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Short Communication

First-trimester maternal serum vitamin D and mode of delivery

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Abstract

Low maternal vitamin D levels have been associated with adverse pregnancy outcome. A recent study has suggested that low maternal vitamin D levels at the time of delivery are also associated with an almost fourfold increase in caesarean section risk. The aim of the present study was to investigate whether there is a difference in maternal serum 25-hydroxyvitamin D (25(OH)D) levels at 11–13 weeks' gestation according to the mode of delivery. Maternal serum 25(OH)D levels were measured at 11–13 weeks' gestation in 995 singleton pregnancies resulting in the birth of phenotypically normal neonates at term. The measured 25(OH)D levels were adjusted for maternal age, BMI, racial origin, smoking, method of conception and season of blood testing, and the adjusted levels (multiple of the median; MoM) were compared between those who subsequently delivered vaginally and those that delivered by caesarean section. Delivery was vaginal in 79·6 % of cases, by emergency caesarean section in 11·6 % and by elective caesarean section in 8·8 %. The median 25(OH)D level in our population was 46·82 (interquartile range (IQR) 27·75–70·13) nmol/l. The adjusted maternal median 25(OH)D levels in the emergency and elective caesarean section groups (0·99, IQR 0·71–1·46 MoM and 0·96, IQR 0·73–1·27 MoM, respectively) were not significantly different from the vaginal delivery group (0·99, IQR 0·71–1·33 MoM; $P=0·53$ and $P=0·81$, respectively). First-trimester maternal serum 25(OH)D levels are similar between women who subsequently have a vaginal delivery and those who deliver by elective or emergency caesarean section.

Key words: Vitamin D: Pregnancy: Caesarean section: Vaginal delivery

Vitamin D has been implicated in the pathogenesis of CVD and diabetes mellitus[1,2]. Recent studies have also reported a link between maternal vitamin D deficiency and adverse pregnancy outcomes such as pre-eclampsia, gestational diabetes and small-for-gestational-age neonates[3–5].

Vitamin D plays an important role in Ca homeostasis, bone mineralisation and muscle performance. The active metabolite of vitamin D, 1,25-dihydroxyvitamin D, binds to a vitamin D-specific nuclear receptor in muscle tissue[6], which leads to *de novo* protein synthesis, muscle cell growth[7] and improved muscle function[8]. A recent case–control study has reported that low maternal serum 25-hydroxyvitamin D (25(OH)D) concentration at the time of delivery was associated with an increased risk of caesarean section (emergency or elective)[9], and this was attributed to the negative effect of vitamin D deficiency on muscle performance and uterine contractions.

The aim of the present study was to assess further possible differences in maternal serum levels of 25(OH)D in the first trimester of pregnancy between women who subsequently have vaginal delivery compared with those who deliver by caesarean section. If vitamin D deficiency is associated with an increased risk of caesarean section due to suboptimal muscle function, this association would have been more marked in women who deliver by emergency caesarean section for failure to progress in labour and/or fetal distress than those who delivered by elective caesarean section.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; MoM, multiple of the median.

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Experimental methods

Study population

The present study was drawn from an ongoing large prospective study, started in March 2006, which aimed to identify early potential biomarkers of pregnancy complications in women attending for their routine first hospital visit in pregnancy. In this visit, which is held at 11–13 weeks of gestation, we record maternal characteristics and medical history, and perform combined screening for aneuploidies[10]. Women attending for this visit are invited to participate in the research study and from those who agree, serum and plasma are stored at −80°C for subsequent biochemical analysis. The present study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the King's College Hospital Research Ethics Committee. Written informed consent was obtained from all subjects/patients.

In the present study, we measured serum 25(OH)D concentration in 1000 singleton pregnancies with no medical complications resulting in the birth, between 37 and 42 weeks' gestation, of a phenotypically normal neonate with birth weight between the 5th and 95th percentiles for gestational age[11].

Outcome measures

The mode of delivery was classified as either vaginal, emergency or elective caesarean section. Emergency caesarean section included all cases where such delivery was undertaken after the onset of labour. Elective caesarean section was performed before the onset of labour.

Sample analysis

Duplicate samples of 100 μl were used to analyse vitamins D_2 and D_3 by liquid chromatography–MS/MS (Prominence HPLC system, equipped with a Phenomenex Luna C8 3 × 50 mm column and AB Sciex API-5000 ESI triple quadrupole; Shimadzu Scientific Instruments). The analysis was performed using the MSMS Vitamin D kit 3075-0010 (PerkinElmer, Inc.). Individual runs were calibrated using National Institute of Standards and Technology Standard Reference Material 2972. The average inter-assay CV for vitamins D_2 and D_3 were 6·6 and 7·3%, respectively, and the intra-assay CV were 6·3 and 6·5%, respectively. The serum 25(OH)D concentration was calculated by adding together the measured vitamin D_2 and D_3 concentrations.

Statistical analysis

Comparison between continuous and categorical variables was done using the Mann–Whitney *U* test and χ^2 test or Fisher's exact test, respectively.

The distribution of serum 25(OH)D was made Gaussian by square root transformation, and normality was assessed using histograms and probability plots. In each case, the measured 25(OH)D was converted into the respective multiple of the median (MoM) after appropriate adjustment for maternal characteristics, including maternal age, BMI, racial origin, smoking, method of conception and season of blood testing[12]. The Kruskal–Wallis test and Mann–Whitney *U* test with *post hoc* Bonferroni correction were used to compare median raw and MoM values of 25(OH)D within and between the vaginal delivery and caesarean section groups.

The statistical software package SPSS 16.0 (SPSS, Inc.) and GraphPad Prism 5 (GraphPad Software, Inc.) were used for data analyses.

Results

Of the 1000 pregnancies, five were excluded from the analysis because the mothers underwent an emergency caesarean section due to previously undiagnosed breech presentation. In the 995 cases, there was vaginal delivery in 796 (80·0%) cases, emergency caesarean section in 111 (11·2%) cases and elective caesarean section in eighty-eight (8·8%) cases. The maternal characteristics of the study group are presented in Table 1. In the emergency caesarean section, compared with the vaginal delivery group, women had higher BMI, were more likely to be of African racial origin and delivered neonates with a higher birth weight percentile. In the elective caesarean section, compared with the vaginal delivery group, maternal age, BMI and neonatal weight percentile were higher and more women were parous and conceived with assisted conception techniques.

Table 1. Maternal and pregnancy characteristics in the vaginal delivery and caesarean section groups

(Medians, interquartile ranges (IQR), number of subjects and percentages)

	Vaginal delivery (*n* 796)		Emergency caesarean section (*n* 111)		Elective caesarean section (*n* 88)	
Maternal characteristics	*n*	%	*n*	%	*n*	%
Maternal age (years)						
Median	31·2		31·5		34·9*	
IQR	26·7–34·9		28·1–35·5		31·5–38·4	
Maternal BMI (kg/m^2)						
Median	23·8		25·8*		25·9*	
IQR	21·8–26·9		23·0–29·2		23·5–29·2	
Season of sampling						
Summer	202	25·4	21	18·9	22	25·0
Other seasons	594	74·6	90	81·1	66	75·0
Racial origin						
Caucasian	471	59·2	47*	42·3	59	67·0
African	253	31·8	49*	44·1	22	25·0
Asian	72	9·0	15	13·6	7	8·0
Parity						
Nulliparous	392	49·2	64	57·7	23	26·1
Parous	404	50·8	47	42·3	65*	73·9
Cigarette smoker	59	7·4	7	6·3	6	6·8
Conception						
Spontaneous	785	98·6	107	96·4	83	94·3
Assisted	11	1·4	4	3·6	5*	5·7
Birth weight in percentile						
Median	49·0		53·3*		59·7*	
IQR	28·9–66·9		30·8–78·7		31·0–76·2	

* All comparisons were made with the vaginal delivery group by the Mann–Whitney *U* test with *post hoc* Bonferroni correction; corrected significance level $P=0·02$.

Table 2. First-trimester maternal serum 25-hydroxyvitamin D levels (nmol/l) in the summer and winter according to the mode of delivery

(Medians and interquartile ranges)

	Summer		Winter	
	Median	Interquartile range	Median	Interquartile range
Vaginal delivery	60·95	63·59–85·81	38·83*	24·03–55·11
Emergency caesarean section	49·02	25·15–75·35	46·82	19·71–55·76
Elective caesarean section	69·03	51·49–86·36	40·80*	24·48–67·36

* Median value was significantly different from that in the summer ($P=0·01$).

Maternal serum 25(OH)D levels increased with maternal age, decreased with BMI, were higher in the summer (June–August; Table 2) or when the conception was assisted. Conversely, its levels were lower in cigarette smokers and in women of African (28·95 nmol/l, interquartile range 19·21–40·93 nmol/l) and Asian (25·45 nmol/l, interquartile range 17·72–44·17 nmol/l) racial origin compared with Caucasians (62·89 nmol/l, interquartile range 45·17–82·36 nmol/l; $P<0·01$ for both comparisons). The median maternal serum 25(OH)D raw and MoM values in the emergency caesarean section group were not significantly different from those in the vaginal delivery or elective caesarean section groups (Table 3). Similarly, there was no significant difference in the incidence of 25(OH)D levels below the 10th percentile, as defined previously[12], between the vaginal delivery group (10·2 %) and either the emergency (10·8 %, $P=0·87$) or the elective caesarean section group (6·8 %, $P=0·45$). In the emergency and elective caesarean section groups, there was no significant difference in the median 25(OH)D MoM between the subgroups of indications for caesarean section and between each of these subgroups and the vaginal delivery group (Table 3).

Discussion

The present study has shown that first-trimester maternal serum levels of 25(OH)D are not significantly different between women who subsequently deliver by emergency or elective caesarean section, compared with those who deliver vaginally.

The rationale for the study was that vitamin D is necessary both for the maintenance of normal Ca levels, which are essential for muscular contractility, and for muscle growth and function[7,8]. Studies in isolated myometrial cells have reported that reduction in the contractility of muscle fibres and the activity of oxytocin or PG could be achieved by lowering the concentration of extracellular Ca or inhibiting the entry of the ion into the cell[13,14]. Ca channel inhibitors can and are being used as a tocolytic for the prevention of preterm delivery[15].

A previous study, which measured maternal 25(OH)D levels at the time of delivery, reported that the median value in 210 women who delivered vaginally was significantly higher than that in forty-three women who had a caesarean section (62·5 *v.* 45 nmol/l), and a 25(OH)D level below 37·5 nmol/l was associated with an almost fourfold increase in the rate of elective/emergency caesarean section[9]. The present study does not support these findings. We have shown no association between the first-trimester maternal serum 25(OH)D levels and the mode of delivery. The large size of our population made it possible to demonstrate a lack of significant difference in maternal 25(OH)D levels between the emergency and elective caesarean section groups and also between the various indications for these procedures. The present study was focused on the first trimester of pregnancy and we cannot exclude the possibility that differences in 25(OH)D levels become apparent only in the third trimester. It could be hypothesised that despite the fact that all women have similar levels of 25(OH)D in the first trimester, those in whom vitamin D levels deteriorate during pregnancy may have an increased

Table 3. Maternal serum 25-hydroxyvitamin D (25(OH)D), raw values (nmol/l) and multiples of the median (MoM), in those having an emergency or elective caesarean section compared with those having a vaginal delivery

(Medians and interquartile ranges)

		25(OH)D (MoM)		25(OH)D (nmol/l)		
Indication for caesarean section	*n*	Median	Interquartile range	Median	Interquartile range	*P*
Vaginal delivery	796	0·99	0·71–1·33	46·6	28·25–69·01	–
Emergency caesarean section	111	0·99	0·71–1·46	42·53	22·91–72·1	0·53
Failure to progress in labour	65	1·00	0·69–1·62	48·19	24·26–75·62	0·25
Fetal distress in labour	46	0·95	0·71–1·34	32·92	20·64–67·54	0·72
Elective caesarean section	88	0·96	0·73–1·27	58·40	28·12–78·89	0·81
Previous caesarean section	41	0·95	0·69–1·28	59·1	27·78–73·3	0·66
Malpresentation	21	0·98	0·74–1·16	56·13	25·9–79·34	0·73
Maternal request	12	0·88	0·74–1·18	61·55	45·6–78·14	0·63
Other*	14	1·18	0·73–1·54	57·95	24·81–97·84	0·32

* Fetal growth restriction (*n* 3); placenta previa (*n* 6); medically indicated (*n* 5).

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risk of caesarean delivery compared with those who better maintain their vitamin D levels. If this were the case, serial measurements of 25(OH)D during pregnancy could be beneficial. Another possible explanation for the differences in findings between the two studies is the methodology for the measurement of 25(OH)D: Merewood *et al.* used competitive protein binding, whereas we used liquid chromatography–MS/MS, which is thought to be the most accurate method[16].

A study in Pakistan reported a lack of difference in maternal 25(OH)D levels between women with a normal delivery and those with an emergency caesarean section that was performed due to cephalopelvic disproportion[17]. It is likely that in a malnourished population with low levels of serum 25(OH)D, possible differences between subgroups according to the mode of delivery could be masked. If this were the case, then the same explanation could be advanced for our inner London multiethnic population where in about 80 % of cases, serum 25(OH)D was below 75 nmol/l, which is considered the cut-off for vitamin D insufficiency in the non-pregnant population[18].

We did not have information on the use of supplemental or amount of dietary intake of vitamin D in the present study population at recruitment. However, there is no reason to believe that women who subsequently had a caesarean delivery were more likely to have a higher oral intake of vitamin D compared with women who deliver vaginally, which could mask the difference between the groups.

In summary, we have found that first-trimester maternal serum 25(OH)D levels are similar between pregnancies resulting in vaginal delivery and those requiring an elective or emergency caesarean section, and therefore it is unlikely that its first-trimester levels play a role in determining the mode of delivery.

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