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Comparison of Serum Vitamin D Level between Normal Pregnancy and Abortion in Outpatient Settings

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Abstract

BACKGROUND: Abortion is pregnancy termination or loss before 20 weeks gestation or with a fetus delivered weighing <500 g. One of the pathogenic mechanisms associated with abortion was immunological factors. The human fetus represents a semi-allograft, which cannot survive without maternal immune tolerance. Vitamin D may be implicated in the risk of miscarriage due to its function as an immune modulator and its potential importance for the maternal-fetal immunologic response

AIM: This study aimed to compare the level of serum Vitamin D in abortion patients and normal pregnant women.

METHODS: This is a cross-sectional study using primary data from a private maternity clinic in October 2020–February 2021. The subjects recruited in this study were 98 women at first-trimester pregnancy with either viable gestation (46 subjects) or abortion (52 subjects). Demographic data (maternal age, gestational age, body BMI, parity level, history of miscarriage, and occupation) and their association to abortion were determined. The serum 25-hydroxyvitamin D [25(OH)D] level was measured and then compared using statistical analysis.

RESULTS: Mean age of the subjects was 30.45 ± 4.56 years and the mean gestational age of the recruitment was 58.31 ± 17.89 days. Abortion group has lower serum 25(OH)D level (16.95 ± 5,51 μg/L) than normal pregnant group (17.89 ± 4.74 μg/L), although it was not statistically significant ($p = 0.527$). The results also showed that there was no statistically significant association between the classification of Vitamin D deficiency, BMI, parity level, history of miscarriage, occupation, and abortion ($p > 0.05$).

CONCLUSION: In our study, we found that abortion patients had lower Vitamin D levels than normal pregnant women, but it was not statistically significant. Abortion also was not associated with BMI, parity level, history of miscarriage, and occupation.

Introduction

Maternal Vitamin D insufficiency during pregnancy is a common issue and a significant public health problem at the global level [1]. The prevalence of Vitamin D deficiency and insufficiency during pregnancy ranges from 27.0% and 91.0% in the United States, 39.0–65.0% in Canada, 45.0–100.0% in Asia, 19.0–96.0% in Europe, and 25.0–87.0% in Australia and New Zealand. Despite being a tropical country with perennial sunshine, Vitamin D deficiency in pregnant women has been reported in Malaysia. A recent study conducted at a tertiary hospital in Kuala Lumpur found that 71.7% of the third trimester pregnant women had Vitamin D deficiency and 21.0% had Vitamin D insufficiency. A recent study conducted in West Sumatera, Indonesia reported the prevalence of Vitamin D deficiency and insufficiency among third trimester pregnant women was 61.3% [2].

Indonesia is a tropical country with abundant sun exposure, as it lies within the equatorial zone. Several studies on Vitamin D status in pregnant women and women of childbearing age have been conducted and have shown that an average of more than 95% of individuals has low Vitamin D status. Last research on West Sumatera showed that the prevalence of first-trimester maternal Vitamin D deficiency and sufficiency were 82.8 and 17.2%, respectively [3].

Low maternal Vitamin D levels during pregnancy have been linked with multiple adverse obstetric outcomes such as maternal osteomalacia, gestational diabetes, preeclampsia, and primary cesarean section. In addition, gestational Vitamin D deficiency is associated with fetal intrauterine growth restriction and various adverse fetal and neonatal health outcomes, including higher risk of premature birth, abortion, low birth weight, neonatal hypocalcemia, and childhood obesity [2]. In addition to its impact on both the early and late trimesters of pregnancy, Vitamin D deficiency is associated with negative impacts on fertility, lactation, perimenopausal syndrome, and the health of postmenopausal women [3].

Pregnancy loss (PL) is an adverse outcome of pregnancy in which conception does not result in a live-born

child. Of clinically recognized pregnancies, 10–15% terminate with spontaneous loss. Early pregnancy loss (spontaneous miscarriage) defined as the spontaneous termination of pregnancy before 12 gestational weeks [4]. Around 73.3 million abortions occurred worldwide every year between 2015 to 2019. Among these, one in three abortions was carried out in dangerous or unsafe settings and almost all of these took place in developing countries. Unsafe abortion also contributes to 4.7–13.2% of maternal deaths each year globally [5]. In Java Island, the most populous island of Indonesia, the incidence of abortion in 2018 is around 42,5/1000 women aged 15–49 [6].

The fetus depends on the maternal supply of Vitamin D, calcium, and phosphorus, which is transmitted across the placenta. In fact, maternal and cord blood 25-hydroxyvitamin D (25[OH]D) are highly correlated in terms of supporting the importance of this vitamin for fetal development [1]. The increased synthesis of 1,25-dihydroxyvitamin D [1,25-(OH)2D] is linked to higher Cytochrome P450 Family 27 Subfamily B Member 1 (CYP27B1) activity in maternal kidney, placental trophoblasts, and decidua. The locally synthesizing 1,25(OH)2D in maternal decidual cells depends on available 25(OH)D in circulation as a substrate for 1α-hydroxylase. It demonstrated that adequate 25(OH) D concentrations were essential during pregnancy. Vitamin D deficiency in the mother could be vertically transmitted to the fetus. We also found that the early pregnancy loss women had a significantly lower 25(OH) D levels than normal early pregnant women and had a low Vitamin D rate of 43.3%; however, 96.7% of normal early pregnant women revealed Vitamin D sufficient [5].

The International Association of Endocrinology defined a Vitamin D level of 21–29 ng/mL as insufficiency and <20 ng/mL as deficiency in adults. The Institute of Medicine suggested that the “Estimated Average Requirement” and “Recommended Dietary Allowance” (RDA) for pregnant women be 400 and 600 IU/day, respectively. The safety dose during pregnancy is not clear, but Hollis *et al.* showed that Vitamin D supplementation of 4000 IU/day for achieving adequate levels was safe and effective in pregnant women [7].

However, there were inconsistent evidence of these abortion-associated mechanisms and also insufficient evidence in the North Sumatera population. To date, there have been a limited number of reports of Vitamin D deficiency and miscarriage and there are some contradictory findings in the literature. This study aimed to compare the level of serum Vitamin D in abortion patients and normal pregnant women.

Methods

This was a cross-sectional study, using primary data from the outpatient department in a private maternity clinic in Medan, North Sumatera, Indonesia, from October 4, 2020 to February 28, 2021. The patients enrolled in this study were women carrying singleton fetuses at <20 weeks of gestation by the 1st day of the last menstrual period which were further divided into two groups: (1) Abortion group: Women who were at <20 weeks gestational age, experiencing vaginal bleeding, and the diagnosis was confirmed by ultrasound. (2) Normal pregnant group: Women who were <20 weeks gestational age with viable fetus confirmed with ultrasound. The exclusion criteria were multiple pregnancies, pregnancy with congenital anomaly, dissatisfaction with the study, and incomplete data. Based on these criteria, 98 subjects were recruited which included 52 subjects on the abortion group and 46 subjects on the normal pregnant group.

Demographic characteristics of the patients (age, gestational age, parity level, history of miscarriage, body mass index, and occupation) were collected by interviewing the mother. The specimen collection and measurement of serum Vitamin D (25[OH]D) levels were done in Pramita Laboratory in Medan, North Sumatera Province, Indonesia. Blood samples were collected from the mother and centrifuged at 3000 r.p.m for 10 min at room temperature. Serum was collected and the Vitamin D quantification was done using the Enzyme-linked immunosorbent assay (ELISA) method. Serum Vitamin D level ≥30 μg/L was considered as sufficiency, the level of 20–29 μg/L was considered as insufficiency, the level of 10–19 μg/L was considered as deficiency, and the level <10 μg/L was considered as severe deficiency.

Statistical analysis was done using SPSS software version 20. Numerical data were displayed as mean ± SD and categorical data as number (%). Shapiro–Wilk test was used to decide the distribution of the numerical data. Mean serum Vitamin D levels of the two groups were compared using the independent-T test as both were normally distributed. Mann–Whitney U test was used to analyze the numerical data that were not normally distributed. Categorical data of the sample were analyzed using either Chi-square or Mann–Whitney U test. $p < 0.05$ was considered statistically significant.

Results

A total of 98 subjects were recruited and further enrolled into the abortion group (52 subjects) and the normal pregnant group (46 subjects). The mean age of the subjects was 30.45 ± 4.56 years and the mean gestational age of the recruitment was 58.31 ± 17.89 days (median 54.00 days and interquartile

Table 1: Demographic characteristics of the subjects

Characteristics	Group				p-value*
	Abortion		Normal pregnant		
	N (%)	Mean (± SD)	N (%)	Mean (± SD)	
Age, years	62 (100)	29.78 (± 4.369)	46 (100)	31.26 (± 4.750)	0.246[a]
Gestational age, days	62 (100)	57.65 (± 13.136)	46 (100)	59.04 (± 22.392)	0.502[a]
Body mass index	62 (100)	24.58 (± 3.612)	46 (100)	27.36 (± 5.586)	0.074[a]
Normal	32 (61.5)		22 (47.8)		0.188[b]
Overweight	16 (30.8)		12 (26.1)		
Obese	4 (7.7)		12 (26.1)		
Parity level	52 (100)		46 (100)		0.592[b]
Nulliparous	24 (46.2)		24 (52.2)		
Primiparous	18 (34.6)		16 (34.8)		
Multiparous	10 (19.2)		6 (13)		
History of miscarriage	52 (100)		46 (100)		0.115[b]
Yes	8 (15.4)		16 (34.8)		
No	44 (84.6)		30 (65.2)		
Occupation	52 (100)		46 (100)		
Homemaker	20 (38.46%)		22 (47.82%)		0.509[b]
Employed	32 (61.04%)		24 (52.18%)		

[a]Independent-T test. [b]Mann–Whitney U, $p < 0.05$ was considered statistically significant.

range 44.50–65.50 days). Table 1 also showed that both groups without significant mean differences in the demographic data including maternal age, gestational age, and body mass index (BMI) ($p > 0.05$). We do not found association between history of miscarriage, parity level, BMI classification, occupation, and abortion ($p > 0.05$).

Figure 1 showed that the abortion group had lower serum 25(OH)D level (16.95 ± 5.51 μg/L) than the normal pregnant group (17.89 ± 4.74 μg/L), although it was not statistically significant ($p > 0.05$). Table 2 revealed that only one subject had a sufficient level of Vitamin D who was in the abortion group. Of the abortion group, 96.2% had either insufficient, deficient, or severely deficient Vitamin D levels versus 100% of the normal pregnant group. We found no significant association between grading of Vitamin D deficiency and abortion ($p > 0.05$).

Table 2: Frequency of Vitamin D deficiency

Vitamin D	Group		Total	p-value
	Abortion	Normal pregnant		
	N (%)	N (%)		
Severe deficiency	4 (7.7)	4 (8.7)	8 (8.2)	0.536*
Deficiency	24 (65.4)	24 (52.2)	48 (59.2)	
Insufficiency	12 (23.1)	18 (39.1)	30 (30.6)	
Sufficiency	2 (3.8)	0 (0)	2 (2)	
Total	62 (100)	46 (100)	98 (100)	

*Mann–Whitney U.

Discussion

Our study showed that the majority of the women (89.8% of total) had either insufficient or deficient serum Vitamin D levels. Only one subject had a sufficient level of Vitamin D who was in the abortion group. There was no association between the classification of Vitamin D deficiency and abortion. This finding was not consistent with a study by Jahantigh *et al.* who found that the frequency of severe Vitamin D deficiency was significantly higher in abortion group than the normal pregnant group [8]. However, a previous study reported that the majority of the women aged 20–50 in North Sumatera were either Vitamin D deficient or insufficient [9].

The serum Vitamin D level of the abortion group was lower than the normal pregnant group, but it was not statistically significant ($p > 0.05$). A meta-analysis by Zhang *et al.* in 2016 which included 10.360 pregnant women reported that there was no significant association between a low level of serum 25(OH)D and an increased risk of pregnancy loss, although an extremely low level (< 20 μg/L) was associated with pregnancy loss [10]. Another meta-analysis by Amegah *et al.* reported that serum Vitamin D level <30 μg/L was not associated with the risk of spontaneous abortion [11]. A previous study by Hou *et al.* reported contrasting results with our study, they found that subjects with pregnancy loss in the first trimester had significantly lower Vitamin D levels than normal pregnant women [5]. Vitamin D had been hypothesized to have effects on pregnancy by its immunomodulatory property that facilitates successful implantation by attenuating decidual T-cells activity. Vitamin D also regulates calcium metabolism in the myometrium that involve in maintaining pregnancy [11]. Although it is biologically plausible, our data did not find this association.

Mitchell *et al.* recorded the Vitamin D deficiency incidence (a serum level of <20 ng/mL) in women during reproductive age to be 31%. Vitamin D status is poorly categorized as an obstetric problem in Iraqi women and little if any study has linked spontaneous abortion to recurrent spontaneous early pregnancy abortion. The cause of pregnancy loss in women with insufficient Vitamin D levels has been investigated by several authors. It is probably mediated by "effector CD4+ T helper (Th) cellular responses in the innate (Th1) and adaptive (Th2) immune systems." Vitamin is proposed to promote them Th2 effect by increasing interleukin (IL)-4, IL-5, and L-13 and preventing then Th1 response of IL-2, IL-1, tumor necrosis factor – alpha, (TNF-α), and interferon gamma (IFN-γ). Vitamin D level is a strong predictor of pregnancy loss in early pregnancy [12].

When an individual is Vitamin D deficient, intestinal calcium and phosphorous absorption decreases, blood ionized calcium levels decline, and parathyroid hormone (PTH) production is enhanced. By raising renal synthesis of 1,25(OH)2D, increasing bone turnover, speeding bone loss, and promoting tubular calcium reabsorption and phosphate excretion increased plasma PTH keeps serum calcium in the normal range [13]. When compared to normotensive control, pregnancy women with preeclampsia had reduced urine calcium excretion, lower ionized calcium levels, greater PTH levels, and lower 1,25-(OH)2 D levels. Low plasma calcium levels trigger numerous typical hypertension mechanisms, including an increase in renal renin and PTH levels. Placental abnormalities that induce reduced active Vitamin D production are considered to be a critical event

in the development of this condition, contributing to lower calcium levels [14].

In this research, of the abortion group, 96.2% had either insufficient, deficient, or severely deficient Vitamin D levels versus 100% of the normal pregnant group. We found no significant association between grading of Vitamin D deficiency and abortion ($p > 0.05$). Contrast with this research result, Elham *et al.* found that mean of 25(OH)D concentration was 22.49 ± 9.22 ng/ml in normal pregnancy group and 30.36 ± 10.03 ng/ml in threatened-abortion patients group and there was a significant difference between the two groups ($p = 0.008$). Serum 25(OH)D levels in threatened-abortion pregnant women are lower than in women with normal pregnancy. Low serum levels of Vitamin D can be considered as a risk factor for threatened-abortion [15]. The study by Yan *et al.* also showed that women with recurrent miscarriage had lower levels of Vitamin D receptor expression in placental villi, decidua, and serum than normal pregnant women, indicating a decrease in Vitamin D receptor expression in pregnancy may be associated with recurrent miscarriages. A study by Kwak-Kim *et al.* also found that Vitamin D deficiency was common in women with repeat pregnancy loss, and those women with Vitamin D deficiency had increased autoimmune and cellular immune abnormalities compared to women with normal Vitamin D levels. A review by Sharif *et al.* also showed that due to the role of Vitamin D in modulating the function of the immune system in maternal-fetal communication and creating a more suitable environment for pregnancy, its deficiency is associated with abortion [16].

This study had some limitations and advantages. One of the limitations in this study did not record the factors affecting Vitamin D levels such as Vitamin D food intake, Vitamin D supplementation, sun-exposure duration, sunscreen appliance, and dressing style. However, this study might be one of a few studies that investigate the association between abortion and Vitamin D levels in Indonesia especially North Sumatera.

Conclusion

In our study, we found that women with abortion had lower serum Vitamin D levels than normal pregnant women, but it was not statistically significant. We also did not find the association between abortion and BMI, parity level, history of miscarriage, and occupation.

Ethical Consideration

Committee has approved all study protocols of Ethics, Nommensen HKBP University, Medan, Indonesia (NO:166A/KEPK/FK/X/2020). All study procedures have following Helsinki's declaration of human rights.

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