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**VITAMIN D SUPPLEMENTATION IN PREGNANCY: A SYSTEMATIC REVIEW**

**HTA Evidence Synthesis:** 10/33 Diagnosis and treatment of vitamin D deficiency during pregnancy


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## BACKGROUND: Why is a systemic assessment of the evidence necessary?

### Epidemiology of vitamin D deficiency

There are very few data on vitamin D levels in pregnant women across a population representative of the UK as a whole; the available studies, however, suggest that vitamin D insufficiency is common in this group. In one cohort in Southampton, composed of white Caucasians, 31% had concentrations of circulating 25(OH)-vitamin D lower than 50nmol/l and 18% less than 25nmol/l(1). A recent US study of a population representative of the national demographic distribution revealed that 80% of black pregnant women had levels less than 50nmol/l; the figures for Hispanic and white pregnant women were 45% and 13% respectively(2). In Asian cohorts in the northern hemisphere the burden is even higher(3-7), possibly reaching 90% or greater: A study of non-pregnant South-Asian women in the North of England, many of whom were of child-bearing age, demonstrated that 94% had circulating levels of 25(OH)-vitamin D <= 37.5nmo/l and 26% <=12.5nmol/l(8); a survey of the UK (non-pregnant) population revealed low levels of 25(OH)-vitamin D in 50%(9). As the main source of vitamin D is synthesis in the skin under the influence of UVB radiation from sun light exposure, ethnicity (dark-skin), covering and northerly latitudes (as in UK) are all major risk factors for insufficiency(10).The vitamin D axis is known to be highly influential in the acquisition of bone mineral and significant changes in women's vitamin D and calcium homeostasis occur during pregnancy in order to provide the fetus with adequate calcium to mineralise its rapidly growing skeleton. Evidence that maternal vitamin D status influences neonatal calcium homeostasis has come from studies of Asian immigrants, among whom reduced serum 25(OH)-vitamin D concentrations are accompanied by increased parathyroid hormone levels. Maternal vitamin D deficiency in pregnancy has been associated with neonatal hypocalcaemia(11) and other adverse birth outcomes, such as craniotabes and widened growth plates, suggestive of rachitic (rickets-like) change(12). Indeed a recent study demonstrated rachitic-like widening of the fetal distal femoral metaphysis relative to its length, scanned by ultrasound at 19 and 34 weeks, in fetuses of mothers with low levels of circulating 25(OH)-vitamin D, implying a relatively early effect(13). Infants of mothers with low vitamin D intake may have lower calcium levels at day four post delivery(14). Anecdotally infant rickets is becoming more common in dark-skinned communities in the UK, probably due to low infant intake of vitamin D from the mother, secondary to maternal deficiency, initially via the placenta in utero and then via breast milk post-natally(15-18). However accurate population-wide epidemiological data are lacking.

### Intervention studies

There have been several, mainly small, intervention studies examining this issue (Table 1): Thus in one study 506 women were supplemented at 12 weeks gestation to 400 iu/day vs 633 placebo(19). Levels of 25(OH)-vitamin D levels were higher in maternal, umbilical cord, and infant serum (day 3 and 6) in the supplemented

group. This was not a randomised trial, but supplemented women from one clinic vs placebo in another clinic. Another study compared 59 Asian women, supplemented with 1000 iu from 28 to 32 weeks(20), with 67 controls. Calcium levels were higher in the supplemented mothers, and there was a lower incidence of symptomatic neonatal hypocalcaemia and growth retardation amongst babies of supplemented mothers. Again in an Asian population(4), 25 mothers were randomised to 1200 iu vitamin D per day, 20 mothers to 600 000 iu twice ($7^{th}$ and $8^{th}$ month), and 75 mothers to placebo. In this study there was no difference in calcium and alkaline phosphatase levels between mothers taking 1200 iu/day and those taking placebo. However, those taking 600 000 iu twice had higher maternal and cord calcium and lower alkaline phosphatase than placebo. In a second study(5) the same group supplemented 100 Asian-Indian women with 600 000 iu twice (again at $7^{th}$ and $8^{th}$ months) vs 100 controls and found again, higher maternal and cord calcium and lower alkaline phosphatase. There have been two studies in French populations: 15 women were randomised to receive 1000 iu per day from $3^{rd}$ trimester vs 15 controls(6). Day 4 neonatal calcium and 25(OH)-vitamin D levels were higher in the supplemented group. In the second study 21 French women received 1000 iu per day in the last trimester and 27 received 200 000 iu once during $7^{th}$ month and 29 acted as controls(7). Here neonatal calcium at day 2 and 6 was similar in all groups, but maternal serum 25(OH)-vitamin D was greater in both intervention groups than in the controls. In the one study to measure bone mineral at birth(21), there was no difference in radial BMC in offspring of 19 Asian mothers who had taken 1000 iu vitamin D per day compared with 45 controls. However this lack of observed effect is likely to reflect both the small numbers of subjects and the poor sensitivity of single photon absorptiometry in measuring the tiny amount of bone mineral in the baby's distal radius.

**Table 1: Trials of vitamin D supplements in pregnancy**

| Trial | No. | Location | Intervention | Outcome | |
|---|---|---|---|---|---|
| Cockburn (1980) | 1139 | Scotland | 400 IU/day or | 25(OH)D maternal | ↑ |
| | | | or placebo | Cord | ↑ |
| | | | | Infant | ↑ |
| Brooke (1980) | 126 | UK | 1,000 IU/day | Ca maternal | ↑ |
| | | Asian | | | |
| | | | or placebo | Cord | → |
| | | | | Neonatal | ↑ |
| | | | | Maternal weight | ↑ |
| Marya (1981) | 120 | Asian | 600,000 IU (x2); | Ca maternal | ↑ |
| | | Indian | 1,200 IU/day | Cord | ↑ |
| | | | or placebo | ALP maternal | ↓ |
| | | | | Cord | ↓ |
| Marya (1988) | 200 | Asian | 600,000 IU (x2); | Ca/P maternal | ↑ |
| | | Indian | or placebo | Cord | ↑ |
| | | | | ALP maternal | ↓ |
| | | | | Cord | ↓ |
| Delvin (1986) | 34 | France | 1,000 IU/day; | 25(OH)D cord | ↑ |
| | | | or no vit D | Neonatal | ↑ |
| Mallet (1986) | 68 | France | 200,000 IU (x1); 1,000 IU/day; or no vit D | 25(OH)D maternal with both regimes | ↑ |

↑ elevation; → no change; ↓ decrease; ALP alkaline phosphatase

**Safety of vitamin D supplementation in pregnancy**

None of these studies listed above has suggested that vitamin D supplementation during pregnancy carries a significant risk. Human beings have evolved to cope with as much as 25,000 iu vitamin D formation daily in

the skin. Although rat studies using the equivalent of 15,000,000 iu per day have resulted in extra-skeletal calcifications, there is no evidence that doses below 800,000 iu per day have any adverse effect. 2 studies(22;23) have examined the children of hypoparathyroid women given 100,000 iu vitamin D daily for the duration of pregnancy and found no morphological or physiological adverse consequences. These children were followed for up to 16 years. Recent work has demonstrated a moderate increase in atopy in children of mothers in the highest quarter of serum vitamin D in pregnancy, where levels were greater than 30 ng/ml (24). However, in this study the numbers were small with only 6 cases of atopy (asthma, eczema) by 9 years in the top quartile of maternal vitamin D, 4 each in the middle quartiles and 2 in the bottom. These numbers, even in the highest quartile, were actually lower than the figure for the general population. Additionally, in the Southampton Women's Survey, there was no association between maternal 25(OH)-vitamin D status and atopic or non-atopic eczema at 9 months of age (unpublished data). Thus, this finding needs to be further examined in larger studies, but suggests, for safety, that the optimal intervention would be to supplement those mothers found to be deficient in vitamin D, rather than all pregnant mothers.

**Maternal vitamin D status, offspring wheezing and diabetes**

In contrast to the findings above, another epidemiological study suggested an inverse relationship between maternal dietary intake of vitamin D in pregnancy and later wheezing in the offspring(25). However, a study of vitamin D supplementation in infants again suggested a positive relationship such that greater infant supplementation was associated with increased later wheezing(26). Hypponen found, in an adult population cohort, that circulating IgE levels (are marker of atopic tendency) were positively related to concentrations of 25(OH)-vitamin D but that this was only apparent at very high concentrations (> 125nmol/l)(27). Animal studies have implicated 1,25(OH)-vitamin D as a modulator of immune balance between a tendency to autoimmunity and atopy, but these studies have again suggested influences in both directions(28). Thus the data are inconsistent, and clearly any studies using dietary intake of vitamin D, rather than blood levels, as the marker of vitamin D status have the potential for confounding by UVB exposure and other lifestyle, anthropometric and health factors. It is possible that the relationships between vitamin D and atopy differ depending on timing (eg in pregnancy or postnatal life), or with 25 or 1,25(OH)-vitamin D, or are U-shaped such that both low and very high levels are detrimental. Finally a birth-cohort study from Finland demonstrated a reduced risk of type 1 diabetes in children who had been supplemented with vitamin D as infants(29).

**Longer term importance of maternal vitamin D repletion for offspring bone size and density**

Recent work has suggested that maternal vitamin D deficiency during pregnancy may not solely influence the offspring's skeleton through overt rachitic change. Evidence is accruing that less profound maternal 25(OH)-vitamin D insufficiency may lead to sub-optimal bone size and density in the offspring post-natally, a situation likely to lead to an increased risk of osteoporotic fracture in the offspring in later life. Evidence that the risk of osteoporosis might be modified by environmental influences in early life comes from two groups of studies: (a) those evaluating bone mineral and fracture risk in cohorts of adults for whom birth and/or childhood records are available; and (b) those studies relating the nutrition, body build and lifestyle of pregnant women to the bone mass of their offspring(30). Cohort studies in adults from the UK, USA, Australia and Scandinavia have shown that those who were heavier at birth or in infancy have a greater bone mass(31-34) and a reduced risk of fracture(35) in later life. These associations remain after adjustment for potential confounding factors, such as physical activity, dietary calcium intake, smoking and alcohol consumption. In a cohort of twins, intra-pair differences in birthweight were associated with bone mineral content in middle age, even among monozygous pairs(36). Mother-offspring cohort studies based in Southampton have shown that maternal smoking, poor fat stores and excessive exercise in late pregnancy all have a detrimental effect on bone mineral accrual by the fetus, leading to reduced bone mass at birth(37).

However, the strongest risk factor for poor bone mineral accrual documented in these mother-offspring cohort studies has been maternal vitamin D insufficiency. There was already some indication of the potential role played by maternal vitamin D status in pregnancy from a retrospective cohort study(38) showing that premature babies who were supplemented with vitamin D had an increased whole body bone mass at age 12 years, but these recent findings provided the first direct evidence for the importance of maternal vitamin D status during pregnancy on the child's skeletal growth. In our mother-offspring cohort, data on anthropometry, lifestyle and diet were collected from women during pregnancy and venous 25(OH)-vitamin D was measured

by radio-immunoassay in late pregnancy(1). Whole body, hip and lumbar spine bone area, BMC and BMD were measured in the healthy, term offspring at age 9 years. 31% of the mothers had reduced (insufficient or deficient) circulating concentrations of 25(OH)-vitamin D in late pregnancy. There was a positive association between maternal 25(OH)-vitamin D concentration in late pregnancy and whole body bone mineral content ($r=0.21$, $p=0.0088$) and density ($r=0.21$, $p=0.0063$) in the offspring at 9 years old, with a suggestion of a threshold effect at 40nmol/l. Both the estimated exposure to ultraviolet B radiation during late pregnancy and use of vitamin D supplements predicted maternal 25(OH)-vitamin D concentration ($p<0.001$ and $p=0.01$) and childhood bone mass ($p=0.03$). Reduced concentration of umbilical-venous calcium also predicted lower childhood bone mass ($p=0.03$), suggesting a possible role for placental calcium transport in this process.

Similar findings, linking reduced maternal 25(OH)-vitamin D concentration with lower offspring bone mass, have come from the Southampton Women's Survey. In this ongoing prospective cohort study of women aged 20-34 years, characterised before and during pregnancy, maternal 25(OH)-vitamin D status was measured by radio-immunoassay in late pregnancy and 556 healthy term neonates underwent whole body DXA within 20 days of birth. Offspring of mothers who were insufficient or deficient (<40 nmol/l) in vitamin D in late pregnancy had lower bone mass than those of mothers who were replete. Thus the mean whole body bone area of the female offspring of deficient mothers was 112 $cm^2$ *vs* 120 $cm^2$ in offspring of replete mothers ($p=0.045$). The mean whole body bone mineral content of offspring of deficient *vs* replete mothers was 59g *vs* 64g ($p=0.046$) respectively. There were weaker associations in the boys and there was no association with maternal alkaline phosphatase. Additionally, maternal UVB exposure during pregnancy was positively associated with whole body bone mineral content in the offspring aged 9 years in the Avon Longitudinal Study of Parents and Children(39).

**Summary**

Maternal vitamin D deficiency is important for maternal health, and also has implications for the offspring. In frank deficiency, most common in dark-skinned/ covered populations in the UK, neonatal hypocalcaemia, craniotabes and infant rickets are an increasing problem. However, evidence is accruing for the longer term implications of milder maternal vitamin D insufficiency in the broader population (including white Caucasian women). Thus children of mothers with low levels of circulating 25(OH)-vitamin D in pregnancy have reduced bone size and density, even in the absence of definite rachitic change. This is likely to lead to reduced peak bone mass and increased risk of osteoporotic fracture in later life. Furthermore maternal vitamin D status has been linked to allergy and asthma in the offspring. Thus the outcomes considered for this proposal will encompass both immediate maternal and neonatal health, but also longer term skeletal development and atopy in the child.

## CONSIDERATIONS FOR APPRAISAL OF DATA

There are several factors which make any study of evidence surrounding vitamin D problematic. Firstly, the main source of vitamin D is from synthesis in the skin by the action of UVB radiation, with dietary intake usually forming a minor contribution to overall levels; secondly the physiology of vitamin D in pregnancy and its role in placental calcium transfer and offspring bone development (both linear growth and mineralisation) is unclear; thirdly the definition of a normal range is difficult, even in non-pregnant populations, and techniques used to measure 25(OH)-vitamin D concentrations have widely different characteristics; fourthly, dose-response and differences between use of vitamin $D_2$ and vitamin $D_3$ are unclear; fifthly post-natal vitamin D intake by the offspring may confound any pregnancy relationships and finally the definition of osteomalacia used is important (clinical syndrome or histological definition from bone biopsy). A detailed appraisal of these factors is given below:

### Photosynthesis and metabolism of vitamin D

Vitamin D is a secosteroid which is synthesized in the skin by the action of sunlight. It plays a crucial role in bone metabolism and skeletal growth(40). Around 95% is acquired via photosynthesis in the skin, with the minority from the diet. There are two dietary forms: $D_2$, from plants, or $D_3$, from animals; the latter mainly found in oily fish and fortified margarines and breakfast cereals(41). Vitamin D is synthesized from the action of sunlight (wavelengths 290- 315 nm) on cutaneous 7-dehydrocholesterol, converting it to pre-vitamin $D_3$(10;40). Once formed, pre-vitamin $D_3$ undergoes membrane-enhanced temperature-dependent isomerisation to vitamin $D_3$(40), which is translocated into the circulation where it binds to vitamin D-binding protein

(DBP)(10). The main determinant of vitamin D synthesis in the skin is the level of sun exposure. The total amount of energy accrued from sunlight is dependent on duration and extent of skin exposure, but also on latitude and season. Thus pigmented skin and covering, particularly relevant to the dark-skinned, and potentially covered ethnic minority groups in the UK, reduce synthesis; using sun-block with a factor higher than 8 almost completely prevents formation of vitamin D(41). At latitudes of 48.5° (Paris, France), the skin is unable to form vitamin D between the months of October through to March(40). In Northern latitudes this results in a seasonal variation in levels of vitamin D, with a peak over the summer months and a trough in the winter(10). Use of sunscreen during the summer may prevent adequate synthesis of vitamin D and subsequent storage in fat for the winter months, thus leading to deficiency; greater adiposity is also associated with reduced levels(10). Circulating vitamin D is converted in the liver to 25(OH)-vitamin D (calcidiol), which is the main circulating store. This step, which involves the cytochrome P450 system, is not tightly regulated and thus an increase in photosynthesis of vitamin D in the skin will lead to an increase in 25(OH)-vitamin D in the circulation(10;42), bound to DBP. Excess 25(OH)-vitamin D is converted to 24,25(OH)-vitamin D which is thought be relatively metabolically inactive(10). The 25-(OH)-vitamin D-DBP complex enters renal tubule cells by membrane-bound megalin transport, where the enzyme 1-α-hydroxylase converts it to $1,25(OH)_2$-vitamin D (calcitriol), which is the active compound(42). Although the kidney is the primary site for conversion of circulating 25(OH)-vitamin D, many tissues, such as macrophages, osteoblasts, keratinocytes, prostate, colon and breast express the 1-α-hydroxylase enzyme(40;43;44). Since anephric patients have very low levels of $1,25(OH)_2$-vitamin D in the blood, it seems likely that these extra-renal sites function at the paracrine level, and do not play a major role in calcium homeostasis(41).

**Food sources, recommended intakes and dose response**

Few foods contain significant amounts of vitamin D. The most effective sources are oily fish (for example salmon, mackerel) and fortified foods such as margarine and breakfast cereal. The amount of vitamin D derived from fish is modest: wild salmon contains around 400 iu per 3.5 oz(10). There is much controversy over the recommended daily intake of vitamin D. Older guidance has suggested 200 iu per day for children and adults up to 50 years old and 400 – 600 iu for older adults(45). However, humans have evolved to synthesise much higher levels of vitamin D in the skin: 30 minutes exposure at midday in the summer sun at a southerly latitude in a bathing suit will release around 50,000 iu into the circulation within 24 hours in white persons(46). Previous guidelines were not based on any rigorous assessment of the effects of levels and more recent dosing studies have shown that supplementation with 200-400 iu per day is unlikely to maintain levels of 25(OH)-vitamin D over winter months, let alone replenish stores in somebody who is frankly vitamin D deficient(47). Thus a daily maintenance dose of around 1000 iu per day may be more appropriate in people without adequate sunshine exposure, with higher initial dosing required to reverse frank deficiency(48).

**Physiology of vitamin D in pregnancy**

During pregnancy there is an increase in $1,25(OH)_2$-vitamin D, which may be largely due to an increase in vitamin D binding protein (DBP)(49). This rise is associated with an increase in intestinal calcium absorption (to around 80% intake), and an absorptive hypercalciuria(49). There does not seem to be a rise in maternal parathyroid hormone or 25(OH)-vitamin D during pregnancy, suggesting that the rise in $1,25(OH)_2$-vitamin D may be due to another factor, such as parathyroid hormone-related peptide, which may be secreted by the placenta(50). Studies of maternal bone mass in pregnancy have been conflicting, but most suggest a probable decrease, with a possibly greater decrease in lactation(51-55). The vitamin D receptor (VDR) appears to develop after birth in the infant intestine, and thus calcium absorption is a passive process immediately after birth(56). The role of vitamin D in utero is uncertain, although 25(OH)-vitamin D does cross the placenta(57). In a mouse model, lack of VDR did not significantly affect placental calcium transport or skeletal mineralisation(56); conversely in the rat, $1,25(OH)_2$-vitamin D did seem to influence placental calcium flux(58). Additionally chondrocytes are an extrarenal source of 1a-hydroxylase activity (and so conversion of 25(OH)-vitamin D to $1,25(OH)_2$-vitamin D(59). This observation therefore suggests a possible mechanism by which maternal 25(OH)-vitamin D status might influence bone size in the fetus. Further evidence to support this notion comes from mouse models in which the gene for 1α-hydroxylase (Cyp27b1) was either knocked out or over-expressed in chondrocytes leading to altered growth plate morphology(60). Few data exist in humans at the level of cell biology, but some suggestions have come from recent epidemiological work described above, in which maternal 25(OH)-vitamin D concentrations positively predicted offspring bone

mass at birth(61), and at 9 years old(1), with umbilical cord calcium concentrations and placental calcium transporters(62) implicated in the mechanisms.

**Normal range and measurement of vitamin D**

Circulating 25(OH)-vitamin D is the major store of vitamin D and is the most appropriate for measurement. $1,25(OH)_2$-vitamin D is an adaptive hormone, and therefore its level will reflect prevailing conditions such as calcium intake, and thus defining a normal level may not be meaningful(41). The concept of what is the normal range for 25(OH)-vitamin D is highly controversial at the moment. Given that humans seem to have evolved to require much higher levels of vitamin D than are observed in the UK currently, the process of measuring levels in a population and defining a lower cut-off of the distribution as deficient is likely not to be valid. Historically in the UK, serum levels have been classed as "replete" (>50 nmol/l), insufficient (25 to 50 nmol/l) or deficient (<25 nmol/l). (Older studies often use ng/ml as the unit of measurement: 1 ng/ml = 2.5 nmol/l). The distinction between replete and insufficient has been made on the basis of whether there is a secondary rise in parathyroid hormone, and deficient as a lower cut off below this level. Previous studies have examined the level of 25(OH)-vitamin D in populations at which a rise in PTH is seen, and this threshold has been around 50 nmol/l(63). However, a proportion of the population do not show a rise in PTH with decreasing 25(OH)-vitamin D levels, possibly as a result of concomitant magnesium deficiency(64). Thus an alternative approach is to explore the relationship between fractional calcium absorption in the bowel and level of 25(OH)-vitamin D. Using this technique there appears to be a threshold where absorption reaches a plateau at levels of around 75-80 nmol/l of 25(OH)-vitamin D(65;66). Consequently one common view currently is that the minimum healthy level of 25(OH)-vitamin D is 75 nmol/l(66). This is further supported by recent work in which bone biopsies were performed at autopsy in 675 subjects and related to 25(OH)-vitamin D levels(67). Here, no mineralisation defects were seen in any subject with 25(OH)-vitamin D > 75 nmol/l, although there was no level below which mineralisation defects were universal. The normal level in pregnancy is difficult to define as there is haemodilution and also a rise in vitamin D binding protein. However, many feel that the proposed standard adult level of 75 nmol/l should apply here as well, in the absence of any specific data(66).

There are several different methods available to measure 25(OH)-vitamin D. The gold standard is seen to be gas chromatography- mass spectrometry (GC-MS), but this technique is slow, expensive and time-consuming. Most labs use commercial kit assays, which are usually radio-immunometric assays (for example, IDS, Diasorin, Nicholls), although a chemi-luminescence assay also exists (Diasorin Liaison). The assays tend to be less accurate than GC-MS and high-performance liquid chromatography (HPLC), and also discriminate less well between the $D_2$ and $D_3$ forms(68). Comparison of the Diasorin RIA kits with HPLC showed good correlation for $D_3$, but $D_2$ tended to be slightly underestimated(69). A national system now exists to standardise measurement of 25(OH)-vitamin across laboratories in the UK (Vitamin D External Quality Assessment Scheme http://www.deqas.org/).

**Infant post-natal vitamin D intake**

Infant feeding, supplementation and sunlight exposure will be strong determinants of post-natal infant 25(OH)-vitamin D levels and bone health(70). Concentrations of 25(OH)-vitamin D in breast milk depend on the mother's blood levels and so if the mother is deficient in vitamin D during pregnancy, she is likely to continue to be deficient through lactation, yielding a double-insult to the child in the absence of adequate sun exposure. Clearly post-natal vitamin D supplementation of either the mother (whilst breast feeding) or the infant directly could confound any early outcomes attributed to maternal vitamin D status in pregnancy.

**Osteomalacia: definition**

Osteomalacia is a bone disease caused by inadequate mineralisation of the bone protein matrix, most often, in the UK, as a result of low levels of vitamin D(71). Inadequate calcium and phosphate are other potential causes, seen more frequently in developing countries or as a result of genetic abnormalities leading to phosphate loss. Although osteomalacia is therefore a histological term, it is used to describe the finding of low vitamin D status in a patient with bone/ muscle pain, weakness, waddling gait, skeletal fragility and appropriate biochemical abnormalities e.g. hypocalcaemia(71). There are very few studies which have examined osteomalacia in pregnancy, although anecdotally the incidence of the clinical syndrome is rising in dark-skinned ethnic minorities in the UK. Clearly the definition of osteomalacia used in studies considered for

this review will be critical as the symptoms of osteomalacia overlap considerably with those of chronic pain syndromes such as fibromyalgia. Bone biopsy is the only way to diagnose osteomalacia histologically, but the interventional nature of this procedure means that it is unsuitable for large scale population studies. One recent study of 675 human subjects at autopsy has demonstrated that there is no threshold in circulating 25(OH)-vitamin D level below which osteomalacic changes on bone biopsy are always seen(72).

## EXISTING EVIDENCE SYNTHESIS

Two previous systematic reviews have been performed in this area. The most recent (Mahomed and Gulmezoglu 2009) from the Cochrane group, asked the question "What are the effects of vitamin D supplementation on pregnancy outcome?", and although published in 2009, the actual searches and conclusions were established in 1999. The authors searched for intervention studies registered on the Cochrane Pregnancy and Childbirth Group trials register (October 2001) and the Cochrane Controlled Trials Register (Issue 3, 2001). Thus more recent work and observational data, plus unpublished evidence were not included. Two trials of vitamin D supplementation in pregnancy (Mallet et al., 1986 and Brooke et al., 1980; see table 1) were assessed worthy of inclusion but the authors concluded that there was insufficient evidence on which to base any recommendations. NICE produced guidelines for antenatal care in 2008 (CG62 http://www.nice.org.uk/nicemedia/live/11947/40115/40115.pdf). Again, the conclusion was that there was insufficient evidence to allow a recommendation regarding vitamin D supplementation in pregnancy, although the authors acknowledged that supplementation may be beneficial in high risk groups. Despite the lack of good evidence for population wide supplementation and the dose chosen, the Department of Health currently recommend that all pregnant women take 400 iu vitamin D daily: (http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/@sta/@perf/documents/digitalasset/dh_107667.pdf).

### MAVIDOS Maternal Vitamin D Osteoporosis Study

NH and CC are currently PI and CI respectively of a large study aimed at testing the hypothesis that vitamin D supplementation during pregnancy of women who have low levels of vitamin D will result in improved neonatal bone mineral content. This randomised, placebo-controlled double-blind trial is underway in Southampton, having recruited over 250 out of 954 participants; it should help to inform public health policy regarding vitamin D supplementation in terms of both bone and other maternal and offspring health outcomes.

A summary of trial methods are given below:

Women will have their vitamin D status assessed when they attend for nuchal fold scanning in the twelfth week of pregnancy. Women with circulating 25(OH)-vitamin D levels between 25-100 nmol/l will be randomised in a double blind design to receive an oral vitamin $D_3$ supplement (1000 iu/day) or placebo at 14 weeks gestation till delivery. Questionnaire data obtained will include parity, sunlight exposure, dietary information, and cigarette and alcohol consumption. Women will be seen again at 19 and 34 weeks pregnancy. Blood samples will be taken at 14 and 34 weeks gestation to measure 25(OH)-vitamin D, PTH and bone biochemistry. Maternal anthropometry will be measured at each time point. At delivery venous umbilical cord blood will be collected, together with umbilical cord and placental tissue. Following delivery, the baby will undergo DXA within the first 14 days after birth. Children will be followed up with yearly assessment of health, diet, physical activity and anthropometric measures, with repeat assessment of bone mass by DXA at age 4. The study will provide opportunities for assessment of childhood endocrine (glucose tolerance), cardiovascular (blood pressure, carotid doppler, echocardiography), neurological (IQ) and immunological (Th1/Th2 balance, atopy/ asthma) outcomes.

## OBJECTIVES OF CURRENT APPLICATION

### Research questions (as outlined in HTA call):

1) What are the clinical criteria for vitamin D deficiency in pregnant women?

2) What adverse maternal and neonatal health outcomes are associated with low maternal circulating 25(OH)-vitamin D?

3) Does maternal supplementation with vitamin D in pregnancy lead to an improvement in these outcomes (including assessment of compliance and effectiveness)?

4) What is the optimal type ($D_2$ or $D_3$), dose, regimen and route for vitamin D supplementation in pregnancy?

We will also seek to answer one additional question:

5) Is supplementation with vitamin D in pregnancy likely to be cost-effective?

## METHODS

We will conduct a systematic review of evidence to address these five research questions.

### Inclusion criteria

Studies will be selected if they fulfil criteria based on the sample studied, the independent variable of interest (exposure), the outcomes and the study design.

*Sample studied*

This must include pregnant women or pregnant women and their offspring.

*Exposure*

This must include either assessment of vitamin D status (dietary intake, sunlight exposure, circulating 25(OH)-vitamin D concentration, 1,25(OH)-vitamin D concentration, PTH concentration) or supplementation of participants with vitamin D or vitamin D containing food e.g. oily fish.

*Outcomes*

Primary: Maternal osteomalacia; Neonatal hypocalcaemia, rickets and reduced bone mass

Secondary: Maternal quality of life, bone mass; Neonatal body composition, later offspring health outcomes (including asthma, diabetes, immune disease)

*Study design*

We will include studies (in any language) which report data on individuals. Ecological studies, and non-human studies will therefore be excluded. Study designs that may be included, together with level of evidence quality according to Centre for Evidence Based Medicine (www.cebm.net/index.aspx?o=1025) are:

| | |
|---|---|
| Level 1a | Systematic review (with homogeneity) of randomised controlled trials |
| Level 1b | Individual randomised controlled trial (with narrow confidence interval) |
| Level 2a | Systematic review (with homogeneity) of cohort studies |
| Level 2b | Individual cohort study |
| Level 3a | Systematic reviews (with homogeneity) of case-control studies |
| Level 3b | Individual case-control study |

We plan to include all studies which contribute relevant information, regardless of the setting. However, the setting will be noted as part of data abstraction and will be used in narrative synthesis. We do not plan to exclude studies on the basis of publication date.

*Study setting and timing*

We plan to include all studies which contribute relevant information, regardless of the setting. However, the setting will be noted as part of data abstraction and will be used in narrative synthesis. We do not plan to exclude studies on the basis of publication date.

### Search strategy for identification of studies

The search strategy has been informed by initial scoping exercises performed by an information specialist with extensive expertise in systematic reviews of effectiveness and observational evidence and will aim to identify studies which describe maternal vitamin D levels/ supplementation in relation to maternal and offspring outcomes which may be suitable for answering the questions posed in the review. Searching will commence with a mapping exercise which will be presented to an advisory group, which will be convened at

the outset of the review. The group's advice will be used to refine areas for assessment and accompanying searches to be performed by the information specialist.

The following resources will be searched from their start dates to the present day:

Completed studies (systematic reviews):

- DARE (CRD)
- Cochrane Database of Systematic Reviews (CDSR)
- HTA database (CRD)

Completed studies (other study types):

- Cochrane Register of Controlled Trials (CENTRAL)
- Medline
- Embase
- Biosis
- Google scholar
- AMED

Ongoing studies:

- National Research Register archive
- UKCRN Portfolio
- Current Controlled Trials
- Clinical Trials.gov

Grey literature:

- Conference Proceedings Citation Index- Science (1990-present)
- Zetoc conference search
- Scientific Advisory Committee on Nutrition website
- Department of Health website
- King's Fund Library database
- Trip database
- HTA website
- HMIC (Health Management Information Consortium database)

- Handsearching of bibliographies of selected papers
- Contacting authors for unpublished findings
- Consultation with experts in several fields including metabolic bone disease, obstetrics, infant nutrition, child development, allergy.

Identification of unpublished research is considered important in order to avoid publication bias. Unpublished observational evidence may be difficult to find since observational studies are not registered in the way that RCTs are. Our approach will be to include all studies (published or unpublished) that satisfy selection criteria for the review, by consulting with experts in the field and by writing to first authors of all included studies. We will attempt to find unpublished studies by publicising our review. There is also a possibility that inclusion of those identified may itself introduce bias, due to over-representation of the findings of groups know to reviewers. This will be assessed at the analysis stage of the review.

**Search terms and scoping exercises**

The information specialist has conducted initial scoping exercises using search terms (both text and MeSH) to identify any studies which might relate maternal vitamin D status/ supplementation to maternal or offspring musculoskeletal outcomes. This preliminary search included Medline from 1950 to present revealed 6501 hits and the information specialist has estimated that the strategy is likely to generate around 15000 de-duplicated hits. The strategy uses generalised and specific approaches (e.g. "Vitamin D" + "Pregnancy" vs "Maternal" + "Vitamin D" + " Deficiency" + "Neonatal"+ "Rickets") to ensure maximum sensitivity. The search terms included in this initial scoping exercise are shown below and a summary of the results of the searches is given in Table 2 (page 13 to 15).

**Search terms used for initial scoping exercise:**

**Circulating vitamin D terms and supplement terms**
(Textword terms):
Covered by **vitamin D.ti,ab.**
"25(OH)-vitamin D".ti,ab.
"25 (OH) vitamin D".ti,ab.
"1,25(OH)2-vitamin D".ti,ab.
"24,25(OH)-vitamin D".ti,ab.
vitamin D-deficient.ti,ab.
Vitamin d deficiency.ti,ab.

"(3 beta,5z,7e)-9,10-secocholesta-5,7,10(19)-trien-3-ol".ti,ab. (0 hits)

Covered by **250HD.ti,ab.**
serum 25OHD.ti,ab.

**"25(OH)-vit D".ti,ab.**

Covered by **Hydroxycholecalciferol.ti,ab.**

25 hydroxycholecalciferol.ti,ab.

(Name of substance terms):
**"19356-17-3 (Calcifediol)".rn.**
**"32222-06-3 (Calcitriol)".rn.**
**"1406-16-2 (Vitamin D)".rn.**
**"64719-49-9 (25-hydroxyvitamin D)".rn.**
**"67-97-0 (Cholecalciferol)".rn.**

Supplement$.ti,ab.
Fortified.ti,ab.

(MeSH terms):
**Vitamin D deficiency/**
Covered by **Exp Vitamin D/**
25-Hydroxyvitamin D 2/
24,25-Dihydroxyvitamin D 3/
Calcifediol/
Calcitriol/
Cholecalciferol/
Dihydrotachysterol/
Dihydroxycholecalciferols/
Ergocalciferols/
Hydroxycholecalciferols/

Vitamins/
Dietary Supplements/
Nutritional Status/

Osteomalacia/
Ricketts/

*Sunlight terms*

(Textword terms):
UVB
UVA
Ultraviolet
**hypovitaminosis D.ti,ab.**
**Vitamin D2.ti,ab.**
**Vitamin D3.ti,ab.**
**Alfacalcidol$.ti,ab.**
**Cacidiol.ti,ab.**
**Calciferol.ti,ab.**
**Calciol.ti,ab. (0 hits)**
**Calcitriol.ti,ab.**
**Cholecalciferol.ti,ab.**
Dehydrocholestrol.ti,ab. (1 not helpful hit)
**dihydrotachysterol$.ti,ab.** (half synthetic Vitamin D analogue)
**Dihydroxycholecalciferol$.ti,ab.**
**dihydroxyvitamin d.ti,ab.**
**Doxercalciferol$.ti,ab.**
**Ergocalciferol.ti,ab.**
**paricalcitol$.ti,ab.**
Sunlight
Sunshine
Sunburn
sun exposure
solar radiation

(MeSH terms):
Ultraviolet Rays/
PUVA Therapy/
Ultraviolet Therapy/
Sunlight/
Sunburn/

*Pregnancy terms*

(Textword terms):
**ante-natal.ti,ab.**
**Antenatal.ti,ab.**
**Babies.ti,ab.**
**Baby.ti,ab.**
**birthweight.ti,ab.**

**Child$.ti,ab.**
**childbear$.ti,ab.**

**Fetal.ti,ab.**
**Fetus.ti,ab.**
**Foetal.ti,ab.**
**Foetus.ti,ab.**

**Infancy.ti,ab.**
**Infant.ti,ab.**
**Maternal.ti,ab.**
**Maternity.ti,ab.**
**Mother.ti,ab.**

**Neonat$.ti,ab.**
**Newborn$.ti,ab.**
**Offspring.ti,ab.**

**post-natal.ti,ab.**

**Postnatal.ti,ab.**
**post-partum.ti,ab.**
**Postpartum.ti,ab.**
**pre-concept$.ti,ab.**
**Preconception$.ti,ab.**
**preconceptual.ti,ab.**
**Pregnan$.ti,ab.**
**Premature.ti,ab.**
**pre-natal.ti,ab.**
**Prenatal.ti,ab.**
**Puerperium.ti,ab.**
**small-for-gestational age.ti,ab.**

**Toddler$.ti,ab.**

(child$ adj5 pre-school).ti,ab.

(MeSH terms):
Covered by **exp "Embryonic and Fetal Development"/**
Fetal Development/

### Methods of the review

We will follow the methods recommended by the Centre for Reviews and Dissemination (CRD), University of York (http://www.york.ac.uk/inst/crd/). Where study designs allow, a meta-analysis may be performed to generate a pooled effect size.

### Screening of abstracts

When applying selection criteria, all abstracts and potentially relevant papers will be independently assessed by two reviewers and decisions shown to be reproducible. Disagreements over inclusion will be resolved through consensus and, where necessary, following discussion with a third member of the review team

### Data extraction

Data extraction will be carried out by two reviewers. Disagreements will be resolved in the same way as for screening of abstracts. Separate forms will be used to mark or correct errors or disagreements and a database of disagreements kept for potential future methodological work.

Data will be abstracted onto an electronic form. This will contain the following items: general information (e.g. date of data extraction, reviewer ID); study characteristics (e.g. study design, inclusion/exclusion criteria,); study population characteristics; method of assessment of vitamin D status; baseline data (e.g. age, sex, ethnicity, measures of vitamin D status/ supplementation); quality criteria; outcomes (what they were and how they were ascertained); confounding factors; analysis (statistical techniques, sample size based on power calculation, adjustment for confounding, losses to follow up); results (direction of relationship, size of effect and measure of precision of effect estimate such as 95% confidence interval or standard error).

An important aspect of data extraction and quality assessment will be to assess whether studies have adequately controlled for important variables that could confound or modify the relationship between maternal vitamin D status and later outcomes. The effect modifiers and confounding factors we will consider important are ethnicity, skin covering, season, sunlight exposure, alcohol intake, smoking, dietary calcium, physical activity, comorbidity (e.g. diabetes), current medication, maternal body mass index, infant feeding/ supplementation and maternal post-natal supplementation if breast feeding. Where study designs allow, a meta-analysis may be performed to generate a pooled effect size. For each study included in the review, we will record whether each of these variables has been measured and whether they were adjusted for in the statistical analysis. This information will then be used in quality assessment.

### Study quality assessment

Study quality assessment will occur at two stages in the review:

1. During data extraction by assessing methodological quality
2. In the analysis of the review findings. Sensitivity analysis may be used to determine whether the overall results are the same when only studies with little risk of bias are included in the analysis.

The quality of included studies will be assessed by the two reviewers, using a checklist of questions. The questions used, while based initially on CRD guidelines, will be refined through piloting and through

agreement with the advisory group. Aspects of quality assessed will include appropriateness of study design, ascertainment of exposure and outcome, and consideration of the effects of important confounding factors. Quality assessment will also incorporate specific issues related to vitamin D (see above for detail). Quality criteria are summarised in Tables 3-5 (pages 16 to 18). The answers to these questions will then be used either in a narrative description of quality, or to produce composite validity scores which will assign a quality level to each study and can be used as means of stratifying studies during synthesis of evidence. Similar tools will be developed for other study designs. Quality assessment tool(s) will be agreed by the advisory group and will be refined during piloting. Vitamin D-specific issues are summarised below:

How is "vitamin D" assessed? (Dietary intake, supplement use, blood levels of 25(OH)-vitamin D, blood levels of 1,25(OH)-vitamin D, PTH concentration)

Are season and sunlight exposures including sunscreen use and skin covering considered?

Is ethnicity and skin pigmentation considered?

How is 25(OH)-vitamin D blood level assessed? What assay is used? Are $D_2$ and $D_3$ forms adequately measured and are quality data (e.g DEQAS) given?

What definition of "normal range" for 25(OH)-vitamin D is used? Is the concentration treated as categorical (e.g. deficient, insufficient, replete) or continuous?

Has infant post-natal vitamin D intake (breast, bottle feeding, supplementation) and sunlight exposure been considered?

Has maternal compliance with supplementation been assessed?

**Synthesis of extracted evidence**

The aim of this part of the review will be to investigate whether effects are consistent across studies and to explore reasons for apparent differences. We intend to use both descriptive (qualitative) and quantitative synthesis, but our capacity to do this will be determined by the evidence available. If any degree of quantitative synthesis or meta-analysis is possible, we will carry it out according to standard procedures(73). This will not be a straightforward step in our review because of the inclusion of studies of different design. Statistical combination of studies of different design could introduce bias. This could be overcome using one of a number of alternative techniques including stratification according to study type, cumulative combination of studies of decreasing strength, and modelling the strength of evidence in a regression analysis where studies are graded according to quality and validity.

**Formation of advisory group**

The role of the advisory group will be to advise on protocol development and review the outputs of the project. Generic expertise required includes review methodology, information science, health economics, qualitative research, epidemiology, statistics and consumer perspectives. The specialist topic areas that will be represented on the group include metabolic bone disease, obstetrics, paediatrics, social care, health visiting and community practice, public health and nutrition. Additionally views and advice on vitamin D supplementation from service users who are participants in existing Southampton studies (Southampton Women's Survey, Southampton Initiative for Health and MAVIDOS Maternal Vitamin D Osteoporosis Study) will be sought. In addition to the local paediatric (Dr Justin Davies, University of Southampton), obstetric (Mr David Howe, University of Southampton) and statistical (Dr Sarah Crozier, Professor Hazel Inskip, University of Southampton) expertise, members of the UK Vitamin D Working Group have agreed to join as part of this advisory process. Thus, under the direction of Professor Nick Bishop (University of Sheffield), this will consolidate expertise in paediatrics (Dr Zulf Mughal, University of Manchester; Dr Nick Shaw, University of Birmingham), obstetrics (Dr Stephen Kennedy, University of Oxford; Mr Robert Fraser, University of Sheffield; Mr Saurabh Gandhi, University of Sheffield), and we will approach Professor Nick Freemantle, Birmingham University, to act as a further advisor on the statistical aspects of the study.

## EXPECTED OUTPUT OF RESEARCH

Recommendations as to normal level of 25(OH)-vitamin D in pregnancy and optimal supplementation strategy to achieve this and thus best health outcomes for mother and child; Final report to HTA programme,

and publication in peer reviewed journal. The work will be presented at national and international conferences such as the annual meetings of the National Osteoporosis Society, Bone Research Society, British Society for Rheumatology, American Society for Bone and Mineral Research, European Calcified Tissue Society, World Congress in Osteoporosis (International Osteoporosis Foundation).

**EXPERTISE IN THE TEAM**

NH has experience of systematic reviews and extensive experience and expertise regarding vitamin D in pregnancy. He is currently PI of a large multicentre randomised-controlled trial of vitamin D supplementation in pregnancy. MKJ, ZAC, EMD, KMG are experts in the role of vitamin D in pregnancy (MAVIDOS). JB is an expert in evidence synthesis and systematic reviews. TT has extensive experience in evidence synthesis. MK will provide expert statistical input. CC has extensive experience of systematic reviews and the role of vitamin D in pregnancy and is currently CI of the MAVIDOS study.

The project timetable is based on predicted search hits of 15,000**,** and an estimate of 100 papers that satisfy review inclusion criteria (based on our knowledge of the literature).

Weeks 1-4: Convene and meet with advisory group, develop and agree protocol for review

Weeks 5-10: Information Specialist executes literature searches

Weeks 11-20: Two reviewers will screen abstracts and select studies for inclusion in review

Weeks 21-24: Develop and pilot data extraction form and quality criteria

Weeks 25-36: Data extraction and quality assessment

Weeks 36-42: Update searches; Data extraction and quality assessment of additional studies identified by screening reference lists, correspondence with first authors and updated searches

Weeks 42-46: Synthesis and meta-analysis

Weeks 46-52: Writing up and dissemination of review findings

**RESOURCES REQUESTED**

| | | |
|---|---|---|
| Information Specialist: 1FTE for 10 weeks: | £ 16450 | (Search strategy and execution) |
| Research Assistant: 2* 0.5FTE for 1 year: | £ 36984 | (Abstract screening, selection, data extraction, quality assessment) |
| Travel costs: | £ 600 | (Advisory Group, unpublished data) |
| Office costs: | £ 500 | (Postage, telephone calls) |
| **Total:** | **£ 54534** | |

**Table 2: Summary of initial scoping exercise using musculoskeletal outcomes**

| Databases and years searched | Terms | Number retrieved | Number of relevant hits |
|---|---|---|---|
| Systematic reviews | | | |
| Cochrane Library: CDSR, current Issue, 2010 http://www.thecochranelibrary.com/view/0/index.html | | | |
| DARE (CRD) 2000-2010 http://www.crd.york.ac.uk/crdweb/ | | | |
| HTA Database (CRD) http://www.crd.york.ac.uk/crdweb/ | | | |
| National Coordinating Centre for Health Technology | | | |

| | | | |
|---|---|---|---|
| Assessment website http://www.hta.nhsweb.nhs.uk | | | |
| Other study types | | | |
| Cochrane Library: CENTRAL, current Issue, 2010 http://www.thecochranelibrary.com/view/0/index.html | | | |
| Medline (OVID) 1950-2010, June Week 1<br><br>(15/6/10) | 1 Pregnan$.ti,ab. 295057<br>2 Preconception$.ti,ab. 1752<br>3 preconceptual.ti,ab. 135<br>4 pre-concept$.ti,ab. 250<br>5 Fetal.ti,ab. 157883<br>6 Foetal.ti,ab. 11957<br>7 Fetus.ti,ab. 43868<br>8 Foetus.ti,ab. 4543<br>9 Newborn$.ti,ab. 104312<br>10 Neonat$.ti,ab. 154612<br>11 Baby.ti,ab. 21290<br>12 Babies.ti,ab. 22884<br>13 Infant.ti,ab. 99951<br>14 Infancy.ti,ab. 29601<br>15 Premature.ti,ab. 68207<br>16 Toddler$.ti,ab. 3913<br>17 Offspring.ti,ab. 33494<br>18 Child$.ti,ab. 770655<br>19 Postnatal.ti,ab. 61090<br>20 Postpartum.ti,ab. 25159<br>21 Maternal.ti,ab. 126587<br>22 Maternity.ti,ab. 10210<br>23 Mother.ti,ab. 58088<br>24 small-for-gestational age.ti,ab. 4212<br>25 pre-natal.ti,ab. 573<br>26 prenatal.ti,ab. 52711<br>27 ante-natal.ti,ab. 267<br>28 post-partum.ti,ab. 6959<br>29 post-natal.ti,ab. 3777<br>30 puerperium.ti,ab. 4552<br>31 childbear$.ti,ab. 6830<br>32 birthweight.ti,ab. 9667<br>33 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 1557322<br>34 Pregnancy/ 609281<br>35 Prenatal Nutritional Physiological Phenomena/ 695<br>36 Pregnancy, High-Risk/ 3586<br>37 Maternal Nutritional Physiological Phenomena/ 988<br>38 Pregnancy Complications/ 62603<br>39 Pregnancy Outcome/ 29721<br>40 Maternal Fetal exchange/ 26212<br>41 Prenatal Exposure Delayed Effects/ 14989<br>42 exp "Embryonic and Fetal Development"/ 163222<br>43 Child Development/ 28583<br>44 Preconception Care/ 981<br>45 Prenatal Care/ 16979<br>46 Postpartum Period/ 14439<br>47 exp infant/ 817413<br>48 Postnatal Care/ 3095<br>49 exp Pregnancy Trimesters/ 27623<br>50 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 2155617<br>51 exp Vitamin D/ 34004<br>52 "1406-16-2 (Vitamin D)".rn. 15518<br>53 "25(OH)-vit D".ti,ab. 15<br>54 25OHD.ti,ab. 424<br>55 hypovitaminosis D.ti,ab. 440<br>56 "19356-17-3 (Calcifediol)".rn. 2398<br>57 "32222-06-3 (Calcitriol)".rn. 11536<br>58 "64719-49-9 (25-hydroxyvitamin D)".rn. 1333<br>59 Vitamin D deficiency/ 5668 | 6501 hits | First 500 refs saved<br><br>(Ref Ids: 82-581 in Ref Man database) |

| | | | |
|---|---|---|---|
| | 60 Vitamin D.ti,ab. 25020<br>61 Vitamin D2.ti,ab. 862<br>62 Vitamin D3.ti,ab. 5527<br>63 Cacidiol.ti,ab. 0<br>64 calciol.ti,ab. 12<br>65 "67-97-0 (Cholecalciferol)".rn. 4441<br>66 Ergocalciferol.ti,ab. 288<br>67 Cholecalciferol.ti,ab. 1086<br>68 Colecalciferol.ti,ab. 21<br>69 Calciferol.ti,ab. 330<br>70 Calcitriol.ti,ab. 2923<br>71 Hydroxycholecalciferol.ti,ab. 1111<br>72 dihydroxycholecalciferol$.ti,ab. 1366<br>73 dihydroxyvitamin d.ti,ab. 3858<br>74 dihydrotachysterol$.ti,ab. 294<br>75 doxercalciferol$.ti,ab. 48<br>76 alfacalcidol$.ti,ab. 297<br>77 paricalcitol$.ti,ab. 180<br>78 Calcitriol/ 11536<br>79 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 45279<br>80 49 and 79 67<br>81 50 and 79 8116<br>82 Animals/ 4579351<br>83 Humans/ 11255304<br>84 82 and 83 1175867<br>85 82 not 84 3403484<br>**86 81 not 85 6501** | | |
| Embase (OVID) 2000-2004, Week 21 | | | |
| BIOSIS 1985- | | | |
| Ongoing studies | | | |
| NRR archive (National Research Register) https://portal.nihr.ac.uk/Pages/NRRArchiveSearch.aspx (14/6/10) | "Vitamin D" and pregnancy [All fields] | 20 | 0 |
| UKCRN Portfolio http://public.ukcrn.org.uk/Search/Portfolio.aspx (14/6/10) | Pregnancy [Title]<br><br>Pregnancy vitamin [research summary] | 41<br><br>2 | 1, poss 2<br><br>1 |
| Current Controlled Trials including MRC Trials dB http://controlled-trials.com/ (14/6/10) | vitamin d AND pregnancy | 207 | 13 (slight overlap with UKCRN) |
| Clinical Trials.gov http://clinicaltrials.gov/ | | | |
| Conferences and grey literature | | | |
| Conference Proceedings Citation Index- Science (1990-present) | | | |
| Trip database http://www.tripdatabase.com/search/advanced | | | |
| King's Fund database http://www.kingsfund.org.uk/library/ (14/6/10) | Pregnancy<br><br>Vitamin d | 528<br><br>15 | <br><br>Poss 2 |
| Scientific Advisory Committee on Nutrition website http://www.sacn.gov.uk/reports_position_statements/index.html (14/6/10) | Browse reports and position statements section | 2 report | 2 reports |
| Department of Health website | Browse reports | | |

| | | | |
|---|---|---|---|
| http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005936 (14/6/10) | | | |
| Zetoc (general & conferences) http://zetoc.mimas.ac.uk/wzgw?id=23685659 | | | |
| Guidelines | | | |
| SIGN http://www.sign.ac.uk | | | |
| NICE http://www.nice.org.uk/nice-web/ | | | |
| National Guidelines Clearinghouse http://www.ahcpr.gov/clinic/assess.htm | | | |

**Table 3: Summary of cohort quality assessment system**

| | **Risk of Bias (score)** | | |
|---|---|---|---|
| *Criterion* | **High (–1)** | **Medium (0)** | **Low (+1)** |
| 1. Study design appropriate? | Ambiguously described, obviously bias inducing or unsuitable for the objectives and stated conclusions | Possibly restricting but reflected in the scope of the objectives and the stated conclusions | Planned to minimise bias and allow generalisability beyond the immediate scope of the objectives |
| 2. Adequate description of study participants? | Little or no information given | Incl/excl and other criteria such as term/ pre-term/ small for gestational age baby given in some way; at least two useful measures including measure of vitamin D status, ethnicity | Incl/excl and other criteria such as term/ pre-term/ small for gestational age baby given in some way; at least three useful measures including measure of vitamin D status, ethnicity with measures of precision |
| 3. How is maternal vitamin D status measured? | Dietary intake only or insufficient information | Blood levels of circulating 25(OH)-vitamin D | Blood levels of circulating 25(OH)-vitamin D, with details of precision, pick up of $D_2$ and $D_3$ and assay used |
| 4. Measurements of outcomes reliably ascertained? | Inadequately explained or obviously unsuitable | Adequate description and reliability/suitability of at least one of the following: instruments, technique/ definition/protocol, people, place | Detailed description and reliability of one and at least adequate description of the others |
| 5. Measurements of later outcomes objective? | Subjective measure, eg bone or muscle pain, wheezing | Ascertained from researcher examination | Objective measure e.g. DXA, bone biopsy, lung function tests |
| 6. Measures of vitamin D intake/ 25(OH)-vitamin D level, bone outcomes rounded? | Measures categorised or rounded very roughly, or if any clear evidence of rounding exists without explanation in the text | Yes, but not by much | No information given and no obvious reason to suspect rounding has occurred; or explicitly stated that measurements were not rounded |
| 7. Consideration for the effects of important confounding factors? (e.g. season, sunlight exposure, calcium intake, maternal compliance, infant feeding) | One factor controlled for in tables, nothing for the others (NB whether they were *measured* or not is irrelevant) | Most factors controlled for in tables, or fewer if one or more is adjusted for in regression | Most factors adjusted for in regression |
| 8. Outcome assessment blind to maternal vitamin D status? | N/A | No details given | Some details or statement given |
| 9. What proportion of the cohort was followed up? | % FU is not given, unclear, or low (below 70%) | % FU is low to average (70-90%) | % FU is high (over 90%) |
| 10. Info on non-participants | Very little or no information, or information given that is adequate but suggests a serious potential for bias | Adequate information given, or information given that is very clear but suggests a moderate potential for bias | Above average information given, none of which suggests a potential for bias |
| 11. Analysis rigorous and appropriate? | No statistical analyses carried out (just tables or description) | Tables of means & differences given with statistical tests (e.g. t-tests), or some regression but without clear/valid measure of association | Regression (or similar technique) used which gives a valid measure of association (e.g. odds ratios, hazard ratios, relative risks) |
| 12. Sample size | Extremely ambiguous, not given, or small (under 100) | Average (100 to 1000) | Large (over 1000) |

**Table 4: Summary of case-control quality assessment system:**

| | Risk of Bias (score) | | |
|---|---|---|---|
| Criterion | **High (–1)** | **Medium (0)** | **Low (+1)** |
| 1. Case definition explicit and appropriate? | Definition and/or incl/excl criteria not given, ambiguous, or clearly unsuitable | Basic definition given; enough to satisfy that chosen cases (and the criteria used to select them) are suitable | Detailed definition and explanation; all suitable cases included |
| 2. How is maternal vitamin D status measured? | Dietary intake only or insufficient information | Blood levels of 25(OH)-vitamin D | Blood levels of circulating 25(OH)-vitamin D, with details of precision, pick up of $D_2$ and $D_3$ and assay used |
| 3. Measurements of outcomes reliably ascertained? | Inadequately explained or obviously unsuitable | Adequate description and reliability/suitability of at least one of the following: instruments, technique/ definition/protocol, people, place | Detailed description and reliability of one and at least adequate description of the others |
| 4. Measurements of later outcomes objective? | Subjective measure, eg bone or muscle pain, wheezing | Ascertained from researcher examination | Objective measure e.g. DXA, bone biopsy, lung function tests |
| 5. Control selection appropriate? | No information at all, ambiguous, or not selected from population of cases or otherwise clearly inappropriate to the study objectives | Selection is from population of cases, and is basically appropriate and similar to cases for all factors other than the outcome of interest, but not optimally, or with incomplete information | Selection is from population of cases in a manner wholly appropriate to the study objectives, and in such a way as to make them as similar as possible to cases in all respects except the outcome of interest |
| 6. Measures of vitamin D intake/ 25(OH)-vitamin D level, bone outcomes rounded? | Categorisation or very rough rounding, or if any clear evidence of rounding exists without explanation in the text | Measures are rounded, but not by much | No information given, and no obvious reason to suspect rounding has occurred.<br>Or: explicitly stated that measurements were not rounded. |
| 7. Setting and population appropriate? | Ambiguously described, obviously bias inducing or unsuitable for the objectives and stated conclusions | Possibly restricting but reflected in the scope of the objectives and the stated conclusions | Planned to minimise bias and allow generalisability beyond the immediate scope of the objectives |
| 8. Outcome assessment blind to vitamin D status? | N/A | No details given | Some details or statement given |
| 9. Analysis rigorous and appropriate? | No statistical analyses carried out (just tables or description), or analysis badly carried out | Tables of means and differences given with statistical tests (e.g. t-tests), or some regression but without clear/valid measure of association | Regression (or similar technique) is used which gives a valid measure of association (e.g. odds ratios, hazard ratios, relative risks) |
| 10. Response rates for:<br>a. cases<br>b. controls<br>(a separate score for each should be given) | Low (<70%) | Medium (70-90%) or not given | High (>90%) |
| 11. Info on representativeness and non-participants | Cases obviously unrepresentative of wider population alluded to in text | Some information on cases and controls lost or excluded, or no information but with no reason to suspect a detrimental lack of representativeness | Detailed information on cases and controls lost or excluded, with numbers and reasons. |
| 12. Sample sizes for:<br>a. cases<br>b. controls<br>(a separate score for each should be given) | Extremely ambiguous, not given, or small (under 100) | Average (100 to 1000) | Large (over 1000) |
| 13. Adequate consideration of important confounding factors? (e.g. season, sunlight exposure, calcium intake, maternal compliance, infant feeding) | One factor matched on or controlled for in tables; nothing for the others (NB whether they were *measured* or not is irrelevant) | Most factors matched on or controlled for in tables, or fewer if one or more is adjusted for in regression | Most factors adjusted for in regression |

**Table 5: Summary of clinical trial assessment system**

| | **Risk of Bias (score)** | | |
|---|---|---|---|
| *Criterion* | **High (–1)** | **Medium (0)** | **Low (+1)** |
| 1. Study design appropriate? | Ambiguously described, obviously bias inducing or unsuitable for the objectives and stated conclusions | Possibly restricting but reflected in the scope of the objectives and the stated conclusions | Planned to minimise bias and allow generalisability beyond the immediate scope of the objectives |
| 2. Are CONSORT guidelines followed? | Not described, not followed or poorly adherent | CONSORT report presented but some data missing | Full adherence to CONSORT guidelines |
| 2. Adequate description of study participants? | Little or no information given | Incl/excl and other criteria such as term/ pre-term/ small for gestational age baby given in some way; at least two useful measures including measure of vitamin D status, ethnicity | Incl/excl and other criteria such as term/ pre-term/ small for gestational age baby given in some way; at least three useful measures including measure of vitamin D status, ethnicity with measures of precision |
| 4. Is randomisation adequate? | No randomisation or not discussed | Some attempt at randomisation | Robust randomisation |
| 5. Is there placebo control and is blinding adequate? | Not controlled, not adequate or not discussed | Placebo control, either not blinded or single blinded | Placebo control, double-blinded |
| 6. Are details of the study medication given? | No details | Some detail e.g. "vitamin D 1000 iu per day" | Full details including $D_2$ or $D_3$, manufacturer, GMP compliant, full regimen. |
| 7. Is change in maternal vitamin D status measured? | N/A | No | Yes |
| 8. Are details of the assay given? | No details | Some details e.g. Diasorin RIA | Fully detail- type, manufacturer, precision, $D_2$/$D_3$ pick up. |
| 9. Measurements of outcomes reliably ascertained? | Inadequately explained or obviously unsuitable | Adequate description and reliability/suitability of at least one of the following: instruments, technique/ definition/protocol, people, place | Detailed description and reliability of one and at least adequate description of the others |
| 10. Measurements of later outcomes objective? | Subjective measure, eg bone or muscle pain, wheezing | Ascertained from researcher examination | Objective measure e.g. DXA, bone biopsy, lung function tests |
| 11. Measures of vitamin D intake/ 25(OH)-vitamin D level, bone outcomes, e.g. BMC rounded? | Measures categorised or rounded very roughly, or if any clear evidence of rounding exists without explanation in the text | Yes, but not by much | No information given and no obvious reason to suspect rounding has occurred; or explicitly stated that measurements were not rounded |
| 12. Consideration for the effects of important confounding factors? (e.g. season, sunlight exposure, calcium intake, maternal compliance, infant feeding) | One factor controlled for in tables, nothing for the others (NB whether they were *measured* or not is irrelevant) | Most factors controlled for in tables, or fewer if one or more is adjusted for in regression | Most factors adjusted for in regression |
| 13. What proportion of the cohort completed the trial? | % FU is not given, unclear, or low (below 70%) | % FU is low to average (70-90%) | % FU is high (over 90%) |
| 14. Info on non-participants | Very little or no information, or information given that is adequate but suggests a serious potential for bias | Adequate information given, or information given that is very clear but suggests a moderate potential for bias | Above average information given, none of which suggests a potential for bias |
| 15. Analysis rigorous and appropriate? | No statistical analyses carried out (just tables or description) | Appropriate statistical techniques but no mention of whether intention to treat or pre protocol | Appropriate statistical techniques and intention to treat primary analysis |
| 12. Sample size | Extremely ambiguous, not given, or small (under 100) | Average (100 to 250) | Large (over 250) |

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