J Musculoskelet Neuronal Interact 2021; 21(2):193-195

Journal of Musculoskeletal and Neuronal Interactions JMNI

Cochrane Corner

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What are the effects of vitamin D supplementation for term breastfed infants to prevent vitamin D deficiency and improve bone health? - A Cochrane Review summary with commentary

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Keywords: Bone, Breastfed, Deficiency, Infants, Vitamin D

The aim of this commentary is to discuss from a rehabilitation perspective the published Cochrane Review "Vitamin D supplementation for term breastfed infants to prevent vitamin D deficiency and improve bone health"[1] by Tan et al.[a], under the direct supervision of Cochrane Neonatal Group. This Cochrane Corner is produced in agreement with Journal of Musculoskeletal and Neuronal Interactions by Cochrane Rehabilitation.

Background

Vitamin D insufficiency and deficiency is common in early childhood because of several factors including insufficient amount of vitamin D in human milk and maternal vitamin D status in pregnancy[2,3]. Recently, there has been increasing interest in the potential benefits of vitamin D replacement during pregnancy, lactation, and early childhood on bone health and growth. The literature indicates the presence of a relationship between maternal vitamin D deficiency and childhood rickets around the world[4]. Serum 25-hydroxy vitamin D (25(OH)D) is the main circulating form of vitamin D. There are different opinions about normal levels of serum 25(OH)D and definition of vitamin D deficiency or insufficiency. According to most authorities, vitamin D deficiency is defined as a serum 25(OH)D below 20 ng/ml (50 nmol/L) and insufficiency as a 25(OH)D of 21-29 ng/ml (52.5-72.5 nmol/L)[5,6]. Many studies have examined different approaches to preventing vitamin D deficiency in infants. A daily 400 IU vitamin D supplement is recommended for healthy breastfed term infants[2]. Although many randomized controlled trails (RCTs) have been conducted on this subject, it is still important to provide evidence-based data about the impacts of vitamin D supplementation in mother-infant pairs and its potential adverse effects. This Cochrane Review[1] aims to identify evidence of the effects of vitamin D supplementation in mother-infant pairs.

The author declares no conflicts of interest.

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[a] This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2020, Issue 12, Art. No.: CD013046, DOI: 10.1002/14651858.CD013046.pub2. (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.
The views expressed in the summary with commentary are those of the Cochrane Corner author and do not represent the Cochrane Library or Wiley.

Vitamin D supplementation for term breastfed infants to prevent vitamin D deficiency and improve bone health

(May Loong Tan, Steven A Abrams, David A Osborn, 2020)

What is the aim of this Cochrane review?

The aim of this Cochrane Review was to determine the impact of vitamin D supplementation in infants and breastfeeding mothers, on vitamin D levels, bone mineralization, and growth in the healthy breastfed term infants.

What was studied in the Cochrane review?

The population addressed in this review was healthy, term, breastfed infants. The interventions studied were any RCTs and quasi-RCTs that assessed the effects of vitamin D supplementation on vitamin D deficiency, bone mineralization, and growth in breastfeeding mother and infants. The intervention was compared (1) vitamin D supplementation of infants or breastfeeding mothers with placebo, sunlight exposure, and no intervention, (2) vitamin D supplementation of infants with breastfeeding mothers. The primary outcome of interest in the review was bone mineral density (dual-energy X-ray absorptiometry), serum 25(OH) D levels, nutritional rickets, and adverse effects including vitamin D toxicity. The secondary ones were serum 25(OH)D levels in the first six months of age (lowest or post-treatment levels), fracture, osteomalacia, and growth.

Search methodology and up-to-dateness of the Cochrane review?

The review authors searched for relevant RCTs and quasi-RCTs in any language that had been published up to May 2020. The electronic searches were employed in the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, MIDIRS, clinical trials registries databases, conference proceedings, and citations.

What are the main results of the Cochrane review?

The review included 19 studies of vitamin D supplementation during breastfeeding (mother-infant pairs, n=2837), nine studies in infants, eight studies in breastfeeding mothers, and six studies in infants versus breastfeeding mothers. There was no study comparing vitamin D supplementation with periods of sunlight exposure in infants.

The review shows that:

Comparison 1: Vitamin D supplementation in infants versus placebo or no treatment

The authors concluded that vitamin D supplementation (400 IU/day) in infants may increase 25(OH)D level (six studies, n=334; mean difference (MD) 22.63 nmol/L, 95% confidence interval (CI) 17.05 to 28.21; low-certainty evidence) and decrease incidence of vitamin D insufficiency (25(OH)D<50 nmol/L) compared with placebo or no treatment (four studies, n=274; risk ratio (RR) 0.57, 95% CI 0.41 to 0.80; low-certainty evidence). They did not find adequate evidence regarding the impact of vitamin D supplementation on the risk of vitamin D deficiency (25(OH) D<30 nmol/L) until six months (two studies, n=122; RR 0.41, 95% CI 0.16 to 1.05), bone mineral content, and incidence of biochemical or radiological rickets (very-low certainty evidence). The authors were uncertain about adverse effects. They did not find any studies to investigate higher doses of vitamin D supplementation (>400 IU/day) in infant compared with placebo.

Comparison 2: Vitamin D supplementation in lactating mothers versus placebo or no treatment

The authors concluded that vitamin D supplementation in breastfeeding mothers may increase 25(OH)D level in infants (seven studies, n=597; MD 24.60 nmol/L, 95% CI 21.59 to 27.60; low-certainty evidence) and decrease incidence of vitamin D insufficiency (25(OH)D<50 nmol/L) (five studies, n=512; RR 0.47, 95% CI 0.39 to 0.57; low-certainty evidence), vitamin D deficiency (25(OH)D<30 nmol/L) (five studies, n=512; RR 0.15, 95% CI 0.09 to 0.24; low-certainty evidence), and biochemical rickets (two studies, n=229; RR 0.06, 95% CI 0.01 to 0.44; low-certainty evidence) compared with placebo or no treatment. They did not find enough evidence to determine the impact of maternal vitamin D supplementation on radiological rickets in infants (three studies, n=536; RR 0.76, 95% CI 0.18 to 3.31; very low-certainty evidence). All breastfeeding mothers included in the studies had a high risk of vitamin D deficiency. The authors were uncertain about the effects of maternal supplementation on infant growth and adverse effects.

Comparison 3: Vitamin D supplementation in infants versus breastfeeding mothers

The authors concluded that vitamin D supplementation in infants (400 IU/day) may increase their 25(OH)D levels (four studies, n=269; MD 14.35 nmol/L, 95% CI 9.64 to 19.06; low-certainty evidence), and decrease incidence of vitamin D insufficiency (25(OH)D<50 nmol/L) (four studies, n=334; RR 0.61, 95% CI 0.40 to 0.94; very low-certainty evidence) and vitamin D deficiency (25(OH)D<30 nmol/L) (four studies, n=334; RR 0.35, 95% CI 0.17 to 0.72; very low-certainty evidence) compared with maternal supplementation (400 IU to >4000 IU/day). They did not find enough evidence to determine the impact of maternal vitamin D supplementation on biochemical rickets in infants. All infants and breastfeeding mothers included in the studies had a high risk of vitamin D deficiency. The authors were uncertain about adverse effects.

Comparison 4: Vitamin D supplementation versus sunlight exposure in infants

The authors did not find studies comparing vitamin D supplementation versus sunlight exposure in infants.

How did the authors conclude?

The authors of the review concluded that vitamin D supplementation of infants (400 IU/day) within first six months increased 25(OH)D level of infants (22.63 nmol/L) and decreased the incidence of vitamin D insufficiency, however, they did not find enough evidence to determine the impact of vitamin D supplementation on vitamin D deficiency and bone health. Moreover, they declared that maternal vitamin D supplementation increased 25(OH)D level of infants (24.60 nmol/L) and decreased the incidence of both vitamin D insufficiency and deficiency in breastfed infants. The authors found that vitamin D supplementation of infants increased the infant 25(OH) D level and decreased the incidence of vitamin D insufficiency/deficiency compared with supplementation of breastfeeding mothers. There was very uncertain evidence about the effects of vitamin D supplementation on bone health in breastfed infants. In infants or mothers with higher risk of vitamin D deficiency, vitamin D supplementation led to a greater increase in 25(OH)D levels. In terms of 25(OH) D levels, high-dose vitamin D supplementation (>4000 IU/day) in breastfeeding mothers had similar results with 400 IU daily vitamin D supplementation in breastfed infants. However, the authors declared that the certainly of evidence for all outcomes was very low to low.

What are the implications of the Cochrane evidence for practice in rehabilitation?

Breastfed infants are at higher risk of vitamin D deficiency because the content of vitamin D in human milk is dependent to the vitamin D intake of breastfeeding mothers[7]. Vitamin D supplementation in children with vitamin D deficiency could result in clinically useful improvements in bone mineralization and peak bone mass, which may lead to decrease in fracture risk in both childhood and later life[8].

There are different strategies to prevent vitamin D deficiency in breastfed infants including maternal or infant vitamin D supplementation regimes[2,7]. Many international guidelines recommend vitamin D supplementation for pregnant women and breastfeeding mother-infant pairs.9 However, the evidence regarding the efficacy and safety of these supplementation regimes is still uncertain. Moreover, the number of studies reporting the impact of vitamin D supplementation on bone health is limited and most studies investigated the impact of vitamin D supplementation in high-risk populations.

Although the authors declared the number of studies that compared different doses of vitamin D supplementation in infants or breastfeeding mothers were insufficient and defined the level of evidences as low or very low, the findings of the current review may provide additional valuable data to optimizing vitamin D supplementation programs in mother-infant pairs. Future studies need to focus on investigating the effective and optimal dosing for maternal and infant supplementation of vitamin D, and identifying the best strategies to increase adherence. Additionally, the use of definite clinical outcomes in different levels of 25(OH)D could improve the certainly of evidence.

From a rehabilitation point of view, vitamin D is known to play an important role in musculoskeletal health and there is need to be aware of the detrimental effects of vitamin D deficiency on growth, bone health, and muscle strength in the pediatric age group, particularly in the children with neuromuscular disorders.

Acknowledgements

The author thanks Cochrane Rehabilitation and Cochrane Neonatal Group for reviewing the contents of the Cochrane Corner.

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