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# OPTIMIZING REPRODUCTIVE HEALTH: A STUDY ON MATERNAL VITAMIN D STATUS AND INTERVENTIONS IN RECURRENT MISCARRIAGES

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**Abstract**
This study explores the correlation between maternal vitamin D status and recurrent miscarriages, encapsulating a comprehensive examination within a case-control framework at Mubarak Hospital's Obstetrics and Gynecology clinic over one year. Amid growing evidence linking environmental and lifestyle factors to miscarriage risk, such as advanced maternal age and non-genetic influences, this research delves into the role of vitamin D, recognized for its immune-modulatory capabilities critical to maternal-fetal tolerance. Given the semi-allogenic nature of the human embryo, vitamin D's immunological function is of particular interest, with the study investigating the precursor hormone, 25(OH)D, as a marker for serum vitamin D concentration. Despite mixed findings on the association between 25(OH)D levels and pregnancy outcomes such as preeclampsia and fetal growth, recent analyses suggest significant risks associated with vitamin D deficiency. This research also highlights the placenta's crucial function in vitamin D metabolism, contributing to its impact on fetal development and the maternal immune response. Preliminary global data indicates a widespread prevalence of vitamin D deficiency among pregnant women, underscoring the public health imperative to address this issue. Through an in-depth analysis involving patient recruitment, blood sample evaluation before the 22nd week of gestation, and meticulous consideration of variables including pregestational BMI and maternal age, the study aims to contribute valuable insights into optimizing reproductive health through vitamin D status intervention.

**Keywords:** Case-control Study, Obstetrics and Gynecology, Pregnancy, Public Health, Recurrent Miscarriages, Vitamin D Deficiency

## Introduction

With a reported prevalence of 12–20%, miscarriage is the most typical unfavorable result of Pregnancy (Everett, 1997). The causes of miscarriages are complex and likely involve more environmental or acquired variables than genetic ones. Finding modifiable miscarriage risk factors may be crucial for public health (Lathi *et al*.,2011). According to a recent Danish study, there are several significant, avoidable risk factors for miscarriage, including advanced mother age, alcohol use, pre-pregnancy BMI, hard lifting, and night shift employment (Nigro *et al*., 2011).

The human embryo is a semi-allograft that depends on the mother's immunological tolerance to survive. Because vitamin D functions as an immune modulator and may be necessary for the maternal-fetal immunologic response, it may be linked to an increased risk of miscarriage (Nepomnaschy *et al*., 2007).

Measuring the quantity of the precursor hormone, 25(OH)D, is the most accurate method of determining the amount of vitamin D in serum. Regarding 25(OH)D concentrations during pregnancy and their associations with unfavorable pregnancy outcomes, there is conflicting data (Jensen et al., 2015). 50 nmol/L of 25(OH)D has been linked to an increased risk of preeclampsia, according to study; however, other studies have not discovered a significant correlation between preeclampsia risk and 25(OH)D concentrations (Feodor Nilsson et al., 2014). However, a recent meta-analysis of cohort studies found a pooled crude OR of 2.09 for preeclampsia if 25(OH)D concentrations during pregnancy were 50 nmol/L (Hewison, 2008).

The evidence regarding the risk of small-for-gestational-age infants is also conflicting. However, in a meta-analysis from the same study, the pooled crude odds were 1.52 for small-for-gestational-age infants if 25(OH)D concentrations throughout pregnancy were 50 nmol/L (Adams & Hewison, 2008). A significant extrarenal location for the conversion of active 1,25-dihydroxycholecalciferol from 25-hydroxyvitamin D3 is the human placenta. In the first and second trimesters, decidua and the placenta exhibit high levels of the converting enzyme and the vitamin D receptor; however, in the third trimester, their expressions decline (Lagishetty *et al*., 2011). Active 1,25(OH)D administration has been shown in animal experiments to enhance endometrial decidualization, and in human trophoblasts, 1,25(OH)D boosts the synthesis of estradiol, progesterone, and human choriogonadotropin (Hewison, 2012).

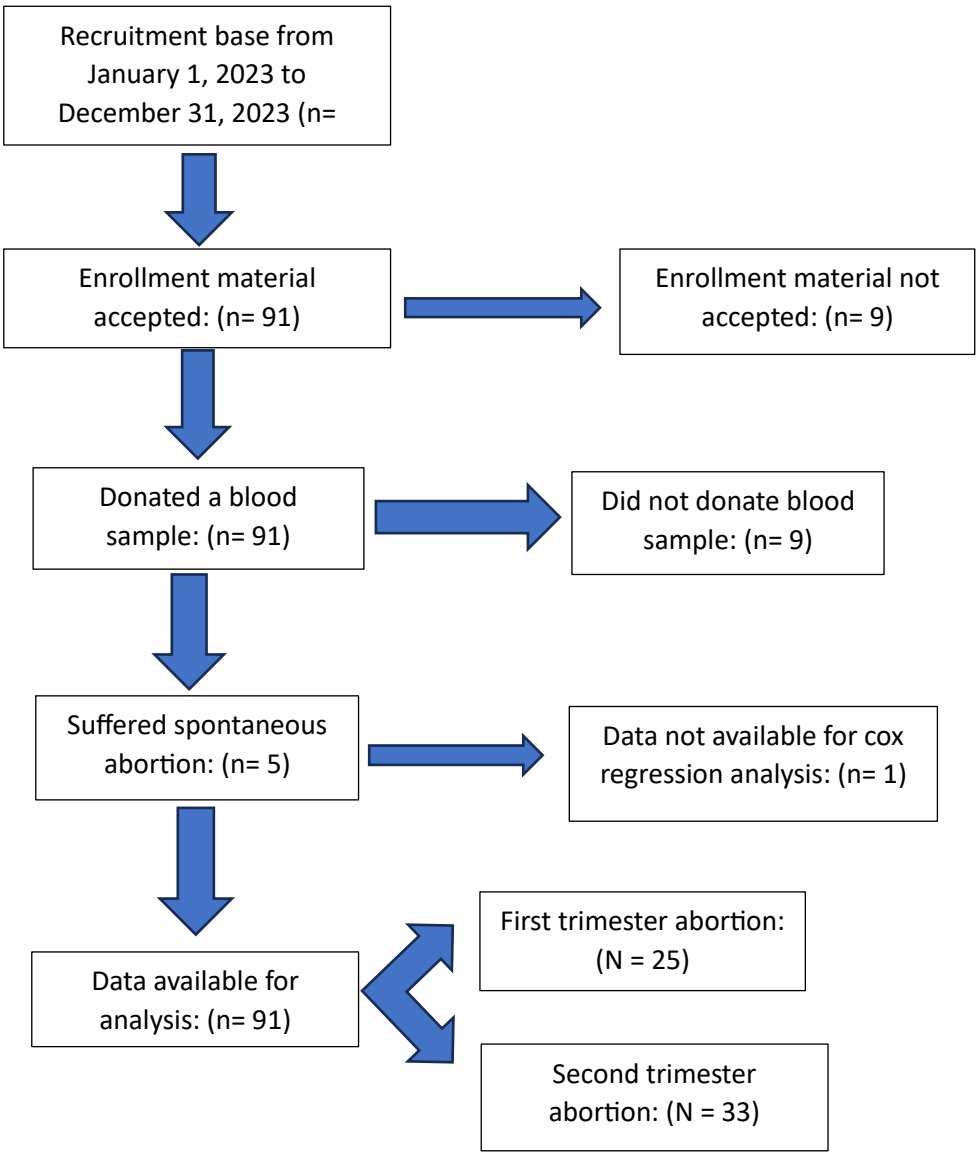
At the maternal-fetal interface, 1,25(OH)2-D3 is believed to have strong anti-inflammatory properties. It upregulates Th17-producing cells, encouraging the Th2 response and regulatory T-cell development. Early in Pregnancy, exposure to elevated levels of inflammatory cytokines increased the expression of the vitamin D receptor and CYP27B1, and in vitro cytokine production and profile were impacted by direct administration of 1,25(OH)2-D3 to stromal cells (Christesen *et al*., 2012). Moreover, 1,25(OH)2-D3 can control HOXA10, an enzyme required for fertility and embryo implantation. Therefore, it is conceivable that earlier in Pregnancy, higher vitamin D concentrations encourage healthy embryonic and fetoplacental development (Wei *et al*., 2013).

A study that analyzed data from multiple studies found that globally, 64% of American pregnant women had vitamin D concentrations below 20ng/ml, and 9% had concentrations below 10ng/ml. In Europe, the percentages were 57% and 23% respectively (Weisman *et al*., 1979). In the Eastern Mediterranean, the percentages were 79% and 46%. In Southeast Asia, the percentages were 87%, and the exact percentage for concentrations below 10ng/ml was unavailable. In the Western Pacific, the percentages were 83% and 13% (Zehnder *et al*., 2002).

**Materials and Methods**

All expectant patients at Mubarak Hospital's gynecological clinic were eligible to participate in the study between January 1, 2023, and December 31, 2023. Recruitment materials were given to one thousand women. Ninety-one patients out of the participants gave a blood sample before twenty-two weeks of gestation.

At the first prenatal appointment, self-reported information was used to gather data on the date of the last menstrual cycle, pregestational BMI, maternal age, and parity. To take seasonal differences in vitamin D levels into consideration, the blood sample season was divided into two categories: May to October and November to April.




Liquid chromatography-mass spectrometry was used to measure the levels of serum 25(OH)D, and concentrations for both 25(OH)-D2 and 25(OH)-D3 were established.

The means were used to report the variables. The Mann-Whitney test or the student's t-test were used for comparisons. The impact of 25(OH)D levels on the risk of miscarriage was examined using a Cox proportional hazards regression model that took age, BMI, parity, and the time of year the blood was drawn into account. Women who miscarried in the first trimester were matched 1:1 on gestational age at the blood sample with women who did not miscarry in order to do the subgroup analysis. Additional adjustments were performed for age, parity, BMI, and the season of blood collection. STATA 12.0 was used for data analysis, and $P < 0.05$ was used as the significance level for two-sided tests.

## Results

Out of the 1000 women who took part in the study, 58 experienced a miscarriage. 20 out of the 91 women whose 25(OH)D concentration was known prior to gestation 22 + 0 weeks experienced a miscarriage. There were 91 women in the final study population, of whom 58 had miscarriages, 25 in the first trimester and 33 in the second. Of these, one woman was diagnosed with miscarriage on the day of blood sampling and was excluded from the study.

**Table 1: Characteristics of Study Participants by Miscarriage Status**

| Characteristics | No Miscarriage (n=1000) | Miscarriage Overall (n=58) | P Value | First-Trimester Miscarriage (n=25) | P Value | Second-Trimester Miscarriage (n=33) | P Value |
|---|---|---|---|---|---|---|---|
| 25(OH)D, nmol/L | 68.0 (6.5–9) | 58.3 (45.60–72.80) | 0.003 | 53.75 (42.90–78.60) | 0.003 | 60.2 (53.50–78.60) | NS |
| Blood sampled in the summer season, n (%) | 35 (10.5) | 32 (55.2) | NS | 14 (48.8) | NS | 18 (54.5) | NS |
| GA blood sampling, d | 28 (8–16) | 72 (66–78.50) | <0.0001 | 67.5 (63–80) | <0.0001 | 77 (71–81.10) | 0.0001 |
| Maternal age, y | 31.45 ± 4.80 | 31.60 ± 6.00 | NS | 31.42 ± 6.30 | NS | 31.55 ± 5.85 | NS |
| Maternal prepregnancy BMI, kg/m² | 24.05 (3.00–3.00) | 24.30 (22.00–28.00) | NS | 24.50 (23.20–28.90) | NS | 24.15 (21.00–27.00) | NS |
| - Nullipara | 72 (7.2) | 32 (55.2) | NS | 15 (60) | NS | 17 (51.5) | NS |
| - Primipara | 50 (4.0) | 24 (41.4) | NS | 9 (36) | NS | 15 (45.4) | NS |
| - Secundipara | 60 (8.9) | 6 (10.3) | NS | 4 (16) | NS | 3 (9.1) | |
| - Tercipara or more | 15 (2.5) | 2 (3.4) | | 2 (8.0) | | | |

Statistical tests used: Student's t-test for parametric data, Mann-Whitney test for nonparametric data, and Fisher's exact test for 2x2 tables. P values represent comparisons with the no-miscarriage group. As appropriate, values are presented as median (IQR) or mean ± SD. Just two miscarried women gave blood in the second trimester, compared to the majority (n = 56; 96.6%) who gave blood in the first trimester. 29 (2.4%) of the 92 participants who did not donate blood before the full 22 weeks of Pregnancy experienced a miscarriage. Miscarriages occurred at a median gestational age of 87 days (IQR: 78–90 days) in the group that gave a blood sample and 88.5 days in the group of women who did not submit a blood sample.

The miscarriage group in the study population had lower maternal serum concentrations of 25(OH)D at the time of sampling (miscarriage median 55.55 nmol/L vs. non-miscarriage median 66 nmol/L; P = 0.002) and had blood samples taken earlier.

The miscarriage group did not differ from the background population in terms of maternal age, BMI, or parity. According to the miscarriage group, women who lost a pregnancy in the first trimester tended to have lower levels of 25(OH)D (P = 0.053) and earlier blood sampling than those who lost a pregnancy in the second trimester.

25(OH)D concentrations in blood samples for both miscarried and non-miscarried women tended to rise with gestational age. In the total adjusted analysis, higher amounts of 25(OH)D were linked to somewhat decreased HRs for miscarriage; however, this relationship did not achieve statistical significance.

Higher 25(OH)D concentrations significantly reduced the risk of first-trimester miscarriage in adjusted Cox regression analyses stratified by first- or second-trimester miscarriage. If concentrations were greater than 50 nmol/L, the miscarriage risk rose.

Additionally, a trend was observed indicating that concentrations of 75 nmol/L were linked to an increased chance of miscarriage. We calculated the post hoc power using the Cox proportional hazards regression/Wald test and the estimates from the proportional hazards model. With 25 cases, the sample size was large enough to have a power of 0.30 and an uncorrected HR of 2.1 for the exposure of interest for first-trimester miscarriage, which was 25(OH)D, 50 nmol/L.

A sample size 92 with 58 cases of first-trimester losses would be required to detect an accurate, unadjusted correlation with a prevalence of 1.5% and a power of 0.80. Our study was not deemed underpowered since we found an adjusted correlation with even fewer case numbers.

There was no proof that low 25(OH)D concentrations enhanced the incidence of miscarriage for second-trimester miscarriages (Table 2). In adjusted analyses, the incidence of miscarriage was unaffected by age, pre pregnancy BMI, parity, and seasonal fluctuation.

**Table 2: Crude and Adjusted Hazard Ratios (HRs) for Miscarriage by 25(OH)D Levels**

| Characteristics | Miscarriage Overall Crude HR (95% CI) | Miscarriage Overall Adjusted HR (95% CI) | First-Trimester Miscarriage Crude HR (95% CI) | First-Trimester Miscarriage Adjusted HR (95% CI) | Second-Trimester Miscarriage Crude HR (95% CI) | Second-Trimester Miscarriage Adjusted HR (95% CI) |
|---|---|---|---|---|---|---|
| 25(OH)D, nmol/L | 1.01 (0.99, 1.02) | 1.00 (0.98, 1.01) | 0.97 (0.95, 0.99) | 0.97 (0.95, 0.98) | 1.02 (0.99, 1.04) | 1.01 (0.99, 1.03) |
| 25(OH)D <50 vs. ≥50 nmol/L | 1.35 (0.80, 2.28) | 1.40 (0.82, 2.40) | 2.30 (1.05, 5.00) | 2.65 (1.15, 6.10) | 0.85 (0.40, 1.85) | 0.80 (0.35, 1.80) |
| 25(OH)D <75 vs. ≥75 nmol/L | 1.75 (0.85, 3.60) | 1.80 (0.88, 3.70) | 5.60 (0.80, 41.50) | 5.85 (0.80, 43.00) | 1.20 (0.55, 2.60) | 1.25 (0.55, 2.70) |

The statistical test used was the Cox proportional hazards regression model, adjusted for the season of blood sampling, parity, maternal BMI, and maternal age. $P < 0.05$.

In the current investigation, miscarried women submitted blood for 25(OH)D analysis at a later date than did women who were carrying healthy babies. Since the entry point for Cox regression analysis was gestational age at the blood sample, it was not possible to adjust for this variable by including it as a covariate. Nonetheless, we conducted an exact matching conditional logistic regression analysis based on gestational age at blood sample (Table 3).

**Table 3: Conditional Matched Case-Control Analysis for Miscarriage by 25(OH)D Levels**

| Characteristics | Miscarriage Overall (n=57 vs. n=57) Crude OR (95% CI) | Miscarriage Overall (n=57 vs. n=57) Adjusted OR (95% CI) | First-Trimester Miscarriage (n=25 vs. n=25) Crude OR (95% CI) | First-Trimester Miscarriage (n=25 vs. n=25) Adjusted OR (95% CI) | Second-Trimester Miscarriage (n=32 vs. n=32) Crude OR (95% CI) | Second-Trimester Miscarriage (n=32 vs. n=32) Adjusted OR (95% CI) |
|---|---|---|---|---|---|---|
| 25(OH)D, nmol/L | 1.01 (0.99, 1.03) | 1.01 (0.99, 1.02) | 0.99 (0.95, 1.03) | 0.98 (0.95, 1.03) | 1.02 (0.99, 1.04) | 1.02 (0.99, 1.04) |
| 25(OH)D <50 vs. ≥50 nmol/L | 1.35 (0.80, 2.28) | 1.40 (0.82, 2.40) | 3.00 (0.95, 10.00) | 4.00 (1.10, 15.00)* | 0.85 (0.40, 1.85) | 0.80 (0.35, 1.80) |

Statistical analysis was used: conditional matched logistic regression with exact matching of gestational age at blood sampling. Covariates in adjusted analysis: maternal age, maternal pre pregnancy BMI, parity, and season of blood sampling.

*$P < 0.05$.

In comparison to women with 25(OH)D concentrations of $50 nmol/L (n = 25), those with concentrations of 50 nmol/L had an OR of 3.86 (95% CI: 1.02, 14.63) for first-trimester miscarriage (n = 25). Additionally, we ran a standard logistic regression analysis on the entire group, accounting for gestational age at blood sampling.

In this investigation, the OR for first-trimester miscarriage (n = 26) was 2.43 (95% CI: 1.02, 14.63) among women with 25(OH)D concentrations of 50 nmol/L as opposed to those with 50 nmol/L.

**Discussion:**

The primary endpoint of this prospective cohort study was the correlation between 25(OH)D concentrations and the subsequent risk of miscarriage. We show that there was a higher chance of miscarriage in the first trimester but not in the second, according to low serum concentrations of 25(OH)D. The usual half-life of 25(OH)D is two weeks, and the risk of miscarriage or severe abnormalities is increased when specific chemicals or medications are exposed during the first trimester. We believed that women who experienced losses before 12 weeks of gestation would most likely have a 25(OH)D concentration similar to our cohort, which consisted primarily of first-trimester blood samples.

As far as we know, no randomized controlled experiment has been conducted to look into how much 25(OH)D is present and how often miscarriages occur. Nonetheless, miscarriage has been examined as a secondary result in a few recent observational studies.

Furthermore, women who lost their Pregnancy showed a nonsignificant trend toward lower 25(OH)D concentrations at 12 weeks of gestation compared to women who delivered a live baby [25(OH)D concentrations: 50.4 6 23.2 nmol/L vs. 57.9 6 24.5 nmol/L]. This was observed in a randomized controlled trial of 25(OH)D supplemental doses (Barrera *et al*., 2008).

Miscarriage and later fetal death up to 34 weeks of gestation were included in the pregnancy loss. A study conducted on an Australian cohort revealed that there was no statistically significant difference in mean 25(OH)D concentrations between 3714 women who experienced no adverse pregnancy outcome and 39 women who miscarried. The concentrations ranged from 53.5 nmol/L (95% CI: 42.4, 61.7) to 56.9 nmol/L (95% CI: 43.9, 70.8) (Boonstra *et al*., 2001).

Our research revealed a relationship between miscarriage in the first trimester and 25(OH)D but not in the second. Different processes and underlying etiologies in the two trimesters may be responsible for this outcome. Additionally, first- and second-trimester losses can be regarded as separate disease entities with differing clinical treatment options. However, the 25(OH)D concentration may potentially be linked to first-trimester miscarriages because it is a better indicator of serum concentrations at the time of miscarriage.

The potential preventive effect of 25(OH)D against miscarriage exists. It has been shown that vitamin D regulates both innate and adaptive immune responses. Numerous immune cells express the vitamin D receptor, part of a system regulating antigen receptor signalling and T-cell activation. The downregulation of Th1 cytokines by active 1,25(OH)2D has been demonstrated, and this has been suggested as an immunotherapy against spontaneous recurrent miscarriages (Vijayendra Chary *et al*., 2015).

Moreover, it has been shown that the placenta secretes proinflammatory cytokines such as TNF-a, IL-6, and interferon-g, which are inhibited by active vitamin The availability of the substrate, 25(OH)D, and the presence of the converting enzyme, CYP27B1, determine the concentration of 1,25(OH)2D. As a result, the cytokine profile and inflammatory response may be directly impacted by the quantity of vitamin D in the human placenta (Joshi *et al*., 2011). Recent research of 133 women who had experienced three or more recurrent miscarriages found that those with 25(OH)D, 30 ng/mL (75 nmol/L) were more likely to experience aberrant cellular immune responses and autoimmune diseases (Andersen *et al*., 2013).

Similarly, in vitro research using endometrial cells from women who experienced spontaneous recurrent miscarriages revealed that 1,25(OH)2-D3 stimulation altered the release of cytokines.

Furthermore, the success of in vitro fertilization and the frequency of bacterial vaginosis, which has been linked to early, late, and recurrent miscarriages, have been linked to vitamin D deficiency (Vigano *et al*., 2006).

As a result, there is strong evidence to suggest that vitamin D plays a role in miscarriage through its active involvement in the feto-maternal immune interface. Worldwide, Pregnancy is frequently associated with vitamin D insufficiency, defined as 25(OH)D levels of either 50 nmol/L or 75 nmol/L. This suggests that hypovitaminosis D may be a significant, avoidable risk factor for miscarriage in the first trimester (Tavakoli *et al.,* 2011).

The study's main advantages include its prospective design, in which the women were unaware of their vitamin D concentrations, the sizeable sample size, and the capacity to account for factors including parity, BMI, and sampling season. We were well-informed about the 25(OH)D concentrations, which are thought to indicate the value at the time of the miscarriage.

We were able to find a correlation between low 25(OH)D and miscarriage, even though our cohort had higher concentrations of 25(OH)D than other studies and our cohort sample included fewer women of non-European ethnic origin than our background population. This suggests that the magnitude of the effect in a less homogeneous population may be even higher than detected.

**Limitations of the study**

- The observational nature of the pregnancy cohort and the low rate of miscarriages—which resulted from the women being enrolled in the late first trimester after Pregnancy was discovered—are the study's limitations.
- Post hoc power analysis showed that our study could have been more underpowered for unadjusted analysis due to the low prevalence of vitamin D deficiency.
- For an optimally designed trial, more samples from pregnant women should have been obtained, and the possibility of an unexpectedly high mean of 25(OH)D should have been factored into the preemptive power calculation.
- Moreover, miscarriage was not detected prior to patient enrollment, and patients who experienced miscarriage gave blood earlier in their pregnancies.
- Additional restrictions included the fact that only 58.6% of participants had their blood samples drawn for early Pregnancy and that women in the cohort's background population did not participate at a rate of 57.1%.
- On the other hand, the frequency of losses was lower in the women who did not provide blood samples, indicating a lower risk of miscarriage.

**Conclusion**

In summary, this study robustly investigates the relationship between maternal vitamin D deficiency and recurrent miscarriages, shedding light on critical aspects of reproductive health and potential intervention strategies. The findings underscore the importance of optimal vitamin D levels for reducing miscarriage risk, highlighting vitamin D's multifaceted role in supporting maternal immune modulation, placental function, and fetal development. The research calls for heightened awareness among healthcare professionals regarding the link between vitamin D status and pregnancy outcomes, advocating for early screening and supplementation as preventive measures against recurrent miscarriages.

Future studies should aim to refine these findings further, exploring tailored vitamin D supplementation protocols that could effectively enhance maternal-fetal health outcomes. This work contributes significant insight into the complex dynamics of Pregnancy and marks a pivotal step towards optimizing reproductive health and well-being through nutritional intervention.

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