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Analysis of maternal serum vitamin D concentrations at birth in women presenting with spontaneous preterm birth: A case-control study

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Abstract

Vitamin D is a potent immune system modulator; its deficiency correlates with increased susceptibility to infections. We evaluated the status of maternal serum vitamin D in women with spontaneous preterm birth. In this case-control study, the maternal serum concentration of vitamin D (25OH D) was measured in 95 women delivering preterm and 92 women having a term birth. Vitamin D sufficiency was found in 79% of the mothers who delivered preterm and 80.4% of the mothers who had term birth (p=0.822). There was a negative correlation between maternal serum concentration of 25 Hydroxyvitamin D and maternal age in the preterm birth group (p=0.043). In conclusion, there was no difference in maternal serum concentrations of 25 Hydroxyvitamin D between women delivering preterm compared to those having term birth. Maternal serum concentration of 25 Hydroxyvitamin D is not associated with occurrence of preterm birth. *(Afr J Reprod Health 2021; 25[2]: 103-109).*

Keywords: Preterm birth, vitamin D, preterm delivery, 25 Hydroxyvitamin D, premature

Résumé

La vitamine D est un puissant modulateur du système immunitaire; sa carence est corrélée à une sensibilité accrue aux infections. Nous avons évalué le statut de la vitamine D sérique maternelle chez les femmes ayant une naissance prématurée spontanée. Dans cette étude cas-témoins, la concentration sérique maternelle de vitamine D (25OH D) a été mesurée chez 95 femmes ayant accouché avant terme et 92 femmes ayant une naissance à terme. Une suffisance en vitamine D a été trouvée chez 79% des mères qui ont accouché prématurément et 80,4% des mères qui ont eu un accouchement à terme (p = 0,822). Il y avait une corrélation négative entre la concentration sérique maternelle de 25 hydroxyvitamine D et l'âge maternel dans le groupe des naissances prématurées (p = 0,043). En conclusion, il n'y avait aucune différence dans les concentrations sériques maternelles de 25 Hydroxyvitamine D entre les femmes ayant accouché avant terme et celles ayant une naissance à terme. La concentration sérique maternelle de 25 hydroxyvitamine D n'est pas associée à la survenue d'un accouchement prématuré. *(Afr J Reprod Health 2021; 25[2]: 103-109).*

Mots-clés: Naissance prématurée, vitamine D, accouchement prématuré, 25 hydroxyvitamine D, prématurée

Introduction

Vitamin D is a fat-soluble secosteroid which has multiple biological effects. It plays a significant role in calcium and phosphate homeostasis and metabolism[1]. Other non-calcium functions of vitamin D have been established. These include modulation of immunity[2,3], stimulation of insulin production[4], effects on myocardial contractility[5,6], promotion of thyroid-stimulating hormone secretion[7–9], and prevention of inflammatory bowel disease[10]. The synthesis of vitamin D involves two hydroxylation processes converting cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) to the biologically active form, 1α, 25 dihydroxyvitamin D (1,25(O.H.)2D) in the liver and kidney[11]. Vitamin D3 is in the majority and is synthesised from cholesterol through a chemical reaction which depends on ultraviolet B-rays[12,13] while vitamin D2 is ingested from diet and supplements[14]. During

pregnancy, 1,25(O.H.)2D is also synthesised by human decidua and placenta tissues[15]. At the same time, the synthesis of 1, 25(OH) 2D by the kidneys is increased. Thus, 1,25(O.H.)2D concentration increases during pregnancy with maximum levels reached during the third trimester[16].

Worldwide, vitamin D deficiency has been reported in women of reproductive age[17]. Despite the sufficient and stable sunny conditions across the tropical countries enabling endogenous production of vitamin D, high prevalence of vitamin D deficiencies in pregnancy and lactating women have been reported in the literature[18–21]. This has been attributed to dark skin pigmentation which is prevalent in these areas and a range of lifestyle factors including the increased time they spend indoors, covered clothing due to the religious customs, liberal use of sun creams for fear of cancer [22]. The deficiency of vitamin D in pregnancy has been associated with various maternal and fetal complications. Maternal adverse effects include preeclampsia[23], gestational diabetes mellitus[24], and preterm birth[25], and fetal complications of small for gestation age, low birth weight, and neonatal hypocalcemia[26].

Preterm birth remains a global health problem with an average preterm birth rate of 11.1% every year[27]. Malawi is one of the countries with a very high preterm birth rate of 18.1%[27]. Various pathological processes have been identified as precursors leading to a common pathway of increased myometrial contractility, cervical dilatation and chorioamnionic membrane weakening and rupture resulting in spontaneous preterm birth (spPTB)[28]. Infections have been causally linked to spPTB[29]. Vitamin D is a potent immune system modulator that its deficiency correlates with increased susceptibility to infections due to impaired localised innate immunity and defective antigen-specific cellular immune response[30].

Considering the high preterm birth rate in Malawi and the vital role which vitamin D play in immune modulation in humans, we evaluated the status of vitamin D in spPTB in a low resource tropical country. The null hypothesis was that there is no relationship between serum concentration of vitamin D and the prevalence of spPTB.

Methods

A case-control study was conducted between June 2016 and March 2017 at Kamuzu Central Hospital (KCH) and Bwaila Hospital (B.H.), public and government-funded tertiary and general hospitals respectively. These two hospitals are 4 kilometres from each other within the city of Lilongwe, in the central region of Malawi. Neonatal services are only available at KCH. The target population was all pregnant women presenting with spPTB at the hospitals. Women presenting with spontaneous preterm birth (gestation 28 - <37 weeks) were recruited as cases and controls were women presenting with spontaneous labour at term (gestation ≥37-41 weeks). The measured outcome was maternal serum concentrations of vitamin D. Women with comorbidities (preeclampsia, gestational diabetes, and heart disease), multiple pregnancies, intrauterine growth restriction (IUGR), fetal anomaly, preterm premature rupture of membrane (PPROM) were excluded from the study. Systematic random sampling was done by allocating numbers to all eligible preterm cases and all with odd numbers recruited in the study. Controls were recruited as they presented in the labour ward and matched to the living area. This study was approved by the ethics committee of the University of Malawi, College of Medicine Research Committee (COMREC) P.05/15/1738.

All data and samples were obtained soon after delivery. After obtaining written informed consent, 5 millilitres of blood was collected from the woman using a regular vacutainer technique. The blood sample was centrifuged at 3000g for 10 minutes within 30 minutes of collection. The serum was stored at -80°C in a screw-top vial until further analysis. Vitamin D metabolites (25 Hydroxyvitamin D_2 and Hydroxyvitamin D_3) were analysed by Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) using Waters Acquity™ *I*-class UPLC system with an autosampler, and a binary solvent delivery system (Waters, Milford, MA) interfaced to Waters Xevo TQ-S benchtop tandem quadrupole mass spectrometer (Waters, Manchester, U.K.). Data was collected in a cross-section way on all maternal demographics, race, wearing of concealed clothing,

education status, HIV status and use of HAART. Gestation age was based on early fetal ultrasound or modified Ballard examination. Determination of haemoglobin was done using HemoCue Hb 301 (HemoCue AB, Angelhalm, Sweden).

Statistical analysis

A value of less than ≤50nmol/L was taken as a threshold to define deficiency of vitamin D; insufficiency was 51 -74 nmol/L and sufficiency were 75-250nmol/L[31]. A sample size of 90 was reached through the power of test calculation. This sample size gives 80% power to detect a significant difference at 5% level of significance. Data were processed using IBM SPSS version 20.0 software and imported into STATA 14.0 for analysis. A binary variable was generated for the primary outcome of spPTB (cases) coded as 1 and term birth (controls) coded 0. One-way frequencies were computed for categorical variables, while mean and standard deviation were calculated for continuous variables that were normally distributed. Log transformation was done where there was a presence of highly skewed data. Two-way associations between independent variables and the outcome variable of preterm birth were investigated using the Student t-test for continuous independent variables and the Chi-squared test for categorical variables. Pearson correlation was used to determine the effect of two values on each other. P-values from all tests of less than 0.05 were considered statistically significant.

Results

There were a total of 187 mothers, 92 were term birth group with mean maternal age of 26.2 years (SD: 5.9), while 95 were preterm births with mean maternal age of 23.9 years (SD: 6.1) participating in the present study (Table 1). All participating women were of the black race and wore no protective clothing. Term births group had significantly higher maternal age compared to preterm birth group (p=0.008). The preterm birth group were more likely to have a haemoglobin of <11g/dl (62/95, 65.3%) compared to term birth group (42/92, 45.7%) (p=0.007). Gravidity, education, Human immunoglobulin Virus (HIV) status and use of HAART were not significantly different between the two groups. Similarly, there was no difference in the concentration of 25(O.H.) D between women delivering preterm and those having a term birth, p=0.822.

The data was further analysed by Pearson correlation to determine the effect of maternal age, gravidity, and birth weight on micronutrients concentrations in the preterm birth group and in the term group. There was a negative correlation between maternal serum concentration of 25(O.H.) D and maternal age (p=0.043), as shown in Figure 1. No correlation was observed between maternal serum concentration of 25(O.H.)D and gravidity (p=0.147) or birth weight (p=0.661) in the preterm birth group.

Similarly there was no correlation between maternal serum concentration of 25(O.H.)D and maternal age (p=0.190) gravidity (p=0.510), and birth weight (p=0.064) in the term birth group, (Figure 2).

Discussion

The present study indicates that there is no difference in maternal concentrations of 25(OH)D between women who delivered preterm and those who had term birth. However, the study found a negative correlation between the maternal concentration of 25(O.H.) D and maternal age in the preterm birth group. Vitamin D sufficiency was found in 79.0% of the mothers who delivered preterm and 80.4% of the mothers who delivered at term, and this was not statistically different. There are no data on serum 25(OH) D concentrations in pregnant women in Malawi. Other published studies from other regions indicate lower concentrations of vitamin D in women delivering preterm. A study in Brazil looking at 92 women with preterm birth, the mean vitamin D concentrations was significantly lower in women having a preterm birth, p=0.011[32]. Another study in Japan found concentrations of 25(O.H.) D significantly different in preterm birth compared to term birth group[33]. The study population in these studies are culturally, environmentally and, nutritionally diverse from the Malawi population.

This study design did not measure the cause-effect association. However, vitamin D deficiency is known to be associated with multiple adverse pregnancy outcomes, including preterm birth[30,34].

Table 1: Maternal clinical characteristics by gestation age (preterm versus term births)

Characteristic	Term births n=92	Preterm births n=95	p-value
Maternal age, Mean(SD†), (years)	26.2(5.9)	23.9(6.1)	0.008*
Gestation, Mean(SD), (weeks)	38.0(1.0)	33.4(2.5)	<0.001*
Black race, N‡ (%)	92(100)	95.0(100)	-
Wearing concealed clothing, N(%)	0 (0)	0(0)	-
Birth weight, Mean(SD) , (kg)	3.1(0.4)	2.1(0.5)	<0.001*
Gravidity 1-2, N(%)	48(52.2)	64(67.4)	0.085
At least secondary education, N(%)	48(52.2)	36(37.9)	0.075
HIV§ positive, N(%)	15(16.3)	13(13.7)	0.300
Use of HAART¶, N(%)	15(16.3)	9(9.5)	0.163
Haemoglobin <11g/dl, N(%)	42(45.7)	62(65.3)	0.007*
25(O.H.)D††, N(%), nmol/L			
≤50 (deficiency)	2(1.1)	4(4.3)	0.822
51-74 (insufficiency)	16(17.4)	16(16.8)	
75-250 (sufficiency)	74(80.4)	75(79.0)	

† standard deviation, ‡ number, § human immunoglobulin virus, ¶ Highly active antiretroviral treatment, * significant values, †† 25 Hydroxyvitamin D
t-test used for continuous variables, Chi-square or Fisher's Exact test used for categorical variables

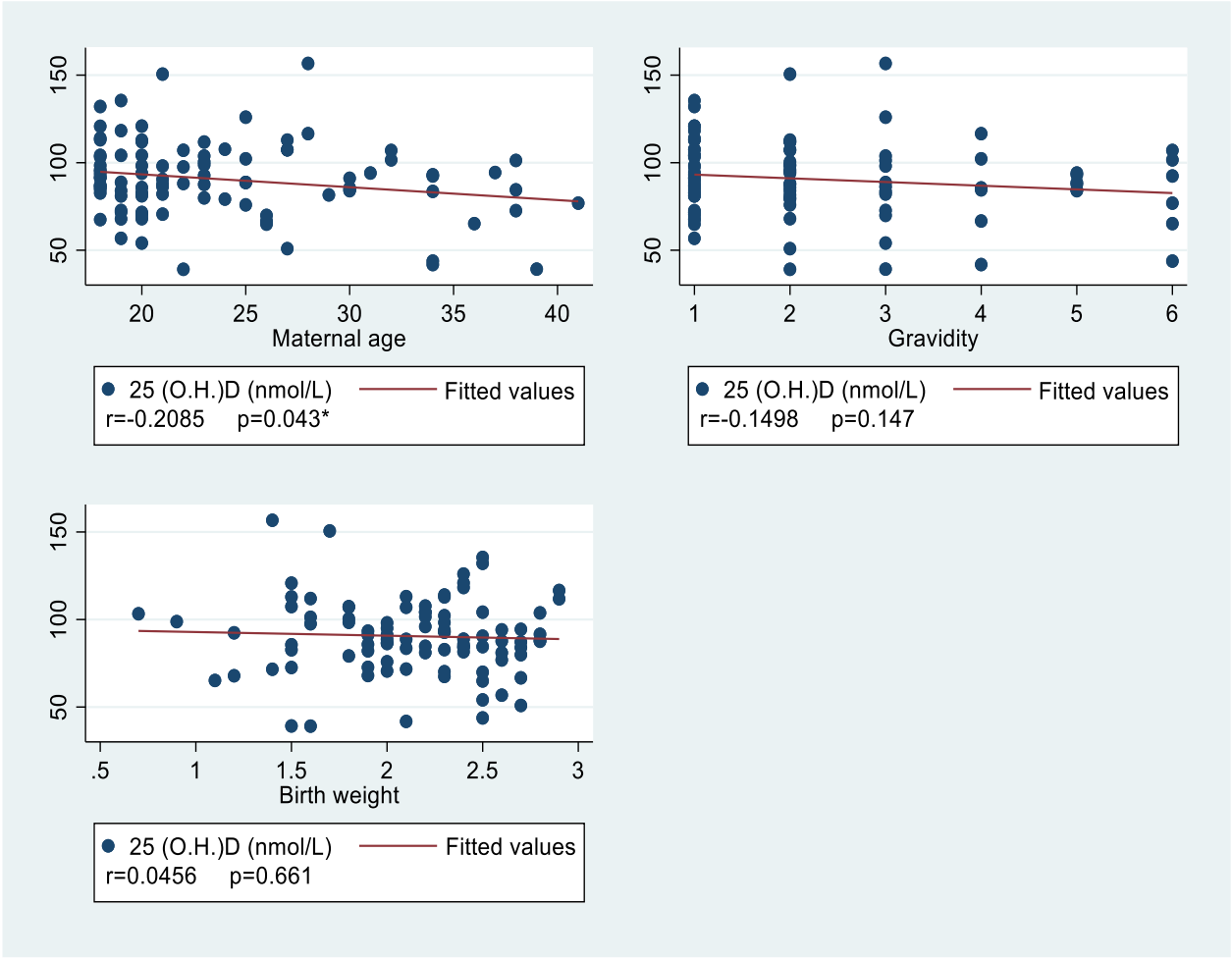

Figure 9: Correlation between maternal serum concentrations 25(O.H.)D and maternal age, gravidity, birth weight respectively in the preterm group

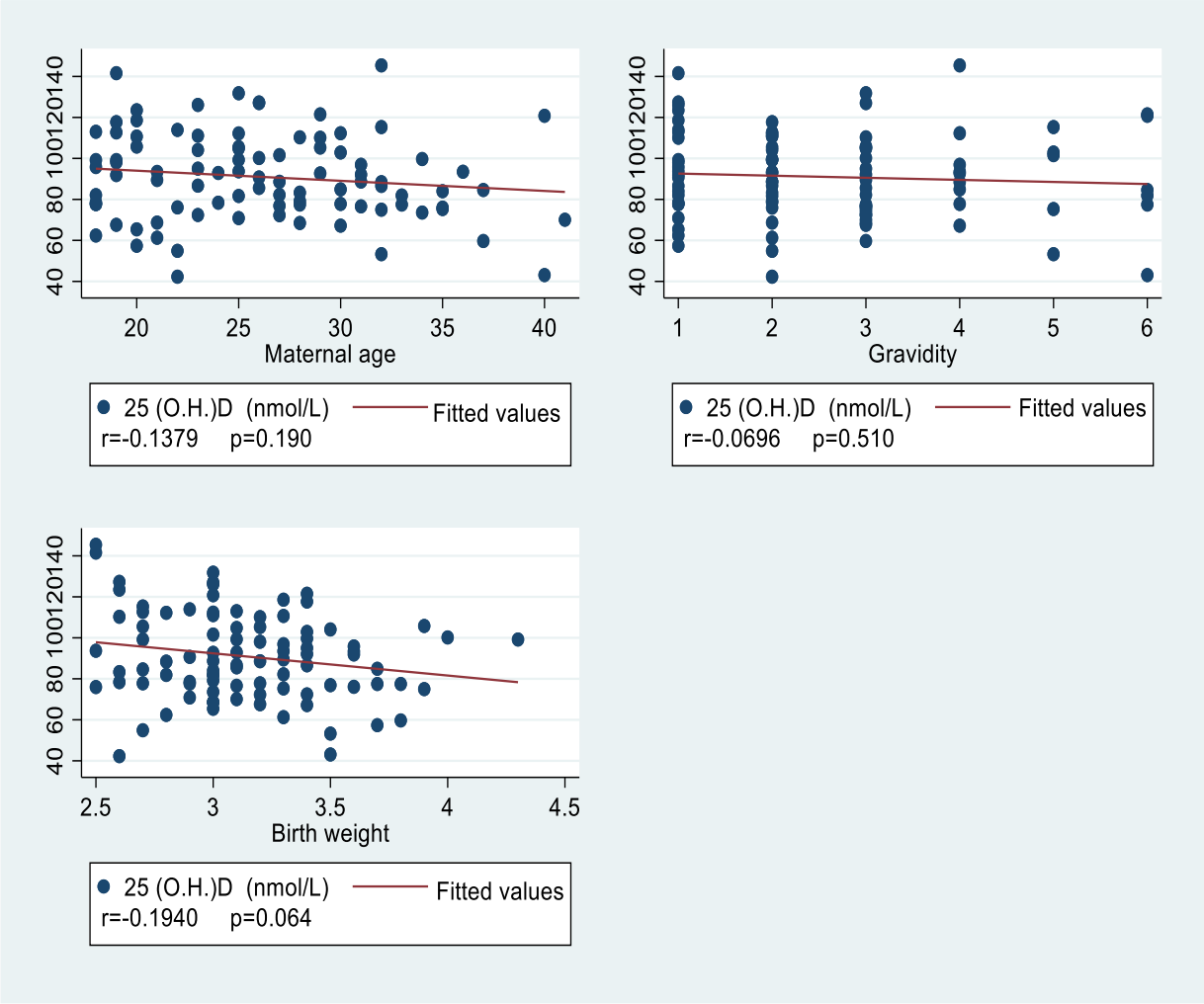

Figure 2: Correlation between maternal serum concentrations 25(O.H.)D and maternal age, gravidity, birth weight respectively in the term birth group

Previous studies had indicated that vitamin D reduces pro-inflammatory cytokines in conditions characterised by inflammation[35]. Inflammation is considered a precursor leading to preterm birth[28]. The difference between term and preterm birth was not seen in our study.

In this study, we observed a significant negative correlation between maternal age and maternal serum concentrations of 25(OH) D in the preterm group which was not present in term birth group. This finding is similar to what previous studies have reported[22,36]. Following changes in social demographics and increasing immobility associated with increasing age, women tend to stay more indoors reducing sun exposure required for vitamin D synthesis[22]. Deficiency of vitamin D is also more prevalent in old age due to endocrine changes accompanying increasing age. These include the development of intestinal resistance to 1,25(O.H.)2D hampering intestinal calcium uptake, decrease in the number of vitamin D receptor in various organs involved in calcium metabolism and reduced activity of 1α-hydroxylase due to decrease in renal function, reducing the activation of vitamin D[37].

When interpreting these results, it should be considered that there was no information on nutrition status and body mass index for the study population. Previous studies had indicated a higher body index to be associated with decreased levels of vitamin D[38]. The adipose tissue sequesters vitamin D. Despite this weakness, the results from

this study add on a body of evidence regarding maternal serum concentrations of vitamin D in term and preterm pregnancies in Malawi women. This study population was from two main hospitals in the central region of Malawi. We don't know if this reflects the general pregnant population in the country.

Conclusion

The study demonstrated the serum concentrations of vitamin D in pregnant women delivering at the two urban hospitals in the central region of Malawi. Serum concentrations of 25(O.H.) D were not significantly different between the preterm and term births. There was a negative correlation between maternal age and serum concentrations of vitamin D in the spPTB group. Considering that there was no correlation between increasing maternal age and maternal serum concentrations of 25(O.H.)D in the term birth group, the study recommends further research confirming this finding in other pregnant women communities' outside the Lilongwe urban, central Malawi and establish a causal relationship if indeed it exists.

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Conflict of interest

The authors have no conflict of interest.

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