



## Original Research Article

# Vitamin D Deficiency; A Potential Risk Factor for Recurrent Miscarriages

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### Abstract:

**Objective:** To determine the association of vitamin D deficiency with recurrent miscarriages in pregnant females. **Study Design:** Case control study. **Place and Duration of Study:** Conducted from 1st June 2025 to 1st September 2025 in Department of Gynecology and Obstetrics LRH Peshawar. **Methodology:** A total of 184 pregnant females aged 20–40 years were included. Ninety-two females with history of two or more pregnancy losses before 24 weeks of gestation were taken as cases, while ninety-two healthy pregnant females without such history were taken as controls. Vitamin D deficiency was considered when serum vitamin D level was less than 20 nanograms per milliliter. Association between vitamin D deficiency and recurrent miscarriage was assessed using Chi square test. **Results:** In this study mean age of participants was  $30.93 \pm 5.80$  years in cases and  $30.59 \pm 6.22$  years in controls. Mean serum vitamin D level was lower in cases ( $18.38 \pm 7.51$  nanograms per milliliter) compared with controls ( $22.06 \pm 8.42$  nanograms per milliliter). Vitamin-D deficiency was observed in 61 (66.3%) cases and 48 (52.2%) controls, showing borderline statistical significance ( $p = 0.051$ ). **Conclusion:** Vitamin-D deficiency was more common in females with recurrent miscarriages and may act as a possible contributing factor in pregnancy loss.

**Keywords:** Body mass index, Pregnancy trimester first, Spontaneous abortion, Vitamin D, Women.

## INTRODUCTION

Recurrent miscarriage is a critical issue faced in the branch of obstetrics and gynecology, causing significant emotional and physical problems for the affected couples.<sup>1</sup> It has been defined as the loss of a pregnancy on two or more occasions before the viability of the fetus, usually before 24 weeks of gestation.<sup>2</sup>

Most miscarriages take place during the first trimester, and the cause of miscarriage remains unknown for many couples.<sup>3</sup> Women experiencing recurrent miscarriage seek medical attention at tertiary centers for comprehensive investigation and management. This condition not only affects the physical health of the woman, but also has a significant effect on the mental and emotional well-being of the couples.<sup>4</sup> Considering that the early stages of pregnancy are critical, any slight change in the environment may cause the failure of the continuation of pregnancy.

There are a multitude of causes for recurrent miscarriages, which include genetic, anatomical, hormonal, immunological, and environmental factors.<sup>5</sup> Chromosomal abnormalities in the embryo are a common cause of miscarriages during early pregnancy. Anatomical abnormalities of the uterus, which include a septate uterus, fibroids, and intrauterine adhesions, also contribute to miscarriages.<sup>6</sup> Endocrine abnormalities such as thyroid disease, diabetes mellitus, luteal phase deficiency, and polycystic ovary syndrome also contribute to miscarriages.<sup>7</sup>

Vitamin D insufficiency is increasingly considered a possible cause of recurrent miscarriages. Vitamin D is a fat-soluble vitamin with a hormone-like action on the body. It is active only in its 1,25-dihydroxyvitamin D form, also abbreviated as 1,25(OH)<sub>2</sub>D.<sup>8</sup> The presence of vitamin D receptors in the endometrium and placenta indicates its possible role in implantation and placental

development.<sup>9</sup> Vitamin D insufficiency may also impair immune modulation at the maternal-fetal interface and the endometrial receptive window. It also regulates the expression of genes involved in implantation and placental invasion. Clinically, vitamin D insufficiency has been documented in women with a history of recurrent miscarriages compared with normal pregnant women.<sup>10</sup> Thus, vitamin D insufficiency may increase the risk of pregnancy loss through immune modulation, placental function, and vascular development. Recurrent miscarriages are commonly reported in tertiary care hospitals of Peshawar, but limited local data is available regarding the role of Vitamin-D deficiency in such patients. Most of the available evidence is from international studies, and regional variations in nutritional status, sun exposure, dietary habits and socioeconomic conditions may influence vitamin D levels in local population. Without local data, it is difficult to assess the true burden and strength of association in this region.

## METHODOLOGY

This study was conducted in the Department of Gynecology and Obstetrics LRH Peshawar from 1st June 2025 to 1st September 2025. Approval was obtained from the Research Review Board of the hospital before starting the study and the study was carried out according to institutional ethical standards. Sample size was calculated by using OpenEpi software with anticipated proportion of Vitamin-D deficiency in cases as 71.7% and in controls as 51.3%,<sup>11</sup> keeping power of test 80% and confidence level 95%. The calculated sample size was 92 in each group, so total sample size was 184. Pregnant females aged 20 to 40 years were included. Cases were pregnant females having history of recurrent miscarriages (Group A).

Recurrent miscarriages were considered when there was history of fetal expulsion before 24 weeks' gestation on 2 or more occasions. Controls were healthy pregnant females without such history (Group B). Patients were excluded if they had anatomical, genetic, endocrine, infectious, immunological causes of pregnancy loss or any oncological diseases. Those taking native vitamin D medications or supplements in last 3 months, pregnancy achieved by assisted reproductive technologies, induced abortions, smoking, drug abuse, and history of use of teratogenic medications like methotrexate, retinoids, misoprostol and NSAIDs were also excluded.

Informed consent was obtained from all the participants before the study began. Demographic data were collected. The study had 92 cases and 92 controls, with matching done for age between the case and control groups.

The study subjects underwent an obstetric history, which included the history of previous miscarriages and the gestational age at which the miscarriage occurred. The study subjects underwent a general physical examination. For the estimation of the serum vitamin D level, 5ml of venous blood samples were collected from the superficial vein in the antecubital fossa of the non-

dominant arm under aseptic precautions. The blood samples were transported to the laboratory within 30 minutes to estimate the serum vitamin D level. The study subjects were followed up until the report was obtained, and the vitamin D level was documented. Vitamin-D deficiency was defined as a serum vitamin D level below 20ng/ml.

Data was analyzed using IBM SPSS version 25. Quantitative variables including age, height, weight, BMI and serum vitamin D level were expressed as mean  $\pm$  SD. Qualitative variables including residence, profession, marriage type and Vitamin-D deficiency were presented as frequencies and percentages. Comparison between cases and controls for Vitamin-D deficiency was done by chi-square test. Data was further stratified by age, BMI and residence. Chi-square test was used with a p value  $\leq 0.05$  taken significant.

## RESULTS

In the present study the mean age of participants in Group A (cases) was  $30.93 \pm 5.80$  years, whereas in Group B (controls) it was  $30.59 \pm 6.22$  years. The mean weight was recorded as  $69.15 \pm 7.96$  kg in Group A and  $68.51 \pm 7.18$  kg in Group B, while mean height was  $159.13 \pm 5.51$  cm and  $158.30 \pm 4.85$  cm in Group A and Group B respectively. The mean BMI was nearly similar between both groups, being  $27.28 \pm 2.53$  kg/m<sup>2</sup> in cases and  $27.32 \pm 2.46$  kg/m<sup>2</sup> in controls.

The mean serum Vitamin D level was observed to be  $18.38 \pm 7.51$  ng/ml in Group A and comparatively higher at  $22.06 \pm 8.42$  ng/ml in Group B. Regarding residence, majority of participants in both groups was belonging to rural areas, with 60 (65.2%) cases and 59 (64.1%) controls living in rural settings, while 32 (34.8%) and 33 (35.9%) were from urban areas in Group A and Group B respectively.

In terms of profession, most participants in both groups were housewives, constituting 79 (85.9%) in Group A and 74 (80.4%) in Group B, while employed females were 13 (14.1%) and 18 (19.6%) respectively. Concerning marriage type, consanguineous marriages was more prevalent in Group A with 63 (68.5%) cases as compared to 47 (51.1%) in Group B, whereas non-consanguineous marriages were reported in 29 (31.5%) and 45 (48.9%) in Group A and Group B respectively (Table 1).

**Table 1. Patient Demographics in Both Groups**

| Variables                | Group A<br>(Cases) n=92 | Group B<br>(Controls)<br>n=92 |
|--------------------------|-------------------------|-------------------------------|
|                          | Mean $\pm$ SD           | Mean $\pm$ SD                 |
| Age (years)              | $30.93 \pm 5.80$        | $30.59 \pm 6.22$              |
| Weight (kg)              | $69.15 \pm 7.96$        | $68.51 \pm 7.18$              |
| Height (cm)              | $159.13 \pm 5.51$       | $158.30 \pm 4.85$             |
| BMI (kg/m <sup>2</sup> ) | $27.28 \pm 2.53$        | $27.32 \pm 2.46$              |

|                                |              |              |
|--------------------------------|--------------|--------------|
| <b>Serum Vitamin D (ng/ml)</b> | 18.38 ± 7.51 | 22.06 ± 8.42 |
| <b>Residence</b>               | n (%)        | n (%)        |
| <b>Rural</b>                   | 60 (65.2%)   | 59 (64.1%)   |
| <b>Urban</b>                   | 32 (34.8%)   | 33 (35.9%)   |
| <b>Profession</b>              |              |              |
| <b>Housewife</b>               | 79 (85.9%)   | 74 (80.4%)   |
| <b>Employed</b>                | 13 (14.1%)   | 18 (19.6%)   |
| <b>Marriage Type</b>           |              |              |
| <b>Consanguineous</b>          | 63 (68.5%)   | 47 (51.1%)   |
| <b>Non-Consanguineous</b>      | 29 (31.5%)   | 45 (48.9%)   |

Vitamin-D deficiency was present in 61 (66.3%) of cases in Group A and 48 (52.2%) in Group B controls, with no Vitamin-D deficiency found in 31 (33.7%) and 44 (47.8%) respectively (p = 0.051) (Table 2).

**Table 2. Comparison of Vitamin-D Deficiency Between the Two Groups n=184**

| <b>Vitamin-D deficiency</b> | <b>Group A (Cases) n=92 n (%)</b> | <b>Group B (Controls) n=92 n (%)</b> | <b>P value</b> |
|-----------------------------|-----------------------------------|--------------------------------------|----------------|
| <b>Yes</b>                  | 61 (66.3%)                        | 48 (52.2%)                           | 0.051*         |
| <b>No</b>                   | 31 (33.7%)                        | 44 (47.8%)                           |                |
| <b>Total</b>                | 92 (100%)                         | 92 (100%)                            |                |

\*Chi-Square Test

In stratified analysis according to age, among participants aged ≤30 years, Vitamin-D deficiency was found in 27 (62.8%) of Group A and 24 (54.5%) of Group B, with p = 0.435 which was not significant. In the age subgroup of >30 years, Vitamin-D deficiency was present in 34 (69.4%) of Group A and 24 (50.0%) of Group B, with p = 0.052 which was also not reaching significance. When BMI was considered, in participants with BMI ≤25 kg/m<sup>2</sup>, Vitamin-D deficiency was seen in 10 (47.6%) of Group A and 9 (47.4%) of Group B (p = 0.987), showing no difference between groups. However, among participants with BMI >25 kg/m<sup>2</sup>, Vitamin-D deficiency was more prevalent in Group A with 51 (71.8%) as compared to 39 (53.4%) in Group B, and this difference was statistically significant (p = 0.023). Regarding residence, in rural participants Vitamin-D deficiency was present in 37 (61.7%) of Group A and 29 (49.2%) of Group B (p = 0.170), and in urban participants it was found in 24 (75.0%) and 19 (57.6%) in Group A and Group B respectively (p = 0.138), both comparisons were not significant (Table 3).

**Table 3. Association of Demographic Variables with**

#### Vitamin-D deficiency

| <b>Demographic Variables</b>  | <b>Sub groups</b> | <b>Group A</b> | <b>Vitamin-D deficiency Yes n (%)</b> | <b>Vitamin-D deficiency No n (%)</b> | <b>P-value*</b> |
|-------------------------------|-------------------|----------------|---------------------------------------|--------------------------------------|-----------------|
| <b>Age (years)</b>            | ≤30               | A              | 27 (62.8%)                            | 16 (37.2%)                           | 0.435           |
|                               |                   | B              | 24 (54.5%)                            | 20 (45.5%)                           |                 |
|                               | >30               | A              | 34 (69.4%)                            | 15 (30.6%)                           | 0.052           |
|                               |                   | B              | 24 (50.0%)                            | 24 (50.0%)                           |                 |
| <b>BMI (kg/m<sup>2</sup>)</b> | ≤25               | A              | 10 (47.6%)                            | 11 (52.4%)                           | 0.987           |
|                               |                   | B              | 9 (47.4%)                             | 10 (52.6%)                           |                 |
|                               | >25               | A              | 51 (71.8%)                            | 20 (28.2%)                           | 0.023           |
|                               |                   | B              | 39 (53.4%)                            | 34 (46.6%)                           |                 |
| <b>Residence</b>              | Rural             | A              | 37 (61.7%)                            | 23 (38.3%)                           | 0.170           |
|                               |                   | B              | 29 (49.2%)                            | 30 (50.8%)                           |                 |
|                               | Urban             | A              | 24 (75.0%)                            | 8 (25.0%)                            | 0.138           |
|                               |                   | B              | 19 (57.6%)                            | 14 (42.4%)                           |                 |

\*Chi-Square Test

#### DISCUSSION

Vitamin-D deficiency was noted in 61 of 92 cases (66.3%) compared with 48 of 92 controls (52.2%), (p = 0.051). However, this almost reaches significance, especially in relation to Vitamin D's role in immune modulation and implantation. Vitamin-D deficiency can lead to defective trophoblast invasion and abnormal immune tolerance at the fetomaternal interface, which are known causes of miscarriages. However, the mean Vitamin D levels were found to be lower in cases than in controls. While the mean Vitamin D levels in cases were 18.38 ± 7.51 ng/mL, those in controls were 22.06 ± 8.42 ng/mL. This indicates that Vitamin D levels are likely to be low in cases of recurrent miscarriages, especially in relation to Vitamin D receptors on uterine NK cells and Treg cells, where Vitamin-D deficiency can lead to abnormal immune tolerance, which is essential for pregnancy.

The present study findings regarding Vitamin-D deficiency in women with recurrent miscarriages was showing considerable agreement with several previously published studies. Vitamin-D deficiency was found in 61 (66.3%) of cases with recurrent miscarriages as compared to 48 (52.2%) in healthy pregnant controls, with a near-significant p value of 0.051. These findings were supported by Radzinsky et al. 11 who also reported significantly higher Vitamin D insufficiency in women with miscarriage (93.3%) versus controls (76.9%),

$p=0.0183$ ), and by Kasim et al.<sup>12</sup> reported that Vitamin D deficiency was present in 95% of females who experienced spontaneous abortion, whereas it was detected in only 17.5% of pregnant women who had no prior history of miscarriage. The near-significant trend observed in present study rather than a fully significant result may be explained by the relatively smaller sample size and the fact that Vitamin-D deficiency was already quite prevalent in both groups, which reduced the statistical power to detect between-group differences. Bezirganoglu Altuntas et al.<sup>13</sup> similarly reported a non-significant difference in mean Vitamin D levels between miscarriage and control groups ( $13.3 \pm 5.7$  vs  $15.5 \pm 6.4$  ng/ml,  $p=0.056$ ), which is closely resembling the borderline significance observed in present study, although they did found severe Vitamin-D deficiency to be a significant independent risk factor.

The mean serum Vitamin D in cases was  $18.38 \pm 7.51$  ng/ml compared to  $22.06 \pm 8.42$  ng/ml in controls, indicating lower Vitamin D status in women with recurrent miscarriages. This pattern was similarly observed by Khudhair et al.<sup>14</sup> who reported mean Vitamin D of  $19.6 \pm 2.86$  ng/ml in RPL group versus  $23.46 \pm 2.93$  ng/ml in non-aborted pregnant group, and by Kurtdereli et al.<sup>15</sup> who demonstrated significantly lower  $25(\text{OH})\text{D}$  levels in miscarriage group ( $8.61 \pm 2.42$  mcg/L) compared to controls ( $16.61 \pm 6.12$  mcg/L,  $p=0.001$ ). The biological explanation for this association is that Vitamin D receptors are expressed on uterine natural killer cells and regulatory T cells, and deficiency in Vitamin D impairs the immunological tolerance at feto-maternal interface, which is necessary for successful implantation and continuation of pregnancy. Du et al.<sup>16</sup> further supported this by demonstrating that Vitamin-D deficiency rates was 76.50% in recurrent spontaneous abortion group compared to 29.51% in women without abortion history, and they also showed that Vitamin D supplementation improved pregnancy outcomes with live birth rate reaching 72.68%, which is providing strong scientific evidence for the causal role of Vitamin D in pregnancy maintenance.

Regarding BMI, Vitamin-D deficiency was significantly more prevalent in cases with BMI  $>25$  kg/m<sup>2</sup>, with 51 (71.8%) cases versus 39 (53.4%) controls ( $p=0.023$ ). This finding was in agreement with Al Luaibi et al.<sup>17</sup> who reported that women with Vitamin-D deficiency had significantly higher BMI ( $26.91 \pm 0.40$ ) compared to those with normal Vitamin D levels ( $24.71 \pm 0.74$ ,  $p=0.0066$ ). The scientific reason for this association is that Vitamin D being a fat-soluble vitamin get sequestered in adipose tissue of overweight individuals, thus reducing its bioavailability in the circulation and leading to functional deficiency even when dietary intake may be adequate.

The limitations of the present study need to be considered for a better understanding of its findings. First, it is a single-center study, meaning it includes only one hospital. This might reduce its generalizability to other populations. Second, it had a limited number of participants, with 92 cases and 92 controls. Although it

is a decent number for a preliminary study, it might reduce its power for finding significant differences, as shown by its  $p$  value of 0.051 for Vitamin-D deficiency. Third, it is possible that measuring Vitamin D levels at one point might have influenced its findings, especially because of its seasonal variation.

## CONCLUSION

The present study has shown that Vitamin-D deficiency is more common in women with recurrent miscarriages than in healthy pregnant women, and therefore this deficiency may be a potential risk factor in recurrent miscarriages. It was observed that body mass index (BMI) was an important factor that may increase the risk of Vitamin-D deficiency in women with recurrent miscarriages, as the incidence of deficiency was significantly higher in overweight women.

### Disclaimer:

Nothing to declare.

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### Conflict of Interest:

The author declare that they have no competing interest related to this research study.

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