Relationship between maternal serum vitamin D deficiency, maternal serum calcium level, and primary caesarean section

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Abstract: Background: Vitamin D deficiency might be responsible for poor muscular performance causing dysfunctional labor, while a rise in intracellular calcium has been proven as a primary trigger for human myometrial contractions. **Objectives:** The aim of our study was to assess the relationship between maternal vitamin D (serum 25-hydroxyvitamin D [25(OH)D]) deficiency, maternal serum calcium level, and primary caesarean section. **Materials and Methods:** This was a case-control study. 75 women who delivered by primary caesarean section after 37 weeks of gestation were taken as cases and another 75 women who delivered vaginally were taken as controls. All patients were subjected to measurement of serum 25(OH)D, and serum calcium within 72 hours following giving birth. Vitamin D deficiency was diagnosed when the serum 25(OH)D level was ≤15 ng/ml and this was compared between cases and controls. **Results:** 33% of women who had primary caesarean section had serum [25(OH)D] less than 15 ng/ml, compared with only 15% of women who delivered vaginally (p = 0.007). In multi-variable logistic regression analysis controlling for maternal age, fetal weight, parity, education level, drank milk in pregnancy, prenatal multivitamin supplements, and infant gender, women with vitamin D deficiency (< 15 ng/ml) were almost 3 times as likely to have a primary caesarean section as women without deficiency (p = 0.048; adjusted odds ratio 2.835, 95% confidence interval 1.701-7.95). In addition, there were no statistically significant differences between median maternal serum calcium levels in women who had caesareans and women who delivered vaginally. **Conclusion**: Vitamin D deficiency was associated with increased odds of the primary caesarean section.
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Keywords: Vitamin D deficiency, serum calcium, caesarean section

1. Introduction

At the turn of the 20th century, rickets ran rampant in the newly industrialized cities of Europe and North America, and rachitic pelvis was a common cause of death in childbirth [1]. Caesarean sections became established, in part, to manage this condition: "malformed pelvises often prohibited normal delivery. As a result, the rate of caesarean section went up markedly." [2]. Although rickets virtually disappeared with the discovery of the vitamin D and its subsequent addition to milk, recent reports suggest its reemergence [3], and that vitamin D deficiency is widespread in industrialized nations [4]. Meanwhile, research into vitamin D deficiency and awareness of its range of acute and chronic consequences have proliferated [5]. Poor muscular performance is an established symptom of vitamin D deficiency [6]. Common reasons for caesareans in industrialized nations include dystocia and failure to progress [7]. Vitamin D deficiency has been associated with proximal muscle weakness as well as suboptimal muscle performance and strength [8]. While serum calcium status, which is regulated by vitamin D, plays a role in smooth muscle function in early labor [9]. Papandreou et al. (2004) reported significantly higher serum calcium levels in pregnant women at the time of vaginal delivery compared with term women not in labor or women who did not labor but delivered by scheduled caesarean. It was speculated that the higher serum calcium levels played a role in the mechanism of initiation of labor. Because vitamin D is critically important for the maintenance of calcium homeostasis, it is possible that vitamin D deficiency, which causes a slight lowering of the serum calcium, is related to both skeletal muscle and smooth muscle strength and may play a role in the initiation of early labor. It is also possible that vitamin D deficiency might be related to specific types of caesareans (such as cephalopelvic disproportion or failure to progress) than to others (such as breech). Recent research suggests that maternal calcium status plays a role both in preterm labor and in the initiation of labor [10].

2. Patients and methods

A total of 150 women who recently give birth within the preceding 72 hours were included in the study. They were randomly selected in March and April 2016 from Al-Azhar university hospitals,

Faculty of Medicine, Al-Azhar University, Cairo, Egypt. The study was started after the approval of the local ethical committee of the faculty of medicine, Al-Azhar University. Informed consent was obtained from each patient before enrollment in the study. Women eligible for the study were those women who had singleton pregnancy and gave birth after 37 weeks of gestation. Women included in this study were divided into 2 groups: group I included 75 women who delivered by primary caesarean section regardless of their parity and group II included 75 women who delivered vaginally (as a control group). Women were illegible if they had a history of parathyroid, renal, or liver disease. Mothers with multiple pregnancy and those having repeat caesarean were also excluded because of the strong causal relationship between primary and repeat caesareans. All patients were subjected to measurement of serum 25-hydroxyvitamin D [25(OH)D], and serum calcium within 72 hours following giving birth. The blood samples were analysed for serum 25(OH)D levels by enzyme immune-assay, using DRG® 25-OH Vitamin D (total) ELISA Kit (EIA-5396) from DRG International, Inc., USA. Vitamin D deficiency was diagnosed when the serum 25 (OH)D level was ≤ 15ng/ml [3].

Statistical analysis

The statistical analysis system (IBM Corp. Released 2017. IBM SPSS Statistics for Mac OS, Version 25.0, Armonk, NY) was used for data management. For each independent/confounding variable, the distribution was tested for normality using Shapiro-Wilk test. Mean and 95% confidence interval (95% CI) were used for normally distributed (parametric) numerical variables. Median and interquartile range (IQR) were used for skewed (non-parametric) numerical variables. Frequency, percentage were used for categorical variables. The statistical significance of differences in vitamin D levels and maternal factors associated with caesarean delivery between cases and controls were analysed using Pearson's chi-squared test ($\chi 2$), t-test and Mann-Whitney U test. P-value less than 0.05 is considered significant. Confounding was controlled with the use of logistic regression. Univariate logistic regression analysis tested all independent variables, followed by a multivariate logistic regression analysis that tested all variables with $P < 0.25$ in univariate analysis. Multi-variable logistic regression analysis was used with LSCS as dependent variable and mother's age, fetal weight, parity, mother's educational level, drank milk in pregnancy, multivitamin supplements, infant gender and maternal serum 25(OH)D level (ng/ml) as independent variables.

3. Results

Indications for caesarean included failure to progress (46 of 75); non-reassuring fetal tracing (21 of 75); and malpresentation such as breech (8 of 75). For the women who had a primary caesarean, the median (IQR) maternal age at childbirth was 26.00 (21-29) years compared to 29.00 (22-33) years for the women who delivered vaginally ($p = 0.046$) (Table 1).

75% of the caesarean group were primigravida, compared to only 27% women who delivered vaginally. Regarding fetal gender, for the caesarean group, 47 fetuses were males compared to 34 fetuses for the control group. There was no statistical significance of differences between the mean fetal weight for the women who had a primary caesarean and who delivered vaginally. Also, there was no statistical significance of differences between the mean maternal BMI for both caesarean and vaginal delivery group. In addition, there was no statistical significance of differences between the median gestational age for both caesarean group and vaginal delivery group. The number of mothers who had secondary education and less was [63 (84%) vs 57 (76%), $p = 0.211$] among the cases and the controls respectively and this was similar. For LSCS and control groups, women who drank milk and woman on multivitamin supplementations prenatally were similar.

Concerning maternal serum calcium, we found no statistically significant differences between median maternal serum calcium levels in women who had caesareans and women who delivered vaginally (Table 2).

Regarding maternal serum vitamin D, we found that women who had caesarean section had a significantly lower median (IQR) 25(OH)D serum level than women who delivered vaginally [16.80 (10.0-20.0) vs. 25.0 (16.40-38.0) ng/ml, respectively, $p = 0.001$] (Figure 1).

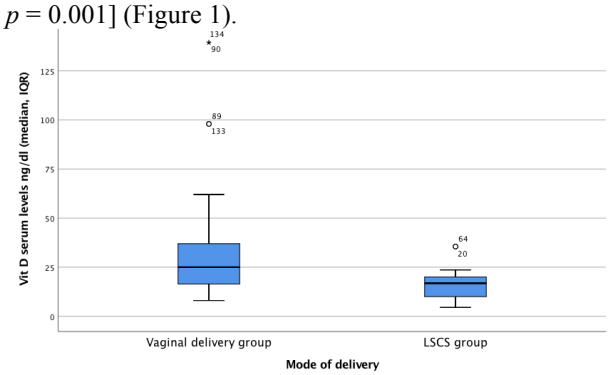

Figure 1. 25(OH)D levels in maternal serum in cases and controls.

We found that 33% of women who had primary caesarean section had serum 25(OH)D less than 15 ng/ml, compared with only 15% of women who delivered vaginally ($p = 0.007$) (Figure 2).

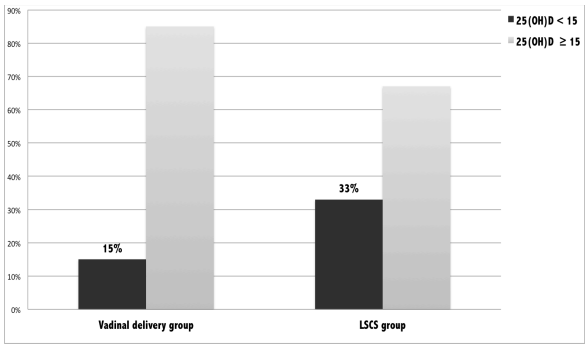

Figure 2. 25(OH)D deficiency in cases and controls.

In multi-variable logistic regression analysis controlling for maternal age, fetal weight, parity, education level, drank milk in pregnancy, prenatal multivitamin supplements, and infant gender, women with vitamin D deficiency (< 15 ng/ml) were almost 3 times as likely to have a primary caesarean section as women without deficiency (p = 0.048; (AOR) 2.835, 95% CI 1.701-7.95). Also, compared with women who had vaginal births, women who had caesareans were significantly more likely to have babies with bigger birth weight (p = 0.032; adjusted odds ratio (AOR) 4.778; 95% CI 1.144-19.961), to be primigravidae (p = 0.001; AOR 7.958; 95% CI 3.832-16.526), to have secondary education and less (p = 0.001; AOR 7.701; 95% CI 2.321-25.553) and to have male fetuses (p = 0.034; AOR 2.024; 95% CI 1.054-3.887) (Table 3).

So, maternal serum 25(OH)D deficiency is associated with increased odds of the primary caesarean section. Primiparity, carrying male fetuses, bigger birth weight, and mother's lower educational level had increased likelihood of primary caesarean section, while maternal age, prenatal drinking milk, and multivitamins supplementation were not statistically significant.

Figure 3. shows the association between mother's increasing 25(OH)D level in nanogram/milliliter and decreasing predicted probability (from multivariate analysis) of having a caesarean section vs. vaginal delivery. Thus, women with the highest serum 25(OH)D had the lowest probability of requiring a caesarean section.

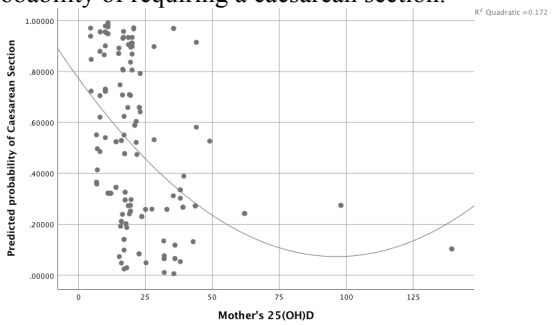

Figure 3. Mother's 25(OH) D level in nanogram/milliliter and predicted probability of primary caesarean section delivery.

Table 1. Characteristics of study sample by mode of delivery

Variables	**Vaginal delivery, n =75**	**Primary LSCS n = 75**	***P* value**
Mother's age (years), Median (interquartile range)	29.00 (22-33)	26.00 (21-29)	0.046 (Mann-Whitney U test)
Mother's BMI (Kg/m2), Mean (95% CI)	28.49 (27.57-29.40)	28.78 (27.84-29.72)	0.661 (Student's t-test)
Parity, n (%) Multipara Primipara	 55 (73%) 20 (27%)	 19 (25%) 56 (75%)	 0.001 (Chi-square)
Gestational age (weeks), Median (interquartile range)	37.0 (37.0-39.0)	37.00 (37.0-39.0)	0.852 (Mann-Whitney U test)
Fetal weight (Kg), Mean (95% CI)	3.02 (2.96-3.08)	3.11 (3.03-3.19)	0.07 (Student's t-test)
Education, n (%) Secondary and less Graduate	 57 (76) 18 (24)	 63 (84) 12 (16)	0.221 (Chi-square)
Drank milk during pregnancy, n (%) No Yes	 55 (73) 20 (27)	 46 (62) 29 (38)	0.117 (Chi-square test)
Prenatal multivitamin supplements, n (%) No Yes	 38 (51) 37 (49)	 29 (39) 46 (61)	0.139 (Chi-square test)
Infant gender, n (%) Female Male	 41 (55) 34 (45)	 28 (37) 47 (63)	0.033 (Chi-square test)

Table 2. Outcomes

Variables	Vaginal delivery, n =75	Primary LSCS n = 75	*P* value
Maternal calcium (mg/dl), Median (interquartile range)	8.30 (7.70-8.50)	8.40 (7.60-8.80)	0.748 (Mann-Whitney U test)
Maternal 25(OH)D (ng/ml), Median (interquartile range)	25.0 (16.40-38.0)	16.80 (10.0-20.0)	0.001 (Mann-Whitney U test)
Maternal 25(OH)D (ng/ml), n (%)			0.007 (Chi-square test)
25(OH)D < 15	11 (15)	25 (33)	
25(OH)D ≥ 15	64 (85)	50 (67)	

Table 3. Multi-variable logistic regression analysis of factors associated with primary caesarean section

Variables	Adjusted OR	95% CI	*P* value
Mother's age	1.079	0.994-1.171	0.070
Fetal weight	4.778	1.144-19.961	0.032
Parity			
Multipara	Ref		
Primipara	7.958	3.832-16.526	0.001
Education			
Graduate	Ref		
Secondary and less	7.701	2.321-25.553	0.001
Drank milk during pregnancy			
Yes	Ref		
No	0.38754	0.149-1.007	0.052
Multivitamin supplements			
Yes	Ref		
No	0.604	0.251-1.458	0.263
Infant gender			
Female	Ref		
Male	2.024	1.054-3.887	0.034
Maternal 25(OH)D (ng/ml)			
25(OH)D ≥ 15	Ref		
25(OH)D < 15	**2.835**	1.011-7.950	**0.048**

4. Discussion

Delivery by caesarean is a common operative procedure experienced by reproductive age women [11]. A Caesarean may be performed for reasons related to the mother or to the fetus including prolonged labor (dystocia), fetal distress, fetal malpresentation or a prior caesarean delivery [12]. Factors that increase risk include older maternal age, obesity, parity, and ethnicity (MacDorman, et al., 2008) along with a more recently defined factor—maternal nutrition [13].

In our analysis, women who were severely vitamin D deficient [25(OH)D less than 15 ng/ml (37.5 nmol/l)] at the time of delivery had almost three times the odds of caesarean birth than women who were not deficient.

One explanation for our findings is the fact that skeletal muscle contains the vitamin D receptor. Vitamin D deficiency has been associated with proximal muscle weakness as well as suboptimal muscle performance and strength [14]. Vitamin D status is also linked to immune status. Certain infections have been associated with preeclampsia [15], and preeclampsia, in turn, increases the odds of caesarean [16]. Vitamin D deficiency may thus be a marker for a compromised immune system and an associated, higher risk of caesarean.

Our data are consistent with a study by Anne, where women with a primary caesarean section had lower concentrations of 25(OH)D measured within 72 hours of delivery than controls who delivered vaginally. That study found that women with 25(OH)D less than 37.5 nmol/liter (15 ng/ml) were almost 4 times as likely to have a caesarean than women with 25(OH)D 37.5 nmol/liter (15 ng/ml) or greater [17]. Also, our data are consistent with a study by Scholl, who examined the association of maternal vitamin D deficiency to risk of caesarean delivery using prospective data in a cohort of 1153 at 13.73 ± 5.6 (SD) completed weeks gestation and concluded

that vitamin D deficiency was linked to a 2-fold increased risk of caesarean for prolonged labor [18].

Suggested explanation for the association of maternal vitamin D deficiency to fetal distress and birth asphyxia is that fetal vitamin D levels are directly related to that of their mothers [19], and vitamin D is not only necessary for optimal skeletal function [20], but also it is important for bone metabolism, as well as for optimal function of striated and smooth muscle strength including heart muscle, and is related to postnatal muscle strength [21]. Birth asphyxia is associated with cardiovascular dysfunction, including low ventricular output, lower left ventricular ejection fraction and increased troponin levels [22]. Congestive heart failure may occur in severe cases of asphyxia [23]. Intrauterine fetal distress is related to an increase in blood pressure, redistribution and a change in fetal heart rate pattern. Therefore, cardiotocography (CTG) is the main instrument of fetal surveillance [24]. It is plausible that vitamin D deficiency could make the fetal heart more vulnerable to fetal distress/birth asphyxia [25].

A study performed in 1994–1995 by Brunvand, found no association between vitamin D deficiency at the time of delivery and obstructed labor in a case-control study of Indian women giving birth in Karachi. Their findings bear little relevance for the present study, however; outcomes were measured only for caesareans due to cephalopelvic disproportion; the sample consisted of largely undernourished impoverished women, and 71% of study participants were severely vitamin D deficient [25(OH)D < 30 nmol/liter]. In addition, the paper does not satisfactorily clarify the use of the term cephalopelvic disproportion [26].

Regarding maternal serum calcium levels, it is well known that the initiation of labor is a complex phenomenon. The role of calcium in the contractions of the uterus seems to be particularly important. Calcium seems to be related to production of prostaglandins and the action of nitric oxidase in the myometrium [27]. It has been proven, that the primary trigger for human myometrial contractions (spontaneous and agonist-induced) is a rise in intracellular calcium [28].

In our study, we demonstrate that there were no statistically significant differences in total calcium levels between women undergoing spontaneous labor and women undergoing caesarean section, and a clear explanation of our finding is that women in both groups had already their labour initiated. In another word, the women undergoing emergency caesarean section experienced at least a period of labour. Our findings are consistent with a study by Bagnoli, where serum levels of calcium were determined in cord blood of 229 newborns. The probands were divided into four groups according to the mode of delivery: (1) Spontaneous delivery (SD); (2) elective caesarean section without labour (ECS); (3) elective caesarean section in labour (ECSL); (4) emergency caesarean section with fetal distress (EMCS). That study showed that newborns in ECS group had significantly lower calcium in cord blood than the other three groups, also, there were similar serum calcium levels in the cord blood of SD, ECSL and EMCS newborns, following the pattern of the calcium levels of their mothers [29].

A salient secondary finding of our study was that there was a strong significant association between primiparity and the increasing likelihood of primary caesarean section, which was seen with multi-variable logistic regression. Another important secondary finding of our study was the strong association between the mother's lower educational level and increase the probability of primary caesarean section. In addition, we found that there was a significant association between bigger birth weight and increase the rate of primary caesarean section. Furthermore, we found that there was a significant association between carrying the male fetus and increased likelihood of primary caesarean section.

Conclusion

While there is no single reason for the continued rise in caesarean delivery, our data suggest that decreasing the number of women at risk of vitamin D deficiency might have important ramifications for women, their pregnancies and the cost of their care. So, adequate vitamin D supplementation during pregnancy to raise blood levels of 25(OH)D above at least 15 ng/ml (37.5 nmol/liter) is recommended to reduce the caesarean section rate.

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Conflicts of interest

There are no conflicts of interest.

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