**Does antenatal cholecalciferol supplementation affect the mode or timing of delivery? Post-hoc analyses of the MAVIDOS randomised controlled trial**

Rebecca J Moon, NIHR Academic Clinical Lecturer in Child Health1,2

Stefania D’Angelo, Statistician1

Sarah R Crozier, Statistician1

Elizabeth M Curtis, Associate Professor in Rheumatology1

Michelle Fernandes, Academic Clinical Lecturer & MRC Clinical Research Training Fellow in Paediatrics1

Alexandra J Kermack, NIHR Academic Clinical Lecturer of Obstetrics and Gynaecology3

Justin H Davies, Consultant in Paediatric Endocrinology2

Keith M Godfrey, Professor of Epidemiology and Human Development1,4

Nicholas J Bishop, Professor of Paediatric Metabolic Bone Disease5,

Stephen H Kennedy, Professor of Reproductive Medicine and Director of the Oxford Maternal and Perinatal Health Institute6

Ann Prentice, Honorary Senior Visiting Fellow7

Inez Schoenmakers, Senior Lecturer8

Robert Fraser, Professor9

Saurabh V Gandhi, Consultant in Obstetrics and Gynaecology9

Hazel M Inskip, Emeritus Professor of Statistical Epidemiology1,4

M Kassim Javaid, Associate Professor in Metabolic Bone Disease10

Aris T Papageorghiou, Professor of Obstetrics and Fetal Medicine6

Cyrus Cooper, Professor of Rheumatology and Director of the MRC Lifecourse Epidemiology Unit1,4,10Ŧ

Nicholas C Harvey, Professor of Rheumatology and Clinical Epidemiology1,4 Ŧ

and the MAVIDOS Trial Group

1. MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK

2. Paediatric Endocrinology, University Hospital Southampton NHS Foundation Trust, Southampton, UK

3. Department of Women’s Health, University Hospital Southampton NHS Foundation Trust, Southampton, UK

4. NIHR Southampton Nutrition Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

5. Academic Unit of Child Health, Sheffield Children’s Hospital, University of Sheffield, Sheffield, UK

6. Nuffield Department of Women’s & Reproductive Health, John Radcliffe Hospital, University of Oxford, Oxford, UK

7. MRC Epidemiology Unit, University of Cambridge, UK; previously at MRC Human Nutrition Research, Elsie Widdowson Laboratory, Cambridge, UK

8. Department of Medicine, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, UK

9. Department of Obstetrics and Gynaecology, Sheffield Hospitals NHS Trust, University of Sheffield, Sheffield, UK

10. National Institute for Health Research (NIHR) Musculoskeletal Biomedical Research Centre, University of Oxford, UK

CC and NCH are joint senior authors

MAVIDOS Trial Group: Nigel K Arden, Andrew Carr, Elaine M Dennison, Richard Eastell, M Zulf Mughal

**Short title:** Antenatal vitamin D and delivery mode

**Corresponding Author and person to whom reprint requests should be addressed:**

Professor Nicholas Harvey,

MRC Lifecourse Epidemiology Centre,

University of Southampton,

Southampton General Hospital,

Southampton.

SO16 6YD

Tel: 023 8077 7624

Fax: 023 8070 4021

Email: nch@mrc.soton.ac.uk

**Disclosure summary**

RJM, SK, IS, RF, SVG, SD, SC, AP, SMR, AJK, MF have nothing to disclose. CC reports personal fees from ABBH, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier and Takeda, outside the submitted work. NCH reports personal fees, consultancy, lecture fees and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, Servier, Shire, Consilient Healthcare and Internis Pharma, outside the submitted work. EMC reports travel support or lecture fees from Eli Lilly, Pfizer and UCB, outside the submitted work. NJB reports remuneration from Internis Pharmaceuticals Ltd, Mero Biopharma, Alexion, Ultragenyx, Pfizer and Rampart BioSciences, outside the submitted work. ATP reports grants from Versus Arthritis, during the conduct of the study. KMG reports reimbursement for speaking at Nestle Nutrition Institute conferences, grants from Abbott Nutrition & Nestec, outside the submitted work; in addition, KMG has a patent Phenotype Prediction pending, a patent Predictive Use of CpG Methylation pending, and a patent Maternal Nutrition Composition pending, not directly related to this work. JHD reports honoraria from Pfizer, SANDOZ and Novo Nordisk. HMI reports grants from Medical Research Council, Versus Arthritis, European Union’s Seventh Framework Programme, during the conduct of the study; and while not directly receiving funding from other bodies, members of her team have received funding from the following companies from other work: Danone, Nestec, Abbott Nutrition. MKJ reports personal fees from Stirling Anglia, Consilient Health and Internis, outside the submitted work. IS reports research funding outside the submitted work from Medical Research Council, Versus Arthritis, UK Department of Health, Academy of Medical Sciences and the University of East Anglia during the conduct of the study.

**Clinical Trial Registry number:** ISRCTN:82927713; EUDRACT:2007-001716-23

**Word Count:** 2877

**Tables:** 2

**Figures:** 2

**Abstract**

**Background**

Observational studies relating maternal 25-hydroxyvitamin D status to timing and mode of delivery have reported inconsistent results. We assessed the effect of antenatal cholecalciferol supplementation on the incidence of preterm birth, delivery mode and post-partum haemorrhage.

**Methods**

MAVIDOS was a randomised, double-blind, placebo-controlled trial of 1000 IU/day cholecalciferol from 14 weeks’ gestation until delivery. Gestational age, mode of delivery (categorised as spontaneous vaginal [SVD], instrumental [including forceps and vacuum extraction] or Caesarean section) and postpartum haemorrhage (>500ml estimated blood loss) were determined from medical records.

**Results**

965 women participated in the study until delivery. Gestation at birth and incidence of preterm birth (cholecalciferol 5.7%, placebo 4.5%, p=0.43) were similar between the two treatment groups. SVD (versus instrumental or Caesarean delivery) was more likely in women randomised to cholecalciferol (RR 1.13, 95%CI 1.02,1.25) due to fewer instrumental (RR 0.68, 95%CI 0.51,0.91) but similar risk of Caesarean delivery (RR 0.94, 95%CI 0.74,1.19). Postpartum haemorrhage was less common in women randomised to cholecalciferol (32.1% compared to placebo (38.1%, p=0.054) overall, but similar when stratified by delivery mode.

**Conclusions**

Antenatal cholecalciferol supplementation did not alter timing of birth or prevalence of preterm birth but demonstrated a possible effect on the likelihood of SVD.

**Key words**: 25-hydroxyvitamin D; pregnancy; cholecalciferol; preterm birth; Caesarean; labour; delivery; post-partum haemorrhage

**Background**

Vitamin D deficiency in pregnancy is common. In a study of predominately White women in the south of the UK, 31% had a serum 25(OH)D <50 nmol/L (typically considered “insufficient”([1](#_ENREF_1))) and 18% <25 nmol/L ( typically considered “deficient” ([1](#_ENREF_1))) in late pregnancy ([2](#_ENREF_2)). In a more ethnically diverse population in London, 36% women had 25(OH)D <25 nmol/L in early pregnancy ([3](#_ENREF_3)). Reports of similarly high prevalence of vitamin D deficiency in pregnancy have also been reported in other countries across Europe ([4-6](#_ENREF_4)), although in Nordic countries where ultraviolet B (UVB) exposure is limited, the reported prevalence of vitamin D deficiency is lower than in some Southern European countries. This reflects higher supplement use and food fortification practices, highlighting the importance of dietary intake to maintain vitamin D status ([7](#_ENREF_7)).

The primary function of vitamin D is in calcium and phosphate homeostasis and severe maternal vitamin D deficiency can result in neonatal hypocalcaemia resulting in seizures, rickets and cardiomyopathy. There is consistent evidence that the incidence of symptomatic neonatal hypocalcaemia can be reduced by antenatal vitamin D supplementation ([8-10](#_ENREF_8)). In the United Kingdom, all pregnant women are advised to take 400 IU/day vitamin D throughout pregnancy ([11](#_ENREF_11)). Similar guidelines also exist in other developed countries ([12-14](#_ENREF_12)). It has also been proposed that 25(OH)D might have other pleiotropic functions. Indeed, the vitamin D receptor is expressed in a wide range of tissues and local conversion of 25(OH)D into the active metabolite 1,25(OH)2D occurs with auto- and paracrine effects, including in the myometrium([15](#_ENREF_15)) and placenta ([16](#_ENREF_16), [17](#_ENREF_17)).

Vitamin D deficiency has been associated with obstetric outcomes in numerous observational studies, including timing and mode of delivery and incidence of postpartum haemorrhage (PPH)([18](#_ENREF_18), [19](#_ENREF_19)), but the study findings are inconsistent ([20](#_ENREF_20), [21](#_ENREF_21)). For example, maternal vitamin D deficiency has been associated with an increased risk ([22-24](#_ENREF_22)), no difference in risk ([25-27](#_ENREF_25)), and reduced risk of preterm birth ([28](#_ENREF_28), [29](#_ENREF_29)). Furthermore, a recent meta-analysis of observational studies suggested that the timing of vitamin D deficiency may be important to the risk of preterm birth, with only deficiency in the second, and not the third, trimester being of potential importance to this outcome ([30](#_ENREF_30)). Several recent observational studies have also shown lower maternal 25(OH)D levels in those requiring Caesarean section compared to vaginal delivery ([31-34](#_ENREF_31)), but observational studies can be confounded by factors that affect both maternal 25(OH)D and risk of needing an operative delivery, such as maternal obesity, gestational weight gain and ethnicity ([35](#_ENREF_35)). Christoph *et al* found vitamin D deficiency reduced the incidence of PPH in an observational study ([19](#_ENREF_19)). In contrast, women in China with gestational diabetes (GDM) who received vitamin D supplementation had a reduced risk of PPH ([36](#_ENREF_36)). Importantly, observational studies have variably adjusted for recognised risk factors for these outcomes. For example, risk factors for preterm delivery include amongst others grand multiparity, previous preterm birth, low socioeconomic status, gestational diabetes, hypertension, vaginal infections, smoking and alcohol use ([37](#_ENREF_37)). Risk factors for instrumental delivery include nulliparity, use of epidural analgesia, older maternal age ([38](#_ENREF_38), [39](#_ENREF_39)), and for PPH are related to increased risk of poor uterine contraction (e.g. polyhdramnios, multiple birth, rapid labour, infection), retained products of conception, trauma or coagulopathy ([40](#_ENREF_40)).

Despite the wealth of observational evidence, there are few data from intervention studies to support the use of vitamin D supplementation to reduce the incidence of preterm birth and rates of Caesarean section ([41](#_ENREF_41)). Further, given the higher risk of PPH in operative and instrumental deliveries ([42](#_ENREF_42)), it is unknown if PPH can be modified by pregnancy vitamin D supplementation, either directly or indirectly due to the effect on delivery mode. We assessed, in this post-hoc analysis, the effect of antenatal cholecalciferol supplementation on the timing and mode of delivery and incidence of PPH in a randomised, placebo-controlled trial ([43](#_ENREF_43)).

**Methods**

***The Maternal Vitamin D Osteoporosis Study (MAVIDOS)***

The MAVIDOS Study was a multicentre, double-blind, randomised, placebo-controlled trial of vitamin D supplementation in pregnancy. The primary outcome was neonatal bone mass. A detailed description of the study methods ([43](#_ENREF_43)) and primary findings have been published previously ([44](#_ENREF_44)).

Women attending one of three United Kingdom (UK) hospitals [University Hospital Southampton NHS Foundation Trust, Southampton, UK (latitude 50.9° North); Oxford University Hospitals NHS Foundation Trust, Oxford, UK (latitude 51.8° North); Sheffield Hospitals NHS Trust (University of Sheffield), Sheffield, UK (latitude 53.4° North)] for early pregnancy ultrasound screening (11-14 weeks’ gestation) between 6th October 2008 and 11th February 2014 were invited to participate in the study. Gestational age was determined using date of last menstrual period (LMP) and with first trimester fetal ultrasonographic crown-rump length measurement used if >7 days’ discrepancy between LMP and scan dates, uncertain LMP date, irregular cycles or hormonal contraception-use within last 3 months. Inclusion criteria were age over 18 years, singleton pregnancy, and gestational age less than 17 weeks based on last menstrual period and ultrasound measurements. Women with known metabolic bone disease, renal stones, hyperparathyroidism or hypercalciuria, those taking medication known to interfere with fetal growth, fetal anomalies on ultrasonography and women already using >400 IU/day vitamin D supplementation were excluded. A screening blood sample was obtained and analysed on the local NHS platform [all three laboratories (Southampton, Oxford and Sheffield) participate in DEQAS vitamin D quality assurance system (http://www.deqas.org/)]. Women with 25(OH)D between 25 and 100 nmol/l and serum calcium <2.75mmol/l were eligible to enrol fully in the study.

***Intervention***

Participants were randomised to either cholecalciferol 1000 IU/day or matched placebo [Merck KGaA, (Darmstadt, Germany)/ Sharp Clinical Services (Crickhowell, UK; previously DHP-Bilcare)], commenced before 17 weeks’ gestation. Packs of medication were randomly assigned in a 1:1 ratio by a computer-generated sequence in randomly permuted blocks of ten, starting randomly midway through the block, and sequentially numbered, before delivery to the study sites, and then dispensed in order by each study pharmacist. The study medication was provided in a single box containing all medication for the whole pregnancy. The participants, individuals providing antenatal and intrapartum care, and all field researchers involved in data collection and sample analysis were blinded to the assignment of the intervention. All participants received standard antenatal care, and could continue self-administration of dietary supplements containing up to 400 IU/day vitamin D. Women wishing to take dietary supplements containing > 400 IU/day vitamin D were excluded from participation in the study, and those who increased their personal supplementation use above this threshold during the study were excluded from the analysis.

***Outcomes***

*Maternal assessments during pregnancy*

Prior to commencing the study medication, and again at 34 weeks’ gestation, the women attended the research centre for a detailed assessment lifestyle and health (smoking, past medical history, current medication use) and use of vitamin D supplementation using interviewer-led questionnaires. Height and weight were measured and used to calculate body mass index (BMI). Compliance with study medication was assessed by pills counts

*Assessment of 25(OH)D*

Non-fasted venous blood samples were obtained on the day that the study medication was dispensed and at 34 weeks’ gestation. Serum was stored at -80°C. 25(OH)D concentration was assessed by chemiluminescence immunoassay (Liaison automated platform, Diasorin, Minnesota, USA). All samples were analysed in a single batch at the end of the study at MRC Human Nutrition Research, Cambridge, UK. Within- and between-assay CV were 4.1 and 6.1 %. Details of assay performance and quality control through participation in DEQAS and calibration against , NIST standards are given elsewhere ([45](#_ENREF_45), [46](#_ENREF_46)).

*Delivery and infant details*

Gestational age at birth and mode of delivery were collected by a research nurse/midwife from participants’ medical records. Preterm birth was defined as delivery before 37 weeks’ completed gestation. Mode of delivery was categorised as spontaneous vaginal delivery (SVD), instrumental vaginal delivery (i.e. forceps and/or vacuum extraction) or Caesarean section (emergency or elective). When a woman started labour spontaneously before the date of a planned Caesarean section and still delivered by Caesarean section, this was categorised as an elective Caesarean. Since delivery mode is associated with differences in blood loss, estimated blood loss (EBL) was extracted from the medical records; post-partum haemorrhage (PPH) was defined as an EBL ≥ 500ml, with major PPH as ≥ 1000ml ([42](#_ENREF_42)). The obstetric team were not involved in this research study and were also blinded to the allocation to cholecalciferol or placebo. Sex and birth weight were also extracted from the medical records.

***Statistical analysis***

The analysis performed here was post-hoc exploratory analysis that was not stated in the original trial protocol ([43](#_ENREF_43)). The analysis was performed on an intention to treat basis. Comparisons between treatment groups were performed using t-tests for normally distributed continuous outcomes, Mann-Whitney U-tests for non-normally distributed data and χ2 tests for categorical variables. Poisson regression with robust standard errors was used to calculate the relative risk of each delivery mode in comparison to all alternative delivery modes; as such Caesarean section was compared to women who did not have a Caesarean section (SVD or instrumental combined) and SVD was compared to those not achieving an SVD (Caesarean section and instrumental combined). This statistical approach will correct estimates in the case of binary outcomes ([47](#_ENREF_47)), but the estimates and confidence intervals were the same when repeated using log-binominal regression models. Given the study design and balanced characteristics of the mothers at baseline, results are presented unadjusted for any covariates. In exploratory analyses we included adjustment for compliance with study medication and assessed for interactions between treatment allocation and maternal age or baseline 25(OH)D status at randomisation. All analyses were performed using Stata v14.2 (Statacorp, College Station, Texas, USA).

***Ethics approval***

The study was approved by the Southampton and South-West Hampshire Research Ethics Committee. MAVIDOS was registered prospectively (ISRCTN:82927713; EUDRACT:2007-001716-23); full approval from UK MHRA was granted, and written, informed consent was obtained from all participants.

**Results**

A total of 1449 women consented to baseline 25(OH)D screening to determine eligibility to participate in the full trial; 59 and 89 women were excluded due to 25(OH)D < 25nmol/l and > 100 nmol/l, respectively. A further 167 women withdrew prior to randomisation. A total of 1134 women were initially randomised, and 965 continued in the study until delivery (Figure 1) with similar proportions in each treatment group at each centres. Maternal characteristics are shown in Table 1. 25(OH)D was similar at baseline in the two groups, but higher in women randomised to cholecalciferol [68.2 nmol/l (SD 21.9 nmol/l)] than placebo [43.4 nmol/l (SD 22.4 nmol/l)] at 34 weeks’ gestation (p<0.001). Compliance with study medication was high in both groups (placebo: median 95.0% IQR 88.2,98.8%; cholecalciferol: median 96.2% IQR 88.9,99.2%). Maternal weight gain from early to late pregnancy did not differ between the two groups (placebo: mean 9.45 kg (SD 3.65 kg); cholecalciferol: mean 9.57 kg (SD 3.55 kg), p=0.63).

*Gestational age and birth weight at delivery*

The proportion of male infants born in each group was similar (placebo 51.7%, cholecalciferol 53.9%, p=0.49). Median gestational age at delivery was 40.3 weeks (IQR 39.3, 41.1 weeks) in women randomised to placebo and 40.3 weeks (IQR 39.1, 41.0 weeks) in those randomised to cholecalciferol (p=0.22). The incidence of preterm birth was also similar (placebo 4.5%, cholecalciferol 5.7%, p=0.43). Birthweight did not differ between the two groups (placebo: mean 3518 g (SD 517 g); cholecalciferol: 3481 g (SD 543 g), p=0.28). Occipitofrontal circumference (OFC) also did not differ (placebo: mean 35.5 cm (SD 1.5 cm); cholecalciferol: 35.4 cm (SD 1.4 cm), p=0.62).

*Mode of delivery*

Mode of delivery differed between the two groups (p=0.016, Figure 2); SVD was achieved in 65.6% of women in the cholecalciferol group compared with 57.9% in the placebo group (RR 1.13, 95%CI 1.02,1.25). The difference results from fewer instrumental deliveries in the cholecalciferol group (13.2%) compared with placebo group (19.4%, RR 0.68, 95%CI 0.51,0.91), whereas delivery by Caesarean section was similar in the two groups (cholecalciferol 21.3%, placebo 22.7%). The overall risk of Caesarean section as opposed to a vaginal (spontaneous or instrumental delivery) was not reduced by cholecalciferol supplementation (RR 0.94, 95%CI 0.74,1.19). 67 women had an elective section and for 21 women the type of Caesarean section was not documented. The findings were similar when these women were excluded, and inclusion of research centre in the models did not alter the findings. The findings were also similar when compliance with the study medication was included in the models. In exploratory analysis, there was no statistical interaction between treatment allocation and maternal age or baseline 25(OH)D status.

*Post-partum haemorrhage (PPH)*

Postpartum haemorrhage occurred in 32.1% of women randomised to cholecalciferol and 38.1% of women randomised to placebo (RR 0.84, 95%CI 0.71,1.00). Findings were similar for major PPH, with wider confidence limits for this less frequent outcome (RR 0.77, 95%CI 0.52,1.15). Overall, PPH was more common in women requiring a Caesarean section (60.0%) or instrumental delivery (55.4%) compared with those who had a SVD (21.0%) (p<0.001) but there was no evidence of a statistical interaction between treatment group and delivery mode on risk of PPH (Table 2).

**Discussion**

*Main Findings of this study*

In this randomised, placebo-controlled trial, 1000 IU/day cholecalciferol during pregnancy in women with an early pregnancy 25(OH)D of 25-100 nmol/l did not alter the gestational age at delivery or the incidence of preterm birth. However, our findings suggest that antenatal vitamin D supplementation might be effective at reducing the need for an instrumental delivery and as a result the associated risk of PPH.

*What is already known on this topic*

A systematic review of intervention studies of vitamin D supplementation has not shown that supplementation reduces the risk of preterm birth ([48](#_ENREF_48), [49](#_ENREF_49)). This is in contrast to many observational studies ([30](#_ENREF_30)) where findings may be affected by confounding and reverse causality. For example, hospital admission and reduced physical activity in women with threatened preterm birth may result in low serum 25(OH)D due to reduced environmental sunlight exposure. Yonetani et al demonstrated that in women requiring hospitalisation for at least 28 days for threatened preterm labour during the second trimester, 25(OH)D reduced from the second to the third trimester by a mean of 13 nmol/l compared to no change in 25(OH)D over the same time period in pregnant women not requiring admission matched for age and season.([50](#_ENREF_50))

*What this study adds*

Supplementation with 1000 IU/day cholecalciferol did result in a difference in mode of delivery. The proportion of women having a SVD in those randomised to cholecalciferol was higher than the placebo group with fewer instrumental deliveries but no difference in Caesarean section. As instrumental delivery is associated with increased risk of perineal trauma, maternal psychological distress and infant morbidity (for example trauma, jaundice, facial nerve injury, intracranial haemorrhage), vitamin D supplementation might reduce these outcomes, although we were not able to assess this directly. Corcoy et al also did not find a reduced rate of Caesarean section following supplementation with 1600 IU/day cholecalciferol compared or placebo ([51](#_ENREF_51)). Yap et al found no difference in delivery mode in women with an increased risk of GDM randomised to 5000 IU/day cholecalciferol compared to 400 IU/day ([52](#_ENREF_52)). Hollis et al found that the proportion of women that achieved a SVD was greater in those randomised to 2000 IU/day or 4000 IU/day during pregnancy compared to 400 IU/day ([53](#_ENREF_53)). Variation in findings likely reflects differences in study design including the populations studied, timing of commencement of supplementation and study size/power.

The mechanism by which vitamin D might increase SVD rates could result from effects on uterine contractility and muscle strength. The VDR has been isolated in human myometrium ([15](#_ENREF_15)), placenta ([17](#_ENREF_17)) and skeletal muscle ([54](#_ENREF_54)) and vitamin D supplementation results in a small increase in skeletal muscle strength in non-pregnant adults ([55](#_ENREF_55)). Although the role of the VDR in smooth muscle is less certain, calcium status is important to contractility and thus may represent an indirect action of vitamin D on myometrium function. Through this effect on contractility, vitamin D deficiency might reduce abdominal wall and/or pelvic muscle floor strength. In one observational study, women with vitamin D deficiency in late pregnancy had lower pelvic floor muscle strength at 8-10 weeks post-partum independent of delivery mode ([56](#_ENREF_56)). Stafne et al showed that vitamin D deficiency during pregnancy was associated with higher rates of urinary incontinence in mid-pregnancy ([57](#_ENREF_57)). However, in these observational studies, findings could be confounded by overall health and physical activity influencing muscle strength, pelvic floor function and vitamin D status. Low pelvic muscle strength has been associated with prolonged first stage of labour in an observational study of 93 women undergoing induction of labour ([58](#_ENREF_58)), and in a randomised controlled trial pelvic training reduced the frequency of prolonged second stage of labour ([59](#_ENREF_59)). Prolonged labour may increase the need for operative intervention although the exact association of pelvic muscle strength with need for operative delivery remains uncertain ([58](#_ENREF_58), [59](#_ENREF_59)). Two studies have previously examined the relationships between maternal 25(OH)D status and prolonged labour. Gernand et al did not identify an increased risk of prolonged first or second stage in women with a low 25(OH)D concentration measured before 26 weeks’ gestation ([60](#_ENREF_60)), whereas Scholl et al found an approximately two-fold greater risk of prolonged labour in women with 25(OH)D<30nmol/l in early pregnancy compared with those with a 25(OH)D level 50-125nmol/l ([61](#_ENREF_61)).

# The observed reduction in PPH by cholecalciferol likely reflects the difference in delivery mode. PPH risk is higher in instrumental and operative deliveries ([42](#_ENREF_42)), and the proportion of women experiencing a PPH in each randomisation group was similar when stratified by delivery mode, although statistical power would be reduced to demonstrate this. Recent meta-analysis of two studies of vitamin D supplementation in women with GDM has also suggested pregnancy vitamin D supplementation might reduce PPH ([36](#_ENREF_36)). Furthermore, in the NiPPeR randomised placebo-controlled trial of periconception and pregnancy myo-Inositol, probiotics, and micronutrient (including vitamin D) supplementation, major PPH was also reduced by the trial product, despite similar number of women requiring Caesarean section ([62](#_ENREF_62)). Although it is difficult to know which nutritional element(s) contributed to the reduction in PPH in NiPPeR, taken together these findings highlight the need for assessment of PPH in other trials of vitamin D supplementation.

As these are hypothesis-generating post-hoc analyses, and the reasons for operative delivery were not documented, future trials would need to focus on delivery characteristics, such as labour timings, use and reasons for any intervention and analgesia, both to confirm our findings and attempt to elucidate the underlying mechanisms. Future studies should additionally aim to establish the benefits of vitamin D supplementation on these outcomes in specific risk groups for both vitamin D deficiency (for example, obesity, prolonged hospital admission or Black, Asian and Minority Ethnic groups) and adverse obstetric outcomes, and with randomisation stratified by factors associated with the biochemical response to vitamin D supplementation ([63-65](#_ENREF_63)) and risk of poor labour outcomes.

Based on our findings, the number of women needed to treat with 1000 IU/day cholecalciferol to prevent one instrumental delivery is 14. As 1000 IU/day cholecalciferol for the duration of pregnancy for one woman in the UK costs approximately £15 (NHS prescribing cost of £1.45 for 30 tablets, British National Formulary 2021), the cost to prevent one instrumental delivery would be approximately £210. This however would be offset against the reduction in maternal and neonatal morbidity, and thus could be a relatively cheap intervention and warrants further investigation. If these findings and the other identified benefits of higher dose antenatal vitamin D supplementation such as increased offspring bone mass ([66](#_ENREF_66)) are replicated in further high quality randomised controlled trials without increased risk of harm, consideration should be given to increasing the recommended pregnancy supplementation guidance to 1000 IU/day in the UK. In the interim, promotion of the current guidelines recommending 400 IU/day vitamin D in pregnancy is appropriate to increase the current low uptake of supplementation ([67](#_ENREF_67)).

*Limitations of this study*

A key limitation was the exclusion of women with 25(OH)D<25nmol/l in early pregnancy due to ethical and governance issues. Further intervention studies are, therefore, required in women with vitamin D deficiency who might particularly benefit from supplementation. Over 95% of the MAVIDOS participants were of White ethnicity, which reflects the local populations from which recruitment occurred but limits the generalisability of the study findings. Data on clothing choices, UVB exposure, dietary intake of vitamin D and previous pregnancy complications and outcomes were not collected. Nonetheless, considering the RCT design of the study and inclusion of all women in the outcomes assessed in these analyses, random distribution of these characteristics between the two groups would be expected. These post-hoc analyses are hypothesis-generating, rather than part of the pre-specified analysis plan for MAVIDOS, which primarily aimed to assess the effect of antenatal cholecalciferol supplementation on offspring bone development ([44](#_ENREF_44)). However, as one of the largest trials of vitamin D supplementation in pregnancy, the MAVIDOS trial provides a unique opportunity to assess the effects of vitamin D supplementation in pregnancy on other outcomes, and preterm birth and delivery mode were chosen based on inconsistent findings in previously published observational studies that highlighted the need for data from intervention studies.

**Conclusions**

In conclusion, in women with a baseline 25(OH)D 25-100nmol/l, 1000 IU/day cholecalciferol during pregnancy did not reduce the incidence of preterm birth but was associated with a modest increase in the proportion who achieved a SVD and reduction in instrumental deliveries. Further trials are required to confirm this finding, and in particular, including women with very low levels of 25(OH)D at baseline.

**Acknowledgements**

This work was supported by grants from the Arthritis Research UK (17702), Medical Research Council (MC\_PC\_21003; MC\_PC\_21001), Bupa Foundation, National Institute for Health Research (NIHR) Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, and NIHR Musculoskeletal Biomedical Research Unit, University of Oxford. IS and AP were funded by the Medical Research Council (MRC) (programme code U105960371). The work leading to these results was supported by the European Union's Seventh Framework Programme (FP7/2007-2013), projects EarlyNutrition and ODIN under grant agreements numbers 289346 and 613977. CC and NCH are joint senior authors. We are extremely grateful to Merck GmbH for the kind provision of the Vigantoletten supplement. Merck GmbH had no role in the trial execution, data collection, analysis or manuscript preparation.

**Figure Legends**

Figure 1: Consort diagram

Figure 2: Mode of delivery in women randomised to placebo or 1000 IU/day cholecalciferol during pregnancy (p=0.03)

Figure 1: Consort diagram



Figure 2: Mode of delivery in women randomised to placebo or 1000 IU/day cholecalciferol during pregnancy



**Table Legends**

Table 1: Characteristics of the women at randomisation

Table 2: Proportion of women experiencing post-partum haemorrhage by randomisation group, stratified by delivery mode

Table 1: Characteristics of the women

|  |  |  |
| --- | --- | --- |
|  | Placebo | Cholecalciferol |
| n | 486 | 479 |
| Age (years), mean (SD) | 30.7 (5.3) | 30.8 (5.1) |
| Smoking at randomisation, % | 7.9 | 8.2 |
| Nulliparous, % | 43.8 | 42.1 |
| BMI at randomisation (kg/m2), median (IQR) | 25.6 (22.9-29.9) | 24.6 (22.3-28.6) |
| Height (cm), mean (SD) | 165.7 (6.6) | 165.4 (6.3) |
| White ethnicity, % | 94.6 | 95.2 |
| 25(OH)D at randomisation (nmol/l), mean (SD) | 45.7 (16.9) | 46.8 (17.4) |
| Participation in moderate/strenuous physical activity in late pregnancy, N (%) | 280 (67.8) | 267 (67.9) |
| Use of additional vitamin D supplementation (up to 400 IU/day) during pregnancy, N (%) | 119 (27.5) | 120 (29.1) |
| Season of delivery, N (%)  |  |  |
| Winter (December-February) | 102 (21.0) | 104 (21.7) |
| Spring (March-May) | 126 (25.9) | 120 (25.1) |
| Summer (June-August) | 130 (26.8) | 122 (25.5) |
| Autumn (September-November) | 128 (26.3) | 133 (27.8) |

BMI, body mass index

Table 2: Proportion of women experiencing post-partum haemorrhage by randomisation group, stratified by delivery mode

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Placebo**  | **Cholecalciferol**  | **Relative risk** |
|  | Total n | PPH, n (%) | Total n | PPH, n (%) |
| **All** | 483 | 184 (38.1) |  476 | 153 (32.1) | 0.84 (0.71, 1.00) |
| **Spontaneous vaginal delivery** | 278 | 62 (22.3) |  313  | 62 (19.8) | 0.89 (0.65, 1.21) |
| **Instrumental vaginal delivery** | 94 | 51 (54.3) |  63 | 36 (57.1) | 1.06 (0.79, 1.40) |
| **Caesarean Section** | 110 | 71 (64.6) |  100 | 55 (55.0) | 0.85 (0.68, 1.07) |
|  | ***Emergency Caesarean Section*** | 63 | 39 (61.9) |  59 | 32 (54.2) | 0.88 (0.65, 1.19) |

Information on mode of delivery for 1 woman was missing

**References**

1. Bouillon R. Comparative analysis of nutritional guidelines for vitamin D. Nature Reviews Endocrinology. 2017; 13:466-79.

2. Javaid MK, Crozier SR, Harvey NC, Gale CR, Dennison EM, Boucher BJ, et al. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. Lancet. 2006; 367:36-43.

3. McAree T, Jacobs B, Manickavasagar T, Sivalokanathan S, Brennan L, Bassett P, et al. Vitamin D deficiency in pregnancy - still a public health issue. Matern Child Nutr. 2013; 9:23-30.

4. Courbebaisse M, Souberbielle JC, Baptiste A, Taieb J, Tsatsaris V, Guibourdenche J, et al. Vitamin D status during pregnancy and in cord blood in a large prospective French cohort. Clin Nutr. 2019; 38:2136-44.

5. Sideri V, Antonakos G, Fretzayas A, Attilakos A, Chrelias C, Papaevangelou V, et al. Hypovitaminosis D in Healthy Pregnant Women and their Newborns in Greece. Endocr Metab Immune Disord Drug Targets. 2019; 19:159-65.

6. Gustafsson MK, Romundstad PR, Stafne SN, Helvik AS, Stunes AK, Mørkved S, et al. Alterations in the vitamin D endocrine system during pregnancy: A longitudinal study of 855 healthy Norwegian women. PLoS One. 2018; 13:e0195041.

7. Itkonen ST, Andersen R, Björk AK, Brugård Konde Å, Eneroth H, Erkkola M, et al. Vitamin D status and current policies to achieve adequate vitamin D intake in the Nordic countries. Scand J Public Health. 2021; 49:616-27.

8. Brooke OG, Brown IR, Bone CD, Carter ND, Cleeve HJ, Maxwell JD, et al. Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. BMJ. 1980; 280:751-4.

9. Cockburn F, Belton NR, Purvis RJ, Giles MM, Brown JK, Turner TL, et al. Maternal vitamin D intake and mineral metabolism in mothers and their newborn infants. BMJ. 1980; 281:11-4.

10. Hashemipour S, Lalooha F, Zahir Mirdamadi S, Ziaee A, Dabaghi Ghaleh T. Effect of vitamin D administration in vitamin D-deficient pregnant women on maternal and neonatal serum calcium and vitamin D concentrations: a randomised clinical trial. Br J Nutr. 2013; 110:1611-6.

11. National Institute for Health and Care Excellence. Vitamin D: increasing supplement use in at-risk groups [PHC56]. <https://www.nice.org.uk/guidance/ph56>; 2014.

12. Perreault M, Atkinson SA, Meyre D, Fusch G, Mottola MF. Summer Season and Recommended Vitamin D Intake Support Adequate Vitamin D Status throughout Pregnancy in Healthy Canadian Women and Their Newborns. J Nutr. 2020; 150:739-46.

13. Ross AC, Taylor CL, Yaktine AL, Del Valle HB. Dietary Reference Intakes for Calcium and Vitamin D 2011.

14. Paxton GA, Teale GR, Nowson CA, Mason RS, McGrath JJ, Thompson MJ, et al. Vitamin D and health in pregnancy, infants, children and adolescents in Australia and New Zealand: a position statement. Med J Aust. 2013; 198:142-3.

15. Vienonen A, Miettinen S, Blauer M, Martikainen PM, Tomas E, Heinonen PK, et al. Expression of nuclear receptors and cofactors in human endometrium and myometrium. J Soc Gynecol Investig. 2004; 11:104-12.

16. Tanamura A, Nomura S, Kurauchi O, Furui T, Mizutani S, Tomoda Y. Purification and characterization of 1,25(OH)2D3 receptor from human placenta. J Obstet Gynaecol (Tokyo 1995). 1995; 21:631-9.

17. Ashley B, Simner C, Manousopoulou A, Jenkinson C, Hey F, M Frost J, et al. Placental uptake and metabolism as determinants of pregnancy vitamin D status. bioRxiv. 2021:2021.03.01.431439.

18. Wang O, Nie M, Hu YY, Zhang K, Li W, Ping F, et al. Association between vitamin D insufficiency and the risk for gestational diabetes mellitus in pregnant Chinese women. Biomed Environ Sci. 2012; 25:399-406.

19. Christoph P, Challande P, Raio L, Surbek D. High prevalence of severe vitamin D deficiency during the first trimester in pregnant women in Switzerland and its potential contributions to adverse outcomes in the pregnancy. Swiss Med Wkly. 2020; 150:w20238.

20. Moon RJ, Harvey NC, Cooper C. ENDOCRINOLOGY IN PREGNANCY: Influence of maternal vitamin D status on obstetric outcomes and the foetal skeleton. Eur J Endocrinol. 2015; 173:R69-83.

21. Harvey N, Holroyd C, Ntani G, Javaid M, Cooper P, Moon R, et al. Vitamin D supplementation in pregnancy: a systematic review. Health Technol Assess. 2014; 18.

22. Perez-Ferre N, Torrejon MJ, Fuentes M, Fernandez MD, Ramos A, Bordiu E, et al. Association of low serum 25-hydroxyvitamin D levels in pregnancy with glucose homeostasis and obstetric and newborn outcomes. Endocr Pract. 2012; 18:676-84.

23. Bodnar LM, Rouse DJ, Momirova V, Peaceman AM, Sciscione A, Spong CY, et al. Maternal 25-hydroxyvitamin d and preterm birth in twin gestations. Obstet Gynecol. 2013; 122:91-8.

24. Bodnar LM, Klebanoff MA, Gernand AD, Platt RW, Parks WT, Catov JM, et al. Maternal vitamin D status and spontaneous preterm birth by placental histology in the US Collaborative Perinatal Project. Am J Epidemiol. 2014; 179:168-76.

25. Schneuer FJ, Roberts CL, Guilbert C, Simpson JM, Algert CS, Khambalia AZ, et al. Effects of maternal serum 25-hydroxyvitamin D concentrations in the first trimester on subsequent pregnancy outcomes in an Australian population. Am J Clin Nutr. 2014; 99:287-95.

26. Ong YL, Quah PL, Tint MT, Aris IM, Chen LW, van Dam RM, et al. The association of maternal vitamin D status with infant birth outcomes, postnatal growth and adiposity in the first 2 years of life in a multi-ethnic Asian population: the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort study. Br J Nutr. 2016; 116:621-31.

27. Rodriguez A, Garcia-Esteban R, Basterretxea M, Lertxundi A, Rodriguez-Bernal C, Iniguez C, et al. Associations of maternal circulating 25-hydroxyvitamin D3 concentration with pregnancy and birth outcomes. BJOG. 2015; 122:1695-704.

28. Zhou J, Su L, Liu M, Liu Y, Cao X, Wang Z, et al. Associations between 25-hydroxyvitamin D levels and pregnancy outcomes: a prospective observational study in southern China. Eur J Clin Nutr. 2014; 68:925-30.

29. Hossain N, Khanani R, Hussain-Kanani F, Shah T, Arif S, Pal L. High prevalence of vitamin D deficiency in Pakistani mothers and their newborns. Int J Gynaecol Obstet. 2011; 112:229-33.

30. Lian RH, Qi PA, Yuan T, Yan PJ, Qiu WW, Wei Y, et al. Systematic review and meta-analysis of vitamin D deficiency in different pregnancy on preterm birth: Deficiency in middle pregnancy might be at risk. Medicine (Baltimore). 2021; 100:e26303.

31. Thomsen CR, Milidou I, Hvidman L, Khalil MR, Rejnmark L, Uldbjerg N. Vitamin D and the risk of dystocia: A case-control study. PLoS One. 2020; 15:e0240406.

32. Augustin H, Mulcahy S, Schoenmakers I, Bullarbo M, Glantz A, Winkvist A, et al. Late Pregnancy Vitamin D Deficiency is Associated with Doubled Odds of Birth Asphyxia and Emergency Caesarean Section: A Prospective Cohort Study. Matern Child Health J. 2020; 24:1412-8.

33. Humadi Al-Maini EH, Abd Al-Kadir IT, Hassan Al-Joboury EA. The correlation of vitamin D level with dysfunctional labour and mode of delivery. J Pak Med Assoc. 2019; 69(Suppl 3):S55-s8.

34. Arora S, Goel P, Chawla D, Huria A, Arya A. Vitamin D Status in Mothers and Their Newborns and Its Association with Pregnancy Outcomes: Experience from a Tertiary Care Center in Northern India. J Obstet Gynaecol India. 2018; 68:389-93.

35. Patel RR, Peters TJ, Murphy DJ. Prenatal risk factors for Caesarean section. Analyses of the ALSPAC cohort of 12,944 women in England. Int J Epidemiol. 2005; 34:353-67.

36. Wang M, Chen Z, Hu Y, Wang Y, Wu Y, Lian F, et al. The effects of vitamin D supplementation on glycemic control and maternal-neonatal outcomes in women with established gestational diabetes mellitus: A systematic review and meta-analysis. Clin Nutr. 2021; 40:3148-57.

37. Ip M, Peyman E, Lohsoonthorn V, Williams MA. A case-control study of preterm delivery risk factors according to clinical subtypes and severity. J Obstet Gynaecol Res. 2010; 36:34-44.

38. Sharma V, Colleran G, Dineen B, Hession MB, Avalos G, Morrison JJ. Factors influencing delivery mode for nulliparous women with a singleton pregnancy and cephalic presentation during a 17-year period. Eur J Obstet Gynecol Reprod Biol. 2009; 147:173-7.

39. Murphy DJ, Strachan BK, Bahl R, the Royal College of O, Gynaecologists. Assisted Vaginal Birth. BJOG: An International Journal of Obstetrics & Gynaecology. 2020; 127:e70-e112.

40. Prevention and Management of Postpartum Haemorrhage. BJOG: An International Journal of Obstetrics & Gynaecology. 2017; 124:e106-e49.

41. Gallo S, McDermid JM, Al-Nimr RI, Hakeem R, Moreschi JM, Pari-Keener M, et al. Vitamin D Supplementation during Pregnancy: An Evidence Analysis Center Systematic Review and Meta-Analysis. J Acad Nutr Diet. 2020; 120:898-924.e4.

42. Royal College of Obstetrics and Gynaecology (RCOG). Prevention and Management of Postpartum Haemorrhage. Green-top Guideline No 52. BJOG: An International Journal of Obstetrics & Gynaecology. 2017; 124:e106-e49.

43. Harvey NC, Javaid K, Bishop N, Kennedy S, Papageorghiou AT, Fraser R, et al. MAVIDOS Maternal Vitamin D Osteoporosis Study: study protocol for a randomized controlled trial. The MAVIDOS Study Group. Trials. 2012; 13:13.

44. Cooper C, Harvey NC, Bishop NJ, Kennedy S, Papageorghiou AT, Schoenmakers I, et al. Maternal gestational vitamin D supplementation and offspring bone health (MAVIDOS): a multicentre, double-blind, randomised placebo-controlled trial. Lancet Diabetes Endocrinol. 2016; 4:393-402.

45. Jones KS, Assar S, Harnpanich D, Bouillon R, Lambrechts D, Prentice A, et al. 25(OH)D2 Half-Life Is Shorter Than 25(OH)D3 Half-Life and Is Influenced by DBP Concentration and Genotype. J Clin Endocrinol Metab. 2014; 99:3373-81.

46. Sempos CT, Vesper HW, Phinney KW, Thienpont LM, Coates PM. Vitamin D status as an international issue: national surveys and the problem of standardization. Scand J Clin Lab Invest Suppl. 2012; 243:32-40.

47. Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC Med Res Methodol. 2003; 3:21.

48. Bialy L, Fenton T, Shulhan-Kilroy J, Johnson DW, McNeil DA, Hartling L. Vitamin D supplementation to improve pregnancy and perinatal outcomes: an overview of 42 systematic reviews. BMJ open. 2020; 10:e032626-e.

49. Palacios C, Trak-Fellermeier MA, Martinez RX, Lopez-Perez L, Lips P, Salisi JA, et al. Regimens of vitamin D supplementation for women during pregnancy. Cochrane Database Syst Rev. 2019; 10:Cd013446.

50. Yonetani N, Kaji T, Hichijo A, Nakayama S, Maeda K, Irahara M. Effect of prolonged hospitalization for threatened preterm labor on maternal and fetal vitamin D levels. Journal of Obstetrics and Gynaecology Research. 2018; 44:1042-8.

51. Corcoy R, Mendoza LC, Simmons D, Desoye G, Adelantado JM, Chico A, et al. The DALI vitamin D randomized controlled trial for gestational diabetes mellitus prevention: No major benefit shown besides vitamin D sufficiency. Clin Nutr. 2020; 39:976-84.

52. Yap C, Cheung NW, Gunton JE, Athayde N, Munns CF, Duke A, et al. Vitamin d supplementation and the effects on glucose metabolism during pregnancy: a randomized controlled trial. Diabetes Care. 2014; 37:1837-44.

53. Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. J Bone Miner Res. 2011; 26:2341-57.

54. Bischoff HA, Borchers M, Gudat F, Duermueller U, Theiler R, Stahelin HB, et al. In situ detection of 1,25-dihydroxyvitamin D3 receptor in human skeletal muscle tissue. Histochem J. 2001; 33:19-24.

55. Beaudart C, Buckinx F, Rabenda V, Gillain S, Cavalier E, Slomian J, et al. The effects of vitamin D on skeletal muscle strength, muscle mass and muscle power: a systematic review and meta-analysis of randomized controlled trials. J Clin Endocrinol Metab. 2014; 99:4336-45.

56. Aydogmus S, Kelekci S, Aydogmus H, Demir M, Yilmaz B, Sutcu R. Association of antepartum vitamin D levels with postpartum pelvic floor muscle strength and symptoms. Int Urogynecol J. 2015; 26:1179-84.

57. Stafne S, Mørkved S, Gustafsson M, Syversen U, Stunes A, Salvesen K, et al. Vitamin D and stress urinary incontinence in pregnancy: a cross-sectional study. BJOG: An International Journal of Obstetrics & Gynaecology. 2020; 127:1704-11.

58. Aran T, Osmanagaoglu MA, Kart C, Guven S, Sahin M, Unsal MA. Failed labor induction in nulliparous women at term: the role of pelvic floor muscle strength. Int Urogynecol J. 2012; 23:1105-10.

59. Salvesen KA, Mørkved S. Randomised controlled trial of pelvic floor muscle training during pregnancy. BMJ. 2004; 329:378-80.

60. Gernand AD, Klebanoff MA, Simhan HN, Bodnar LM. Maternal vitamin D status, prolonged labor, cesarean delivery and instrumental delivery in an era with a low cesarean rate. J Perinatol. 2015; 35:23-8.

61. Scholl TO, Chen X, Stein P. Maternal vitamin D status and delivery by cesarean. Nutrients. 2012; 4:319-30.

62. Godfrey KM, Barton SJ, El-Heis S, Kenealy T, Nield H, Baker PN, et al. Myo-Inositol, Probiotics, and Micronutrient Supplementation From Preconception for Glycemia in Pregnancy: NiPPeR International Multicenter Double-Blind Randomized Controlled Trial. Diabetes Care. 2021; 44:1091-9.

63. Moon RJ, Cooke LDF, D'Angelo S, Curtis EM, Titcombe P, Davies JH, et al. Maternal and fetal genetic variation in vitamin D metabolism and umbilical cord blood 25-hydroxyvitamin D. J Clin Endocrinol Metab. 2022.

64. Moon RJ, Harvey NC, Cooper C, D'Angelo S, Crozier SR, Inskip HM, et al. Determinants of the Maternal 25-Hydroxyvitamin D Response to Vitamin D Supplementation During Pregnancy. J Clin Endocrinol Metab. 2016; 101:5012-20.

65. Moon RJ, Harvey NC, Cooper C, D'Angelo S, Curtis EM, Crozier SR, et al. Response to Antenatal Cholecalciferol Supplementation Is Associated With Common Vitamin D-Related Genetic Variants. J Clin Endocrinol Metab. 2017; 102:2941-9.

66. Curtis EM, Moon RJ, D'Angelo S, Crozier SR, Bishop NJ, Gopal-Kothandapani JS, et al. Pregnancy Vitamin D Supplementation and Childhood Bone Mass at Age 4 Years: Findings From the Maternal Vitamin D Osteoporosis Study (MAVIDOS) Randomized Controlled Trial. JBMR Plus. 2022; n/a:e10651.

67. Yamanouchi L, Srinivasan M, Barlow N, Basu A. Level of adherence to vitamin D supplementation guidelines in an antenatal centre in Birmingham, UK, and its effect on biochemical and obstetrical outcomes: a single-centre cross-sectional study. BMJ Open. 2021; 11:e048705.