Adipose tissue sequesters vitamin D, reducing its bioavailability, while also contributing to insulin resistance through lipotoxicity and inflammatory pathways. Failure to adequately adjust for BMI in analyses can lead to overestimation of vitamin D's role in GDM development.

Ethnicity is another important confounder. Darker skin pigmentation reduces cutaneous vitamin D synthesis, while certain ethnic groups also have higher baseline GDM risk due to genetic predisposition and lifestyle factors [65]. Many studies include ethnically diverse participants but do not stratify analyses by ethnicity, potentially obscuring subgroup-specific effects or leading to residual confounding. Similarly, cultural practices such as clothing styles and dietary habits influence both vitamin D status and metabolic health.

Seasonal variation in UVB exposure is a known determinant of serum 25(OH)D levels and can coincide with seasonal fluctuations in diet and physical activity [66]. Without adjusting for the season of blood sampling, observed associations between low vitamin D and GDM may partially reflect seasonal lifestyle changes rather than a direct causal effect. This issue is particularly relevant in high-latitude countries where differences between summer and winter vitamin D levels can be substantial.

Measurement variability adds further complexity. Different assays for 25(OH)D quantification, including immunoassays and liquid chromatography–tandem mass spectrometry, can produce divergent results, especially at lower concentrations [67]. Moreover, the lack of universally accepted cut-off values for vitamin D deficiency complicates comparisons across studies. Some classify deficiency as <20 ng/mL, others as <30 ng/mL, leading to inconsistent prevalence estimates and potentially different associations with GDM risk.

Finally, observational studies cannot prove causation. While temporality is often established—vitamin D is measured before GDM diagnosis—reverse causality is possible in studies measuring vitamin D later in pregnancy. Additionally, residual confounding from unmeasured variables such as dietary patterns, magnesium status, or genetic polymorphisms in vitamin D metabolism may still bias results [68]. Randomized controlled trials can address causality but face their own limitations, including small sample sizes, variability in supplementation protocols, and ethical challenges of withholding supplementation in severely deficient women.

Clinical Implications and Screening Strategies

The potential link between first-trimester vitamin D deficiency and GDM development carries important clinical implications for antenatal care. If confirmed by high-quality evidence, routine early-pregnancy screening for serum 25(OH)D could be integrated into existing first-trimester laboratory panels alongside hemoglobin, ferritin, and infectious disease screening [69]. This approach would

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allow identification of women at risk before significant metabolic derangements occur, enabling targeted supplementation and lifestyle counseling.

Vitamin D supplementation is relatively inexpensive, widely available, and generally safe at recommended doses, making it an attractive preventive strategy if efficacy in reducing GDM risk is validated [70]. Given that many prenatal vitamins already contain vitamin D, clinicians could individualize dosing based on baseline status. For severely deficient women, higher initial doses may be warranted, followed by maintenance supplementation throughout pregnancy. Such interventions could be especially valuable in high-risk groups, including those with obesity, darker skin pigmentation, limited sun exposure, or a history of GDM.

Incorporating vitamin D status into GDM risk prediction models may improve early detection of high-risk pregnancies. Current models often rely on nonmodifiable factors such as age, parity, and family history, as well as early-pregnancy BMI. Adding a modifiable biomarker like vitamin D could enhance predictive accuracy and provide a target for intervention [71]. However, before this can be implemented, standardized cut-offs for deficiency during pregnancy and consensus on optimal supplementation regimens are necessary.

From a public health perspective, fortification of staple foods with vitamin D has been shown to improve population vitamin D status, but whether such measures reduce GDM incidence remains unknown [72]. Population-based strategies may be more cost-effective in regions with high prevalence of both vitamin D deficiency and GDM. However, targeted screening in antenatal care may still be needed to ensure adequate status in individuals with unique risk factors or suboptimal response to fortification programs.

Conclusion

Evidence from observational studies, meta-analyses, and mechanistic research suggests a probable association between first-trimester vitamin D deficiency and an increased risk of developing gestational diabetes mellitus. The biological plausibility is supported by vitamin D's role in β-cell function, insulin sensitivity, inflammation modulation, and placental health. However, the strength of this association varies across populations and study designs, reflecting the influence of confounding factors such as BMI, ethnicity, seasonality, and assay variability.

Interventional trials indicate that supplementation—particularly when initiated in the first trimester and targeted to deficient women—may reduce gestational diabetes incidence, but results remain inconsistent. The heterogeneity in dosage, timing, and baseline status across studies complicates direct comparisons and limits the formation of universal clinical guidelines. At present, routine vitamin D screening in pregnancy is not universally recommended, but high-risk groups may benefit from early testing and tailored supplementation strategies.

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Given the public health implications of gestational diabetes and the safety profile of vitamin D supplementation, further high-quality, large-scale randomized trials are needed to clarify causality and define optimal intervention protocols. In the interim, incorporating vitamin D assessment into antenatal care for women at high risk of deficiency appears reasonable, with the dual aim of supporting maternal metabolic health and improving perinatal outcomes.

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