

Vitamin D supplementation in pregnancy: a systematic review

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Scientific summary

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Background

Low levels of serum 25-hydroxyvitamin D [25(OH)D] have been observed in many populations, including pregnant women. Studies have demonstrated associations between low levels of serum 25(OH)D during pregnancy and maternal/offspring health outcomes. However, many of these studies are observational in nature and it is unclear whether or not the current evidence base allows definite conclusions to be made regarding the optimal maternal circulating concentration of 25(OH)D during pregnancy, and how this might best be achieved. The aim of this work was to provide a systematic review of the current evidence base linking maternal 25(OH)D status to both maternal and offspring health outcomes, in order to answer the specific questions below.

Objectives

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

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

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

What is the optimal type (D₂ or D₃), dose, regimen and route for vitamin D supplementation in pregnancy?

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

Methods

Data sources

Completed studies (systematic reviews): Database of Abstracts of Reviews of Effects (DARE), Centre for Reviews and Dissemination (CRD), Cochrane Database of Systematic Reviews (CDSR), Health Technology Assessment (HTA) database. Completed studies (other study types): Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Bioscience Information Service (BIOSIS), Google Scholar, Allied and Complementary Medicine Database (AMED). Ongoing studies: National Research Register archive, United Kingdom Clinical Research Network (UKCRN) Portfolio, Current Controlled Trials, ClinicalTrials.gov. Grey literature: Conference Proceedings Citation Index-Science (1990–present), The British Library's Electronic Table of Contents (Zetoc) conference search, Scientific Advisory Committee on Nutrition (SACN) website, Department of Health website, The King's Fund Library database, Trip database, HTA website, Health Management Information Consortium (HMIC) database. Bibliographies of selected papers were hand-searched for additional studies. We contacted first authors and experts in several fields including metabolic bone disease, obstetrics, infant nutrition, child development and allergy for any unpublished findings. Citations were independently reviewed by two reviewers according to CRD guidelines.

Inclusion and exclusion criteria

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

Sample studied

Pregnant women or pregnant women and their offspring.

Exposure

Either assessment of vitamin D status [dietary intake, sunlight exposure, circulating 25(OH)D concentration] or supplementation of participants with vitamin D or food containing vitamin D (e.g. oily fish).

Outcomes

Primary: maternal osteomalacia, neonatal hypocalcaemia, rickets and reduced bone mass.

Secondary: maternal quality of life, neonatal body composition, and later offspring health outcomes (including asthma, diabetes mellitus and immune disease).

Study design

Observational studies (case-control, cohort, cross-sectional), intervention studies.

Studies were excluded if they were not written in English, were non-human studies, did not measure maternal vitamin D status in or immediately after pregnancy or supplement participants with vitamin D in pregnancy, or where an outcome of interest was not measured. Systematic reviews were not included in the formal review, but were used as a potential source of additional references via hand-searching.

Data extraction

Data extraction was carried out by two reviewers. Disagreements were resolved in the same way as for screening of abstracts according to CRD guidelines. Separate forms were used to mark or correct errors or disagreements, and a database was kept for potential future methodological work. Data were abstracted onto an electronic form. This contained 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); and results [direction of relationship, size of effect, and measure of precision of effect estimate such as 95% confidence interval (CI) or standard error].

Assessment of validity and quality

Quality assessment of studies occurred first during data extraction and second in the analysis of review findings. The quality of included studies was assessed by the two reviewers, using a checklist of questions. The questions used, although based initially on CRD guidelines, were refined through piloting and agreement with the advisory group. Aspects of quality assessed included appropriateness of study design, ascertainment of exposure and outcome, and consideration of the effects of important confounding factors. Quality assessment also incorporated specific issues related to vitamin D. Quality data were used in narrative description of quality, and to produce composite validity scores with which to assign a quality level to each study such that studies could be stratified during synthesis of evidence.

Data synthesis

The aim of this part of the review was to investigate whether or not effects were consistent across studies and to explore reasons for apparent differences. We used both descriptive (qualitative) and quantitative synthesis; our capacity for the latter was determined by the evidence available. Where meta-analysis was possible, we used standard analytical procedures. Only independent studies were meta-analysed. Thus, where a study contained two treatment arms, these were not included in the same analysis. We used the *Q*-statistic to define statistical heterogeneity, with a $p < 0.1$ to define statistical significance. The I^2 statistic (percentage of variability in the results that is due to heterogeneity) was used to quantify the degree of heterogeneity across studies. Results were presented as forest plots, either as random-effects models

(REMs), if significant heterogeneity was detected, or as fixed-effects models if minimal heterogeneity was detected. All analysis was performed using Stata v11.0 (StataCorp LP, College Station TX, USA).

Results

Included/excluded studies: 22,961 citations were identified from the initial database search up to 3 January 2011. A subsequent additional search from 3 January 2011 to 18 June 2012 identified another 2448 citations, yielding a total of 25,409 citations. A further 66 citations were identified from other sources (e.g. grey literature and bibliographies). After duplicate citations were removed, 16,842 citations were screened. Of these, 16,669 were excluded on the basis of the content of the title and/or the abstract (if available). A further eight papers could not be found despite thorough searching; thus, 16,677 records were excluded. A total of 165 full-text articles were retrieved for detailed assessment and, of these, 76 papers were included in the review. A total of 89 papers retrieved for assessment were excluded. Around a third of these ($n = 34$) were abstracts. Twenty-one papers had no relevant maternal or offspring outcome; 11 papers had no estimate of maternal vitamin D status; 10 papers used data from other papers included in the review; eight papers were either review articles, letters, editorials or commentaries with no new results; one paper was of a non-human study; and four papers reported on an outcome not assessed in any other paper (maternal breast cancer, offspring schizophrenia, offspring multiple sclerosis and offspring influenza A). The results relating to the specific research questions are detailed below.

What are the clinical criteria for vitamin D deficiency in pregnant women? The highly heterogeneous and variable quality of the identified studies resulted in an evidence base that did not allow this question to be reliably answered, in terms of either biochemical relationships or disease outcomes. *What adverse maternal and neonatal health outcomes are associated with low maternal circulating 25(OH)D? Does maternal supplementation with vitamin D in pregnancy lead to an improvement in these outcomes (including assessment of compliance and effectiveness)?* The results relevant to these two study questions are itemised by individual health outcomes below.

Birthweight

Nineteen observational studies were identified. Composite bias scores ranged from -2 to $+8$, with seven of the 19 studies scored as having a low risk of bias. Six studies demonstrated a significant positive relationship between maternal vitamin D status and offspring birthweight; one study found a significant negative association. Of the remaining studies, seven suggested a non-significant positive association between the two variables and three found a non-significant negative association.

Nine intervention trials were identified. Seven of these studies were rated as having a high chance of bias on the composite score (-2 to -9); only the two most recent studies were assessed as having a low risk of bias (composite bias score of 5 and 10). Sample sizes ranged from 40 to 350 patients and interventions were highly variable. Three studies demonstrated significantly greater birthweight in offspring of supplemented mothers. The remainder showed no significant difference in infant birthweight regardless of supplementation (birthweight was non-significantly higher in the supplemented group in two of these, non-significantly lower in the supplemented group in one, and was not presented in the remaining two).

Meta-analysis of three observational studies found weak positive associations between log-transformed maternal 25(OH)D concentrations and offspring birthweight after adjustment for potential confounders [pooled regression coefficient 5.63 g/10% change in maternal 25(OH)D, 95% CI 1.11 g to 10.16 g].

Birth length

Twelve observational studies were identified. One study was assessed as having a high risk of bias (composite score -2 , high risk) with the others demonstrating composite scores between $+1$ and $+8$. Two studies found a significantly positive relationship between maternal vitamin D status and offspring birth length; however, neither study directly measured maternal serum 25(OH)D concentration in

pregnancy. Of the remaining studies, four showed a non-significant positive association and four showed a non-significant inverse association. A further study observed a significant positive association between maternal vitamin D status and offspring length at 1 month.

Two intervention trials were identified. Both were assessed to have a high risk of bias (composite bias score of both -2 , high risk). In one, birth length was higher in the offspring of women supplemented with vitamin D than in the offspring of unsupplemented women; the other found no significant association but a trend towards higher birth length in the supplemented group. Both studies were assessed to have a high risk of bias.

Head circumference

Eleven observational studies were identified, none of which found a significant relationship between maternal vitamin D status and offspring head circumference. Composite bias scores ranged from -2 to $+8$, with six studies having a low risk of bias. There was a non-significant trend towards greater head circumference with greater maternal vitamin D status in five studies, and a non-significant inverse relationship in four studies.

Two intervention studies were identified, both of which were assessed as having a high risk of bias (composite bias score -2 in both). One study demonstrated significantly greater offspring head circumference in supplemented mothers; the other found no association, but a non-significant trend towards greater head circumference in supplemented mothers.

Offspring bone mass

Eight observational studies were identified, all of which were assessed as being of medium to low risk of bias, with composite bias scores ranging from $+3$ to $+7$. Five studies demonstrated a significant positive relationship between maternal vitamin D status and offspring bone outcomes [which included whole-body, lumbar, femoral and tibial bone mineral content (BMC), and whole-body and lumbar spine bone mineral density (BMD)]. Of the remaining studies, no significant association was observed between maternal vitamin D status and offspring radial and whole-body BMC.

One intervention study was identified, which found no difference in offspring forearm BMC (measured within 5 days of birth) between supplemented and unsupplemented mothers. There was a non-significant trend towards higher forearm BMC in the supplemented group. This study was assessed to have a high risk of bias.

Offspring anthropometry and body composition

Six observational studies were identified, four of which demonstrated a significant relationship between maternal vitamin D status and offspring body composition and anthropometric variables (including skinfold thickness, lean mass and fat mass). Two studies found no significant relationship between maternal vitamin D status and the offspring anthropometric variables measured. Composite bias scores ranged from $+3$ to $+8$, indicating a medium to low risk of bias. Two intervention studies were identified; both were assessed to have a high risk of bias (composite bias score -2 for both). One demonstrated no effect of maternal vitamin D supplementation on offspring triceps skinfold thickness, whereas the other did find evidence of a positive effect.

Offspring asthma and atopy

Ten observational studies were identified. Five studies found a significantly reduced risk of offspring asthma or atopy with higher maternal vitamin D status; conversely, three studies found a significant positive association between maternal vitamin D status and offspring risk of asthma or atopy. The remaining two studies found no significant association between late-pregnancy 25(OH)D and lung function in offspring aged 6–7 years. All but one study were judged to be at moderate to high risk of bias, and no intervention studies were identified.

Offspring born small for gestational age

Seven observational studies were identified. All achieved a composite bias score of between +1 and +7, indicating a low to medium risk of bias. One study found a significantly increased risk of infants being small for gestational age (SGA) if maternal 25(OH)D was < 30 nmol/l. A second study found a U-shaped relationship between SGA and maternal 25(OH)D concentration in white women only, with the lowest risk between 60 and 80 nmol/l. No relationship was seen in black women. A third study of pregnant women with early-onset pre-eclampsia found significantly lower serum 25(OH)D in those women with SGA infants compared with the control groups. The four remaining studies found no significant relationship; two of these found a non-significant trend towards greater SGA risk in women with lower vitamin D status. Data were not given for the other two studies.

Two intervention trials were identified, one judged at low risk of bias and the other at high risk of bias, and neither of which found a significant difference in SGA risk in women supplemented with vitamin D compared with unsupplemented mothers. There was, however, a non-significant trend towards higher SGA risk in the unsupplemented group in both studies.

Offspring preterm birth

Seven observational studies were identified, ranging from low to high risk of bias. One study found that the risk of threatened premature delivery was significantly increased in mothers with lower 25(OH)D. Six studies found no significant relationship. No intervention trials were identified.

Offspring type 1 diabetes mellitus

Three observational studies were identified, judged to be at medium or low risk of bias. One study found a significantly increased risk of type 1 diabetes mellitus in the offspring of mothers with lower concentration of 25(OH)D in late pregnancy. The remaining studies found no significant relationship. No intervention studies were identified.

Offspring low birthweight

Three observational studies were identified, with composite bias scores ranging from -2 to +3, indicating a medium to high risk of bias. One study found a significantly reduced risk of low-birthweight offspring with adequate, compared with inadequate, maternal vitamin D and calcium intake. The remaining studies found no significant association. No intervention studies were identified.

Offspring serum calcium concentration

One observational study, at low risk of bias, was identified which found no significant association between maternal 25(OH)D at delivery and offspring cord calcium.

Six intervention trials were identified, all judged to be at high risk of bias (composite scores -9 to -1). Offspring serum calcium was significantly higher in the supplemented group in five of these studies. The remaining study found a non-significant trend towards higher cord blood calcium in the supplemented group. Meta-analysis of the intervention studies demonstrated a weak positive association (mean difference in serum calcium concentration in offspring of supplemented vs. unsupplemented mothers: 0.05 mmol/l, 95% CI 0.02 mmol/l to 0.05 mmol/l). Factors which might increase risk of symptomatic hypocalcaemia, such as ethnicity and breast (compared with formula) feeding, were not adequately addressed.

Offspring blood pressure

Two observational studies were identified, judged to be at medium risk of bias, and neither of which found a significant relationship between maternal 25(OH)D concentration and offspring blood pressure. No intervention trials were identified.

Pre-eclampsia

Eleven observational studies were identified, judged to be at low to medium risk of bias. Five studies found a significant inverse relationship between maternal vitamin D status and risk of pre-eclampsia; the remaining six studies found no significant relationship. Meta-analysis was possible for four studies, suggesting an inverse relationship between 25(OH)D and pre-eclampsia risk, but did not achieve statistical significance. One intervention trial was identified; no difference in risk of pre-eclampsia was seen in mothers supplemented with vitamin D compared with unsupplemented women.

Gestational diabetes mellitus

Eight observational studies were identified, judged to be at low to medium risk of bias. Three studies found a significant inverse relationship between risk of gestational diabetes mellitus and maternal vitamin D status. No intervention studies were identified.

Caesarean section

Six observational studies were identified, judged to be at low to medium risk of bias. Two studies found an inverse relationship between risk of caesarean section and maternal vitamin D status. The remaining four studies found no significant relationship, although a non-significant inverse trend was observed in two studies (the remaining two studies did not provide adequate data to assess trend). No intervention trials were identified.

Maternal bacterial vaginosis

Three observational studies were found, judged to be at low to medium risk of bias, and all of which found that lower maternal 25(OH)D was significantly associated with an increased risk of bacterial vaginosis in pregnancy. No intervention trials were identified.

What is the optimal type (D₂ or D₃), dose, regimen and route for vitamin D supplementation in pregnancy?

The marked variation in dose, route, study population, methods of exposure and outcome evaluation, and lack of comparative investigations, meant that the evidence base was insufficient to reliably answer this question.

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

No studies including health economic evaluations in relation to specific disease outcomes were identified.

Conclusions

There was some evidence to support a positive relationship between maternal vitamin D status and offspring birthweight (meta-analysis of observational studies), neonatal calcium concentrations [meta-analysis of randomised controlled trials (RCTs)] and offspring bone mass (observational studies). Recurring themes in each disease area included marked heterogeneity between studies in terms of design, definition of exposure and outcome, dose, timing, route, statistical analysis, treatment of potential confounding factors. In no single disease area did the evidence base unequivocally support the use of vitamin D supplementation during pregnancy.

Implications for health care

The fundamental conclusion is that the current evidence base does not allow the study questions to be definitively answered. It is therefore not possible to make rigorously evidence-based recommendations regarding maternal vitamin D supplementation during pregnancy.

Recommendations for research

This systematic review has identified important gaps in the evidence, and further high-quality research is clearly needed. In many areas, well-designed large prospective cohort studies are most appropriate as the next step. In others, the evidence base is sufficient to suggest RCTs. Without such a rigorous approach, there is a risk that public health policy will be made on the basis of optimistic evaluations of conflicting and heterogeneous studies. Although modest doses of vitamin D during pregnancy are likely to be relatively safe, at least in the short term, there is a dearth of long-term data to inform the potential long-term effects of maternal vitamin D supplementation on offspring health. As with most interventions, it is probably optimistic to expect that there will be no risk of adverse events.

Study registration

This study is registered as PROSPERO CRD42011001426.

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