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ORIGINAL ARTICLE

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Association of Vitamin D Levels in Reproductive Immunologic Disorders

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ABSTRACT

Background: Reproductive health has always been an important part of any discussion about women's health. Recurrent pregnancy loss (RPL) is a devastating reproductive problem. It affects approximately 0.5 to 1% of women attempting pregnancy and 5% of couples trying to conceive. There are several causes of RPL; however, despite work-up, half of the cases remain unexplained.

Methodology: This is a cross-sectional study using convenience sampling wherein women aged 19–45 years and pregnant patients without a history of abortion were recruited.

Results: A total of 75 women were equally distributed among the women with RPL, women with infertility, and normal pregnant women. Normal pregnant women are significantly younger and have significantly longer sun exposure. Vitamin D deficiency is significantly higher among those with RPL and infertility.

Conclusion: In summary, normal pregnant women are younger and have more sun exposure. In the RPL arm, most of them have 3 abortions. The majority of women with RPL and infertility have hypovitaminosis D, but there is no significant difference in the vitamin D levels with regard to the number of abortions. Vitamin D deficiency is significantly higher in the infertile group. Still, no significant difference in vitamin D insufficiency was observed between the RPL group and the infertility group. Normal pregnant women have significantly higher mean vitamin D.

Keywords: vitamin D, recurrent pregnancy loss, reproductive immunologic disorders, antiphospholipid antibody syndrome, infertility

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INTRODUCTION

Reproductive health has always been an important part of any discussion about women's health.[1] Recurrent pregnancy loss (RPL) is a devastating reproductive problem. It affects approximately 0.5 to 1% of women attempting pregnancy and 5% of couples trying to conceive.[2]

There are many causes of recurrent pregnancy loss, such as infection, chromosomal abnormalities, immunologic factors, and maternal anatomic factors. Early pregnancy loss, also referred to as miscarriage or spontaneous abortion, is defined as the loss of a clinical pregnancy before 20 completed weeks of gestational age (18 weeks after fertilization) or, if gestational age is unknown, the loss of an embryo or fetus of 400 grams.[3]

The definition of recurrent pregnancy loss has long been debated and differs among international societies. For the European Society for Human Reproduction and Embryology and the Royal College of Obstetricians and Gynaecologists, RPL refers to three consecutive pregnancy losses, including nonvisualized ones. However, according to the American Society for Reproductive Medicine, it is defined as two or more clinical pregnancy losses (documented by ultrasonography or histopathologic examination), but not necessarily consecutive.

Around 15% of all clinically recognized pregnancies result in spontaneous loss, and only 30% of all conceptions result in a live birth.[4] Incidence of RPL is approximately 1 in 300 pregnancies.[4] Studies suggest that the risk of miscarriage in subsequent pregnancies is 30% after 2 losses, compared with 33% after 3 losses among patients without a history of a live birth.[4] Recurrent pregnancy loss can also be classified either as primary or secondary. Primary RPL is defined as RPL without a previous viable pregnancy beyond 24 weeks of gestation, while secondary RPL, on the other hand, is an episode of RPL after 1 or more previous pregnancies progressing beyond 24 weeks of gestation.[5]

Several pathogenic mechanisms associated with RPL were described, which include parental chromosomal abnormalities, untreated hypothyroidism, uncontrolled diabetes mellitus, certain uterine anatomic abnormalities, and antiphospholipid antibody syndrome. Other etiologies include additional endocrine disorders, heritable and/or acquired thrombophilias, immunologic abnormalities, infections, and environmental factors. However, despite work-up, still half of the cases remain unexplained.

Pregnancy loss adversely affects the mother's present health, grief response, subsequent pregnancy, psychological problems, and social or economic condition. It has a relevant emotional impact on women and their partners. Feelings of shame, guilt, isolation, and sometimes anger are common and can intensify with repeated losses, which can affect the marital relationship. Currently, we have an increasing number of referrals of recurrent pregnancy loss seen in the department here in our institution, wherein alloimmune and autoimmune causes are the most common reasons. The prevalence of antiphospholipid antibody syndrome (APS) in women with RPL varies according to studies, from as low as 6% to as high as 42%, but it is generally accepted to be 5%–20%.[3] However, at this time, no studies were done locally associating recurrent pregnancy loss with vitamin D levels.

Vitamin D, or calciferol, is a steroid hormone known for its roles in bone metabolism and phosphate homeostasis. It is mainly synthesized in the skin following exposure to sunlight and is obtained to a lesser extent from the diet.[7] Vitamin D metabolites include both genomic and non-genomic effects.[6] Genomic effects affect the classical target organs like the kidney, intestine, skeletal muscle, bone, and parathyroid glands.[6] However, vitamin D receptors have also been demonstrated in most 'non-classical' target tissues in the body, including smooth muscle, heart muscle, cells of the immune system, liver, brain, thyroid, colon, gonads, skin, and prostate.[6] Vitamin D receptor (VDR) and the enzymes involved in hydroxylation of vitamin D are also present in the human placenta and decidua, which may associate its importance in reproductive function and may serve as a risk factor for RPL.[6] During exposure to the ultraviolet rays in sunlight, 7-dehydrocholesterol converts into VD3 (cholecalciferol).[7] In the liver, vitamin D undergoes its first enzymatic conversion by the mitochondrial form of 25-hydroxylase, resulting in 25-hydroxyvitamin D or 25(OH)D (calcidiol), the major circulating form of VD. The second enzymatic conversion occurs mainly in the kidney by 1α-hydroxylase (CYP27B1) and 24α-hydroxylase (CYP24) resulting in 1,25-dihydroxyvitamin D or 1,25(OH)2D (calcitriol), the active metabolite of VD.[8]

Maternal 25(OH) D crosses the placenta and represents the main pool of VD in the fetus. These changes occur in the placenta and the systemic circulation, suggesting that the placenta is an important site of VD metabolism in pregnancy.[9] The role of VD during normal pregnancy is that it stimulates the maternal innate immunity and suppresses the adaptive immunity. These alterations in the maternal-fetal interface promote immune tolerance and prevent fetal rejection.[10] Normal pregnancy is exemplified by a shift from a type 1 to a type 2 immune response.

Ota et al.,[11] and Chen et al.,[12] reported that the majority of women with recurrent pregnancy loss (RPL) had low vitamin D levels, which can be related to poor obstetrical outcomes.

Ota et al., showed that females with RPL and low vitamin D levels had a higher prevalence of antiphospholipid antibodies, antinuclear antibodies, anti-single-stranded DNA antibodies, and thyroperoxidase antibodies than women with RPL and normal vitamin D levels. This study also showed that in vitro VD3 reduced NK cytotoxicity, suppressed secretion of type 1 cytokines (TNF-α, INF-γ), and increased secretion of type 2 cytokines (IL-10), promoting a shift from type 1 to type 2 immunity, a response favorable for a successful pregnancy.

Chen et al., noted that most women with RPL had insufficient or deficient vitamin D levels, and the number of spontaneous abortions (SA) was higher in those women with abnormal vitamin D levels.

Ibrahim et al.,[13] evaluated the immunomodulatory role of VD3 in preventing SA in cases of RPL. The study revealed that IFN-γ was significantly downregulated after VD3 treatment and was associated with successful pregnancy.

Infertility affects 186 million worldwide. Rudick et al., observed that the clinical pregnancy rate progressively decreases with declining vitamin D status in non-Hispanic whites, but not in women of Asian ethnicity.[14]

A study by Ozkan et al., conducted in New York in 2010, showed that women with higher vitamin D levels were more likely to have a positive outcome of in vitro fertilization (IVF). They concluded that vitamin D supplementation in vitamin D-deficient subjects could improve fertility outcomes.[15]

In a retrospective study done by Li et al., in California in 2012 in women of reproductive age, it was observed that the majority of infertile women had low vitamin D levels. They also noted that high BMI, Asian and blacks were all at risk of vitamin D deficiency, especially Asian women.[16]

According to the Endocrine Society Clinical Practice Guidelines, deficiency is defined as serum 25-hydroxyvitamin D levels <20 ng/mL, and insufficiency as levels between 21 and 29 ng/mL. For pregnant women, the Institute of Medicine recommends an intake of 600 IU of vitamin D. Meanwhile, the US Endocrine Society recommends at least 1,500 to 2,000 IU of vitamin D. Both societies agree that the upper intake limit for vitamin D is 4,000 IU/day.

OBJECTIVES

General objective

This study aims to correlate the vitamin D levels of patients with reproductive immunologic disorders like infertility and recurrent pregnancy losses.

Specific objectives

1. To compare the demographic data of patients who had reproductive immunologic disorders and the normal pregnant women without any history of abortion.
2. To compare the level of vitamin D between patients with reproductive immunologic disorders and normal pregnant patients.
3. To associate the vitamin D level of patients with RPL and the number of abortions.

METHODOLOGY

Study setting

This study was conducted in the University of the Philippines – Philippine General Hospital (UP-PGH) since it is a tertiary hospital and a training institution, hence many patients with recurrent pregnancy losses were referred here. The institution has capable specialists in immunology who have assessed and properly managed patients with pregnancy loss.

Study design

This was a cross-sectional study using convenience sampling.

Study population and sampling technique

This study included inpatient and outpatient referrals of reproductive immunologic disorders in women aged 19-45 years old and pregnant patients without a history of abortion in the PGH.

Inclusion Criteria

- All pregnant women ages 19-45 who had a history of reproductive immunologic disorders, defined as 2 or more pregnancy losses not necessarily consecutive, and those without a history of abortion.
- New and old cases seen in both the inpatient and outpatient departments in the PGH with reproductive immunologic disorders and women without a history of abortion.
- All pregnant women who had regular menstrual cycles and had not used hormones or vitamin D for at least 3 months.
- All pregnant women without any treatment given for the history of pregnancy, excluding aspirin.
- All pregnant patients with reproductive immunologic disorders that were fully worked up for pregnancy loss, like antiphospholipid antibody (APS) panel (SCT/DRVVT, APTT, anti-cardiolipin IgM and IgG, antiB2 glycoprotein IgM and IgG), anti-nuclear antibody (ANA), natural killer cells (NK cell), lymphocyte antigen tests (LAT), and anti-sperm antibodies.

Exclusion criteria

- Patients who have known structural uterine anomalies.
- Patients who have known thyroid, parathyroid, or adrenal disorders, type 1 diabetes, and known malignancy will be excluded.
- Pregnant patients already on heparin, Vitamin D supplementation, and steroids for at least 4 weeks.
- Pregnant patients without work-up for reproductive immunologic disorders.

Data collection procedure

This is a cross-sectional study using convenience sampling wherein enrolled subjects were given a general questionnaire including the participants' sociodemographic characteristics and information about prior abortion, sunscreen usage, diseases, medications, and use of food supplements.

Baseline vitamin D levels were measured during the interview after completing the questionnaire. Approximately 5 mL of whole blood was collected by venipuncture into a plain red-top tube. The staff collected the extraction in the radioimmunoassay (RIA) laboratory. The excess blood samples were disposed appropriately by the RIA staff. Samples were placed in a yellow bag and stored in a secure room for 2 weeks. After 2 weeks, a designated machine measured the radioactivity of the samples, and if the results were low, the samples were disposed of properly as contagious waste.

In vitro determination of total 25-hydroxyvitamin D was measured using the Beckman Coulter Radioimmunoassay (California). According to the Endocrine Society, vitamin D deficiency is below 20 ng/mL or 5 nmol/L; vitamin D insufficiency is levels ranging from 21 to 29 ng/mL or 525 to 725 nmol/L; and sufficient if above 30 ng/mL. No repeat vitamin D determinations were done since no treatment was given to the patients.

The data were collected and tabulated.

Sample size

At 95% confidence level and confidence interval, the minimum total sample size required for this study is at least 75 patients. Specifically, since there are three groups in the study, each group should have at least 25 participants. This is based on the known recurrent pregnancy loss in the Philippines of 5%. The sample size for this study accounts for a 0.05 alpha error probability and at least 80% power. MedCalc statistical software version 18.9 was used to calculate the sample size.

Statistical analysis

The data was thoroughly checked for completeness, accuracy, and consistency. Means, standard deviations, proportions, and percentages were used to describe and summarize the data. A one-way ANOVA F-test was used to compare mean Vitamin D levels among the three groups (RPL, Infertility, Control). Tukey's Kramer pairwise comparisons were also used to follow up on significant ANOVA results. Additionally, to determine the association between RPL and Vitamin D deficiency classifications, Fisher's exact test was used. All tests of significance were at 5% level. MedCalc statistical software was used to perform statistical computations.

Scope and delimitations

The limitations of this research included the following: 1) it was dependent on the recollection of the patient and on the accuracy and completeness of information given, and 2) pregnant patients with no work-up were not included.

Ethical considerations

The study protocol was submitted to the UP-PGH Ethics and Review Board (ERB) for review and approval. The study was conducted only upon the ERB's approval.

All information gathered was kept confidential, and participants' privacy was maintained throughout. Participants' names were not disclosed outside the research group, in accordance with the National Data Privacy Act (Republic Act No. 10173, or the Data Privacy Act of 2012). Identifiable information (e.g., names) was coded and known only to the principal investigator. They were not released to any other person, nor used for publication/presentation. Names were only available to the patient's doctor, the principal investigator, and the staff of the Section of Allergy and Immunology. The information gathered and used in data analysis and interpretation was kept confidential within the limits of the law. There were no significant risks that the participant incurred during the study. No expenses were paid by the participant in this research.

RESULTS

A total of 75 women were included, equally distributed among the following groups: women with RPL, women with infertility, and women with normal pregnancies. Table 1 shows significant differences in their mean age, where those who are normal pregnant women are significantly younger (26 years old) as compared to women with infertility (35 years old). Results also show that those in control are significantly more able to attain a high school education (72%). In comparison, there are significantly more women who were able to pursue vocational education in women with RPL (16%) and infertility (24%), as compared to none among normal pregnant women. Employment status is the same across the three groups, as most of them are housewives. Significant differences also exist in gravidity: normal pregnant women are mostly gravida 1 (36%), whereas those with RPL are mostly gravida

Table 1. Comparison of the descriptive characteristics of the three groups

Variables	Women with RPL (n = 25)	Women with infertility (n = 25)	Control (n = 25)	*p*-value
Age (years), mean ± sd	32.8 ± 5.9	35.4 ± 4.5	26.0 ± 6.9	0.0001*
Educational attainment, n, %				
College	9 (36.0)	10 (40.0)	7 (28.0)	0.5939ns
High School	12 (48.0)	9 (36.0)	18 (72.0)	0.0241*
Vocational	4 (16.0)	6 (24.0)	0 (0.0)	0.0159*
Occupation, n, %				
Employed	11 (44.0)	10 (40.0)	7 (28.0)	0.4767 ns
Housewife	14 (56.0)	15 (60.0)	18 (72.0)	
Gravidity, n, %				
1	0 (0.0)	0 (0.0)	9 (36.0)	0.0001*
2	9 (36.0)	0 (0.0)	7 (28.0)	0.0011*
3	11 (44.0)	0 (0.0)	3 (12.0)	0.0001*
4	1 (4.0)	0 (0.0)	4 (16.0)	0.0642 ns
≥5	0 (0.0)	0 (0.0)	2 (8.0)	0.1081 ns
None	0 (0.0)	25 (100.0)	0 (0.0)	0.0001*
Number of abortions, n, %				
0	0 (0.0)	25 (100.0)	25 (100.0)	0.0001*
2	17 (68.0)	0 (0.0)	0 (0.0)	0.0001*
3	6 (24.0)	0 (0.0)	0 (0.0)	0.0001*
≥4	2 (8.0)	0 (0.0)	0 (0.0)	0.1081 ns
Minutes exposure to sun (minutes)	14.7 ± 14.8	3.9 ± 4.7	25.0 ± 33.7	0.0040*

**significant, ns not significant*

F test through One Way ANOVA for continuous data, Fisher Exact test for Categorical

Table 2. Vitamin D levels in women with RPL, infertility and normal pregnant women

Variables	Women with RPL (n = 25)	Women with infertility (n = 25)	Control (n = 25)	*p*-value
Deficiency	5 (20.0)	11 (44.0)	1 (4.0)	0.0024*
Insufficiency	16 (64.0)	14 (56.0)	13 (52.0)	0.6166ns
Sufficiency	4 (16.0)	0 (0.0)	11 (44.0)	0.0002*

**significant, ns not significant, Fisher exact test*

Table 3. Level of Vitamin D in comparison among women with RPL, infertility and normal pregnant women

Group	Mean (ng/mL)	SD	Median (ng/mL)	Minimum (ng/mL)	Maximum (ng/mL)	*p*-value
RPL	23.85	12.57	23.85	1.63	64.6	0.027*
Infertility	20.53	6.01	21.1	8.3	27.9	
Normal	28.22	10.06	29.27	8.1	48.79	

**significant, ns not significant, F Test through One Way ANOVA,*

Tukeys Kramer for Pairwise Comparison, Infertility has significantly lower mean than Normal

3 (44%). The number of abortions is significantly higher among those with RPL, as none in the control group has experienced it. Moreover, none of the women across all groups use sunscreen, while women in the normal group have significantly longer sun exposure (25 minutes) than women with infertility (around 3.9 minutes).

Table 2 compares Vitamin D levels across the three groups, showing that deficiency is significantly higher among those with RPL (20%) and infertility (44%) than among normal pregnant women (4%). On the other hand, sufficiency is significantly higher among normal pregnant women (44%) as compared to only 16% and none among women with RPL and infertile women, respectively.

Table 3 presents the actual vitamin D levels and shows that normal pregnant women have a significantly higher mean Vitamin D level of 28.22 ng/mL than infertile women

Table 4. Level of Vitamin D across number of abortions

Number of Abortions	n	Mean (ng/mL)	SD	*p*-value
Two (2)	17	24.4	13.5	0.651ns
Three (3)	6	24.9	8.4	
Four and Above (≥4)	2	15.7	19.9	

**significant, ns not significant, F Test through One Way ANOVA*

(20.53 ng/mL). Additionally, the mean of 23.85 ng/mL among women with RPL is not significantly different from the 20.53 ng/mL of infertile women.

Table 4 compares the mean vitamin D across different numbers of abortions; the *p*-value of 0.651 indicates that the means are not significantly different.

Since the majority of subjects in the control group were younger and gravida 1, a post hoc analysis was conducted to examine Vitamin D levels across age groups and gravidity status.

Table 5 uses the vitamin D classification to compare the three age groups, with no significant differences noted. The resulting *p*-value denotes that the amount of vitamin D is not significantly different across different age groups. This table shows that women aged 30-39 in the infertility and RPL arms have lower vitamin levels than women in other age groups.

Table 6 compares the number of gravidities and vitamin D classification across the three arms. Results show that nulliparous women are more likely to have deficient

Table 5. Age and vitamin D classification in women with RPL, infertility and normal pregnant women

	Deficient	Insufficient	Sufficient	*p*-value
Infertility				
19-29	1 (9.1)	0 (0.0)	0 (0.0)	0.64
30-39	8 (72.7)	10 (71.4)	0 (0.0)	
40 and above	2 (18.2)	4 (28.6)	0 (0.0)	
RPL				
19-29	2 (40.0)	5 (31.2)	1 (25.0)	0.8656
30-39	3 (60.0)	8 (50.0)	2 (50.0)	
40 and above	0 (0.0)	3 (18.8)	1 (25.0)	
Normal				
19-29	1 (100.0)	10 (76.9)	7 (63.6)	0.8596
30-39	0 (0.0)	3 (27.3)	3 (27.3)	
40 and above	0 (0.0)	0 (0.0)	1 (9.1)	
Overall				
19-29	4 (23.5)	15 (34.9)	8 (53.3)	0.4652
30-39	11 (64.7)	21 (48.8)	5 (33.3)	
40 and above	2 (11.8)	7 (16.3)	2 (13.3)	

Table 6. Gravidity and vitamin D classification

	Deficient	Insufficient	Sufficient	*p*-value
Infertility				
None	11 (100.0)	14 (100.0)	0 (0.0)	-
1 to 2	0 (0.0)	0 (0.0)	0 (0.0)	
3 and above	0 (0.0)	0 (0.0)	0 (0.0)	
RPL				
None	0 (0.0)	0 (0.0)	0 (0.0)	1.0000
1 to 2	2 (40.0)	6 (37.5)	1 (25.0)	
3 and above	3 (60.0)	10 (62.5)	3 (75.0)	
Normal				
None	0 (0.0)	0 (0.0)	0 (0.0)	0.2077
1 to 2	0 (0.0)	10 (76.9)	6 (54.5)	
3 and above	1 (100.0)	3 (23.1)	5 (45.5)	
Overall				
None	11 (64.7)	14 (32.6)	0 (0.0)	0.0014
1 to 2	2 (11.8)	16 (37.2)	7 (46.7)	
3 and above	4 (23.5)	13 (30.2)	8 (53.3)	

vitamin D (64.7%). At the same time, those with 3 or more pregnancies are more likely to have sufficient vitamin D. However, despite this, there is still no significant difference in vitamin D levels across gravidity levels in the three groups.

DISCUSSION

Recurrent pregnancy losses and infertility are both physically, emotionally, and financially devastating for the couple and the entire family. Several studies have shown that vitamin D has a critical role during pregnancy. It is one of the key factors in immune regulation, balancing both pro- and anti-inflammatory cytokines at the maternal-fetal interface. Pregnant women have a higher vitamin D requirement than non-pregnant women, so they are more prone to lower vitamin D levels. In pregnancy, vitamin D deficiency correlates with increased pregnancy complications like preterm delivery, small for gestational age babies, and pre-eclampsia. Studies in several countries have examined associations between vitamin D levels and pregnancy outcomes; however, in our country, no studies have been conducted yet.

A total of 75 women were recruited for this research, equally distributed among the 3 groups: specifically, normal pregnant women, pregnant women with a history of recurrent pregnancy loss, and infertile women, all in the childbearing age. Results show that the mean age of women with no losses was 26.0 ± 6.9, 32.8 ± 5.9 for women with recurrent pregnancy loss, and 35.4 ± 4.5 for those with infertility. Ghaedi et al.,[6] reported a mean age of 30.43 ± 5.44 for participants with RPL, which is almost identical to the result we obtained. The study on Iranian women was mostly housewives (86.7%) with a median gravidity of 4 in RPL, while ours revealed that most RPL participants were gravida 3, and similarly, the majority of our participants were housewives. As for minutes of sun exposure, the control arm, which consisted of normal pregnant women, had greater sun exposure (25.0 ± 33.7) than the RPL (14.7 ± 14.8) and infertile groups (3.9 ± 4.7). Shaygannejad et al.,[17] reported a direct association between sun exposure and vitamin D serum concentrations across all participants, consistent with our study.

Ghaedi et al.,[6] observed that 33.3% of those with RPL have vitamin D deficiency. As for this study, participants with RPL and who are infertile also had vitamin D deficiency, 20% and 44%, respectively. Ota et al.,[11] noted that in RPL patients, 41% have vitamin D insufficiency and 22% have vitamin D deficiency. Chen et al.,[12] made a study on vitamin D and women with recurrent miscarriages, showing 51.5% of the women had vitamin D insufficiency, while 13.1% had deficiency. Compared with the abovementioned studies on RPL and vitamin D, our study had a higher percentage of participants with decreased vitamin D levels: 64% insufficient and 20% deficient. Wu et al.,[18] showed that 50% of infertile women had vitamin D deficiency and 37% had insufficiency. In a retrospective cohort study by Rudick et al.,[14] the authors observed that among infertile patients, 37% had insufficient vitamin D levels and 21% were deficient. In this study, 44% had a deficiency and 56% had an insufficiency in the infertile group, findings comparable to those of the aforementioned studies. According to the global epidemiology of vitamin D status,[19] vitamin D insufficiency is prevalent across Asia in all age groups and both sexes. This may be taken into account in this study, where 13% have insufficiency and 1% with vitamin D deficiency in the control arm despite adequate sun exposure.

A cross-sectional study of RPL in Iranian women reported a median vitamin D level of 14.20 ng/mL,[6] whereas our findings were 23.85 ng/mL, which is higher. Chen et al.,[12] reported that, among participants with RPL, the mean vitamin D level was 23.9 ± 2.6 ng/mL in the insufficient group and 16.8 ± 2.7 ng/mL in the deficient group. Li et al.,[16] on the other hand, observed that 68.6% of infertile women had vitamin D levels <32 ng/mL and 22.2% <20 ng/mL, whereas in our study, the mean vitamin D level in the infertile arm was 20.53 ng/mL. This research showed that normal pregnant women have a significantly higher mean vitamin D level (28.22 ng/mL) than infertile women (20.53 ng/mL). Still, there was no significant difference in vitamin D levels between RPL and infertile women.

A cross-sectional study in Iran showed that women with 4 or more abortions had a mean vitamin D of 9.20, 11.50 in those with 3 abortions, and 11.50 in participants with 2 abortions, concluding that the lower the vitamin D level, the higher the number of abortions in RPL women. However, for this study, there is no significant difference in the mean level of vitamin D with the number of abortions.

A study by Hagenau et al., showed that vitamin D levels are lower in those aged under 15 and over 75.[20] Children have higher lean mass with growth are linked to the increase in consumption of vitamin D.[21] In the elderly dermal production of vitamin D decreases significantly with noted 50% decline in renal function and calcium absorption.[21,22] Our study showed no significant difference in vitamin D levels across the age groups since our study did not include those below 15 years old and more than 75 years old.

Lastly, in the Odense Child Cohort prospective study and a study conducted in China, nulliparous women had higher vitamin D levels than multiparous women, with a noted decrease in vitamin D levels as parity increased.[23,24] Aji et al., from India had a similar result with our study, wherein nulliparous women have lower vitamin D levels

as compared to their multiparous counterparts.[25] But despite a slightly lower vitamin D level for the nulliparous women, there is still no significant difference as compared to those women with increased parity.

CONCLUSION

In summary, normal pregnant women are younger in age and have longer sun exposure compared to those with RPL and infertility. In the RPL arm, most of them have 3 abortions. The majority of women with RPL and infertility have hypovitaminosis D, but there is no noted significant difference in the vitamin D levels with regard to the number of abortions. Vitamin D deficiency is significantly higher in the infertile group, but no significant difference was noted in vitamin D insufficiency from the RPL group as compared to that of the infertility group. Normal pregnant women have significantly higher mean vitamin D levels than infertile women. Age and gravidity did not differ significantly in vitamin D levels across the three groups.

Recommendations

For future studies, the authors recommend a larger sample size or a randomized controlled trial to corroborate further the role of vitamin D in increasing fertility rates. Vitamin D testing for this research was conducted only once, a study in which vitamin D levels per trimester may be measured to monitor trends. A study can also be conducted on vitamin D supplementation in pregnant patients and on monitoring pregnancy outcomes.

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Statement of Authorship

The authors certified fulfillment of the ICMJE authorship criteria.

Author Disclosure

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