

Relationship Between *Helicobacter pylori* Infection, Serum Vitamin D3 Level and Spontaneous Abortion

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Background: The effects of vitamin D3 (VD3) on pregnancy outcomes remain obscure. Thus, this study aims to investigate the relationship between maternal *H. pylori* infection, low VD3 level, and spontaneous abortion.

Methods: This research is conducted in Shahid Ali Qader Consultant Clinic in Sulaimaniyah city in which 100 women with a history of abortion and 100 women with no history of miscarriage were included. Serum detection of anti-*H. pylori* IgG, IgA, and VD3 were done using enzyme-linked immunosorbent assay (ELISA) technique.

Results: The mean of VD3, *H. pylori* IgG, and IgA in patients and control group cases was determined and analyzed statistically.

Conclusion: *H. pylori* infection and VD3 play a significant role in early pregnancy loss. Blood group A and O are more prone to spontaneous abortion.

Keywords: miscarriage, bacterial infection, vitamin deficiency, antibody detection, ABO grouping

Introduction

The infection with *Helicobacter pylori* considered one of the most dreaded diseases in all age groups and both sexes, especially in undeveloped countries.^{1,2} The bacterium attacks the gastric wall and leads to severe acute infection or sometimes asymptomatic chronic infection. Recent researches confirmed that *H. pylori* infection is a leading cause of peptic ulcers and gastric carcinoma, especially in adult mature peoples.² Additionally, studies reported a direct correlation between *H. pylori* infection and several extra-gastric diseases.³

Spontaneous abortion is the loss of a fetus before 20th weeks of pregnancy that mainly occurs due to fatal genetic problems, or other reasons (non-chromosomal reasons) such as infections and immunological dysfunction. There is evidence indicates that the local inflammation such as *H. pylori* infection may not be confined to the digestive tract, but it can spread to involve the extra- gastrointestinal tract, which may impact reproductive capacity negatively. VD3 deficiency and/or insufficiency could enhance the danger of several chronic sicknesses including immunological dysfunction.^{4,5} *H. pylori* infection is associated with several pathologies during pregnancy, such as pre-eclampsia and recurrent intrauterine death that is mainly characterized by placentation failure that leads to miscarriage cases.⁶

Vitamin D or cholecalciferol is an important hormone that has a potential effect on bone metabolism and mineral homeostasis.^{7,8} It has been found that the increased risk of first-trimester miscarriage is directly associated with low

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concentrations of VD3.⁹ However, the impact of VD3 on pregnancy outcomes remains unclear. Therefore, this study aims to find a relationship between maternal *H. pylori* infection, low VD3 level, and spontaneous abortion.

Methodology

This research is a case-control study, conducted in Shahid Ali Qader Consultant Clinic in Sulaimaniyah city for a period of 10 months starting from January 2019 to October 2019. In this study, 100 women were involved aged between 19 and 49 years old with 5 weeks to 20 weeks of pregnancy loss. Simultaneously, 100 women who have no history of miscarriage and not pregnant during data collection with previous normal delivery were included as a control group. Demographic data were collected including age, parity, number of abortions, dyspepsia, time of dyspepsia, and blood groups. Blood from all women of both groups was collected for the detection of anti-*H. pylori* IgG, IgA (1425-300 *H. pylori* IgG, 1625-300 *H. pylori* IgA, Germany), and VD3 (Bioactiva Diagnostica, BD200BA 25(OH) Vitamin D Kit, Germany) using enzyme-linked immune-sorbent assay (ELISA) technique, using Monobind Inc., USA. Both anti-*H. pylori* IgG and IgA antibodies were previously endorsed in a huge series of *H. pylori*-positive and -negative individuals. Virtually, the existence of *H. pylori*-specific IgG antibody is the only biomarker for chronic infection with this microorganism; thus, it is not a sign of acquisition of the infection, whereas specific IgA antibody is a more specific biomarker for a recently acquired infection with *H. pylori*.¹⁰

The normal value of *H. pylori* IgG is < 8.0 AU/mL and for IgA is < 1.2 Ndx. While VD3 levels are classified into 3 major groups according to the classification of the Institute of Medicine⁴ as follows: sufficient > 30 ng/mL; insufficient ranged between 20 and 30 ng/mL; and deficient < 20 ng/mL.

Written informed consent was obtained from the patients prior to enrollment in the study. All experiments were performed in accordance with the Declaration of Helsinki and approved by the College of Nursing, University of Sulaimani, Iraq.

Inclusion Criteria

Any women attended Shahid Ali Qader Consultant Clinic in Sulaimaniyah city with a spontaneous loss of a fetus from 5th to 20th weeks of pregnancy.

Exclusion Criteria

Any women with medical disorders such as diabetes, hypertension, bronchial asthma, chronic renal, liver or endocrine

disorder, induced or septic abortion, history of trauma during the current pregnancy, uterine and cervical congenital anomalies, received medications that influence bone metabolism and VD3 and calcium intake during the 4th weeks before assessment. Also, blood diseases such as leukemia or thalassemia, malignant, or bone disease were excluded from this study.

Statistical Analysis

All data were analyzed using Excel and SPSS (Version 24) program. The statistical significance of the difference in mean between groups (cases and control) was assessed using an independent sample *t*-test while comparing several groups (more than 2 groups) determined using ANOVA test. Chi-square test was used to find an association between different qualitative variables as between maternal age groups or positivity of IgG and cases and control. P value considered a significant difference when ($p \leq 0.05$) and highly significant differences when ($p \leq 0.01$).

Results

The mean age of the examined subjects that ranged from 19 to 49 years old is 31.98 ± 6.83 and 35.01 ± 8.09 for both cases and control groups, respectively, without significant difference ($p > 0.05$) (Table 1). The mean VD3 for both cases and controls is 9.72 ± 6.22 and 15.77 ± 9.06 ng/mL, respectively, with a highly significant difference ($p \leq 0.001$) (Figure 1). A highly significant difference ($p < 0.01$) was noticed in the mean of *H. pylori* IgG and IgA between cases (9.44 ± 4.44 vs 6.19 ± 2.37) and control (1.09 ± 0.41 vs 0.54 ± 0.18) groups, respectively (Table 1).

In this study, no significant difference was demonstrated between the age groups in both cases and control ($p > 0.05$), but the age of most women complained from abortion ranged between 30 and 39 years old. Out of 200 women, 52% and 17% were positive for *H. pylori* infection in cases and control groups, respectively, with a highly significant difference ($p < 0.01$) (Table 2).

Table 1 Age, Vitamin D3, and *H. Pylori* Antibody Levels of the Participants

Parameter	Mean \pm SD		P-value
	Cases	Control	
Age	31.98 ± 6.83	35.01 ± 8.09	0.06
Vitamin D3 (ng/mL)	9.72 ± 6.22	15.77 ± 9.06	< 0.001
<i>H. pylori</i>	9.44 ± 4.44	6.19 ± 2.37	< 0.01
IgG			
IgA	1.09 ± 0.41	0.54 ± 0.18	< 0.01

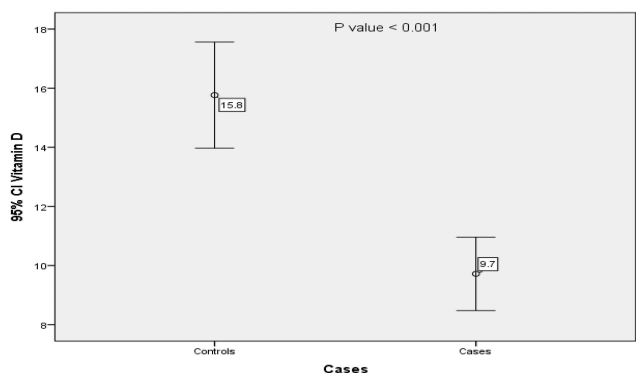


Figure 1 Shows CI % of vitamin D3 (ng/mL) for both cases and control groups which is highly significant ($p \leq 0.001$) when compared.

Additionally, the author revealed that 70% of women had an abortion at a gestational period of 5–10 weeks followed by 11–15 weeks (25%), then 16–20 weeks (5%) (Figure 2). On the other hand, it is observed that 67% of women had the 1st miscarriage, then 18% had 2nd abortion and 15% of women had more than 2 abortions (Figure 3).

The risk associated with *H. pylori* infection (IgG and IgA) such as age, blood group, dyspepsia, the number of abortions is shown in Table 3 in which no significant difference was demonstrated between the age groups and the *H. pylori* IgG and IgA levels ($p > 0.05$), while there is an increment in the *H. pylori* IgG level with increasing age and the highest level being found among the 40–49 years old group.

Furthermore, the author demonstrated that a higher mean of *H. pylori* IgG and IgA levels had blood group type A, followed by type O, then other blood groups with a highly significant difference ($p < 0.01$). Among, examined subjects, only 19 females were complained from dyspepsia more than 6 months with positive *H. pylori* infection (IgA) with significant differences ($p < 0.01$), while there is no significant

Table 2 Age distribution of the Study Population with the Percentage of *H. Pylori* Infection

Parameter		Case %	Control %	P-value
Maternal age (years)	19–29	37	28	0.08
	30–39	46	42	
	40–49	17	30	
	Total	100	100	
<i>H. pylori</i> IgG	Positive	52	17	< 0.01
	Negative	48	83	
	Total	100	100	

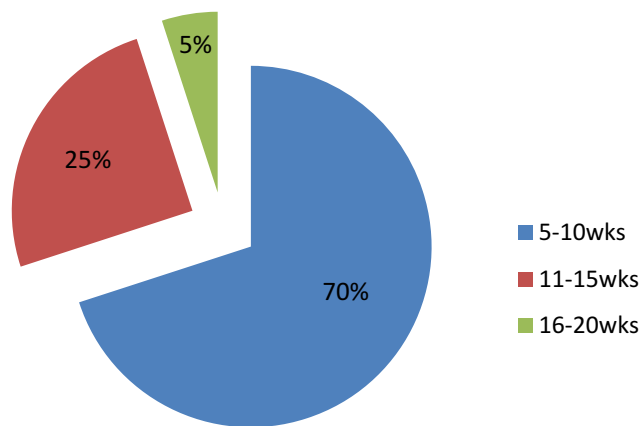


Figure 2 Shows the gestational period at the time of abortion in women of the case group (weeks).

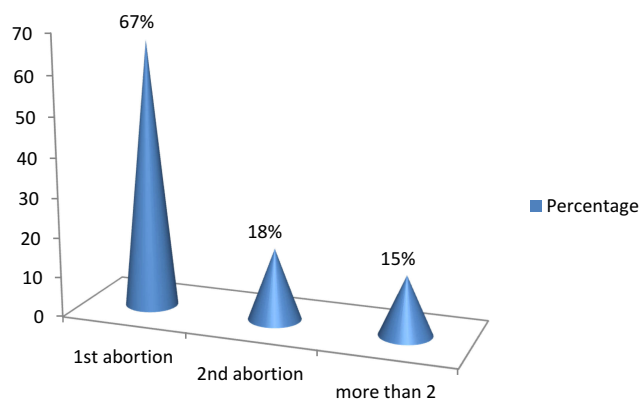


Figure 3 Shows the percentage of abortions in examined subjects.

relationship between female complained from dyspepsia > 6 months and *H. pylori* infection (IgG).

Simultaneously, there are highly significant differences ($p < 0.01$) between *H. pylori* infection (IgG and IgA) and many abortions. The higher mean of *H. pylori* IgG level (11.93 ± 5.44) noticed with more than 2 abortions and a higher mean of *H. pylori* IgA level (1.46 ± 0.50) noticed with 1 abortion only (Table 3).

Moreover, there are low serum VD3 in both control and case groups while there are no changes in the level of VD3 concerning age ($p > 0.05$). Besides, there was a significant difference ($p < 0.05$) in the mean of VD3 concentration between *H. pylori*-positive (9.91 ± 5.43 and 16.97 ± 5.2) and *H. pylori*-negative (6.91 ± 4.17 and 11.35 ± 7.28) in both control and cases, respectively (Table 4).

Finally, VD3 deficiency in women complained abortion is noticed in blood groups of types A and O (7.98 ± 3.36 and 7.63 ± 5.11), respectively, with a highly significant difference ($p < 0.01$). Also, VD3 deficiency revealed in women that complained of dyspepsia but without

Table 3 *H. Pylori* (IgG and IgA) Level with Selected Risk Factors Among Cases

Characteristic	IgG/Cases			Ig A/Cases		
	No.%	Mean ± SD	P-value	No.%	mean ± SD	P-value
Age groups (Years)						
19–29	37	8.38±3.21	0.23	37	0.86± 0.54	0.15
30–39	46	9.91±5.69		46	0.77± 0.27	
40–49	17	10.12±4.71		17	0.63± 0.39	
Blood groups						
A	24	12.91±4.85	< 0.01	24	1.5 ± 0.29	< 0.01
B	26	7.92±3.14		26	0.73± 0.35	
AB	3	7.37±1.48		3	0.63± 0.15	
O	47	9.22±4.67		47	1.3± 0.50	
Dyspepsia > 6 months						
Yes	19	10.89±2.05	0.11	19	1.59± 0.62	< 0.01
No	81	9.10±4.78		81	0.69± 0.28	
No. of abortions						
One	40	10.71±4.05	< 0.01	40	1.46± 0.50	< 0.01
Two	40	6.93±2.83		40	0.65± 0.30	
More than two	20	11.93±5.44		20	0.68± 0.29	

Table 4 Vitamin D3 Level Among Control and Case Groups Concerning Age Distribution and *H. Pylori* Infection

Characteristic	Vitamin D3(ng/mL)/Control			Vitamin D3 (ng/mL)/Cases		
	No.%	Mean ± SD	P-value	No.%	Mean ± SD	P-value
Age groups(Years)						
19–29	2	14.87±7.88	0.40	37	10.28±6.35	0.77
30–39	42	15.02±8.51		45	9.50± 5.56	
40–49	30	17.65±10.7		17	9.08± 7.76	
<i>H. pylori</i>						
Positive	17	9.91±5.43	<	52	6.91± 4.17	<
Negative	83	16.97±5.2	0.05	48	11.35± 7.28	0.05

significant difference ($p = 0.02$). Lastly, VD3 deficiency was noticed more in women with more than 2 abortions (8.67 ± 5.97) than a woman with 2 abortions and 1 abortion (9.25 ± 6.56 , 9.73 ± 6.10), respectively (Table 5).

Discussion

To our knowledge, this is the first study investigating the relation of VD3 level and the existence of *H. pylori* with recurrent abortion in Iraq. The parental age, genetic, hormonal, immunological, and environmental factors are considered as the main causes of most miscarriages in humans. Instantly, it is confirmed that maternal age is the strongest known risk factor;^{11–13} for this reason, in this study, the population (patients and controls) were

comparable and no significant difference between them excludes the age factor.

In the current study, a highly significant difference was noticed in the mean of *H. pylori* IgG and IgA between cases and control groups which is near to other studies revealed a statistically significant difference between cases and controls.¹⁴

Miscarriage is the most common problem in pregnancy, in which the major mechanisms responsible for pregnancy loss are not always clear. Hence, some efforts are being done to determine new factors like chronic infection with *H. Pylori*.^{15,16}

Researchers suggested that *H. pylori* infection may have a role in the pathogenesis of different pregnancy-related

Table 5 Vitamin D3 Level with Selected Risk Factors Among Cases

Characteristic	Vitamin D3 Concentration(ng/mL) Among Cases		P-value
	No. %	Mean \pm SD	
Blood group			< 0.01
A	24	7.98 \pm 3.36	
B	26	11.07 \pm 6.63	
AB	3	21.00 \pm 11.36	
O	46	7.63 \pm 5.11	
Dyspepsia			0.02
Yes	19	9.00 \pm 5.87	
No	80	12.75 \pm 6.90	
Number of abortions			0.66
One	40	9.73 \pm 6.10	
Two	40	9.25 \pm 6.56	
More than two	20	8.67 \pm 5.97	

ailments through various mechanisms such as pro-inflammatory cytokines release, oxidative stress, pre-eclampsia, and cross-reaction between specific anti-*H. pylori* antibodies and antigens localized in placental tissues. In most cases, *H. pylori* infection acquired before gestation, but it is extensively assumed that hormonal and immunological alteration arising during pregnancy could activate latent *H. pylori* with a negative impact not only on maternal health.¹⁷

In agreement with Shalabi et al, it was found that 52% of abortion cases are *H. pylori* seropositive, compared to 17% in control groups that are without a history of previous abortion, with a highly significant difference.¹⁴ *H. pylori* infection may appear as an asymptomatic syndrome and if left untreated, it progresses to a gastric disease especially during pregnancy. In opposite to our result, Golmahammadlou et al reported that there is no relation between *H. pylori* infection and miscarriage.¹⁸

Also, many studies have reported a high prevalence of *H. pylori* infection among healthy and non-healthy individuals worldwide.^{19,20}

Additionally, the author reported that 70% of women had an abortion at the gestational period between 5 and 10 weeks. This finding is not agreed with Shalabi et al¹⁴ outcome. Also, it was revealed that 67% of women had an abortion in the first miscarriage; this finding is in line with Kirchner et al¹⁹ that concludes *H. pylori* infection associated with first miscarriage. On the other hand, Cardaropoli et al reported significantly higher *H. pylori*

seropositive women with a miscarriage compared to controls, while the existence of maternal serum antibodies against *H. pylori* not occurred with repeated abortion.²¹ These findings suggest a relationship between *H. pylori* infection and implantation/placentation failure, possibly due to a cross-reaction between antibodies against *H. pylori* and placental tissue.⁶

No significant association between the age groups and the *H. pylori* (IgG and IgA) level was found, while there is an increment in the *H. pylori* IgG level with increasing age especially more than 40 years old. This finding is inconsistent with Shelbi et al who observed a statistically significant link between the increase in age and *H. pylori* infection.¹⁴

Moreover, the author showed a strong correlation between blood group types A and O with *H. pylori* infection (IgG and IgA) which is consistent with other studies^{22,23} in which they noticed that blood group type O is associated with increased risk of *H. pylori* infection compared to non-O blood group. The H antigen expressed in the duodenal mucosa by using type II oligosaccharide precursor and this antigen is not adapted to A or B antigens in blood group type O, which points to the fact that there is a positive correlation between this blood group and *H. pylori* infection.^{24,25} Additionally, the author noticed that blood group type B and AB patients were less prone to *H. pylori* infection and this finding is supported by previously conducted researches.^{26,27} While Ayalew et al²⁸ showed no correlation between ABO blood group and *H. pylori* infection.

In this study, the author observed a statistically significant link between dyspepsia in patients with more than 6 months of pregnancy that has been diagnosed with positive *H. pylori* infection (IgA), but there is no link between female complained from dyspepsia > 6 months with *H. pylori* infection (IgG). These findings may be explained by local accumulation of CD8+ T cells, reducing CD4+ T cells, and augmented macrophages around the duodenal crypts persevered for months after the acute infectious, signifying impaired cessation of the inflammatory response even after sufficient removal of the infecting pathogen.²⁹ *H. pylori* do not appear to invade the gastric mucosa, but rather release various toxins that ultimately exert tissue damage; among these are mucinase, phospholipase, neutrophil-activating protein A, heat shock protein 60, cytotoxin associated gene A protein (CagA), and vacuolating cytotoxin A (VacA).

The higher mean of *H. pylori* IgG level is reported with several abortions more than 2, and a higher mean of *H. pylori* IgA level was noticed with one abortion in this study. The IgG test is widely used in epidemiological studies and not affected by local changes in the stomach that could lead to false-negatives, this test cannot distinguish between current and past infections because *H. pylori* IgG persist even after the disappearance of this bacterium,³⁰ thus the mucosal CagA-specific IgA antibodies are produced during the acute phase of gastric inflammation. The relevance of IgA testing remains controversial, and both IgA and IgG serum antibodies persist even if the *H. pylori* infection is eradicated. The role of antibody testing in differentiating active *H. pylori* infection from past infection and/or completion of therapy is therefore limited. Seropositivity to CagA has been broadly used to detect infections with virulent *H. pylori* strains.^{10,30,31}

In this study, the mean VD3 among cases was more deficient with a highly significant difference than controls. Our result is supported by Hou et al who reported that serum VD3 levels are higher in women with normal pregnancies than in those with first trimester miscarriages, suggesting that VD3 deficiency is associated with pregnancy loss.³²

VD3 plays an important immunological role at the fetal–maternal interface, as its role in the pathogenesis of recurrent spontaneous abortion has also begun to attract attention. It is the best indicator of nutritional status in clinical practice because of its long half-life and relative stability.⁴ A recent study conducted by Li et al reported that VD3 levels in the decidua are associated with inflammatory cytokine production, suggesting that VD3 may play a role in the etiology of recurrent spontaneous abortion.³³

Our study agrees with Takaoka et al that found low serum VD3 levels among reproductive age in Japanese women,³⁴ in addition to Masoumpour et al who observed that serum level of vitamin D did not decline with age.³⁵ In contrast to these results, Nasri and Ardalan, and Bischof et al found a positive association of ages with VD3 level.^{36,37}

Yang et al³⁸ concluded that VD3 was a protective factor in *H. pylori* infection. Moreover, VD3 can improve the success rate of *H. pylori* eradication that supports our finding since there were no changes in the level of VD3 about age ($p > 0.05$), but there was a significant difference in the mean of VD3 concentration between *H. pylori*-positive and *H. pylori*-negative

in both groups (control and cases), in addition to other studies agree with our results.^{39–41} VD3 plays an important role in gastric mucosa homeostasis and host protection from *H. pylori* infection.⁴² VD3 may reduce the risk of infection through multiple mechanisms; by increasing innate immunity by modulating the production of AMPs and cytokine response. Moreover, VD3 helps in support and elevate the activity of monocytes and macrophages, that way contributing to a powerful systemic antimicrobial effect.^{43,44} VD3 is also known to regulate the expression of AMPs cathelicidin and β -defensin, which kill the bacteria. Although the effect of cathelicidin has been demonstrated only in macrophages infected with *Mycobacterium tuberculosis*, antibacterial action against Gram-negative and Gram-positive bacteria has also been reported. In the VD3-deficient state, the infected macrophage is unable to produce sufficient 1,25-(OH)D₂ to upregulate the production of cathelicidin and β -defensin, thus rendering them unable to kill the *H. pylori* strains. Emerging evidence suggests that VD3 might be a good prophylactic and possibly therapeutic antimicrobial agent for the control and eradication of *H. pylori*.^{45,46}

Highly significant associations between VD3 deficiency in women complained from abortion and blood group types A and O which in line with Al-Fartosi who concluded that a clear increase in several individuals for blood group A in-patients with repeated abortion, and this factor may need to consider in future investigations.⁴⁷

Conclusion

The author concluded that *H. pylori* infection and VD3 play a significant role in early pregnancy loss, as well as blood group, type A and type O, which are more prone to spontaneous abortion in infected individuals. Also, VD3 levels in all women were very low, thus suggesting giving vitamin D to pregnant women according to the instructions of gynecologists.

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Disclosure

The author reports no conflicts of interest in this work.

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