**Maternal gestational vitamin D supplementation and offspring bone health: a multicentre randomised, double-blind, placebo-controlled trial (MAVIDOS)**

**Research in context**

**Evidence before this study**

We conducted a systematic review of studies relating maternal vitamin 25(OH)-vitamin D concentrations, UVB exposure, dietary vitamin D intake, or use of vitamin D supplements during pregnancy to maternal and offspring health outcomes.[1](#_ENREF_1) Major electronic databases (including, but not limited to, PubMed, Embase, Web of Science) were searched from their inception until June 2012. This was complemented by interrogation of grey literature and hand searching of reference lists. Two independent reviewers undertook all assessments, and the study was performed in accordance with PRISMA guidelines. We identified eight observational studies relating maternal gestational vitamin D status to offspring bone mass, all of which were assessed as being of medium to low risk of bias. Of these, five demonstrated a significant positive relationship between maternal vitamin D status and offspring bone outcomes[2-6](#_ENREF_2) [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.[7-9](#_ENREF_7) Differences in study design did not permit meta-analysis. We identified one small intervention study,[10](#_ENREF_10) judged to be at high risk of bias, which found no difference in offspring forearm BMC (measured within five days of birth) between supplemented and un-supplemented mothers. We subsequently updated the search to August 2014, identifying two further observational studies, both judged to be low to medium risk of bias: one, using the ALSPAC cohort, demonstrated no association between maternal 25(OH)-vitamin D concentrations in pregnancy and offspring bone mass at 9 years.[11](#_ENREF_11) In contrast, the second study, from the Australian Raine cohort, documented positive relationships between maternal gestational 25(OH)-vitamin D concentrations offspring bone mass at 20 years.[12](#_ENREF_12)

**Added value of this study**

There was no difference in the primary outcome (neonatal whole body BMC) between offspring born to mothers supplemented with vitamin D during pregnancy compared with mothers randomised to placebo. However, amongst the pre-specified secondary analyses, there was an interaction between treatment and season, with the suggestion of a benefit for offspring neonatal bone mineral content with treatment for deliveries during winter months. Although biologically plausible, this intriguing finding clearly requires replication in further studies before it can provide a basis for alterations to clinical care.

**Implications of all the available evidence**

Vitamin D supplementation during pregnancy is already recommended in many countries, including the UK. Observational studies have provided conflicting evidence regarding associations between maternal 25(OH)-vitamin D status and offspring intrauterine bone development. The MAVIDOS study, whilst negative for its primary outcome, has demonstrated that 1000 IU cholecalciferol daily is sufficient to ensure the majority of pregnant women are replete in 25(OH)-vitamin D, and that such a strategy is safe.

References

1. Harvey NC, Holroyd C, Ntani G, et al. Vitamin D supplementation in pregnancy: a systematic review. *Health Technology Assessment (Winchester, England)* 2014; **18**(45): 1-190.

2. Weiler H, Fitzpatrick-Wong S, Veitch R, et al. Vitamin D deficiency and whole-body and femur bone mass relative to weight in healthy newborns. *CMAJ* 2005; **172**(6): 757-61.

3. Viljakainen HT, Saarnio E, Hytinantti T, et al. Maternal vitamin D status determines bone variables in the newborn. *J Clin Endocrinol Metab* 2010; **95**(4): 1749-57.

4. Viljakainen HT, Korhonen T, Hytinantti T, et al. Maternal vitamin D status affects bone growth in early childhood--a prospective cohort study. *Osteoporos Int* 2011; **22**(3): 883-91.

5. Javaid MK, Crozier SR, Harvey NC, et al. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. *Lancet* 2006; **367**: 36-43.

6. Sayers A, Tobias JH. Estimated maternal ultraviolet B exposure levels in pregnancy influence skeletal development of the child. *J Clin Endocrinol Metab* 2009; **94**(3): 765-71.

7. Akcakus M, Koklu E, Budak N, Kula M, Kurtoglu S, Koklu S. The relationship between birthweight, 25-hydroxyvitamin D concentrations and bone mineral status in neonates. *Annals of Tropical Paediatrics* 2006; **26**(4): 267-75.

8. Dror DK, King JC, Fung EB, Van Loan MD, Gertz ER, Allen LH. Evidence of associations between feto-maternal vitamin D status, cord parathyroid hormone and bone-specific alkaline phosphatase, and newborn whole body bone mineral content. *Nutrients* 2012; **4**(2): 68-77.

9. Prentice A, Jarjou LM, Goldberg GR, Bennett J, Cole TJ, Schoenmakers I. Maternal plasma 25-hydroxyvitamin D concentration and birthweight, growth and bone mineral accretion of Gambian infants. *Acta Paediatr* 2009; **98**(8): 1360-2.

10. Congdon P, Horsman A, Kirby PA, Dibble J, Bashir T. Mineral content of the forearms of babies born to Asian and white mothers. *Br Med J (Clin Res Ed) JID - 8302911* 1983; **286**(6373): 1233-5.

11. Lawlor DA, Wills AK, Fraser A, Sayers A, Fraser WD, Tobias JH. Association of maternal vitamin D status during pregnancy with bone-mineral content in offspring: a prospective cohort study. *Lancet* 2013.

12. Zhu K, Whitehouse AJ, Hart PH, et al. Maternal vitamin D status during pregnancy and bone mass in offspring at 20 years of age: a prospective cohort study. *J Bone Miner Res* 2014; **29**(5): 1088-95.