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Vitamin D in regulating immune response in patients with recurrent pregnancy loss: a case-control study

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ABSTRACT

BACKGROUND Recurrent pregnancy loss (RPL) is linked to lower vitamin D levels and altered immune responses, though unclear mechanisms. This study aimed to identify the effect of vitamin D on the balance between interleukin (IL)-10/IL-17A in women with RPL.

METHODS This case-control study was conducted at the Bint Al-Huda Teaching Hospital, Thi-Qar Governorate, Iraq, from August 2022 to March 2023. Three study groups were included: RPL (47 women), non-aborted pregnant (40 women), and control (38 women). The sera concentrations of IL-17A, vitamin D, and IL-10 had been quantitatively detected using ELISA. SPSS was used for statistical analysis.

RESULTS Women with RPL had significantly lower vitamin D levels (19.6 ng/ml) and higher IL-17A levels (35.66 ng/l) than the non-aborted pregnant (23.46 ng/ml, 24.04 ng/l) and control groups (25.69 ng/ml, 19.87 ng/l). IL-10 levels were substantially depleted in the RPL group (3.96 pg/ml), leading to a statistically lower IL-10/IL-17A ratio (0.19) than in the non-aborted pregnant (0.58) and control (1.60) groups. Regression analysis revealed a valuable positive association between vitamin D and IL-17A in all groups and between vitamin D and IL-10/IL-17A ratio in RPL and control groups. Vitamin D was also significantly associated with IL-10 in the non-aborted pregnant group. However, no statistical relationship was reported between vitamin D and IL-10 levels in the RPL and control groups.

CONCLUSIONS Increased IL-17A and decreased IL-10 contributed to unexplained RPL. The IL-10/IL-17A ratio predicted endometrial function, and vitamin D affects these cytokines, potentially reducing inflammation.

KEYWORDS abortion, interleukin-10, interleukin-17A, recurrent pregnancy loss, vitamin D

Spontaneous recurrent pregnancy loss (RPL) is defined as the spontaneous loss of three or more pregnancies before 20 weeks of gestation.[1] The cause of RPL is complex and multifactorial. Known causes include chromosomal abnormalities, hormonal factors, autoimmune conditions, anatomical issues, and viral agents; however, approximately 50% of the cases remain unexplained. Among these unexplained cases, maternal immunity may be crucial for fetal rejection. A delicate balance between the activity of the maternal immune system and the embryo's immune-mediated control is essential for an effective pregnancy.[2] During gestation, the mother's immune response should tolerate the growing fetus; however, disrupted tolerance may lead to RPL or spontaneous abortion. This theory suggests that immune system dysregulation significantly contributes to the pathophysiology of unexplained RPL.

Regulatory T cells (Treg) inhibit self-reactive lymphocytes, which support the concept of immune

tolerance necessary for a successful pregnancy. Treg decreases the immune defense through cell-to-cell contact or by secreting inhibitory interleukins (ILs), such as IL-10, and transforming growth factor-beta (TGF-β). These cells are crucial for establishing and maintaining tolerance by regulating T helper (Th) 17 (Th17) cells, which are associated with inflammatory processes during the advanced stage of miscarriage.[3] An imbalance between Treg and Th17 cells, due to either increased Th17 cells or decreased Treg levels, can lead to pregnancy-related disorders, including RPL. These findings highlight the importance of regulating the Treg/Th17 balance as a potential therapeutic target for RPL therapy.[2] Pro-inflammatory cytokines produced by Th17 cells associated with allograft rejection may compromise pregnancy, whereas anti-inflammatory cytokines secreted by Treg can promote fetal allograft tolerance and improve pregnancy outcomes.[4] Controlling the immune response against fetal antigens through cytokine balance may enhance fetal survival. Therefore, the equilibrium between pro-inflammatory and anti-inflammatory ILs may explain the pathogenic mechanisms underlying RPL.

Vitamin D, a key immune regulator involved in maintaining the Treg/Th17 balance, has garnered significant research interest. Insufficient or deficiency of vitamin D correlates with the severity and prevalence of disorders. The immune inhibitory properties of vitamin D enable it to modulate immune response and tolerance.[5] It influences various cytokines, including those from Th1 cells, dendritic cells, Th2 cells, B cells, monocyte cells, Treg, and macrophage cells, either by inhibition or upregulation.[6] Moreover, vitamin D can activate Treg cells and inhibit Th17 cells.[7] Certain studies have found that vitamin D is involved in the pathogenicity of RPL,[2,7] with an increased incidence of RPL being linked to vitamin D deficiency, enhancing cellular autoimmunity. This is evidenced by an increased Th1/Th2 ratio, a higher percentage of $CD56^+$ natural killer cells and $CD19^+$ B cells, and the incidence of many peripheral blood (PB) autoantibodies. Additionally, vitamin D supplementation has been shown to reduce cellular immunity dysregulation.[8] Determining the optimal doses of vitamin D supplementation and monitoring maternal vitamin D levels during pregnancy is increasing interest among researchers. However, the specific role and fate of vitamin D in regulating the Treg/Th17 ratio in women with RPL is limited. Since vitamin D supplementation is crucial for a successful pregnancy due to its role in maintaining appropriate immune function,[9] this study aimed to elucidate the modulatory functions of vitamin D on the IL-10/IL-17A balance in women with RPL, highlighting its potential as a therapeutic target.

METHODS

This case-control study was conducted at Bint Al-Huda Teaching Hospital, Thi-Qar Governorate, Iraq, between August 2022 and March 2023. Participants were recruited from the same hospital and categorized into three groups: the RPL group comprised 47 women aged 18–37 years with unexplained consecutive pregnancy loss; the non-aborted pregnant group included 40 normal pregnant women aged 19–38 years; and the control group included 38 healthy, fertile, and non-pregnant women aged 18–36 years.

RPL was assessed, treated, and evaluated according to the American Society for Reproductive Medicine Practice Committee guidelines. All women in the RPL group had experienced two or more consecutive pregnancy losses and had no chronic or autoimmune diseases associated with RPL, no anatomical anomalies, no recent surgery or blood transfusions, non-smokers, non-obese, not under corticosteroid or biological therapy, and had standard body mass index (BMI) (18.5 to 24.9 kg/m^2).[10] Women in the non-aborted pregnant group had at least one successful pregnancy with normal labor, had no history of any common diseases related to RPL, no miscarriage history, no autoimmune, chronic, or infectious diseases, no recent surgery and blood transfusions, and not under biological or immune-inhibitor drugs. The non-aborted pregnant women also had a normal BMI. The control group was selected using the same criteria as the non-aborted pregnancy group. None of the participants in this group were pregnant during sample collection. Approximately 5 ml of PB was collected during the luteal phase of all participant's menstrual cycles. The samples were centrifuged at 700 × *g* at 4°C for 10 min. The sera was then aspirated and frozen at −80°C in 0.5 ml aliquots until biomarker analysis.

Ethical approvals were obtained following the Declaration of Helsinki. All participants data were collected with ensured anonymity and verification that they lived in the Thi-Qar Governorate and attended Bint Al-Huda Teaching Hospital. This research was

revised and approved by the Medical Research Ethics Committee of Southern Technical University, Al-Nasiriyah Technical Institute, Iraq (No. 4912, 3 December 2024).

Vitamin D examination

Serum vitamin D levels were measured and titrated using enzyme-linked immunosorbent assay (ELISA) with a 25-OH vitamin D total ELISA kit (Demeditec Diagnostics GmbH, Germany). The assay was performed in duplicate of each sample and standard for all participants. Vitamin D levels were classified as low (<20 ng/ml), normal (20–30 ng/ml), and high (>30 ng/ml).

ILs levels examination

Serum levels of IL-17A and IL-10 were measured and titrated using human IL-17A (Shanghai YL Biont, China) and IL-10 (Demeditec Diagnostics GmbH) ELISA kits, respectively. Assays were duplicated for each sample and standard based on the manufacturer's instructions. IL-17A and IL-10 levels were classified as low (<20 ng/l and <5 pg/ml), moderate (20–30 ng/l and 5–10 pg/ml), and high (>30 ng/l and 10 pg/ml) based on control subjects. The IL-10/IL-17A ratio was determined for each participant by dividing IL-10 by IL-17A concentration. The ratio was categorized as follows: low (<0.5), moderate (0.5–1), and high (>1).

The normal values of vitamin D, IL-17A, IL-10, and the IL-10/IL-17A ratio are determined based on a control group of healthy individuals matched for age, gender, and other relevant factors. Reference ranges are typically expressed as mean (standard deviation). However, these reference ranges may vary across different populations due to genetic, environmental, and physiological factors.

Statistical analysis

Statistical analysis was performed using the SPSS software version 22 (IBM Corp., USA), with the findings presented as frequencies, means, and standard deviations. Differences in categorical variables were analyzed using the chi-square test, with Yates correction and Fisher's exact test applied whenever

Table 1. Vitamin D, IL-17A, and IL-10 levels in RPL, non-aborted pregnant, and control groups

Variables	Study groups						
	RPL (n = 47)	$p^{\dagger}$	Non-aborted pregnant (n = 40)	$p^{\ddagger}$	Control (n = 38)	$p^{\S}$	Total (n = 125)
Vitamin D level (ng/ml), mean (SD)*	19.6 (2.86)	<0.001	23.46 (2.93)	0.07	25.69 (3.85)	<0.001	22.71 (3.21)
Low, n (%)	26 (55)		2 (5)		0 (0)		28 (22)
Normal, n (%)	21 (45)	<0.001¶	36 (90)	0.2**	29 (76)	<0.001††	86 (69)
High, n (%)	0 (0)		2 (5)		9 (24)		11 (9)
IL-17A level (ng/l), mean (SD)*	35.66 (23.14)	0.002	24.04 (6.40)	0.06	19.87 (5.5)	<0.001	27.14 (16.89)
Low, n (%)	15 (32)		4 (10)		20 (53)		39 (31)
Moderate, n (%)	13 (28)	0.02¶	34 (85)	0.3**	13 (34)	0.04††	60 (48)
High, n (%)	19 (40)		2 (5)		5 (13)		26 (21)
IL-10 level (pg/ml), mean (SD)*	3.96 (2.86)	<0.001	13.87 (4.59)	0.09	18.20 (5.26)	<0.001	11.46 (8.99)
Low, n (%)	40 (85)		0 (0)		0 (0)		40 (32)
Moderate, n (%)	1 (2)	<0.001¶	0 (0)	0.11**	0 (0)	<0.001††	1 (1)
High, n (%)	6 (13)		40 (100)		38 (100)		84 (67)
IL-10/IL-17A ratio,* mean (SD)	0.19 (0.12)	<0.001	0.58 (0.23)	0.023	1.60 (2.77)	<0.001	0.74 (1.65)
Low (<0.5), n (%)	41 (87)		17 (42)		2 (5)		60 (48)
Moderate (0.5–1), n (%)	3 (6.5)	0.007¶	19 (48)	0.021**	17 (45)	0.003††	39 (31)
High (>1), n (%)	3 (6.5)		4 (10)		19 (50)		26 (21)

IL=interleukin; RPL=recurrent pregnancy loss; SD=standard deviation

*Ratio was calculated by dividing the IL-10 by the IL-17A levels for each subject; one-way analysis of variance: †RPL x non-aborted pregnant, ‡non-aborted pregnant x control, §RPL x control; statistical difference between biomarker frequency (%) of study groups: ¶RPL x non-aborted pregnant, **non-aborted pregnant x control

Table 2. Vitamin D correlation with IL-17A, IL-10, and IL-10/IL-17A ratio

Variables, mean (SD)	Vitamin D levels														
	RPL group (ng/ml)					Non-aborted pregnant group (ng/ml)					Control group (ng/ml)				
	Low (n = 26)	Normal (n = 21)	High (n = 0)	r	*p*	Low (n = 2)	Normal (n = 36)	High (n = 2)	r	*p*	Low (n = 0)	Normal (n = 29)	High (n = 9)	r	*p*
IL-17A level (ng/l)	23.6 (11.2)	50.5 (15.5)	0 (0)	0.613	**<0.001**	21.4 (0.28)	25.7 (2.4)	49.6 (0.47)	0.579	**<0.001**	0 (0)	11.6 (3.1)	22.4 (9.3)	0.507	**<0.001**
IL-10 level (pg/ml)	1.2 (0.9)	5.1 (2.3)	0 (0)	0.182	0.2	10.9 (0.21)	12.9 (4.7)	33.5 (0.41)	0.504	**<0.001**	0 (0)	18 (5)	18.8 (6.1)	0.010	0.9
IL-10/IL-17A ratio*	0.03 (0.01)	0.32 (0.13)	0 (0)	0.275	**0.04**	0.51 (0.1)	0.58 (0.23)	0.68 (0.05)	0.158	0.3	0 (0)	1.01 (0.6)	3.5 (2.1)	0.354	**0.02**

IL=interleukin; RPL=recurrent pregnancy loss; SD=standard deviation
*Ratio was calculated by dividing the IL-10 by the IL-17A levels for each subject

applicable. Associations between vitamin D levels and IL-17A, IL-10, and the IL-10/IL-17A ratio were assessed using a simple linear regression test. The findings were considered statistically significant with $p<0.05$.

RESULTS

As shown in Table 1, most participants in the RPL group had lower vitamin D levels than those in the control and non-aborted pregnant groups. However, vitamin D levels were similar between non-aborted pregnant and control groups. Overall, the lowest vitamin D levels were observed in the RPL group.

Serum IL-17A levels were significantly higher in the RPL group, with 40% of the patients having high IL-17A levels and a mean concentration of 35.66 (23.14) ng/l. No significant differences were observed between the non-aborted pregnant and control groups (Table 1). Additionally, the RPL group had the highest frequency of low IL-10 levels and the lowest mean titer of IL-10 level. No differences in IL-10 levels between the non-aborted pregnant and control groups were observed (Table 1). A higher frequency of low IL-10/IL-17A ratios was observed in the RPL group than in other groups. Non-aborted pregnant women showed a higher frequency of low IL-10/IL-17A ratios. The IL-10/IL-17A ratio was lowest in the RPL group (Table 1).

Regression analysis revealed a positive association between vitamin D and IL-17A levels across all study groups. However, a significant positive association between vitamin D and IL-10 levels was observed in the non-aborted pregnant group. A positive association was observed between vitamin D levels and IL-10/IL-17A ratio in the RPL and control groups. In contrast, no significant association between vitamin D concentration and IL-10/IL-17A ratio was observed in the non-aborted pregnant group (Table 2).

DISCUSSION

This study revealed that women with RPL had significantly depleted vitamin D levels and higher IL-17A levels than normal pregnant and healthy non-pregnant women. IL-10 levels were also significantly lower in the RPL group than the control group. Positive correlations between vitamin D and IL-17A levels were observed in all groups, whereas a notable relationship between vitamin D and IL-10 levels was observed only in the non-aborted pregnant group. Furthermore, this

study revealed a higher percentage of women with RPL who had low vitamin D levels than non-aborted pregnant and control women, which is consistent with previous studies.[2,9] Notably, a prior prospective cohort study revealed a correlation between adequate preconception vitamin D levels and an increased percentage of live births and pregnancies, suggesting that vitamin D sufficiency is more beneficial before conception; therefore, vitamin D levels should be elevated before rather than during early gestation.[11]

The IL-17A levels in the RPL group were significantly higher than those in the non-aborted pregnant and control groups in this study. The IL-17 pro-inflammatory cytokine family has multiple functions in terms of host defense, autoimmunity, and inflammation, with IL-17A being the most well-characterized.[12] Elevated IL-17A levels reflect dysregulated, aberrant systemic, and local inflammatory processes, leading to endometrial tissue damage, extracellular matrix degradation, and implantation failure. Moreover, higher IL-17 concentrations have been reported in the PB of participants with diseases such as preeclampsia and RPL.[13,14] IL-17 can interact with other mediators, such as IL-8, contributing to the endometriosis pathophysiology via the activation of prostaglandins, matrix metalloproteinases, and cyclooxygenase-2, all of which are crucial in eutopic endometrial changes. Additionally, IL-17 enhances the synthesis of IL-8, which activates the phosphatidylinositol 3-kinase/protein kinase B signaling pathway. This pathway is aberrantly stimulated in endometriosis, resulting in its overexpression.[12] Women with endometriosis had higher sera concentrations of inflammatory mediators, like IL-17, IL-1A, and IL-6,[15] and this condition is often presented in patients with unexplained infertility during laparoscopy.[16] Therefore, it is possible that some participants in this study had asymptomatic, undiagnosed endometriosis.

A previous study has reported that IL-10 and TGF-β may function as immunosuppressive mediators.[17] This finding revealed a significantly lower level of IL-10 in women with RPL than the non-aborted pregnant and control groups. Women with unexplained RPL may have impaired immunosuppressive ability due to higher IL-17 levels and lower Treg counts. Both IL-10 and TGF-β play a crucial role in maintaining maternal-fetal tolerance during pregnancy by inhibiting the expression of IL-17.[18] This is reflected in our findings, where IL-10 levels were higher in non-aborted pregnant and control groups, accompanied by the lowest IL-17A levels. Similarly, another study reported an increased incidence of RPL in mice treated with recombinant IL-17, which resulted in lower IL-10 and TGF-β concentrations.[19] This suggests that elevated IL-17 expressions in the feto-maternal interface stimulate abortion. Treg transfusions may be effective in preventing unexplained RPL. Furthermore, the adoptive transfusion of IL-10-producing Tregs in pregnant mice decreases miscarriage rates and elevates the IL-10 levels.[19] Overall, these findings emphasize the need for a shift from pro-inflammatory to anti-inflammatory cytokines during normal pregnancies, confirming the crucial role of the balance between Th17 and Tregs and their cytokine profile in the outcome of gestation.

Additionally, elevated levels of forkhead box P^{3+}-$IL\text{-}17^{+}$ T-cells in the PB of patients with unexplained RPL suggested a shift from Treg to Th17 cells, contributing to RPL pathophysiology.[2] Our study supported the findings above, where IL-10/IL-17A level in women with RPL was significantly lower than in non-aborted pregnant and control groups. The reduction in IL-10/IL-17A levels in the RPL group aggravated the Treg/Th17 immune imbalance. Another study has shown that PB immune cells from healthy, fertile women produce more IL-10 than those from women with unexplained infertility undergoing *in vitro* fertilization.[1] Furthermore, higher concentrations of IL-17 and IL-23 have been reported in the decidua of women with RPL and in their sera.[18] IL-17-secreting $CD4^{+}$ T cells were significantly higher in women with RPL, and Tregs with less suppressive activity of IL-17 were found in women with RPL than those in the control group.[20] These observations speculate that Tregs may have a limited inhibitory effect on IL-17 in women with RPL. Additionally, the pro-inflammatory Th17 driven by IL-17A in women with RPL, coupled with low and defective IL-10-producing Treg, negatively impacts fertility and increases the risk of miscarriage. Immunomodulatory therapies may help restore the function and number of IL-10-producing Treg cells.

Our findings revealed a positive association between vitamin D levels and IL-17A, IL-10, and the IL-10/IL-17A ratio across all groups. These findings suggest that vitamin D may significantly influence PB cytokine levels in women with RPL and an IL-10/IL-17A imbalance. Previous studies have reported a positive relationship between Treg and Th17 cell

counts and vitamin D levels, with vitamin D potentially re-establishing the Treg/Th17 value.[2] Several previous studies have investigated the effect of vitamin D supplementation on the immunological factors associated with RPL. Notably, the study by Rafiee et al[21] revealed that vitamin D and paternal lymphocyte treatment in patients with RPL could lower the Th17 and Th/Treg ratios in their PB. Decreased vitamin D levels may be associated with the dysregulation of IL-10 and IL-17A levels, contributing to adverse pregnancy complications. Another study revealed that vitamin D activities can lower the synthesis of pro-inflammatory mediators such as interferon-γ and IL-17A, as well as the values of the Th17-associated markers.[22] Additionally, vitamin D decreases the synthesis of prostaglandin E2, which influences the differentiation of intermediate Th17/Treg cells into Th17 cells.[23] Based on these findings, we suggest that vitamin D supplementation may elevate the IL-10 levels relative to IL-17A levels, reducing inflammation and improving pregnancy outcomes, thus making vitamin D an effective treatment option. However, further research is needed to elucidate the regulatory mechanisms of the immune system during implantation and gestation.

This study highlights a decreased IL-10/IL-17A ratio in the systemic circulation of women with RPL, which corroborates the low serum IL-10/IL-17A ratio as a strong candidate biomarker for the deterioration of endometrial function. An elevation in Th17-associated cytokines and depletion of Treg-related cytokines play roles in pregnancy complications among women with unexplained RPL. Balanced immune regulation between anti-inflammatory and inflammatory cytokines is critical for enhancing implantation and fetal preservation until delivery. These findings suggest that immune system regulation, vitamin D, and RPL are correlated, laying a theoretical rule for further research into the pathogenesis of unexplained RPL. In the future, vitamin D may serve as a viable immunoregulatory supplement for women with RPL and dysregulated immune systems.

The major limitation of this study was the inability to collect serum samples after pregnancy loss due to the immune system instability. We measured IL-17A and IL-10 levels in the PB circulation of women with unexplained RPL, non-aborted pregnant women, and controls to assess the systematic immune response in patients with unexplained RPL. However, PB cytokines alone may not be the most accurate indicator of immunological changes during pregnancy,[24] and the major concern is to evaluate the levels of biomarkers within the tissue biopsies related to pregnancy outcomes.

In conclusion, vitamin D influences the IL-10/IL-17A balance in RPL, potentially leading to an elevation in IL-10/IL-17A levels and a reduction in the inflammatory response. These findings confirm that vitamin D modulates the immune response in RPL by enhancing IL-10, suppressing IL-17A, reducing inflammation, and supporting a pregnancy-friendly environment. This immune balance improves uterine conditions and may increase the chances of successful pregnancy.

Conflict of Interest

The authors confirm no conflict of interest in this study.

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