Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies

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Cite this as: *BMJ* 2013;346:f1169
doi: 10.1136/bmj.f1169

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;346:f1169

bmj.com
- Research: Effect of weekly vitamin D supplements on mortality, morbidity, and growth of low birthweight term infants in India up to age 6 months (*BMJ* 2011;342:d2975)
- Research: Calcium supplements with or without vitamin D and risk of cardiovascular events (*BMJ* 2013;342:d2040)
- Research: Effects of vitamin D supplementation on bone density in healthy children (*BMJ* 2011;342:c7254)
- Research: Fall prevention with supplemental and active forms of vitamin D (*BMJ* 2009;339:b3692)

STUDY QUESTION

What is the association between maternal levels of serum 25-hydroxyvitamin D (25-OHD; the best measure of vitamin D status in humans) and pregnancy and neonatal outcomes?

SUMMARY ANSWER

Vitamin D insufficiency is associated with adverse pregnancy outcomes and birth variables.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Existing data support the hypothesis that vitamin D insufficiency during pregnancy may be associated with an increased risk of pregnancy related diseases. This systematic review and meta-analysis of observational studies found that vitamin D insufficiency is associated with an increased risk of gestational diabetes, pre-eclampsia, and small for gestational age infants. Pregnant women with low 25-OHD levels had an increased risk of bacterial vaginosis and lower birth weight infants, but not delivery by caesarean section.

Summary of pooled odds ratio and weighted mean difference for low 25-hydroxyvitamin D levels and pregnancy outcomes and birth variables

Outcome	No of studies	Pooled odds ratio (95% CI)
Gestational diabetes	10	1.49 (1.18 to 1.89)
Pre-eclampsia	7	1.79 (1.25 to 2.58)
Small for gestational age	6	1.85 (1.52 to 2.26)

Selection criteria for studies

We carried out an electronic search of Medline (1966 to August 2012), PubMed (2008 to August 2012), Embase (1980 to August 2012), CINAHL (1981 to August 2012), the Cochrane database of systematic reviews, and the Cochrane database of registered clinical trials, supplemented with manual searches of bibliographies and conference proceedings. Two reviewers independently selected studies that reported on the association between serum 25-OHD level during pregnancy and the outcomes of interest.

Primary outcomes

We assessed the association between low 25-OHD level and pregnancy outcomes (pre-eclampsia, gestational diabetes, bacterial vaginosis, caesarean section) and birth variables (small for gestational age, birth weight, birth length, and head circumference).

Main results and role of chance

Of 3357 citations, 31 studies met our criteria for inclusion in the final analysis. We used random effects models to pool adjusted odds ratio for low 25-OHD levels compared with sufficient levels. Insufficient 25-OHD levels were associated with gestational diabetes (pooled odds ratio 1.49, 95% confidence interval 1.18 to 1.89), pre-eclampsia (1.79, 1.25 to 2.58), and small for gestational age infants (1.85, 1.52 to 2.26). Pregnant women with low 25-OHD levels had an increased risk of bacterial vaginosis and lower birth weight infants, but not delivery by caesarean section.

Bias, confounding, and other reasons for caution

The studies varied in their definitions of 25-OHD insufficiency. Our analysis used cut-offs that were most commonly reported among studies eligible for inclusion in our review. The identified studies used a cut-off of less than 75 nmol/L to define insufficiency for pregnancy outcomes and less than 37.5 nmol/L for birth variables. The included studies varied in study quality and did not always control for important potential confounding variables. Furthermore, many of the studies included were of case-control design, which could overestimate the effect size of the associations. Clinical and statistical heterogeneity were identified across studies, and a variety of sensitivity analyses were conducted to evaluate the robustness of our pooled estimates and to identify possible sources of heterogeneity. These analyses showed that pool estimates did vary when stratified by study design and 25-OHD quantification method, suggesting the importance of these two factors in contributing to heterogeneity.

Study funding/potential competing interests

FA and TN received studentship funding from the University of Calgary Institute for Public Health (Markin Fund for Health and Society); DMR is supported by an AISH (Alberta Innovate Health Solutions) population health investigator award; SCT is supported by an AISH salary support; and MO'B is supported by AISH, the Canadian Institute of Health Research, and the Canadian Foundation for Healthcare Improvement. These agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Ultrasound imaging for lumbar punctures and epidural catheterisations: systematic review and meta-analysis

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Cite this as: *BMJ* 2013;346:f1720
doi: 10.1136/bmj.f1720

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;346:f1720

STUDY QUESTION

Can ultrasound imaging reduce the risk of failed lumbar punctures and epidural catheterisations, when compared with standard palpation methods?

SUMMARY ANSWER

Ultrasound imaging can significantly reduce the risk of failed lumbar punctures and epidural catheterisations.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Many randomised controlled trials have evaluated the role of ultrasound imaging for lumbar punctures and epidural catheterisations, but none was powered to show a significant effect on the ability to reduce failed procedures. This meta-analysis shows a significant beneficial effect of ultrasound imaging.

Selection criteria for studies

We identified clinical trials that randomly allocated patients to either ultrasound imaging or a non-imaging technique for the performance of a lumbar puncture or epidural catheterisation. We searched for trials in Medline, Embase (from inception to May 2012), and the Cochrane Central Register of Controlled Trials (to the second quarter of 2011), without restriction by language or publication status.

Primary outcome(s)

The primary outcome of interest was the number of failed procedures, defined as a lumbar puncture with an inability to obtain cerebrospinal fluid or an epidural catheterisation with an inability to place a catheter or provide adequate analgesia. Secondary outcomes included the number of traumatic procedures, number of insertion attempts, number of needle redirections, and time taken to perform the procedure.

Main results and role of chance

We identified 14 randomised trials. In total, 674 patients were assigned to the ultrasound group and 660 to the control group. Twelve studies were meta-analysed for our primary outcome. There were six failed procedures of 624 in the ultrasound group compared with 44 failed procedures of 610 in the control group. Ultrasound imaging reduced the risk of failed procedures with a risk ratio of 0.21 (95% confidence interval 0.10 to 0.43, P<0.001). The number needed to treat with ultrasound imaging to reduce one failed procedure was 16. Subgroup analysis showed that the effect of ultrasound imaging on reduction of failed lumbar punctures versus epidural catheterisations was similar (P=0.92 for interaction). For secondary outcomes, ultrasound imaging reduced the risk of traumatic procedures with a risk ratio of 0.27 (0.11 to 0.67, P=0.005) and a number needed to treat of 17. Ultrasound imaging also reduced the number of insertion attempts by a mean difference of −0.44 (−0.64 to −0.24, P<0.001) and the number of needle redirections by a mean difference of −1.00 per procedure (−1.24 to −0.75, P<0.001). Time to perform the procedure could not be meta-analysed because reported measures were too heterogeneous across studies.

Summary of outcomes for ultrasound imaging groups versus control groups

	Effect (95% CI)	P	I^2 (%)
No of failed procedures (12 studies)			
Risk ratio	0.21 (0.10 to 0.43)	<0.001	0
Absolute risk reduction	0.063 (0.041 to 0.084)	—	—
Number needed to treat	16 (12 to 25)	—	—
No of traumatic procedures (5 studies)			
Risk ratio	0.27 (0.11 to 0.67)	0.005	0
Absolute risk reduction	0.059 (0.023 to 0.095)	—	—
Number needed to treat	17 (11 to 44)	—	—
No of insertion attempts (8 studies)			
Mean difference	−0.44 (−0.64 to −0.24)	<0.001	73
No of needle redirections (8 studies)			
Mean difference	−1.00 (−1.24 to −0.75)	<0.001	69

Bias, confounding, and other reasons for caution

Our meta-analysis was limited by the methodological quality and outcome reporting of its component studies. Only one study fulfilled all seven quality measures in a modified version of the CLEAR-NPT, a quality assessment tool. Only one study was double blinded. Individuals performing the ultrasound imaging were study investigators who generally had high levels of experience and special interest in the technique. Many of the studies were in the setting of obstetric anaesthesia, and thus included a patient population composed of young, collaborating, healthy women. These features could limit the external validity of our findings. Other important outcomes, such as postdural puncture headaches, were not often reported and could not be synthesised.

Study funding/potential competing interests

FS is supported by a research fellowship from the Pediatric Oncology Group of Ontario (POGO) Research Unit. LS is supported by a New Investigator Award from the Canadian Institutes of Health Research. All researchers were independent from funders and declare no other interests.

Cardiovascular events after clarithromycin use in lower respiratory tract infections: analysis of two prospective cohort studies

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Cite this as: *BMJ* 2013;346:f1235
doi: 10.1136/bmj.f1235

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;346:f1235

STUDY QUESTION Is the use of clarithromycin in the setting of acute exacerbations of chronic obstructive pulmonary disease (COPD) or community acquired pneumonia associated with excess cardiovascular events?

SUMMARY ANSWER In our cohorts, the use of clarithromycin in the setting of acute exacerbations of COPD or community acquired pneumonia was associated with increased cardiovascular events.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Previous observational studies have suggested an increased risk of cardiovascular events at the time of clarithromycin administration, and a meta-analysis of 17 antibiotic trials in coronary heart disease showed that macrolides increased long term mortality. Clarithromycin may be associated with increased cardiovascular events over the following year when it is used to treat acute exacerbations of COPD or community acquired pneumonia.

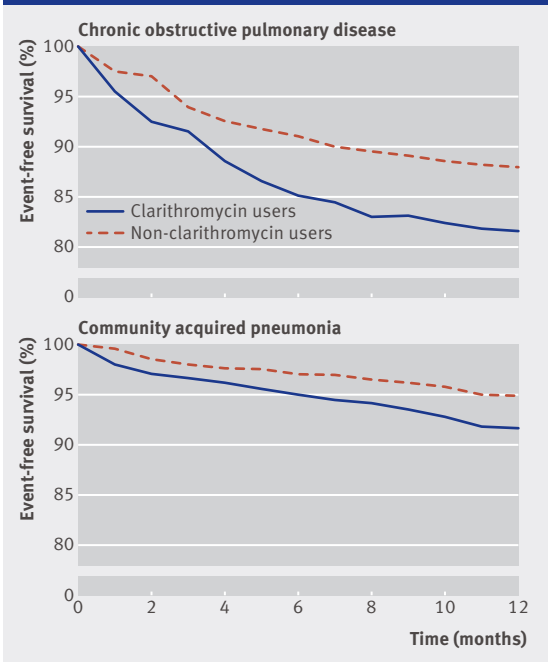
Participants and setting
We analysed two prospectively collected datasets: a multicentre observational study of patients admitted to hospital with acute exacerbations of COPD and the Edinburgh pneumonia study. The COPD dataset includes patients admitted to one of 12 hospitals around the United Kingdom between 2009 and 2011. The Edinburgh pneumonia study cohort includes patients admitted between 2005 and 2009.

Design, size, and duration
The COPD cohort included 1343 patients, and the community acquired pneumonia cohort included 1631. We classified all patients who received at least one dose of clarithromycin during their hospital admission as macrolide users and compared them with patients who did not receive any macrolide antibiotics during their admission. Cardiovascular events (hospital admission for acute coronary syndrome, myocardial infarction, arrhythmia, decompensated heart failure, or cardiac arrest) were identified from national records in the case of the COPD cohort or case note review in the community acquired pneumonia cohort. We used Cox proportional hazards regression to calculate hazard ratios after adjustment for covariates.

Primary outcome
The primary outcome was association between use of clarithromycin and first hospital admission due to a cardiovascular event within one year.

Main results and the role of chance
During one year of follow-up, 268 cardiovascular events occurred in the COPD cohort and 171 in the community acquired pneumonia cohort. After multivariable adjustment, clarithromycin use was associated with an increased risk of cardiovascular events after acute exacerbation of COPD (hazard ratio 1.50, 95% confidence interval 1.13 to 1.97) or community acquired pneumonia (1.68, 1.18 to 2.38). This association persisted after matching for the propensity to receive clarithromycin. Longer durations of clarithromycin use were associated with more cardiovascular events. Use of β lactam antibiotics or doxycycline was not associated with increased cardiovascular events, suggesting a clarithromycin specific effect.

Cox adjusted survival curves for cardiovascular events in two cohorts



Bias, confounding, and other reasons for caution
We attempted to limit bias by adjusting for all measured confounders, but bias due to unrecorded factors may remain. Patients with more severe illness are more likely to be prescribed clarithromycin in community acquired pneumonia, so clarithromycin may be a marker for more severe infection rather than a direct cause of cardiovascular events, although we attempted to limit this by adjusting for severity scores. The results of this study show an association, but its methods cannot prove causation.

Generalisability to other populations
The results are likely to be generalisable to similar populations, as the data were from unselected hospital admissions and a similar effect was seen in both cohorts and in a previous randomised controlled study.

Study funding/potential competing interests
This study received no specific funding.

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Cost effectiveness of telehealth for patients with long term conditions (Whole Systems Demonstrator telehealth questionnaire study): nested economic evaluation in a pragmatic, cluster randomised controlled trial

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Cite this as: *BMJ* 2013;346:f1035
doi: 10.1136/bmj.f1035

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;346:f1035

bmj.com
- Research: Effect of telehealth on quality of life and psychological outcomes over 12 months (Whole Systems Demonstrator telehealth questionnaire study) (*BMJ* 2013;346:f653)
- Research: Effect of telehealth on use of secondary care and mortality (*BMJ* 2012;344:e3874)

STUDY QUESTION

Is it cost effective to add "telehealth" services to standard support and treatment for people with long term conditions?

SUMMARY ANSWER

There is a low probability that telehealth is a cost effective addition to standard support and treatment for people with long term conditions.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Evidence on the economic effect of telehealth is scarce, and some recent reviews have described the quality of economic evaluations as poor. It is unlikely that the community based telehealth intervention evaluated in this study is cost effective, based on analysis of health and social care costs and outcomes after 12 months, and with reference to the National Institute for Health and Clinical Excellence's recommended willingness to pay threshold of £30 000 per QALY.

Design

An economic evaluation was nested within a pragmatic, cluster randomised controlled trial. The primary outcome was incremental cost per QALY gained.

Main results

We undertook net benefit analyses of costs and outcomes for 965 patients (534 receiving telehealth; 431 usual care). The adjusted mean difference in QALY gain between groups at 12 months was 0.012. Incremental cost of the telehealth intervention per QALY gained was £92 000 (€106 700; $142 600). The probability of telehealth being cost effective was 11% at a willingness to pay threshold of £30 000 per QALY gained, and exceeded 50% only if willingness to pay values exceeded about £90 000.

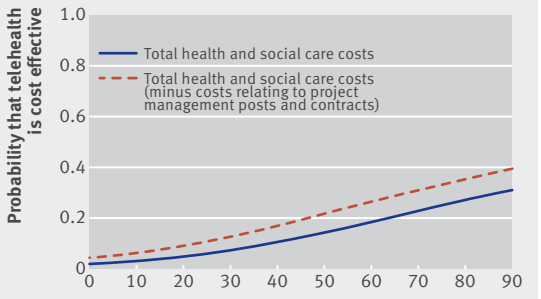
Source(s) of effectiveness

A telehealth trial conducted in three English regions recruited 3230 participants with a long term condition (heart failure, chronic obstructive pulmonary disease, or diabetes). A nested questionnaire study examined telehealth acceptability, effectiveness, and cost effectiveness. Participants offered the intervention received a package of telehealth equipment and monitoring services for 12 months, in addition to standard health and social care available in their area.

Data sources

The evaluation took a health and social services perspective, including costs of hospitals, primary care, community healthcare, medications, social care, and the intervention. Participants completed questionnaires measuring primary and secondary outcomes and service use in health and social care. The time horizon was one year.

Cost effectiveness acceptability curve: QALY



Results of sensitivity analysis

We explored the effect of varying telehealth equipment costs and telehealth support costs if telehealth services had operated at maximum capacity. Total annual mean costs for the telehealth group were less under these new scenarios, and in some cases seemed more cost effective. For example, reducing equipment costs by 80% in combination with reduced support costs resulted in a 61% likelihood that telehealth was cost effective for a willingness to pay threshold of £30 000 per QALY.

Limitations

Limitations included the use of self reported data: participants may have under-reported service use if they were frequent users. We assumed that costs between nine and 12 months of treatment could be multiplied up to a yearly cost. The timeframe of the evaluation could have been too short to show improvements in health related quality of life. The extent to which costs and outcomes differed between participants who completed 12 month follow-up and those who did not (38% of the baseline sample) was not known. The analyses were adjusted for baseline demographic and cost covariates that might influence participants' decision to complete at long term follow-up.

Study funding /potential competing interests

This is an independent report commissioned and funded by the Policy Research Programme in the Department of Health. Some authors have carried out evaluative work funded by government or public agencies but these have not created competing interests.