Original Article

Vitamin D deficiency in pregnancy – still a public health issue

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Abstract

The objectives of this study were to quantify the prevalence of vitamin D insufficiency and deficiency in pregnancy, explore associated risk factors and discuss the public health implications. The study used retrospective analysis of randomly selected data. This is the first report on serum vitamin D levels in an unselected multi-ethnic population of pregnant women collected between April 2008 and March 2009. Women with sufficient stored serum were randomly selected from among all women who delivered between April 2008 and March 2009. Serum vitamin D levels were determined using liquid chromatography coupled to tandem mass spectrometry. Vitamin D levels were analysed with respect to ethnicity (marking skin tone), calendar quartile, body mass index (BMI), trimester and parity. Deficiency was defined as <25 nmol L^{-1}, insufficiency 25–75 nmol L^{-1} and adequacy >75 nmol L^{-1}. Three hundred and forty-six women were included and represented the total population regarding skin tone, quartile, BMI, gestation and parity. Overall, 18% [95% confidence interval (CI): 15–23%] of sample women had adequate vitamin D levels; 36% were deficient, 45% insufficient. Among women with dark skin, only 8% (95% CI: 5–12%) had adequate levels compared with 43% (95% CI: 33–53%) of those with light skin. Obese women were found have significantly lower vitamin D levels than non-obese women. Vitamin D deficiency and insufficiency are prevalent year-round among pregnant women in North West London, especially those with darker skin. Existing supplementation guidelines should be supported; however, other measures are required to improve status among all women.

Keywords: vitamin D, supplementation, public health, pregnancy, deficiency/insufficiency.

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Introduction

'Epidemiologists aim to identify modifiable causes of disease, this often being a prerequisite for the application of epidemiological findings in public health programmes, health service planning and clinical medicine' (Smith 2011). Maternal vitamin D deficiency is a significant public health issue, which if prevented has the potential to bring about health improvement. There is little population data available to quantify the degree of deficiency among UK pregnant women. The lack of high-quality evidence has hampered the implementation of vitamin D deficiency prevention programmes (DeLuca 2004; Lerch & Meissner 2007; Pearce & Cheetham 2010; De-Regil *et al*. 2012). The Royal College of Obstetricians and Gynaecologists (RCOG 2009) and the National Institute for Health and Clinical Excellence (NICE 2008) recommend that all pregnant women should take a multivitamin supplement containing 10 μg of vitamin D daily. They note groups at risk of deficiency should be targeted and suggest that the Department of

Health (DoH) consider universal free provision of supplements. However, they also suggest that the benefit for low-risk women is unclear, and evidence regarding timing and optimal dosing during pregnancy is lacking (Hypponen & Boucher 2010; Finer *et al.* 2012).

Newborn infants derive their vitamin D entirely from maternal vitamin D stores, and following birth their stores are 60% to 70% of maternal levels (Waiters *et al.* 1999). Thus, if maternal levels are deficient (<25 nmol L^{-1}), infant levels will be low. Vitamin D deficiency during pregnancy adversely affects health, growth and development of the offspring; severe deficiency causes rickets and poor bone mineralisation in childhood (Lerch & Meissner 2007). Vitamin D deficiency can also cause infant hypocalcaemia, tetany, seizures (Madhusmita *et al.* 2008) and cardiomyopathy (Maiya *et al.* 2008). Deficiency also has health consequences for the mother, with severe vitamin D deficiency causing osteomalacia (Mawer & Davies 2001). Vitamin D insufficiency (<75 nmol L^{-1}) has been implicated in the aetiology of many other illnesses (Bjelakovic *et al.* 2011) including: autoimmune diseases (type I diabetes, multiple sclerosis, inflammatory bowel disease and rheumatoid arthritis), infectious diseases (tuberculosis), cardiovascular disease, chronic pain disorders and some forms of cancer (Holick 2004). The causal mechanisms of many of these associations are yet to be fully elucidated.

Changes in laboratory measurement techniques over the past 30 years, from the original radioimmunoassay (RIA) to the reformulated RIA and current liquid chromatography coupled to tandem mass spectrometry (LC-MS), have resulted in confusion and misinterpretation of longitudinal trends in population vitamin D status (Binkley *et al.* 2004).

The majority of vitamin D is obtained through exposure of the skin to sunlight (ultraviolet B light in the range 270–290 nm). At this wavelength, 7-dehydrocholesterol in skin is converted to pre-vitamin D, which isomerises to vitamin D3 and is then metabolised by the body to its active and inactive metabolites (DeLuca 2004). Increased skin pigmentation reduces vitamin D synthetic capacity by up to 10 times (Clemens *et al.* 1982). Melanin absorbs ultraviolet light and blocks some of the frequencies required for vitamin D production, and therefore dark-skinned people require greater exposure to sunlight than light-skinned people. Long-sleeved clothing worn in colder climates or for religious reasons block light penetration into skin, as does sunscreen. At latitudes above approximately 52° light between 270 nm and 290 nm is only available from spring through to autumn, and little or no sunlight of an appropriate wavelength is available for endogenous production during the winter months (Hypponen & Power 2007).

Endogenously synthesised vitamin D (or ingested vitamin D) is metabolised in the liver to produce the prohormone, 25-hydroxyvitamin D [25(OH)D]. This circulates bound to vitamin D-binding protein and is stored in muscle and adipose tissue. There are two routes by which the 25(OH)D can be processed, first, the classical route in which one hydroxylation of 25(OH)D takes place in the kidney to produce the active metabolite 1,25-dihydroxyvitamin D. This process is tightly controlled by the prevailing calcium concentration. It is widely accepted that the best measure of vitamin D status is the measurement of

Key messages

- This study confirms a high prevalence of vitamin D deficiency and insufficiency in pregnant women. Those at greatest risk are dark-skinned and obese.
- Due to the potentially serious and long-term nature of the health sequelae associated with vitamin D deficiency, public health policy should be strengthened to ensure effective vitamin D supplementation and further consider food fortification. There needs to be an agreement on optimal dosing.
- Both health professionals and the public need educating in regard to the benefits of vitamin D and how to access supplements and safe sun exposure.
- More prescriptive supplementation guidelines that could benefit specific 'at-risk' populations should be considered, as should offering supplements to all pregnant women free of charge.

25(OH)D in peripheral blood. 1,25-dihydroxyvitamin D increases intestinal absorption of calcium from the gut, and regulates renal tubular re-absorption of calcium in concert with parathyroid hormone. More recent insights suggest that 25(OH)D acts as a pro-hormone. It is delivered to other tissues where it is converted into the active metabolite 1,25-dihydroxyvitamin D and exerts its effect through paracrine actions on vitamin D receptors on adjacent cells inducing anti-inflammatory, immune and neuro-modulatory effects (Holick 2004). Vitamin D receptors have been found on cells throughout the body including skin, parathyroid gland, intestine, bone, kidney, pituitary gland, ovary, lymphocytes, liver, brain, heart and skeletal muscle (Mawer & Davies 2001; Maiya et al. 2008).

Some vitamin D are obtained from the diet, through the ingestion of oily fish, certain fortified foods and vitamin D supplements. Ingested vitamin D is metabolised in the same manner as that endogenously produced. The average UK diet is not rich in vitamin D-containing foods. Women aged between 19 and 64 years consume an average of 2.7 μg of vitamin D per day from food sources, compared with the 10 μg recommended as per the daily UK dietary reference value (Scientific Advisory Committee on Nutrition 2007). About 15% of the adult population and 25% of the young adult population (aged 19–24 years) were previously found to be vitamin D deficient with serum levels <25 nmol L^{-1} (Ruston et al. 2004; Hypponen & Power 2007). However, as sun exposure is also associated with eye and skin disease, recommendations to maximise skin production must be balanced against risks (Binkley et al. 2007).

There is particular concern regarding the vitamin D status of pregnant women in the UK. The prevalence of deficiency in certain high-risk groups (including women of South Asian, African, Caribbean or Middle Eastern origin, those with diets low in vitamin D, pre-pregnancy obesity and limited sun exposure) has been estimated to range from 50% to 84%. Up to 90% of the South Asian female population living in the UK may be vitamin D deficient (Dijkstra et al. 2007; RCOG 2009; Hypponen & Boucher 2010). Vitamin D supplementation during pregnancy improves maternal vitamin D status and has been associated with improved growth during the first year of life (Brunvand et al. 1996), a reduction in the incidence of rickets, reduced risk of wheezing and type 1 diabetes during childhood (Holick 2004; Robyn et al. 2008). Reduction in maternal risk includes pre-eclampsia (Haugen et al. 2009; Robinson et al. 2010), bacterial vaginosis (Bodnar et al. 2009), which may influence premature labour and caesarean section rates (Merewood et al. 2009). This is possibly because vitamin D deficiency is related to poor muscular performance adversely influencing labour. Also, it may be that the caesarean rate increases with fetal distress due to infection or pre-eclampsia, which is linked to vitamin D deficiency as outlined above.

A review of the role of vitamin D is due to be published in 2014 by the UK Scientific Advisory Committee on Nutrition (SACN) (Scientific Advisory Committee on Nutrition 2007). NICE (2008) and SACN have both recommended surveys of vitamin D status be performed among pregnant women. This study sets out to establish the prevalence of vitamin D deficiency among the multi-ethnic population of pregnant women living in North West London and to explore risk factors that might explain insufficiency/deficiency in this community. However, the findings are relevant and applicable in an international context.

Methods

25(OH)D levels were measured in randomly selected (Microsoft Excel number randomisation) serum samples from the antenatal clinic at an outer London district general hospital, which has approximately 5000 births per year. A database containing information on ethnicity (self-reported), body mass index (BMI), parity, date and gestation at booking is routinely maintained for all women from booking onwards. At the initial booking visit, routine blood samples are collected (NICE 2008). Serum from these samples is stored for 2 years as per national protocol (DoH 2003). 25(OH)D levels were retrospectively analysed using LC-MS, which is widely accepted as the gold standard test (Maunsell et al. 2005). This method has been shown to be comparable to established immunoassay techniques and performs

well in a Vitamin D External Quality Assessment Scheme (DEQAS) (Maunsell *et al.* 2005). Results were divided into three thresholds: deficiency, where levels were equal to or under 25 nmol L^{-1}, insufficiency 25–74 nmol L^{-1} and adequacy: levels over 75 nmol L^{-1}.

Results were analysed in relation to skin tone, date of sample, BMI, trimester and parity. Ethnicities listed as African, Afro-Caribbean or Asian were included in the 'dark skin' group and those listed as White British, Irish and White European were included in the 'light skin' group. The calendar year was broken down into quartiles, January to March, April to June, July to September and October to December, to assess seasonal variations in vitamin D due to endogenous production from sun exposure. Women were classified as obese if their BMI was greater than 30 kg m^{-2}.

The sample size was calculated in order to estimate the prevalence of mothers with vitamin D deficiency to within 5% of the true population value. It was assumed that approximately 50% of mothers would have a vitamin D deficiency based on Dutch data and with a 95% confidence level, it was calculated that 384 subjects were required for the study. Prior approval was obtained from the Brent Ethics Committee (REC ref 08/HO717/78).

25(OH)D levels were summarised using the median and interquartile range. Multiple linear regression was used to examine the association between maternal characteristics and 25(OH)D levels. Due to a skewed distribution of 25(OH)D levels, the data were log transformed before analysis. For ease of interpretation, the regression coefficients were back transformed to the original scale, and can be interpreted in the form of ratios. Statistical analysis was performed using Stata version 9.2 (Stata Corp. LLP, College Station, TX, USA). Multiple logistic regression analysis was carried out to determine which maternal factors were independently associated with low 25(OH)D and adjusting for other maternal characteristics.

Results

Of the 4799 women who gave birth between April 2008 and March 2009, 4732 had data available on the database. Of this group, 384 women were randomly selected from the database, 346 of whom had sufficient serum for analysis and were included in the study. There was no statistically significant difference in skin colour, parity, BMI, gestation or quartile at presentation between the women included in the sample and the rest of the maternity population for 2008 to 2009 (results not presented). The positively skewed distribution of 25(OH)D is illustrated in Fig. 1.

Among the sample women, the vast majority had insufficient levels of 25-OH vitamin D. Only 18% [95% confidence interval (CI): 15–23%] of women had adequate levels, and this varied according to skin tone, seasonality and BMI (Table 1).
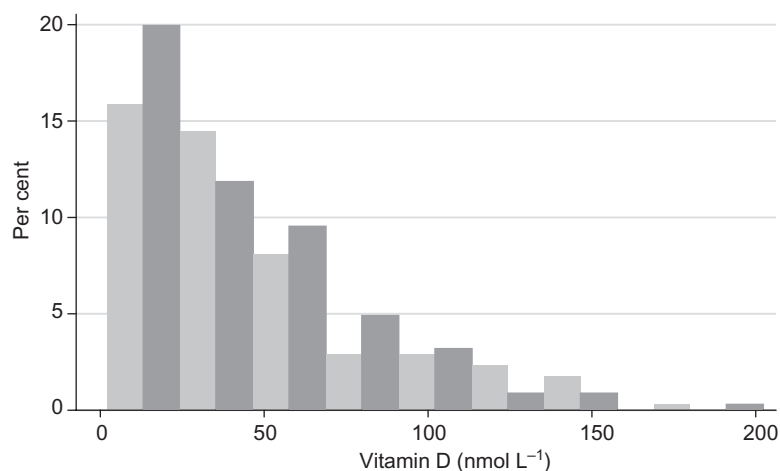

Fig. 1. Histogram illustrating the distribution of serum 25 OH vitamin D among sample women.

Table 1. Serum 25(OH)D levels among sample women by variable

Variable	Category	Vitamin D (nmol L⁻¹)	Vitamin D classification		
		Median (IQR)	Adequate (>75nmol L⁻¹)	Insufficient (25–74nmol L⁻¹)	Deficient (<25nmol L⁻¹)
			n (%)	n (%)	n (%)
Total	(n = 346)	35 (19, 64)	64 (18%)	156 (45%)	126 (36%)
Skin tone	Light (n = 103)	64 (41, 102)	44 (43%)	49 (48%)	10 (10%)
	Dark (n = 243)	26 (15, 45)	20 (8%)	107 (44%)	116 (48%)
Quarter	Jul–Sep	38 (22, 76)	22 (26%)	38 (45%)	25 (29%)
	Oct–Dec	38 (18, 66)	15 (19%)	37 (46%)	29 (36%)
	Jan–Mar	26 (12, 48)	8 (11%)	31 (41%)	37 (49%)
	Apr–Jun	32 (20, 60)	19 (18%)	50 (48%)	35 (34%)
BMI‡	<30 (n = 277)	36 (20, 64)	52 (19%)	128 (46%)	98 (35%)
	≥30 (n = 43)	26 (13, 51)	5 (12%)	18 (42%)	20 (47%)
Trimester†	First	36 (21, 64)	30 (20%)	67 (46%)	50 (34%)
	Second	33 (17, 64)	29 (18%)	69 (43%)	64 (40%)
	Third	29 (17, 54)	3 (10%)	17 (57%)	10 (33%)
Parity*	0	36 (18, 66)	34 (20%)	77 (45%)	62 (36%)
	1	40 (22, 65)	24 (22%)	50 (45%)	36 (36%)
	2+	33 (17, 48)	6 (10%)	28 (47%)	26 (26%)

BMI, body mass index; IQR, interquartile range. *Three patients with missing parity values. †Seven patients with missing trimester values. ‡25 patients with missing BMI values.

There was an independent association between serum 25(OH)D levels and quartile of year. The levels taken between January and March were 30% lower than those taken between July and September. In addition, there was an independent association between BMI and serum 25(OH)D level. While 86.6% of the women in our sample were not obese, the 13.4% who were had significantly lower serum 25(OH)D levels. There were no significant associations noted between serum 25(OH)D and parity or trimester at booking (Table 2).

Vitamin levels in dark-skinned women were significantly lower than for women with light skin. Only 8% (95% CI: 5–12%) of women with dark skin had adequate levels, compared with 43% (95% CI: 33–53%) of women with light skin (Tables 2, 3).

Discussion

The discovery of vitamin D in the 1920s and the subsequent elimination of rickets must rank as one of medicine's great achievements (Steenbock 1924), and yet the re-emergence of rickets and other forms of vitamin D deficiency in this generation may prove to

Table 2. Logistic regression analysis showing the effect of maternal characteristics upon vitamin D levels

Variable	Category	Ratio (95% CI)	P-value*
Skin tone	Light	1	<0.001
	Dark	0.43 (0.35, 0.55)	
Quarter	July–September	1	0.002
	October–December	0.78 (0.59, 1.02)	
	January–March	0.60 (0.46, 0.78)	
	April–June	0.84 (0.66, 1.07)	
BMI	<30 kg m²	1	0.04
	≥30 kg m²	0.76 (0.57, 0.99)	
Trimester	First	1	0.16
	Second	0.83 (0.68, 1.01)	
	Third	0.96 (0.68, 1.37)	
Parity	0	1	0.25
	1	1.06 (0.86, 1.30)	
	2+	0.85 (0.66, 1.08)	

BMI, body mass index; CI, confidence interval. *P-values reflect overall effect of each variable upon vitamin D levels.

be the greatest failure in the UK's public health programme. We found high rates of vitamin D insufficiency and deficiency year-round among all women in this study. Women with dark skin had lower median serum 25(OH)D levels and were more likely to be

Table 3. Percentages of women with adequate serum vitamin D levels, total and by skin tone

Group	Number adequate	% adequate (95% CI)
All women	64/346	18% (15%, 23%)
Light skin tone	44/103	43% (33%, 53%)
Dark skin tone	20/243	8% (5%, 12%)

CI, confidence interval.

either insufficient or deficient compared with women with light skin.

Compared with the summer quarter (July–September) 25(OH)D levels were significantly lower during January to March due to lack of ultraviolet light in the UK in the winter months. Obese women were more likely than non-obese women to have inadequate levels. This has been reported in previous studies and may be related to decreased bioavailability of vitamin D from cutaneous stores or its deposition in body fat (Wortsman *et al*. 2007). We found no association between vitamin D level and parity or trimester at booking.

Longitudinal follow-up is required to determine the natural history of vitamin D status during pregnancy as well as the clinical consequences of suboptimal levels for different groups of women and their children. Well-designed randomised controlled trials of vitamin D supplementation during pregnancy are needed to evaluate its efficacy in improving maternal vitamin D status and clinically relevant outcomes. Current recommendations encouraging supplementation during pregnancy should be supported and strengthened. Similarly, public health initiatives advising on diet and sun exposure should be reviewed to improve effectiveness. Optimal supplementation dosing and methods of administration must be determined, and research on vitamin D metabolism in women of different skin colours and BMIs should be encouraged (De-Regil *et al*. 2012). It appears that additional measures are needed to improve pre- and antenatal vitamin D status, particularly among at-risk women living at higher latitudes. Routine food fortification, as occurs in many countries, should be considered, balanced against safety concerns. Food fortification has the advantage of supplementing the whole population seemingly without any detrimental

effects. In fact, O'Donnell *et al*. (2008) demonstrated in a systematic review covering nine randomised controlled trials from 1966 to June 2006 that, although the trials were small and imperfect, they evidenced that vitamin D supplementation improved vitamin D status in adults. It is important to ensure fortification is appropriately quality-assured.

In the UK, there is evidence of poor public awareness of the consequences of vitamin D deficiency in pregnancy and early infancy (Chandaria *et al*. 2011). Professional awareness of current DoH recommendations is poor (Jain *et al*. 2011; Ling *et al*. 2011), and efforts to strengthen this should improve outcomes.

Limitations

As this was a retrospective study using stored serum samples and a maternity database, information regarding diet, supplementation and sun exposure was not available. Our results may not be generalisable to populations living at different latitudes or of different ethnicity. As skin colour was extrapolated from self-reported ethnicity, imprecision of this as a proxy measure may have affected our results. For future studies, the use of a reflectometer could be considered (Binkley *et al*. 2007). Furthermore, because serum samples were taken at the first antenatal visit, we are unable to report on the efficacy of counselling as regards to vitamin D supplementation or dietary uptake during pregnancy.

Conclusion

This is the first study reporting serum vitamin D status of an unselected group of pregnant women from a multi-ethnic population living in London. We have shown a high prevalence of vitamin D deficiency (36%) and insufficiency (45%) among all pregnant women in North West London, particularly those with darker skin (48% and 44%, respectively). Serum vitamin D levels are lowest during the winter months and among obese women. As inadequate levels of vitamin D impact on maternal and child health optimising maternal, vitamin D status should be a public health priority. Efforts should be made to heighten awareness of the importance of maintaining adequate

levels, particularly among high-risk women. More prescriptive supplementation guidelines that could benefit the 'at-risk' population should be considered, as should offering supplements to all pregnant women free of charge.

Conflicts of interest

Professor M Blair was advisor to Department of Health on the Healthy Child Programme from December 2008 to March 2010.

Contributions

TMc is the first author and corresponding author. BJ contributed in the study design and write-up. TM and SS performed laboratory work and data entry. LB contributed in the results presentation and write-up. PB was the statistician and contributed also in the results presentation. SR was the laboratory lead and biochemical expert and contributed in results writing. MB contributed in the study design, write-up and overall academic supervision.

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