

Vitamin D Levels in Pregnant Congolese Women and Their New-Borns, and the Association with Neonatal Outcomes – A Pilot Study

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Abstract

Background: This study was thus undertaken to study the estimation of vitamin D levels in pregnant women and their newborns in DRC and to study its association with various neonatal outcomes.

Methods: Observational study done on 569 pregnant women and their newborn babies. Sample obtained from maternal serum and cord blood from the placental end during peripartum period. The data was analysed to estimate the prevalence of vitamin D levels in mothers and newborns and to identify association, if any, between maternal vitamin D levels and neonatal outcomes.

Results: 464 mothers had sufficient vitamin D (VDS) levels (≥ 30 ng/dL) and 105 had vitamin D deficiency (VDD) with mean maternal serum vitamin D level of 35.63ng/ml (SD 6.18, range 9.2-39.8). All the newborns (n=569) were vitamin D deficient (< 30 ng/ml). The percentage of LBW babies born to VDD mothers was 18.09%, which was very similar to the percentage of LBW babies born to VDS mothers (18.31%) ($p=0.76456749$). The incidence of caesarean section was 58.09% in the vitamin D deficient (VDD) group as compared to 19.61% in the sufficient (VDS) group ($p<0.0005$). The incidence of preterm births was 10.77% in the sufficient group (VDS) as compared to 17.14% in the vitamin D deficient (VDD) group ($p=0.038$).

Conclusion: Our findings will help health professionals, policy makers, and the general public in Africa aware of the high prevalence of vitamin D deficiency and the associated health risks.

Introduction

Vitamin D is a fat-soluble secosteroid, 1,25 dihydroxy vitamin D [1,25(OH) 2D] and is required for calcium and phosphorous homeostasis, bone mineralization and skeletal growth contributing for overall musculoskeletal growth^[1]. There are multiple sources of vitamin D, plants- fresh and sun dried mushroom, animal- cod liver oil, egg yolk, Salmon, tuna etc., supplements and sunlight^[2]. Vitamin D deficiency is a major global public health issue with around 1 billion people worldwide having vitamin D deficiency^[3]. The status of vitamin D in pregnant women are on an average lower than equivalent non-pregnant women's levels which may be partly explained by increased fetal demands for vitamin D^[4]. The circulatory vitamin D is converted to its active form by an enzyme 1 α -hydroxylase, contained within the placenta^[5]. Maternal vitamin D status depends on consumption, absorption and metabolism of dietary vitamin D, which significantly effects the fetal vitamin status^[6]. Recent studies have reported a link between maternal vitamin D deficiency and adverse pregnancy outcomes such as pre-eclampsia^[7], gestational diabetes^[8], small-for-gestational-age^[9], Caesarean section^[10] and bacterial vaginosis^[11]. Vitamin D deficiency in women can cause pelvic deformities, which poses increased risk of obstructed labor leading to assisted/instrumental delivery^[11]. Multiple neonatal complications such as neonatal hypocalcemia, impaired growth, decreased bone mineral density, skeleton deformity, low birth weight and prematurity are associated with low vitamin D levels in pregnancy^[12]. Globally, more than 20 million infants are born with low birthweight. The number of low birthweight babies is concentrated in two

regions of the developing world: Asia (72%) and Africa (22%)^[13]. Influence of vitamin D on skeletal growth provides a possible explanation for its association with LBW^[14]. An estimated 15 million babies are born prematurely every year^[15] and vitamin D is being increasingly researched for its protective effect against the risk for preterm births due to its role in immunomodulatory and anti-inflammatory processes^[16, 17]. Vitamin D also regulates the calcium concentration across the myometrial cell membranes thus influencing its contractility and preventing onset of preterm labour^[18]. Although, there is ambiguity in the optimal serum concentration of vitamin D, levels above 30 ng/mL (75 nmol/L) is considered sufficient; 21–29 ng/mL (51–74 nmol/L) insufficient and below 20 ng/mL (50 nmol/L) is considered deficient^[12, 19]. The recommended levels for special groups such as pregnancy are higher than 30 ng/mL^[20]. Recent studies also suggest association of vitamin D with cancer, cardiovascular disease, diabetes and immunity, however enough high quality evidence is still lacking to support a cause-and-effect relationship^[21].

Vitamin D deficiency, as mentioned above is associated with infectious as well as non-communicable diseases. The burden of infectious diseases is enormous in Africa, and the prevalence of non-communicable diseases is on a sharp rise^[22]. As per WHO (2014) the estimated burden of non-communicable diseases will overhaul that of communicable diseases in Africa by 2030, due to lifestyle changes related to rapid urbanisation^[23].

Previous studies and reports of vitamin D prevalence and association have reported that vitamin D deficiency exists in African populations, but these reviews had hardly any studies from Africa and none of them quantified the overall prevalence in the population.

This study was undertaken to study the prevalence of vitamin D levels pregnant women and newborns and to study its association with various neonatal outcomes.

To the best of our knowledge, this is the first study of its kind, in the Democratic Republic of Congo (DRC), and also in Africa.

Materials And Methods

Study design:

It was an observational, cross-sectional epidemiological study.

Inclusion criteria:

1. Healthy pregnant Congolese women and their newborn.

Exclusion criteria:

1. Pregnancy losses, spontaneous abortion and still birth.
2. Twin/triplet were excluded because of their high risk of PTB, LBW, LSCS [24].
3. Metabolic bone disease
4. Type 1 diabetes and malabsorption diseases
5. Known history or evidence of Rheumatoid arthritis, Thyroid, Parathyroid, Adrenal diseases, Hepatic or Renal failure.

Methodology

A total of 569 individuals were recruited into the study group after applying inclusion and exclusion criterion. The Institutional Ethics Committee approved the study protocol and informed consent was obtained from the study subjects. The data for this observational study included cord blood samples taken during peri-partum period, maternal and neonatal medical records data were collected from birth register and ANC card diary from the hospital. The primary objective of this project was to assess the vitamin D status in maternal serum, cord blood and to study its association with various neonatal outcomes (birth weight, mode of delivery, preterm births and small for gestational age). Vitamin D deficiency was defined as serum levels of 25(OH)D less than 30 ng/dL [20].

Observations And Results

1. Maternal vitamin D levels:

A total of 569 samples of maternal serum were analyzed for serum 25(OH)D levels in this study. 464 mothers had sufficient vitamin D (VDS) levels (≥ 30 ng/dL) and 105 had vitamin D deficiency (VDD). The mean maternal serum 25(OH) D level was 35.63 ng/ml (SD 6.18, range 9.2–39.8) (Table 1).

Table 1
CLASSIFICATION OF MATERNAL 25(OH) D LEVELS.

Maternal 25(OH) levels	
n	569
Mean (ng/ml)	35.63
SD	6.18
Range (ng/ml)	9.2–39.8
VDS (%)	464 (81.54%)
VDD (%)	105(18.45%)
*VDS = Vitamin D sufficient, VDD = Vitamin D deficiency.	

2. Cord blood (Neonatal) vitamin D levels:

All the newborns (n = 569) were vitamin D deficient (< 30 ng/ml). The median 25(OH)D level was 12.22 ng/mL, mean 13.529, SD = 3.794, range = 7.9–27 ng/mL. 317 newborns were males with median 25(OH)D level = 12.22 ng/mL, mean = 13.60, SD = 3.805, max = 27 ng/mL, min = 7.9 ng/mL. 252 were females with median 25(OH)D level = 12.3 ng/mL, mean = 13.44, SD = 3.776, max = 27 ng/mL, min = 8.2 ng/mL. The difference in levels of vitamin D between male and female newborns was not significant (p = 0.089).

3. Birth weight:

Out of 569 newborns, 104 (18.27%) were low birth weight (LBW) and 465 (81.27%) were normal birth weight (NBW). The mean cord blood 25(OH) D level in the NBW neonates was 13.44 ng/ml (SD 4.19, range 7.9–24) and in the LBW neonates was 13.56 ng/ml (SD 3.69, range 8.2–27), the difference was not statistically significant (p value < 0.77).

The percentage of LBW babies born to VDD mothers was 18.09%, which was very similar to the percentage of LBW babies born to VDS mothers (18.31%). These results were not statistically significant (p = 0.76456749).

Table 2
STATUS OF VITAMIN D IN MOTHERS AND LBW/NBW

	n	LBW	NBW
VDS mothers	464	85(18.31%)	379(81.68%)
VDD mothers	105	19(18.09%)	86(81.09%)
Total	569	104(18.27%)	465(81.72%)
P value	0.76		
*VDD-vitamin D deficient, VDS- vitamin D sufficient, LBW-Low birth weight, NBW-Normal birth weight			

4. Mode of delivery:

152 (26.71%) newborns were born by Caesarian section (LSCS) and 417 (73.28%) by spontaneous vaginal delivery. The mean cord blood 25(OH)D level of the neonates born by vaginal delivery was 14.05 ng/ml (SD 3.86, range 8.2–27) whereas those born by LSCS was 12.11 (SD 3.18, range 7.9–22), which was significantly lower (p value < 0.00000042).

The incidence of LSCS was 58.09% in the vitamin D deficient (VDD) group as compared to 19.61% in the sufficient (VDS) group. The difference was found to be statistically significant (p < 0.0005).

Table 3
RATE OF LSCS AND VAGINAL DELIVERY IN VDS AND VDD MOTHERS

	n	LSCS	VD
VDS mothers	464	91(19.61%)	373(80.38%) 18.27%
VDD mothers	105	61(58.09%)	44(41.90%) 81.72%
Total	569	152(26.71%)	417(73.28%) 100%
P value	0.0005		
*VD- vaginal delivery, LSCS- lower segment caesarean sectio, VDS = Vitamin D sufficient VDD = Vitamin D deficiency			

5. Preterm:

Out of the total 569 deliveries, **501 (88.04%)** occurred at term (≥ 37 weeks period of gestation) and **68 (11.95%)** were preterm (< 37 weeks period of gestation). The mean cord blood 25(OH)D level of preterm neonates was 12.68 ng/ml(SD 3.85, range 7.9–22) and term neonates was 13.63 ng/ml(SD 3.76, range 8.2–27). The difference in values was statistically significant (p value = 0.035).

Out of 464 vitamin D sufficient mothers, 50(10.77%) delivered before term and 414(89.22%) delivered at term. Out of 105 vitamin D deficient mothers, 18(17.14%) delivered before term and 87(82.85%) delivered at term. The incidence of preterm births was **10.77%** in the sufficient group as compared to **17.14%** in the vitamin D deficient group. This difference was statistically significant (p = 0.038). The rate of preterm delivery was 1.59 times higher in mothers with vitamin D deficiency.

Table 4
RATE OF TERM VS PRETERM NEWBORNS IN VDS AND VDD MOTHERS

	n	Preterm	Term
VDS	464	50(10.77%)	414(89.22%)
VDD	105	18(17.14%)	87(82.85%)
TOTAL	569	68 (11.95%)	501 (88.04%)
			100%
P value	0.038		
* VDS = Vitamin D sufficient VDD = Vitamin D deficiency			

6. Small for gestational age (SGA):

On segregating the neonates on the basis of expected birth weight as per period of gestation calculated by Fetal Weight Equation (Hadlock et al) (84), **476(83.65%)** neonates had weight appropriate for gestational age (AGA) whereas **93(16.34%)** were small for gestational age (SGA). The mean cord blood 25(OH)D level of AGA and SGA neonates were similar (p = **0.99**).

The percentage of SGA babies born to mothers with VDD was 13.97%, which was very similar to the percentage of SGA babies born to mothers with Vitamin D sufficiency at 17.24% (**p value = 0.40**).

Table 5
RATE OF SGA AND AGA IN VDS AND VDD MOTHERS

	n	SGA	AGA
VDS	464	80(17.24%)	384(82.75%)
VDD	105	13(12.38%)	92(87.61%)
TOTAL	569	93 (16.34%)	476 (83.65%)
			100%
P value	0.40		
* VDS = Vitamin D sufficient VDD = Vitamin D deficiency, SGA = small for gestational age, AGA = appropriate for gestational age			

Discussion

A total of 569 cord blood samples were collected in DRC from Congolese mothers and their new-borns and were analyzed for 25(OH)D levels. The mean maternal serum 25(OH) D level was 35.63 ng/ml (SD 6.18, range 9.2–39.8). The classification of maternal 25(OH) D levels was done as per US Endocrine society in which 464(81.54%) mothers were found to have sufficient (≥ 30 ng/ml) and 105(18.45%) deficient Vitamin D levels (Table 1). Majority of mothers (81%) were having sufficient vitamin D levels. This finding is in contrast to many other studies which had found high prevalence of vitamin D deficiency during pregnancy^[5, 25].

In present study, none of the neonates(n = 569) had sufficient 25(OH)D (≥ 30 ng/ml) as per US Endocrine society classification of vitamin D deficiency. Sachan^[26] et al conducted a study to determine the prevalence of Osteomalacia and Hypovitaminosis D in Pregnant women and cord blood. They included 117 cord blood samples and observed high prevalence of Hypovitaminosis D(< 20 ng/ml) with 95.7% (mean 8.4 ng/ml) of neonates deficient in vitamin D. These findings corroborated with findings in our study. A prospective Cohort Study, conducted in Shanghai by Yu^[27] et al with a birth cohort of 1071 infants to estimate the prevalence of vitamin D in cord blood and maternal blood found that 36.3%(388) were having 25(OH)D < 20 ng/ml and 84.1%(900) had < 30 ng/ml 25(OH)D. Bowyer's^[5] et al found 98(11%) of 901 neonates deficient in Vitamin D (< 25 nmol/l or 10 ng/ml) as compared to 100.00% vitamin D deficiency observed in current study. These findings were different from our study which could be attributed to defining criteria for vitamin D deficiency in cord blood as < 10 ng/ml in Bowyer's study against < 30 ng/ml in present study. Hence, high prevalence of vitamin D deficiency in newborns was observed in above studies similar to our study (99.99%) which affirms that vitamin D deficiency is a major health problem and can possibly adversely affect neonatal outcomes.

This study attempted to evaluate the association (if any) between the maternal vitamin D levels and neonatal birth weight. 104 (18.27%) newborns were low birth weight (LBW) and 465 (81.27%) were normal birth weight (NBW)(Table 2). The percentage of LBW corroborates with the prevalence of LBW in south Asia (20%)^[28, 29]. The percentage of LBW babies born to VDD mothers was 18.09%, which was very similar to the percentage of LBW babies born to VDS mothers (18.31%) ($p = 0.76456749$). Hence, vitamin D status in maternal blood during peri-partum period was not associated with LBW as per our study. These findings were similar to an observational study CR Gale et al^[30], in which 596 pregnant women were recruited and maternal 25 (OH)-vitamin D concentrations were measured in late pregnancy. There was no statistically significant association seen between maternal Vitamin D and weight at birth ($P = 0.247$). Morley and Carlin studied the relationship between maternal vitamin D and PTH concentrations at less than 16 and 28-week gestation and offspring birth size. 374 out of 475 (79%) women completed the study and they found no evident relationship between birth size and maternal vitamin D levels^[31]. However, Alison D Gernand et al^[32] reported higher birth weight in babies born to the mother with vitamin D status ≥ 37.5 nmol/L than the mothers with levels < 37.5 nmol/L. They further noticed a nonlinear relation between 25(OH)D and birth weight in which birth weight increased by 3.6 g per 1 nmol/liter increase in maternal 25(OH)D up to 37.5 nmol/liter and then leveled off thereafter. The results obtained in this study were incongruous to our findings. The possible explanation could be large sample size (n =

2146), maternal serum being analyzed in first trimester as compared to our study in which the samples were drawn during perinatal period and different cut off points to classify serum vitamin D levels.

The relationship between maternal vitamin D levels and mode of delivery was also studied. Out of the total 569 cases, 417 (73.28%) delivered vaginally and 152 (26.71%) underwent LSCS (Table 3). Out of 105 vitamin D deficient mothers, 61(58.09%) underwent LSCS in comparison to 91(19.61%) of the vitamin D sufficient mothers and this difference was highly significant ($p < 0.00001$). The rate of Cesarean deliveries was 2.96 times higher in mothers who had deficient vitamin D levels (< 30 ng/ml). Merewood A^[33] (2009) obtained similar results with fourfold increase in rates of caesarean section in women with vitamin D levels below 37.5 nmol/liter ($p = 0.012$) after controlling for race, age, education level, insurance status and alcohol use. Another result similar to our study was reported by Scholl^[34] during his analysis of a cohort of 1153 low-income pregnant women in which vitamin D deficiency was linked to a 2-fold increased risk of cesarean. However, Sakineh et al^[35] (2015) in a triple blind randomized controlled trial on 126 pregnant ladies, found no relation between vitamin D and mode of delivery. This result is not consistent with the results of present study. The possible explanation for this finding is that over one third (34.1%) of caesarian deliveries in the study by Sakineh et al were due to previous caesarian surgery or elective caesarian delivery.

Out of the total of 569 deliveries, 501(88.04%) occurred at term (≥ 37 weeks period of gestation) and 68 (11.95%) were preterm (< 37 weeks period of gestation) (Table 4). The incidence of preterm births have been reported to range from 5–7% of live births in developed countries, but are estimated to be substantially higher in developing countries^[36]. Beck S^[37] et al estimated that 9.6% of all births worldwide in 2005 were preterm and approximately (85%) of these preterm births were concentrated in Africa and Asia. The findings in these studies are close to figures in current study (11.95% preterm births). The incidence of preterm births was 10.77% in the vitamin D sufficient group (≥ 30 ng/ml) as compared to 17.14% in the vitamin D deficient group ($p = 0.038$). The rate of preterm delivery was 1.59 times higher in mothers with vitamin D deficiency and the difference was statistically significant. Perez-Ferre^[38] et al. also observed that maternal vitamin D deficiency increased the risk of premature delivery with Odds Ratio of 3.31 (95% CI 1.52–7.19). A systematic review and meta-analysis consisting of 24 studies reported the association between maternal blood vitamin D levels and adverse pregnancy outcomes including preterm birth, preeclampsia and gestational diabetes mellitus (GDM)^[39]. The results revealed that women with circulating vitamin D level less than 20 ng/mL (50 nmol/L) in pregnancy had an increased risk of preterm births [OR 1.58 (1.08–2.31)], preeclampsia [odds ratio (OR) 2.09 (95% confidence intervals 1.50–2.90)] and GDM [OR 1.38 (1.12–1.70)]. The cut off levels for vitamin D deficiency in both the above studies was taken at 20 ng/mL (50 nmol/L) in contrast to current study (vitamin D deficiency < 30 ng/ml) despite which the results were similar and statistically significant ($p = 0.038$). This indicates that even vitamin D levels between 20–30 ng/ml are associated with increased risk of preterm births. A systematic review by De-Regil and Luz Maria,^[40] et al from the cochrane database reported that vitamin D supplementation during pregnancy reduces the risk of preterm births compared to no intervention or placebo (8.9% versus 15.5%; RR 0.36; 95% CI 0.14 to 0.93). The results corroborate with current study, however current study did

not take vitamin D supplementation during pregnancy into account. Various other studies have shown that both maternal and neonatal 25(OH)D concentrations do not have any association with the risk of preterm births. In a randomized controlled trial by Yu^[41] et al, no significant difference in gestational age at delivery was found. In an RCT by Hollis BW^[42] et al, vitamin D supplementation with 50–100 mcg/day did not alter gestational duration compared with vitamin D supplementation of 10 mcg/day. A prospective study conducted by Hossain^[43] et al which included 75 mothers alongwith their newborns. Maternal vitamin D levels for sufficiency was taken as 30 ng/mL (75 nmol/L) similar to current study. Hossain et al found higher maternal and cord blood vitamin D status to be associated with shorter gestational periods ($r = 0.33$, $p = 0.003$). This finding is in contrast to current as well as most other studies which could be explained by relatively small sample size (75 vs 569 in current study).

The percentage of SGA babies born to mothers with VDD was 13.97%, which was very similar to the percentage of SGA babies born to mothers with Vitamin D sufficiency at 17.24% (p value = 0.40) (Table 5). The findings of current study concurred with Farrant, Hannah JW, et al^[44]. However Leffelaar^[45] et al in a large multiethnic study found higher risk of SGA in women with deficient vitamin D levels (OR = 2.4, 95%CI 1.9-3.2).

The possible reasons for the contrasting results in the relation between vitamin D and various neonatal outcomes can be due to several variables such as pre-pregnancy BMI, arbitrary cut-off values for vitamin D, smoking status (including second hand smoke), socioeconomic status, physical activity (pre-pregnancy as well as during pregnancy), ethnicity, geographical location, season of birth, emotional distress^[46] etc. However, potential role of vitamin D cannot be undermined in mitigating risk for Caesarean section and preterm births as seen in current study.

The strength of this study is that a large sample size (569) with relatively uniform population in terms of socioeconomic status was studied. Secondly, sampling for vitamin D was done during the peripartum period when levels of vitamin D are not falsely high as compared to first and second trimester^[47]. Thirdly, this study was done exclusively on Congolese ladies, to find race-specific correlation.

The prevalence of vitamin D deficiency is high in Africa, and DRC is no exception, and our study reiterates this. Public health strategies in DRC should escalate efforts to prevent, detect, and treat vitamin D deficiency, particularly in new-borns, women, and urban populations.

LIMITATION

The limitation of the study was that factors such as pre-pregnancy BMI, vitamin D supplementation, smoking/other substance use etc. were not taken into account.

Conclusion

All the neonates (100%) were deficient in Vitamin D, with no significant difference between male and female neonates. The rate of preterm delivery was 1.59 times higher in mothers with vitamin D deficiency and the difference was statistically significant. The rate of Cesarean deliveries was 2.96 times higher in mothers who had deficient vitamin D levels. Maternal vitamin D status during late pregnancy (peripartum period) did not have any statistically significant effect on the neonatal birth weight and small for gestational age. Our findings may help to increase awareness of these problems and promote the vitamin D supplementation to neonates.

Declarations

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Taken

CONSENT FOR PUBLICATION

Given

Availability of data and materials

Yes

AUTHORS' CONTRIBUTIONS

All authors have contributed partly or wholly in all or at least 3 of - Study conception and design, Acquisition of data, Analysis and interpretation of data, Drafting of manuscript, Critical revision.

COMPETING INTERESTS

Nil

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Nil

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