Original Article

Cord serum vitamin D in a South China birth cohort

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Background and Objectives: Vitamin D deficiency during pregnancy has been associated with many adverse pregnancy and birth outcomes. Low serum 25-hydroxyvitamin D (25OHD) levels (<30 nmol/L) increases the risk of nutritional rickets. This study aimed to investigate the concentration of cord serum 25OHD in a birth cohort in Guangzhou, China and determine whether maternal lifestyle factors had any effect on these levels. **Methods and Study Design:** A total of 854 pregnant women giving birth between Dec 2016 and Dec 2017 were recruited to this study. Basic information was obtained from the clinical database. A voluntary retrospective pregnancy lifestyle questionnaire was completed by 388 participants. The concentration of serum 25OHD, calcium, phosphorus, and alkaline phosphatase (ALP) were measured in umbilical cord blood. **Results:** The mean (SD) of cord serum 25OHD was 44.7 (16.7) nmol/L. The prevalence of cord 25OHD <30 nmol/L was 22.2% and 70.4% had levels <50 nmol/L. The prevalence of vitamin D deficiency is higher in infants born in winter months (31% <30 nmol/L and 76% <50 nmol/L), compared to those born in the summer (12% <30 nmol/L and 64% <50 nmol/L). Infants born to women taking a vitamin D containing supplement had approximately 10 nmol/L higher levels of 25OHD than those who did not supplement their diets. **Conclusions:** Summer born infants have higher serum 25OHD levels at birth, but there are still infants being born with vitamin D deficiency. Vitamin D containing supplement use during pregnancy was effective in raising cord serum vitamin D levels.

Key Words: vitamin D, 25-hydroxyvitamin D, birth cohort, umbilical cord blood, infant

INTRODUCTION

Vitamin D deficiency during pregnancy has been associated with an increased risk of pre-eclampsia,[1] gestational diabetes,[2] fetal growth restriction,[3] pre-term birth,[4] and small for gestational age babies.[5] In the most extreme cases, even with an adequate intake of calcium, vitamin D deficiency can lead to rickets.[6] Low serum 25-hydroxyvitamin D (25OHD) levels (<30 nmol/L) have an increased risk of childhood nutritional rickets.[7] Serum 25OHD levels are commonly used to indicate vitamin D status.[8] However routine 25OHD screening is not carried out at birth in China, even though 25OHD is a reasonable monitoring parameter for prevention of rickets.

At the time of birth, the vitamin D status of a newborn infant is completely dependent on their mother. The Institute of Medicine (IOM) in the USA defines serum 25OHD concentration <30 nmol/L as vitamin D deficiency; and <50 nmol/L as vitamin D insufficiency, based on evidence from bone health studies.[9] There is an ongoing debate regarding serum 25OHD cut off levels, with the USA Endocrine Society suggesting that serum 25OHD concentrations need to reach >75 nmol/L to achieve over all health.[10]

Guangzhou is located in Southern China (latitude 23°N), with abundant sunshine and distinctive seasons (average 2200-3000 sunshine hours per year). The traditional concept of female beauty in China is to be pale skinned; Chinese woman therefore often stay indoors during sunny weather or when outdoors cover their skin with clothing, an umbrella and/or sunscreen to avoid sunlight. This is especially true during pregnancy. One study carried out in a population of 5823 pregnant Chinese women (15-18 weeks gestational age) based in Wuxi, China, reported 40.7% women had serum 25OHD level <30 nmol/L and additional 38% had levels between 30-50 nmol/L.[11]

Serum 25OHD concentration is closely related to body calcium and phosphorus hemostasis. In addition, elevated bone specific alkaline phosphatase (BALP) is also a reflection of bone mineralization disorders, alkaline phosphatase in infancy is mainly of bone origin.[12] When calci-

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um salt precipitation for bone formation is insufficient, secretion of BALP is increased by bone cells. This study aimed to investigate the concentration of serum 25OHD, calcium, phosphorus, and alkaline phosphatase (ALP) in cord blood of a cohort of infants born in Guangzhou across a calendar year; and to evaluate maternal lifestyle factors that may affect cord 25OHD levels at birth.

METHODS

Study design

A total of 854 participants on a completely voluntary basis with successful cord blood collection were officially registered to our study in the delivery suite of Guangzhou Women and Children's Medical Center (GWCMC) between Dec 2016 and Dec 2017, covering 12 calendar months. Written informed consent was taken from all mothers prior to collection of umbilical cord blood samples. Cord blood samples were kept at 4°C until centrifuged (15 mins at 3000g) and serum stored at −80°C until required for analysis. The inclusion criteria were: apparent normal pregnancy, singleton, and vaginal delivery. To ensure as normal a population as possible we excluded delivery by Cesarean section as these are often indicated for complications of pregnancy. Clinical variables were extracted from the clinical database including the birth season, birth weight, infant length, gestational length (days), gravity, parity, infant sex, maternal age, BMI at delivery. A telephone call was made to each participant by Department of Children Health Care to inform them of the return for their first clinical visits. Patients were lost to follow up due to refusal to continue participation and postponement of the appointment. A voluntary retrospective pregnancy lifestyle questionnaire was completed by 388 participants at the first clinical visit post delivery, by the date of 15th December 2018, but not all mothers answered all of the questions. Relevant questions included vitamin D and/or calcium containing supplement use, supplementation duration while pregnant, supplementation frequency and dosage, physical activity (indoors/outdoors) during pregnancy (frequency and duration), maternal/paternal smoking habits, sunscreen/umbrella use, gestational weight gain, education levels. This study was conducted according to the Declaration of Helsinki guidelines, and all procedures were approved by Guangzhou Women and Children's Medical Center Ethical Review Board (approval number: 2018012201).

Analytical methods

Total serum 25-hydroxyvitamin D (25OHD2 plus 25OHD3) was determined using enzyme immunoassay (Immuno Diagnostic System, AC-57SF1, Boldon, UK), which was traceable to the isotope dilution-liquid chromatography/tandem mass spectrometry (ID-LCMS/MS) 25OHD Reference Method Procedure (RMP). The ID-LCMS/MS RMP is traceable to the National Institute of Standards and Technology Standard Reference Material (NIST SRM) 2972. This 25-hydroxyvitamin D EIA assay is certified by the CDC Vitamin D Standardization Certification Program (VDSP). The inter- and intra-assay coefficients of variation were both below 5%. Quality control analysis was carried out on a daily basis.

Concentrations of serum calcium, phosphorus, and overall enzyme activity of total non-tissue specific alkaline phosphatase were determined by Hitachi 7600 automatic biochemical analyzer in the diagnostic laboratory of GWCMC. The inter- and intra-assay coefficients of variation were both below 2%. Quality control analyses were carried out on a daily basis.

Statistical analysis

Statistical analysis was conducted using PASW® Statistics Version 20.0 (SPSS, IBM® USA). The distribution of all variables was tested by Kolmogorov-Smirnov. Descriptive statistics (mean and SD; median and interquartile range; frequency and percentage) were determined for all variables. Primary correlations were explored using Pearson's test (parametric) and Spearman's test (non-parametric). Determinants of 25OHD were explored in unadjusted models and determinants that had a p value <0.1 were included in the multivariate model. The residuals of the multiple linear regression model were slightly deviated from the normal distribution; therefore, square-root transformation for the 25OHD, was used, and the residuals were approximately normally distributed when the regression model was repeated. However, because the regression models on the original scale and the square-root transformation scale identified the same factors as significantly associated with 25OHD, we report the results from the linear regression model without transformation. All tests were 2-sided at the 5% statistical significance level, $p<0.05$ being considered statistically significant.

RESULTS

Principle characteristics

A total of 854 subjects were recruited to this study, their principle characteristics are presented in Table 1. The mean (SD) of cord serum 25OHD was 44.7 (16.7) nmol/L. A total of 388 participants completed the retrospective lifestyle questionnaire during pregnancy. In this cohort of women, the percentage of vitamin D containing supplement users was high at 87%, but their average consumption time frame was 5 months during pregnancy, and they tended to only take the supplement while pregnant. The average daily dosage of vitamin D was 448 IU/day, combined with an average calcium dosage of 422 mg/day. More than half of our cohort used sun protection methods including umbrella, full coverage clothing or sun cream when they went outdoors during pregnancy. Cord 25OHD levels were not associated with any birth parameters including birth weight, infant length and gestational age.

Prevalence of vitamin D deficiency

In the total cohort the prevalence of cord 25OHD <30 nmol/L was 22% and 70% had levels <50 nmol/L. Only 6% had 25OHD levels >75 nmol/L and none were >125 nmol/L. When the data was split into two seasonal groups: summer (May-Oct) and winter (Nov-Apr), the infants born in summer had higher 25OHD concentrations than the infants born in winter ($p<0.001$). The prevalence of vitamin D deficiency is higher in infants born in winter months (Nov-April, n=463), where 31% had 25OHD <30 nmol/L and 76% <50 nmol/L, and among those infants

Table 1. Principle maternal and infant characteristics of the subjects enrolled in the study (n=854)

	Total (n=854)	Completed the questionnaire (n=388)	Did not complete questionnaire (n=466)
Maternal Age (y)	30.7±4.3	30.9±4.3	30.5±4.2
Primary parity (%)	39.8	42.1	38.3
Maternal weight at delivery (kg)	64 (59, 70)	65 (60, 71)	64 (60, 70)
Maternal height (m)	160 (157, 163)	160 (157, 164)	160 (158, 163)
Maternal BMI at delivery (kg/m^2)	25 (23.4, 27.2)	25.2 (23.5, 27.5)	25.1 (23.3, 26.9)
Preterm birth (%)	2.3	1.0	3.4
Infant sex – male (%)	55.4	53.5	56.3
Infant birth weight (kg)	3.23 (3.0, 3.48)	3.24 (3.01, 3.51)	3.24 (3.01, 3.48)
Infant birth length (cm)	50 (49, 51)	50 (49, 51)	50 (49, 51)
Cord serum 25OHD (nmol/L)	42.8 (31.7, 54.2)	43.5 (32.1, 55.2)	42.0 (31.0, 52.6)
Cord serum total calcium (mmol/L)	2.66 (2.56, 2.76)	2.66 (2.57, 2.76)	2.65 (2.56, 2.76)
Cord serum inorganic phosphorus (mmol/L)	1.67 (1.54, 1.78)	1.69 (1.55, 1.82)	1.65 (1.52, 1.76)
Cord serum ALP (U/L)	165 (136, 204)	167 (141, 206)	163 (131, 197)
Received University education % (n 283)†		79.2	
Gestational weight gain (kg) (n 387)†		12.5 (9.0, 15.8)	
Use of an antenatal supplement containing vitamin D (%) (n 377)†		86.5	
Use of sun protection (including umbrella, sun cream etc.) (%) (n 388)†		58.8	
Paternal smoking (%) (n 381)†		40.7	

BMI: body mass index; 25OHD: 25-hydroxyvitamin D; ALP: bone alkaline phosphatase.
†Data from lifestyle questionnaire (n=388)
Mean±SD (all such values) and median; interquartile range in parentheses (all such values); used in the case of non-normally distributed variables

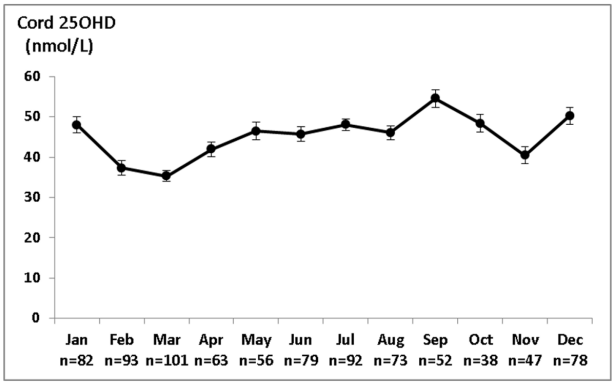

Figure 1. Seasonal variation in cord serum total 25OHD (mean±SEM) by calendar month in Guangzhou, China (n=854).

born in the summer season (n=391), there were 12% <30 nmol/L and 64% <50 nmol/L. Serum 25OHD concentrations were stratified according to month of delivery and a low mean cord 25OHD <50 nmol/L was seen in most months apart from September (Figure 1).

A total of 377 subjects had data for vitamin D containing supplement use during pregnancy, the mean 25OHD levels were much higher in infants born to supplement using mothers (n=325), mean (SD) 47.0 (17.5) nmol/L compared to infants born to non-supplement using mothers (n=52), mean (SD) 36.3 (12.8) nmol/L. The risk of infants born with <30 nmol 25OHD levels were also increased in non-supplement taking mothers, 39.2% compared to 19.4% in supplemented subjects.

Determinates of cord serum 25OHD

A final multiple linear regression model was built using the total number of participants (n=854) and taking into account season of birth, calcium concentration, maternal age and parity, with an overall adjusted r^2=0.052, p<0.001 (Table 2). The season of birth is a strong predictor of cord 25OHD concentration and summer (May-Oct) born infants had much higher 25OHD concentrations than those born in the winter months (Nov-Apr), adjusted mean difference (95% CI) (nmol/L) of [6.4 (4.2, 8.6), p<0.001]. In addition, maternal age at birth [0.6 (0.3, 0.8), p<0.001] and serum calcium [6.9 (2.1, 11.7), p=0.005] also significantly predicted cord 25OHD. Cord serum ALP levels negatively correlated with 25OHD (r=-0.07, p=0.03) but the association was not strong enough when other covariants were taken into account to predict cord 25OHD levels (p>0.1). A strong negative interaction was found between serum calcium and phosphorus (r=0.3, p<0.001), therefore, phosphorus was excluded in the final model.

Among the subgroup (n=388) who completed the lifestyle during pregnancy questionnaire, the use of vitamin D containing supplements during pregnancy had a significant impact on cord 25OHD levels [10.9 (5.8, 16.0), p<0.001], adjusting for season, maternal age, parity, education level, sun protection, outdoor activity, gestational weight gain, while other factors failed to have a significant effect (data not shown), possibly due to the limited number of participants who completed the questionnaire. Sun protection strategies including umbrella and sun cream use during pregnancy had no impact on infant 25OHD levels. In addition, outdoor activity during pregnancy was limited and had no effect on infant 25OHD levels at birth.

DISCUSSION

This is the first study performed in Southern China (23ºN) investigating the vitamin D status of umbilical cord blood. We demonstrate a high prevalence of low cord 25OHD

Table 2. Modifiers of serum 25-hydroxyvitamin D (nmol/L) in a birth cohort in Guangzhou China (n=854)

	25OHD Mean (SD)	Adjusted estimate (95% CI)	*p* value
Season of birth			
Winter (Nov-Apr) (n=463)	41.9 (17.3)	Reference	
Summer (May-Oct) (n=391)	47.9 (15.3)	6.44 (4.2, 8.6)	<0.001
Calcium (mmol/L)		6.9 (2.1, 11.7)	0.005
Age (year)		0.6 (0.3, 0.8)	<0.001
Parity			
1 (n=340)	45.1 (17.3)	Reference	
2 and more (n=514)	44.4 (16.3)	-2.0 (-4.1, -0.03)	0.05

concentrations, 22.2% <30 nmol/L and 70.4% <50 nmol/L across a calendar year in Guangzhou among 854 newborn infants; only 6.3% had 25OHD >75 nmol/L and none >125 nmol/L. In other parts of China, vitamin D deficiency has also been reported in umbilical cord blood samples. Yu et al reported a prevalence of 36.3% <50 nmol/L among 1030 infants born in Shanghai (30ºN).[13] In Hangzhou (30ºN), Zhuang et al reported more than 90% had cord serum 25OHD concentrations <50 nmol/L among 522 infants (article not in English).[14] In Beijing (40ºN), among 70 newborns, 93% had serum 25OHD concentrations <50 nmol/L.[15] In Chengdu (30ºN), among 77 infants born at the end of summer, 44% had 25OHD <37.5 nmol/L.[16] Vitamin D deficiency has also been reported in cord blood in other parts of the word. In New Zealand (41ºS), Camargo et al reported 19% of newborns had 25OHD levels <25 nmol/L, 57 % had levels <50 nmol/L and only 27% had levels of 75 nmol/L or higher among 929 infants.[17] Haggarty et al reported a prevalence of 50% <25 nmol/L among 1205 newborns in the UK (57ºN).[18] A study carried out in Iran (34ºN) reported a prevalence of 34% <12.5 nmol/L and 86% <25 nmol/L in umbilical cord samples of 552 winter born infants.[19] No comparable large population studies have been performed at or below latitude of 23ºN.

Summer born infants had a reduced rate of low 25OHD concentrations, but the sunny season did not protect infants from being born with vitamin D deficiency. Even among infants born during summer months (May-Oct), there was still a significant proportion with low 25OHD concentrations. One of the main reasons might be Chinese women prefer to stay indoors or wear sun protection when they go outside. However, maternal outdoor activity during pregnancy failed to have an impact on offspring's 25OHD levels at birth in the present study, though these results might also reflect the poor response rate to the life-style questionnaire. The use of sun protection during pregnancy does not have any effect on newborn 25OHD levels, therefore, the habit of staying indoors might have a greater impact on 25OHD levels during pregnancy than the use of sun protection during the limited time spent outdoors. Even though Guangzhou has distinctive seasons, 25OHD concentrations did not reflect this as it would elsewhere.[20,21] This is probably due to the subtlety of the seasonal shift as well as the effectiveness of sun protection and the habitual shade seeking behaviour of Chinese women when they go outdoors in sunny weather.

In this study we have shown that vitamin D containing supplement use during pregnancy is very effect in increasing cord 25OHD levels. Among the subjects who completed the questionnaire, the majority of them (87%) were taking a vitamin D or vitamin D containing supplement during pregnancy but these did not reach the recommended daily amount of 600 IU.[7] There are limited foods which naturally contain high levels of vitamin D, except oily fish and UV radiated Mushrooms. Supplementation and food fortification are very important sources of vitamin D when sunlight is limited. However, vitamin D fortification in food is lacking in China. Vitamin D supplement use during pregnancy is on a voluntary basis, and often only started towards the end of the first trimester of pregnancy. In addition, in China 25OHD levels are not included in routine antenatal care to raise health awareness of vitamin D deficiency in pregnancy. Given there is a limited source of vitamin D fortified foods in China, vitamin D supplementation is probably the most effective way in preventing vitamin D deficiency during pregnancy and subsequently early infancy.

An interesting finding of the present study was that cord serum 25OHD levels were positively correlated with maternal age. In the sub-cohort of subjects who have completed the questionnaire, we found that maternal age was positively associated with university education level (r=0.138, p=0.04). Higher education not only effects the decision to take supplementation but also improved dietary and lifestyle choices, which may explain these results. Research shows that the vitamin D status of a newborn is strongly correlated to maternal vitamin D status, while the concentration of serum 25OHD of umbilical cord blood is usually lower than the maternal value, 60-80% of the maternal levels.[19,22,23] The strong correlations between maternal and infant 25OHD levels re-emphasize the need to prevent vitamin D deficiency during pregnancy. In addition, education programs that highlight that limited amounts of direct sun exposure are beneficial to a woman's overall health need to be implemented.

One limitation of our study is the analytical measurement of serum 25OHD levels using Emzym Immunoassay (EIA). Measurement of vitamin D metabolites in serum can be challenging because of their hydrophobic nature and due to the fact they are tightly bound to vitamin D binding proteins (DBP). Variations exist in measuring serum 25OHD concentrations among different methods, and also among different analytical laboratories. LC-MS/MS is regarded as the "gold standard reference" method when the US National Institute of Standards and Technology (NIST) standard reference materials (SRM) are applied, which hugely reduced the inter-laboratory

variation in the analytical performance of LC-MS/MS to measure serum 25OHD.[24] However, this method is not widely available for clinical use. We used the IDS EIA in GWCMC to determine total serum 25OHD for diagnostic purposes, which might over estimate 25OHD levels especially in cord blood serum.[25,26]

Abundant sunshine and a summer birth could not protect infants from being born with vitamin D deficiency. This study re-emphasizes the need for vitamin D supplementation during pregnancy, even in a climate with high sunshine hours.

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AUTHOR DISCLOSURES

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