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Horizons in Nutritional Science

Avoidance of vitamin D deficiency in pregnancy in the United Kingdom: the case for a unified approach in National policy

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Prevalence of hypovitaminosis D in Western populations is high; pregnant women are identified as a high-risk group, especially if dark skinned. Consequences of severe clinical vitamin D deficiency in pregnancy can be life threatening to the newborn, while lesser degrees of hypovitaminosis D may have important long-term implications for offspring health. Past experiences with routine provision of 10 μg/d (400 IU/d) to all pregnant mothers suggest that this dose is sufficient to prevent overt neonatal complications of vitamin D deficiency. Recent data suggest that supplementation with dosages above 10 μg/d may be required for optimal health in the mother and child; however, further research is required for the assessment of the benefits and safety of supplementation with higher dosages. Lack of unified advice on vitamin D supplementation of pregnant mothers in the UK hinders the implementation of primary prevention strategies and is likely to leave some deficient mothers without supplementation.

Vitamin D: Pregnancy: Deficiency: Policy

Mothers have protected their babies from rickets by spending time outdoors and taking cod liver oil for almost 100 years, from before vitamin D was discovered. Now that avoidance of mid-day sunlight is advised, and cod liver oil is no longer used in pregnancy, we have seen rickets and other features of vitamin D deficiency re-emerge[1].

What is the scale of the problem in the UK?

Hypovitaminosis D affects adults in epidemic proportions in Western societies[2,3], which is a problem aggravated by Western lifestyles with long hours of indoor work and by avoidance of sunshine aimed at reduction in skin cancer risks (Table 1). Vitamin D deficiency (< 25 nmol/l) is more common in women than in men (for example, 9·2 *v.* 6·6 %, respectively, in British 45-year-olds)[4], and pregnancy is known to represent a particularly high-risk situation. However, as we will discuss in the following section, in the UK, there is currently no consensus on advice on vitamin D supplementation to pregnant women or generally agreed guidelines for relevant health care providers. Lack of consistent guidance leads to mixed messages, which make it difficult to effectively implement strategies for the primary prevention of vitamin D deficiency.

The return of rickets in the UK

There is a long history of population-based approaches for the prevention of vitamin D deficiency in Britain[5]. By the mid-19th century, it was appreciated that rickets was prevented and cured by summer sunshine or by taking cod liver oil[6]. The discovery of vitamin D in the 1920s led to regular outdoor 'airing' of infants and routine cod liver oil consumption by many mothers and children[5,6]. Indeed, neonatal/infantile hypocalcaemia and rickets had virtually disappeared by the 1930s. As a result of this knowledge, ergocalciferol was added to National Dried Milk during World War II, and cod liver oil was included as one of the five welfare foods distributed by the Ministry of Food to expectant/nursing mothers and young children[7]. Since World War II, vitamin D supplementation has been consistently recommended during pregnancy[5,8,9]. However, after the war, uncontrolled vitamin D fortification of baby milks and baby foods provided intakes of up to 100 μg/d (4000 IU/d), which caused many cases of infantile hypercalcaemia[5,10,11]. Uncontrolled vitamin D fortification was then banned[11], followed by resurgence of rickets in immigrant communities during the 1960s[5,12,13]. Cod liver oil remained available at antenatal clinics, but uptake was poor in immigrant populations[14]. Routine offers of cod liver oil (rich in vitamin A)

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; DoH, Department of Health.

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Table 1. Barriers to adequate vitamin D intake and sunlight-induced skin synthesis in pregnancy

Factor affecting intake/synthesis	Consequence
Diet is a poor source of vitamin D. Vitamin D content is high only in oily fish; moderate in eggs; low in meat and supplemented breakfast cereals; very poor in milk, butter and other dairy products unless fortified. Margarine is routinely fortified in the UK, but only to the concentration naturally present in butter	Insufficient intake of vitamin D through diet
SACN (2004) advice is to avoid eating oily fish of more than two portions per week in pregnancy to avoid excessive intakes of harmful pollutants (mainly, dioxins, polychlorinated biphenyls and mercury)[60]. Links (accessed on 1 August 2008): SACN: http://www.sacn.gov.uk/pdfs/fics_sacn_advice_fish.pdf	Restricted dietary intake of vitamin D due to limited oily fish consumption in pregnancy
UK Department of Health advice not to take cod liver oil in pregnancy (since October 1990) to avoid excessive intakes of vitamin A content due to shown teratogenicity[15]	Elimination of cod liver oil as a source of vitamin D during pregnancy
Latitude	Increasing declination of the sun with distance from the equator reduces UVB reaching the earth's surface
Dimming due to atmospheric dust clouds and/or pollution	Reduces UVB reaching the earth's surface
Clothing, in particular all-over clothing and veiling	Reduces skin exposure to available UVB
Avoidance of sunlight to reduce skin cancer risks or to maintain/improve appearance using hats, sunscreens and avoidance of sunlight between 11.00 and 15.00 hours	All reduce exposure to sunlight containing UVB effective for inducing skin synthesis of vitamin D
Working indoors/shift work	Reduced time spent outdoors during daylight hours, with window glass blocking UVB radiation
Recreational habits: preference for indoor activities, such as watching television and using computers over outdoor activities	Reduced exposure to UVB due to less time spent outdoors
Lack of outdoor exercise due to possible pregnancy-related restrictions	Reduced exposure to UVB due to less time spent outdoors
Lack of holidays in the sun due to possible pregnancy-related travel restrictions	Limited opportunity to boost vitamin D reserves to cover periods of low synthesis in the latitude of residence
Periods of hospitalisation due to pregnancy-related complications	Reduced exposure to UVB due to less time spent outdoors

SACN, Scientific Advisory Committee on Nutrition.

to pregnant mothers ceased in the 1990s following formal advice from the Chief Medical Officer when the teratogenicity of excessive vitamin A intake was appreciated[15]. No provision was made for continued vitamin D supplementation of pregnant mothers. This left women dependent on the combination of a national diet known to be poor in vitamin D and sun-induced skin synthesis that is effective in increasing serum 25-hydroxy-vitamin D (25(OH)D) concentrations only for 5–6 months of the year[4,8]. The benefits of modest supplementation of immigrant mothers had been demonstrated in the UK by the 1990s[5,16], suggesting that the resurgence of rickets was predictable and largely preventable had routine vitamin D supplementation been continued[5].

Current conflicts in advice

The UK Department of Health (DoH) re-enforced their advice[17] for pregnant and breast-feeding mothers to ensure that they achieved intakes of vitamin D (10 μg/d (400 IU/d)) in 2007. This followed recommendations of the Scientific Advisory Committee on Nutrition[8] (Table 2) and a resurgence of rickets, especially in immigrant communities with high prevalence of vitamin D deficiency[3,18–21]. DoH advice effectively endorses supplementation as diet provides little vitamin D, and sunlight-induced synthesis is limited in Britain[4,8].

The recent DoH re-enforcement of vitamin D supplementation in pregnancy coincided with a conflict in advice being developed by the National Institute for Health and Clinical Excellence on Antenatal Care ('healthy pregnant mothers should not be routinely supplemented with vitamin D', September 2007) and on Maternal and Child Nutrition (endorsing existing DoH guidelines, July 2007). The final recommendation was made by the National Institute of Health and Clinical Excellence Guideline Review Panel, and, in contrast to current DoH guidance, it did not endorse vitamin D supplementation for all pregnant women. Instead, it stated that 'all women should be informed... about the importance for their own and their baby's health of maintaining adequate vitamin D stores during pregnancy and whilst breastfeeding', and that 'in order to achieve this, women may choose to take 400 IU/d as in the Healthy Start Multivitamin supplement'[22,23]. Continuing confusion in the UK recommendations is highlighted by the inclusion of vitamin D as one of the vitamins to be provided free of charge to low-income mothers as part of the Healthy Start Scheme (previously known as the Welfare Food Scheme), despite the relatively weak social differences in vitamin D status seen in the UK[4] and the lack of systematic implementation of vitamin D supplementation recommendations for other pregnant mothers. There have also been severe problems in the distribution of Healthy Start vitamins, with manufacturing being stopped due to 'lack of demand'[24]. Currently, the UK is the only one of the thirty-one European countries with a recommended daily vitamin D intake of 0 for women of child-bearing age[25], and therefore, the UK is doing nothing to reduce the risk of women becoming vitamin D deficient before they become pregnant.

Conflicting advice on maternal vitamin D intake is not unique to the UK. The North American health authorities are debating,

Table 2. UK sources of current advice on vitamin D supplementation in pregnancy and conflicts on who should be supplemented

1998: Committee on Medical Aspects of Food and Nutrition Policy[17]
Reference nutrient intake for all pregnant and lactating women: 10 μg/d (400 IU/d): recommendation was set in 1991 and endorsed in 1998. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005936*
2004: National Health Service. 'Healthy start'[61]
Supplements containing 10 μg/d of vitamin D offered free of charge to pregnant and breast-feeding women eligible under the Healthy Start Scheme. Eligible women include pregnant women and families with children under the age of 4 years who are on income support, income-based jobseeker's allowance or who receive child tax credit with an income of £15 575 a year or less (2008/9). http://www.healthystart.nhs.uk/*
2007: Scientific Advisory Committee on Nutrition: Update on vitamin D[8]
Explicit reiteration that all pregnant and breast-feeding women should consider taking daily supplements of vitamin D, 10 μg/d (400 IU/d), to ensure their requirement for vitamin D is met and to ensure adequate fetal stores for early infancy. http://www.sacn.gov.uk/reports_position_statements/position_statements/update_on_vitamin_d_-_november_2007.html*
2007: Department of Health Vitamin D Campaign
Encouragement to pregnant and breast-feeding women to boost their intake of vitamin D in the darker winter months, if necessary by taking supplemental vitamin D (10 μg as in Healthy Start Supplements). Women who consider themselves being at risk of vitamin D deficiency encouraged to seek measurement of serum concentrations. http://www.wired-gov.net/wg/wg-news-1.nsf/0/651D8117086E1C76802573BF00267D65?OpenDocument*
2008: National Institute of Health and Clinical Excellence[22,23]
Importance and benefits of maintaining adequate vitamin D storages to be made known to all pregnant and breast-feeding women at the booking appointment, with advice that women may choose to take 10 μg/d (400 IU/d). Particular focus to be given to high-risk women including the obese, women with limited skin exposure to sunlight or who are of South Asian, African, Caribbean or Middle Eastern descent (in 'Antenatal Care', also women who eat a diet particularly low in vitamin D), uptake of Healthy Start Supplements encouraged in those who are eligible. 'Maternal and Child Nutrition' (March 2008): http://www.nice.org.uk/nicemedia/pdf/PH011guidance.pdf* 'Antenatal Care' (March 2008): http://www.nice.org.uk/nicemedia/pdf/CG062NICEguideline.pdf

* All links are as accessed on 9 July 2009.

not about whether to supplement vitamin D, but only about the dosage of vitamin D that should be provided. The Canadian Paediatric Society recently recommended that 'all pregnant mothers should take vitamin D 50 μg/d (2000 IU/d) throughout pregnancy'[26], while shortly afterwards, the Federal Department of Health Canada re-enforced its recommendation of 5 μg/d (200 IU/d) for pregnant and breast-feeding women, publicly discounting the recommendations of the Paediatric Society. Currently, the European Commission recommends 10 μg/d (400 IU/d) vitamin D during pregnancy[27], while the WHO recommendation is set at 5 μg/d (200 IU/d)[28].

Gaps in the evidence and differences in its interpretation

Inconsistency in advice given by health authorities can arise from differences in the interpretation of available evidence and in the perceived importance of vitamin D deficiency in pregnancy. Furthermore, opinions about the safety of dosages >10 μg/d (400 IU/d) in pregnancy differ[8]. As reviewed above, historical data suggest that the recommended dosage of 10 μg/d (400 IU/d) is safe and effective in preventing severe clinical vitamin D deficiency, rickets in children and osteomalacia in adults[5,9]. However, the physiological effects of 1,25-dihydroxyvitamin D (the active hormonal metabolite) are known to extend beyond Ca metabolism and bone health, and evidence is accumulating to suggest that vitamin D intakes required to achieve optimal benefits are likely to be much higher[29,30].

Vitamin D in pregnancy

The importance of vitamin D during pregnancy is suggested by the presence of nuclear vitamin D receptors and of the vitamin D-activating 1-α-hydroxylase enzyme in pregnancy-specific tissues such as the decidua and placenta[31]. Circulating maternal concentrations of 1,25-dihydroxyvitamin D rise from early in the first trimester and increase progressively during gestation, being twice as high in late pregnancy than postpartum or in non-pregnant controls[31]. These physiological changes are accepted as important for ensuring fetal Ca supplies and for inducing immunological adaptations required for successful maintenance of pregnancy[31]. There is evidence for alterations in vitamin D metabolism in women with pre-eclampsia[32–36], with recent studies suggesting reductions in the incidence with higher maternal vitamin D status[37] and intake[38]. The immunomodulatory effects of 1,25-dihydroxyvitamin D, which have been proposed to explain the associations with pre-eclampsia[36], would also be biologically relevant for reduction in the risk of miscarriage[39], and could explain the recent observations for higher success rates for *in vitro* fertilisation for women with higher compared to lower 25(OH)D concentrations[40]. Preliminary data from a randomised placebo controlled trial of high-dose vitamin D supplementation in pregnancy (100 μg/d, presented in the Vitamin D Workshop in Bruges, October 2009) suggested that supplementation at these dosages was safe and did not lead to elevations in maternal Ca levels[41]. They also reported reductions in the rate of preterm births and pregnancy-related complications. However, full evaluation of these data will need to wait for the formal publication of the findings.

Maternal vitamin D deficiency and offspring health

Vitamin D status in neonates is related to maternal vitamin D status (serum 25(OH)D)[20,42,43]. Randomised trials show maternal and cord 25(OH)D to increase after maternal vitamin D supplementation[43–45]. Neonatal complications of extreme maternal vitamin D deficiency are life threatening (e.g. severe hypocalcaemic fits with high risks of resultant brain damage[20] and neonatal heart failure[46]) in addition to the well-recognised

British Journal of Nutrition

risks of fractures and rickets. The evidence for the severe complications of vitamin D deficiency comes from an expanding series of case reports. For obvious ethical reasons, these rare complications have not been, and they are unlikely ever to be, examined by randomised trials of supplementation. Indeed, experience has already shown that trials proposing to randomise mothers with low serum 25(OH)D concentrations are deemed unacceptable by most ethics committees, and approvals have been granted only to investigate the influences of vitamin D supplementation in women who are not severely deficient (serum 25(OH)D >25 nmol/l). Vitamin D insufficiency has been associated with dose-wise reductions in bone mineral content in offspring[47] and perinatal growth restriction[43], and also with increased risk of immunological disorders such as type 1 diabetes[48,49] and acute respiratory infection[50]. The range of maternal and offspring health outcomes associated with maternal vitamin D status has been the subject of a number of recent reviews[51–54]. The only end-point for possible adverse effects of maternal vitamin D 'repletion' is the association of high maternal 25(OH)D concentrations with increased atopy and asthma risks in the offspring[55], which is a finding challenged by reports suggesting beneficial effects of higher *v.* lower maternal vitamin D intakes on early childhood wheezing[56]. Overall, the available evidence suggests unequivocal benefits for avoidance of vitamin D deficiency during pregnancy, while the possible risks of milder forms of hypovitaminosis D provide promising scope for the prevention of a number of disorders. However, vitamin D dosages required to reach serum concentrations currently considered 'optimal' for health are likely to be higher than 10 μg/d[57,58] and, as Scientific Advisory Committee on Nutrition and National Institute of Health and Clinical Excellence state, larger dosages in pregnancy require formal safety assessment[8,22,23].

The public health problem, what is being done and what more should be done

As stated in the Scientific Advisory Committee on Nutrition Update on Vitamin D[8], there is concern that vitamin D 'recommendations are overlooked by health professionals, as well as by the general public', and further that the 'uptake of vitamin drops in the UK is very low even amongst those entitled to receive free supplies'. The recent provision of supplements containing 10 μg (400 IU) of vitamin D to pregnant/breast-feeding women and their offspring should lead to improvements in the situation, provided that the supply chain problems can be overcome[24].

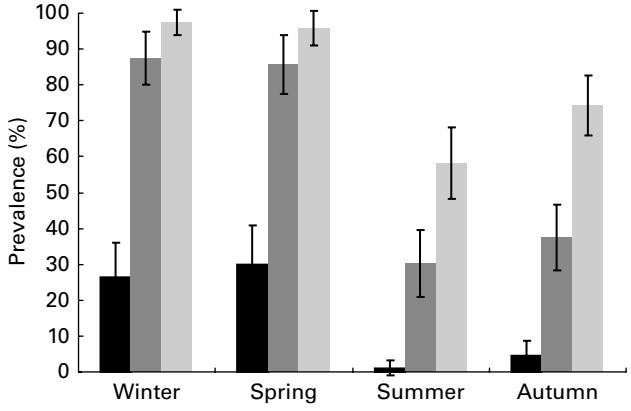

Fig. 1. Prevalence of hypovitaminosis D in pregnant White women living in Southern England (Avon Longitudinal Study of Parents and Children study[59], pilot sample, *n* 354). Error bars represent 95 % CI for prevalence. ■, <25 nmol/l; ■, <50 nmol/l; ■, <75 nmol/l.

British immigrants are recognised as at 'high risk' of hypovitaminosis D, but the problem is also common in pregnant White women, even when living in the Southern England[47]. As can be seen in Fig. 1, 90 % of white pregnant mothers in the Avon Longitudinal Study of Parents and Children[59] had 25(OH)D concentrations <50 nmol/l during winter and spring; 28 % were seriously deficient (<25 nmol/l), and virtually no one reached 75 nmol/l (currently considered optimal). Over the year, 60 % of expectant mothers (approximately 403 000 English/Welsh women) are likely to require vitamin D supplementation for avoidance of serum 25(OH)D <50 nmol/l (90 % being White). Over 150 000 mothers will have deficiency (<25 nmol/l), and 59 % of these being White (estimated from data presented in Fig. 1 and published prevalence rates for non-White British immigrants[57]). As seen in Fig. 1, hypovitaminosis D in White women in the UK is largely a problem during winter and spring, suggesting that treatment during these seasons would benefit most women.

The UK Health Minister emphasised (December 2007) that 'women should contact their GP for a blood test if they think they may be lacking the vitamin' (Table 2). However, this approach does not allow for the high prevalence of hypovitaminosis D, for the high cost of serum 25(OH)D assays (currently approximately £10·50–£25 depending on the assay and laboratory) or for the undesirability of delays in starting supplementation while awaiting results. Indeed, given the data that have been discussed already, it can be argued that relatively little is gained by measuring individual 25(OH)D concentrations since routine supplementation of a pregnant/breast-feeding woman at 10 μg/d (400 IU/d) can currently be provided for £3·64/year[24].

Conclusions

The prevalence of hypovitaminosis D in expectant mothers in Britain is unacceptably high. We, therefore, suggest that all pregnant mothers should be offered vitamin D supplementation throughout the pregnancy to provide cheap, safe and effective prevention of overt vitamin D deficiency. As shown by previous UK experience[5,16], 10 μg/d (400 IU/d) of vitamin D should be enough to prevent the major bony and life-threatening complications of severe clinical deficiency. Higher doses may well be needed to achieve adequate neonatal vitamin D repletion[25,57], but well-designed randomised controlled trials are urgently needed to establish the potential benefits (and safety) of higher maternal vitamin D intakes.

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NS British Journal of Nutrition

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