Medicines Adverse Reactions Committee

Meeting date	11/06/2026	Agenda item	3.2.1
Title	**Safety of colecalciferol 50,000 IU capsules in pregnancy**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**	**Sponsor**	
Colecalciferol	Vit.D3	Multichem NZ Limited	
PHARMAC funding	Fully funded.		
Previous MARC meetings	Not applicable.		
International action	Not applicable.		
Prescriber Update	Not applicable.		
Classification	Prescription medicine		
Usage data	[redacted]		
Advice sought	**The Committee is asked to advise:** • Whether any changes to the colecalciferol data sheet information on use in pregnancy are recommended based on the available clinical data.		

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1 PURPOSE

In 2024 Medsafe reviewed the Vit.D3 (colecalciferol 50,000 IU capsule) data sheet, as it had been noted that the quality of the data sheet could be improved. During this review the safety sections of the data sheet were compared to equivalent medicines approved by recognised regulatory authorities. As a result, in October 2024 the data sheet was updated to list a contraindication to use in pregnancy and state that a lower strength formulation should be used in line with the reviewed data sheets. Medsafe has since received correspondence from New Zealand Formulary requesting a review of this contraindication, as they had received complaints from physicians.

Vit.D3 (colecalciferol 50,000 IU capsule) is the only approved and available colecalciferol (monotherapy) medicine. Pharmac also funds a liquid drop formulation (colecalciferol 400 IU/drop) which is a dietary supplement rather than an approved medicine.

This memo reviews the available information relevant to the safety of colecalciferol in pregnancy, and whether there is any information on use of 50,000 IU monthly.

2 BACKGROUND

2.1 Vitamin D

Vitamin D is involved in the regulation of calcium and phosphate in the body. Vitamin D increases absorption of dietary calcium which is needed for adequate bone mineralisation.

There are two forms of vitamin D: colecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Colecalciferol is produced in the skin in response to sunlight and both colecalciferol and ergocalciferol can be obtained in modest amounts from food.

2.1.1 Vitamin D deficiency

Vitamin D status is defined by 25(OH)D levels. Vitamin D insufficiency is defined as 25(OH)D <50 nmol/L and deficiency is defined at <25 nmol/L. [1]

Table 1: Reference ranges for 25-hydroxyvitamin D

Vitamin D insufficiency		Vitamin D deficiency	
<50 nmol/L	<20 ng/mL	<25 nmol/L	<10 ng/mL

The Institute of Medicine (now the National Academy of Medicine; NAM) Committee (USA) published dietary reference values for vitamin D in 2011. The IOM Committee considered that 25(OH)D levels above 125 to 150 nmol/L should be avoided, although not known to be associated with hypercalcaemia. The basis for this was that bone health benefits and maximal calcium absorption are seen at levels of 50 nmol/L, and that some epidemiological studies have found possible negative effects on all-cause mortality, chronic disease, falls and fractures at 25(OH)D levels between 75 nmol/L and approximately 120 nmol/L. However it was acknowledged that there is uncertainty around these data, and noted that similarly high levels have been seen with sun exposure. [2]

The Institute of Medicine (IOM) set a recommended dietary allowance (RDA) of 600 IU vitamin D per day in adult females, and the same RDA was applied to pregnancy and lactation. [3] A tolerable upper intake level (UL) was set at 4,000 IU per day, based on a no observed adverse effect level (NOAEL) of 10,000 IU per day. [2]

Low vitamin D levels are linked to bone conditions such as rickets in children and osteoporosis and osteomalacia in adults. During pregnancy, vitamin D supports normal growth and development of the fetus. Transplacental passage of maternal 25-hydroxycolecalciferol (25(OH)D) is the only source of vitamin D for the

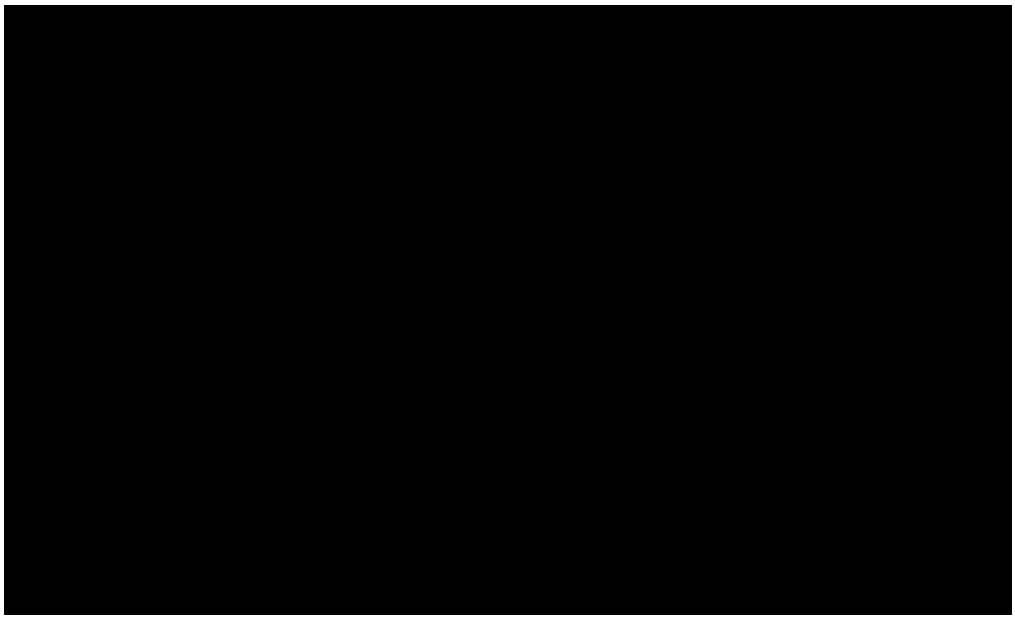
fetus. Some observational studies describe associations between low vitamin D levels in pregnancy and other adverse maternal and infant outcomes, but the evidence is insufficient to confirm a causal relationship. [1, 4, 5]

Risk factors for low vitamin D levels include dark skin, sun avoidance, wearing veils and full-body-coverage clothing, malabsorption syndromes, obesity and older age. People living in cold, southern regions may be at risk of deficiency if they don't get enough sun exposure during winter. [4]

The 2008/09 New Zealand Adult Nutrition Survey found that the overall annual mean level of vitamin D for New Zealand adults was 63.0 nmol/L. The majority of adults (68%) were vitamin D sufficient, while 27% had insufficient levels and 5% were deficient. The prevalence of deficiency was not significantly different across age groups, between men and women, and residence in northern, central and southern parts of New Zealand. However, prevalence of deficiency peaked during the months of August, September and October (figure 1). During these months, the prevalence of deficiency was highest in southern parts of New Zealand (figure 2). [6]

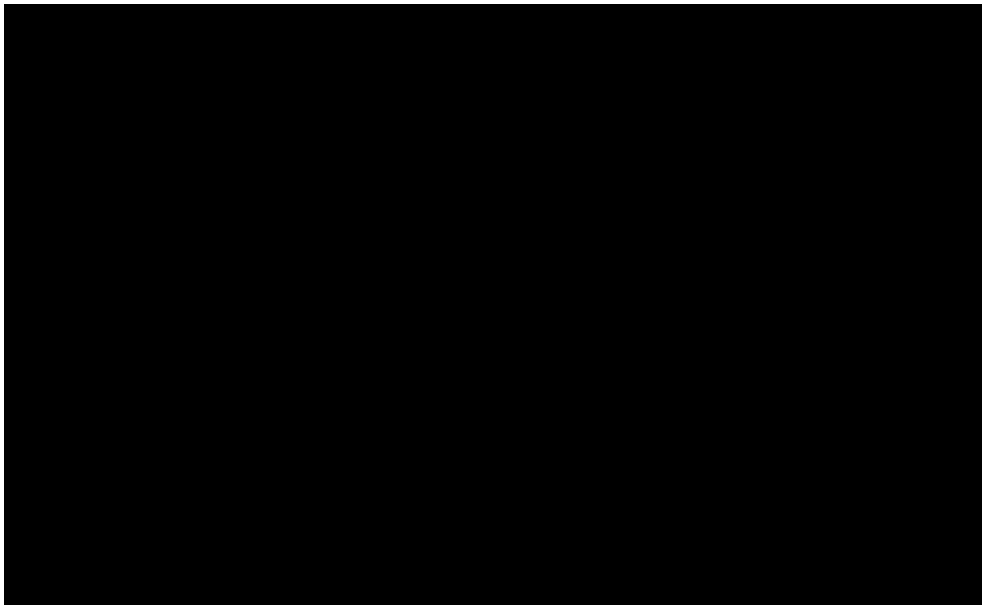
A South Auckland study found that 10% of pregnant participants were vitamin D deficient and 31% were insufficient at 27 weeks gestation, with higher prevalence among Māori, Pacific and participants of other ethnicities compared to European participants. [7] A Dunedin longitudinal study found vitamin D insufficiency at one or more time-points in 65% and 76% of mothers and their infants, respectively. [8]

Figure 1: Prevalence of vitamin D deficiency by month among adults aged 15 years and over (unadjusted prevalence) in the 2008/09 New Zealand Adult Nutrition Survey.



Source: Mason K, Templeton R and Weerasekera D. 2012. Vitamin D status of New Zealand adults: Findings from the 2008/09 New Zealand adult nutrition survey. Ministry of Health.

Figure 2: Prevalence of vitamin D deficiency by region during August, September and October among adults aged 15 years and over (unadjusted prevalence), in the 2008/09 New Zealand Adult Nutrition Survey.



Source: Mason K, Templeton R and Weerasekera D. 2012. Vitamin D status of New Zealand adults: Findings from the 2008/09 New Zealand adult nutrition survey. Ministry of Health.

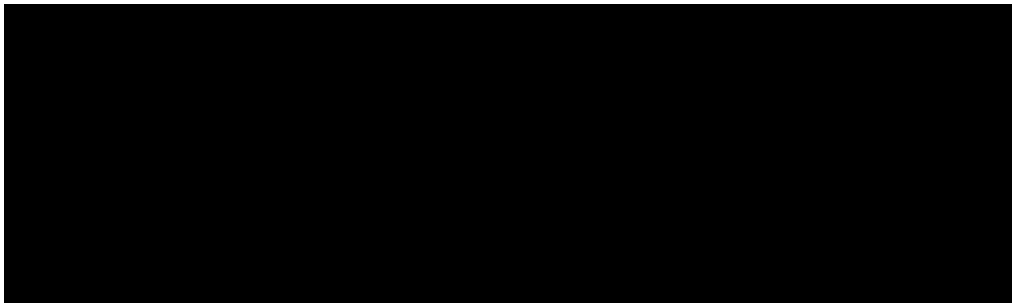
2.1.2 Vitamin D metabolism

When skin is exposed to sunlight, ultraviolet B (UVB) radiation triggers the conversion of 7-dehydrocholesterol to colecalciferol. Vitamin D is fat soluble and is thought to distribute into adipose tissue in the form of colecalciferol, which is in equilibrium with the concentration in plasma.

Colecalciferol is converted to 25-hydroxyvitamin D (25(OH)D; calcidiol) in the liver, and is further hydroxylated by 1-alpha-hydroxylase in the kidney to form the biologically active compound 1,25-dihydroxyvitamin D ($1,25(OH)_2D$; calcitriol) (figure 3). [9]

$1,25(OH)_2D$ stimulates its own degradation via induction of CYP24A1. Conversion of 25(OH)D to 1,25(OH)D also occurs in other tissues, including the placenta, but are thought to be minor contributors to overall levels. [4, 10, 11]

Figure 3: Metabolic activation of vitamin D3 to its hormonal form, 1,25(OH)2D3



Source: DeLuca HF. 2004. Overview of general physiologic features and functions of vitamin D. The American Journal of Clinical Nutrition 80(6): 1689S-1696S. DOI: 10.1093/ajcn/80.6.1689S (accessed 6 May 2026).

2.1.3 Functions of vitamin D

Calcitriol ($1,25(OH)_2D$) is part of an endocrine feedback system that maintains serum calcium and phosphate levels required for bone mineralisation. Control of serum calcium is also required for the functioning of the neuromuscular junction, vasodilatation, nerve transmission, and hormonal secretion. [12]

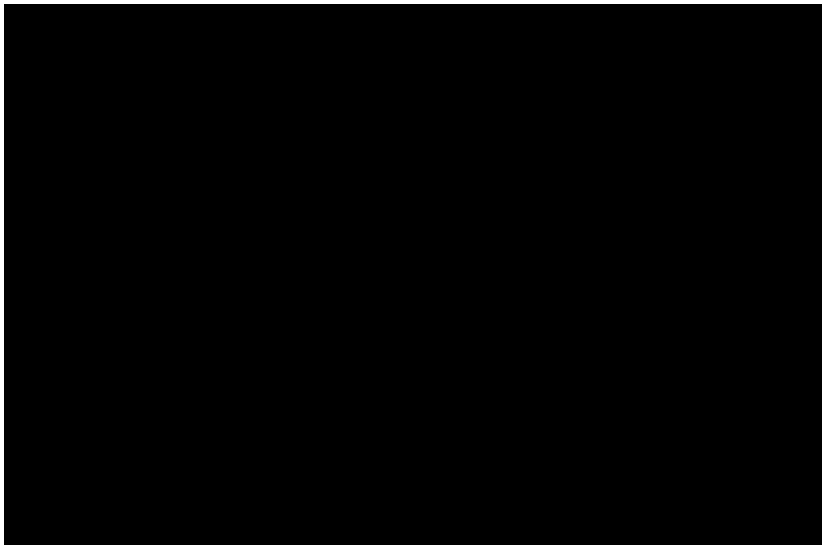
When serum calcium levels decrease, the calcium sensing receptor of the parathyroid gland signals the secretion of parathyroid hormone (PTH). PTH then increases 1-alpha-OHase activity in the kidney resulting in increased conversion of 25(OH)D to calcitriol. Calcitriol then increases calcium and phosphate absorption via the intestine and increases calcium and phosphate reabsorption in the kidney. Calcitriol also induces osteoclast formation and activation to increase bone resorption. PTH also stimulates osteoclasts directly. As the serum calcium level rises to the normal range, PTH secretion decreases (figure 4). [12]

If serum calcium is too high, the C cells (parafollicular) cells of the thyroid gland secrete calcitonin which inhibits bone resorption. Binding of calcitriol to the vitamin D receptor (VDR) also supresses parathyroid gene expression and cell proliferation. Serum phosphorus levels are also involved in the regulation of calcitriol formation. [12]

During pregnancy, adaptations occur to facilitate transfer of large amounts of calcium to the fetus during the third trimester. The main changes are increased production of calcitriol and greatly increased intestinal absorption of calcium. There is also increased calcium excretion in the urine. [13]

Vitamin D receptors are also present in many other tissues not involved in calcium and phosphate metabolism, such as immune cells, but other functions of vitamin D are not well understood. [12]

Figure 4: Endocrine feedback system that maintains serum calcium levels: Involvement of vitamin D and parathyroid hormone (PTH).



CT = calcitonin; PTG = parathyroid gland.
Source: Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. 2011. Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC): National Academies Press.

2.1.4 Vitamin D toxicity

The clinical manifestations of vitamin D toxicity are caused by hypercalcaemia (corrected calcium >2.6 mmol/L). Symptoms of hypercalcaemia include nausea, vomiting, constipation, abdominal pain, thirst, polyuria and mental status changes, but mild hypercalcaemia may be asymptomatic. Severe or prolonged hypercalcaemia may lead to acute kidney injury, nephrocalcinosis, arrythmias and death. Hypercalcaemia has generally been reported at plasma 25(OH)D concentrations above 375-500 nmol/L although a safe level has not been established. [14, 15]

The mechanism of vitamin D toxicity is not well understood. One hypothesis is that excessive circulating concentrations of 25(OH)D (and vitamin D itself) can displace 1,25(OH)2D from the vitamin D-binding protein, leading to excessive unbound 1,25(OH)2D which causes hypercalcaemia via increased calcium absorption and bone resorption. [16]

A published literature review identified 13 publications describing cases of symptomatic vitamin D toxicity, of which 9 were in adults. The vitamin D doses reported in these cases ranged from 50,000 IU/day to 2,604,000 IU/day with marked hypercalcemia (total calcium between 11.1 and 23.08 mg/dL) and serum 25(OH)D concentrations above 150 ng/mL (275 nmol/L). Symptoms included abdominal pain, vomiting, anorexia, weakness, dehydration, altered mental status, acute kidney injury and nephrocalcinosis requiring hospitalisation. [17]

A retrospective chart review at a single hospital identified 127,932 measurements of 25(OH)D from 73,779 patients between the years 2000 and 2016. There were 89 patients with 25(OH)D >120 ng/mL (300 mmol/L) of whom 53 had a concomitant total calcium measurement. There were 7 patients that had elevated total calcium of whom 4 had symptoms of toxicity. The patients were aged 3 to 70 years and had received 40,000 to 150,000 IU vitamin D per day, with 25(OH)D of (194 to 496 ng/mL 485 to 1,240 nmol/L) and total serum calcium of 9.6 to 19.8 mg/dL. Symptoms included gastrointestinal disturbance, nephrocalcinosis, renal failure and altered mental status. No cases of toxicity were identified with 25(OH)D levels below 120 ng/mL (300 nmol/L). [18]

Fatal outcomes have been reported in adults who received 5,200,000 IU over one month and 500,000 IU daily for 6 months. [19, 20] A fatal outcome was reported in a 10-year-old boy who inadvertently received 600,000 IU per day for 21 days. [21] A literature review of 138 paediatric vitamin D toxicity cases identified 6 cases with fatal outcome, all in children aged younger than two years. [22]

Reports of vitamin D toxicity were generally associated with either mislabelled/misformulated medicines or fortified foods with extremely high vitamin D content, accidental or deliberate excessive administration by patients or caregivers, dispensing errors, or inappropriate prescribing. [23]

There has been concern that high doses of vitamin D could have negative effects over time, such as decreased bone mineral density, but this effect has not been confirmed. [24]

2.1.5 Safety of vitamin D supplementation in pregnancy

The recognised safety concern associated with vitamin D supplementation is hypercalcaemia. The experiences of women with primary hyperparathyroidism indicate that hypercalcaemia during pregnancy can cause significant maternal, fetal and neonatal complications if untreated. Maternal complications include nephrolithiasis, pancreatitis, hyperemesis gravidarum, pre-eclampsia and hypercalcaemic crisis. Fetal complications include intrauterine growth restriction, preterm delivery and miscarriage, with miscarriage being more common in those patients with a serum calcium greater than 2.85 mmol/L. Neonatal complications include hypocalcaemia. [25]

There are a few published case reports of neonatal hypercalcaemia following high maternal intake of vitamin D supplements (see section 3.5). Case reports of teratogenicity associated with excess vitamin D intake were not identified.

There are limited safety data on vitamin D supplementation during pregnancy, particularly the use of high intermittent (eg, weekly or monthly) doses. The available data from clinical trials is summarised in section 3. A key safety consideration is whether high intermittent doses of colecalciferol are associated with a higher risk of maternal hypercalcaemia compared to equivalent daily doses. Other theoretical safety concerns include:

- Whether increases in maternal circulating vitamin D metabolite concentrations lead to abnormal fetal calcium metabolism, even in the absence of maternal toxicity.
- Whether a rapid increase in the maternal serum vitamin D_3 concentration can cause toxicity via upregulated production of $1,25(OH)_2D_3$ during pregnancy.

- Whether there are safety implications associated with other differences in vitamin D metabolism during pregnancy (eg, extra-renal metabolism).
- Whether colecalciferol can form toxic metabolites (ie, toxicity without hypercalcaemia). [16]

In clinical studies, key safety parameters are maternal and cord blood serum calcium and the incidence of hypercalcaemia. Hypercalciuria may precede hypercalcaemia and can be monitored through via urine calcium to creatinine ratio (ca:cr). Hypercalciuria is also a potential risk factor for renal stones, although this has not been linked to vitamin D supplementation. Levels of 25(OH)D and markers of vitamin D and calcium metabolism are of interest in interpreting results but are not safety parameters in themselves. [16]

2.1.6 Animal data on vitamin D supplementation in pregnancy

Local and international product information for colecalciferol state that high doses have been associated with fetal abnormalities in animal studies. International product information states that animal studies have not shown teratogenic activity at doses equivalent to those used therapeutically (see section 2.2).

A 2011 review article by Roth et al summarises the available animal data regarding teratogenicity. [16]

- Studies in rats have shown growth restriction, impaired osteogenesis, placental damage and mortality at cumulative vitamin D doses during pregnancy of 26 to 90 mg/kg but not at doses ≤5.2 mg/kg. The effects were dose dependent but not clearly mediated by maternal or fetal hypercalcemia.
- In rabbits, cumulative doses of ≥4.7 mg/kg caused growth restriction and high mortality, but cumulative doses as low as 0.88 mg/kg caused non-calcified vascular lesions in offspring. A ten-fold lower dose of 0.088 mg/kg did not cause vascular lesions but was associated with poor maternal weight gain. The review noted that in rabbits, serum calcium levels vary widely and rise proportionately with dietary calcium, which is passively absorbed independently of vitamin D.
- In cows, doses of ~1 mg/kg colecalciferol administered within the month before calving were associated with severe hypercalcaemic toxicity. The adverse effects on offspring were not described. Whereas pregnant rats have been observed to be relatively resistant to vitamin D toxicity compared with non-pregnant rats administered equivalent doses, pregnant cows were found to be more susceptible to vitamin D toxicity than non-pregnant cows.
- A series of studies in rabbits and rats published in the 1960 to 1980s reported specific craniofacial and aortic abnormalities in the offspring of dams given extremely high doses of vitamin D. The author noted that this caused concern about a possible association between vitamin D and Williams syndrome in humans, which is now known to be caused by a mutation in the elastin gene. A few more recent studies have found histological changes in the aorta and coronary arteries of rat pups and piglets.

2.1.7 Funded colecalciferol products

There are two funded colecalciferol products: Vit.D3 (colecalciferol 50,000 IU capsule) and Clinician's Vitamin D (colecalciferol 7,500 IU/mL). Vit.D3 capsules are the only approved and available colecalciferol monotherapy medicine.

Vit.D3 (colecalciferol 50,000 IU) capsules are indicated for the treatment of vitamin D deficiency in adults and the prevention of vitamin D deficiency in high-risk adults. The dose for treatment of deficiency (<25 nmol/L) is 50,000 IU daily for 10 days, then 50,000 IU monthly. The dose for treatment of insufficiency (≥25 nmol/L) is 50,000 IU monthly. The dose for prevention of deficiency in high-risk adults is 50,000 IU every two to three months. [26]

Clinician's Vitamin D liquid is a dietary supplement rather than an approved medicine and therefore does not make therapeutic claims.

2.1.8 Usage of colecalciferol products

In 2024, 427,344 people received 1.29 million dispensings of colecalciferol 50,000 IU capsules, and approximately 38,528 people received 54,946 dispensings of colecalciferol 7,500 IU/mL oral liquid. [27]

[redacted]

2.2 Data sheets

New Zealand data sheets and international product information are summarised in table 2. For countries with differences in information between products, multiple examples are given. Australia has product information for a colecalciferol 7,000 IU weekly capsule formulation only and this is included in the table.

Most of the reviewed product information for colecalciferol 50,000 IU contains information recommending against use in pregnancy with instruction to use a lower strength formulation. Contraindications to use in pregnancy were identified for some products in the UK and Ireland and the others state that use in pregnancy is not recommended.

In addition to the information listed below, the New Zealand data sheet states that 25(OH)D concentration, calcium, phosphate, parathyroid hormone, and alkaline phosphatase (ALP) monitoring should be considered for populations at high risk of vitamin D deficiency. It also states that there is an increased risk of hypercalcaemia if Vitamin D3 is given with calcium and phosphate, and that calcium concentrations should be monitored in those situations.

Table 2: Summary of pregnancy information in New Zealand and international product information

4.1 Indications	4.2 Dosage	4.3 Contraindications	4.6 Pregnancy	5.3 Preclinical data
New Zealand - Vit.D3 (50,000 IU capsule) [26]				
Treatment of vitamin D deficiency in adults. Prevention of vitamin D deficiency in high-risk adults.	-	Pregnancy	Vit.D3 50,000 IU capsules should not be given to pregnant women and a lower strength formulation should be used. There are no or limited data available on the use of colecalciferol in pregnant women. Overdose of vitamin D has been associated with foetal abnormalities in animals. The recommended daily intake for pregnant women is generally 400 IU.	-
Australia - Ostevit-D One-A-Week (7,000 IU capsule) [28]				
Treatment of vitamin D deficiency in adults and adolescents. Prevention of vitamin D deficiency in high-risk individuals.	-	-	Vitamin D3 is a therapeutic good which is exempted from pregnancy classification by TGA. There is no available data on the teratogenic effects of colecalciferol. However, hypercalcaemia during pregnancy may lead to congenital disorders in the offspring and neonatal hypoparathyroidism. Despite these risks, untreated maternal hypoparathyroidism possesses a greater risk to the fetus than the potential hypercalcaemia from vitamin D therapy. The use of vitamin D3 supplements during pregnancy is well tolerated, with little risk of adverse outcomes during pregnancy for the mother and neonate. Limited evidence shows that maternal vitamin D supplementation is associated with reduced risk of pre-eclampsia and gestational diabetes mellitus for the mother. There were also improved health outcomes for the neonate including reduced risk of pre-term birth and small for gestational age and, increased length and head circumference.	-

4.1 Indications	4.2 Dosage	4.3 Contraindications	4.6 Pregnancy	5.3 Preclinical data
UK - Colecalciferol 50,000 IU (Crescent Pharma) [29]				
Treatment of Vitamin D deficiency. Target populations: Adults	Pregnancy and breastfeeding: Due to lack of clinical data, Colecalciferol Capsule is not recommended.	-	In pregnancy and lactation the high strength formulation is not recommended and a low strength formulation should be used. There are no or limited amount of data from the use of colecalciferol in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data). The recommended daily intake for pregnant women is 400 IU, however, in women who are considered to be Vitamin D3 deficient a higher dose may be required (up to 2000 IU/day- 10 drops with the oral drops presentation). During pregnancy women should follow the advice of their medical practitioner as their requirements may vary depending on the severity of their disease and their response to treatment.	Colecalciferol has been shown to be teratogenic at high doses in animals. At doses equivalent to those used therapeutically, colecalciferol has no teratogenic activity.
UK - Ditralia 50,000 IU orodispersible films [30]				
Initial treatment of vitamin D deficiency (serum levels < 25 nmol/l or < 10 ng/ml) in adults. Prevention of vitamin D deficiency in adults with an identified risk. As an adjunct to specific therapy for osteoporosis in adult patients with vitamin D deficiency or at a risk of vitamin D deficiency.	-	-	During pregnancy and breast-feeding this high dosed product is not recommended and a lower dosed product should be used. During pregnancy and breast-feeding adequate vitamin D intake is necessary. There are no or limited amount of data from the use of colecalciferol in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). Vitamin D deficiency is harmful for mother and child. However, overdose of vitamin D must be avoided during pregnancy, as prolonged hypercalcaemia may lead to physical and mental retardation, supravalvular aortic stenosis and retinopathy of the child. Where there is a vitamin D deficiency the recommended dose is dependent on national guidelines, however, the maximum recommended dose during pregnancy is 4 000 IU/day vitamin D3. <Product name> is not recommended during pregnancy.	At doses far higher than the human therapeutic range teratogenicity has been observed in animal studies.

4.1 Indications	4.2 Dosage	4.3 Contraindications	4.6 Pregnancy	5.3 Preclinical data
UK – DELTIUS 50,000 IU capsule [31]				
Initial treatment of clinically relevant vitamin D deficiency in adults.	Pregnancy and breastfeeding: DELTIUS 50.000 IU capsules is not recommended.	-	DELTIUS 50.000 IU capsules are not recommended in pregnancy and lactation. A low strength formulation should be used. There are no or limited amount of data from the use of colecalciferol (vitamin D3) in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data). Long-term overdose must be avoided during pregnancy, since the resulting protracted hypercalcaemia may lead to physical and mental retardation, supravalvular aortic stenosis and retinopathy in the child. The recommended daily intake for pregnant women is 400 IU, however, in women who are considered to be vitamin D3 deficient a higher dose may be required (up to 2000 IU/day – 10 drops with the oral drops presentation). During pregnancy women should follow the advice of their medical practitioner as their requirements may vary depending on the severity of their disease and their response to treatment. Treatment of pregnant women with high-dose vitamin D is not recommended.	Colecalciferol is teratogenic at high doses in animals. At doses equivalent to those used therapeutically, colecalciferol has no teratogenic activity. Microcephaly, cardiac malformations and skeletal abnormalities were observed in the offspring. Offspring from pregnant rabbits treated with high doses of vitamin D had lesions anatomically similar to supravalvular aortic stenosis and offspring not showing such changes show vasculotoxicity similar to that of adults following acute vitamin D toxicity. Colecalciferol is also fetotoxic in mice with fewer and smaller offspring from pregnant mice receiving medium and high dose Vitamin D.
UK – Choli-D3 and InVita (50,000 IU capsule) [32, 33]				
Treatment of vitamin D3 deficiency.	Pregnancy and breastfeeding: Due to lack of clinical data, Choli-D3 50,000 IU Capsules is not recommended.	Pregnancy	Similar to above.	Colecalciferol has been shown to be teratogenic at high doses in animals. At doses equivalent to those used therapeutically, colecalciferol has no teratogenic activity.

4.1 Indications	4.2 Dosage	4.3 Contraindications	4.6 Pregnancy	5.3 Preclinical data
Ireland - altavitaD3 50,000 IU soft capsules [34]				
Treatment of vitamin D3 deficiency.	Pregnancy and breastfeeding: Due to lack of clinical data, altavitaD3 is not recommended.	Pregnancy	In pregnancy the high strength formulation not recommended and a low strength formulation should be used. There are no or limited amount of data from the use of colecalciferol in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data). The recommended daily intake for pregnant women is 400 IU, however, in women who are considered to be Vitamin D3 deficient a higher dose may be required (up to 2000 IU/day- 10 drops with the oral drops presentation). During pregnancy women should follow the advice of their medical practitioner as their requirements may vary depending on the severity of their disease and their response to treatment.	Colecalciferol has been shown to be teratogenic at high doses in animals. At doses equivalent to those used therapeutically, colecalciferol has no teratogenic activity.
Canada – Euro-D (5,000, 10,000 and 50,000 IU capsule) [35]				
The treatment of refractory rickets (vitamin D resistant rickets) The treatment of hypoparathyroidism	-	-	Safety of doses in excess of 400 IU (10 µg) of Vitamin D3 daily during pregnancy has not been established. Maternal hypercalcemia, possibly caused by excessive Vitamin D intake during pregnancy, has been associated with hypercalcemia in neonates, which may lead to supravalvular aortic stenosis syndrome, the features of which may include retinopathy, mental or growth retardation, strabismus and other effects. Hypercalcemia during pregnancy may also lead to suppression of parathyroid hormone release in the neonate, resulting in hypocalcaemia, tetany and seizures.	-

4.1 Indications	4.2 Dosage	4.3 Contraindications	4.6 Pregnancy	5.3 Preclinical data
Canada - JAMP-Vitamin D (2,000, 5,000, 10,000, 25,000 and 50,000 IU capsule) [36]				
Treatment and prevention of vitamin D deficiency Management and prevention of primary and corticosteroid-induced osteoporosis, in conjunction with calcium Treatment of refractory rickets (vitamin D resistant rickets) Treatment of familial hypophosphatemia Treatment of hypoparathyroidism	-	-	The recommended daily dose of Vitamin D in pregnant women in Canada is 600 IU (15 mcg) daily. Studies have shown safe use of Vitamin D at doses up to 4000 IU (100 mcg) daily during pregnancy although studies in animals have shown reproductive toxicity. Avoid the use of vitamin D in excess of the recommended dietary allowance during pregnancy unless potential benefits outweigh the possible adverse effects. Hypercalcemia during pregnancy may also lead to suppression of parathyroid hormone release in the neonate, resulting in hypocalcaemia, tetany and seizures. Severe deficiency of vitamin D during pregnancy can result in maternal osteomalacia and lead to significant morbidity in both mother and fetus.	-
United States - Decalcitrol (50,000 IU tablet) [37] (Classified as high potency supplement.)				
Colecalciferol Tablets are essential for absorption of calcium and necessary for healthy and strong bones. Hypoparathyroidism Refractory rickets, Familial hypophosphatemia	-	-	Category C. For protection of fetus, use of vitamin D above RDA should be avoided during normal pregnancy unless in the judgment of the physician, potential benefits in a specific, unique case outweigh the significant hazards involved. Safety of >400 IU daily has not been established.	-

3 SCIENTIFIC INFORMATION

3.1 Position statements and guidance

Local and international position statements and guidance relevant to vitamin D supplementation in pregnancy are summarised below.

3.1.1 Committee on Toxicity (United Kingdom): Statement on the potential effects of excess vitamin D intake during preconception, pregnancy and lactation (2022) [15]

As part of a review by the Scientific Advisory Committee on nutrition (SACN), the Committee on Toxicity was asked to consider whether exposure to excess vitamin D would pose a risk to maternal health. Key points from the statement are summarised below.

Vitamin D status in pregnancy

- There is a lack of data on what constitutes a healthy vitamin D status in pregnant women. There is no agreement on whether 25(OH)D requirements are higher during pregnancy. The Scientific Advisory Committee on Nutrition (SACN) did not recommend a separate reference nutrient intake (RNI) for pregnant women, as the RNI of 10 mcg/day (400 IU/day) is inclusive of pregnant and lactating women.
- Conversion of vitamin D to 25(OH)D does not appear to be altered in pregnancy. However, conversion of 25(OH)D to $1,25(OH)_2D$ is increased, with levels rising two to three-fold from a non-pregnant adult.
- 25(OH)D is transported via the placenta to the fetus and also converted there to $1,25(OH)_2D$ or 24,25-dihydroxyvitamin D ($24,25(OH)_2D$).

Excess vitamin D – human health studies and case reports

- Hypervitaminosis D can lead to hypercalcaemia (a total calcium concentration greater than 2.75 mmol/L), causing deposition of calcium in soft tissues, demineralisation of bones and irreversible renal and cardiovascular toxicity. Hypercalcaemia has been reported at plasma 25(OH)D concentrations above 375-500 nmol/L.
- Hypercalcaemia can also lead to hypercalciuria (when urinary excretion of calcium exceeds 250 mg/day in women and 275-300 mg/day in men).
- High oral doses of vitamin D supplements have been shown to have toxic effects, such as hypercalcaemia, dehydration and tissue calcification.
- After a 1951 survey for the UK Ministry of Health showed that some children were receiving up to 35,000 IU per day (875 mcg/day) due to supplementation and fortification of foods, vitamin D levels in cod-liver compounds and dried milk were halved in 1957. Following this there was a marked decrease in the number of infantile hypercalcaemia cases in the early 1960s.
- Vomiting, nausea, constipation, and diarrhoea were reported as signs and symptoms of vitamin D overdosing in Danish infants who consumed a liquid vitamin D supplement that contained 150 mcg (6,000 IU) of vitamin D3 per drop. Infants that consumed this supplement received 750 mcg/day (30,000 IU). The Danish Health Authorities identified 18/150 children (under the age of 2) who had consumed this vitamin D supplement, and had severe hypercalcemia with ionized calcium levels of >1.49 mmol/L. 25(OH)D levels were >150 nmol/L in 87/150 children.
- Stoss (From the German *stossen* meaning 'to push') therapy is a single high oral or intramuscular dose of vitamin D administered at 2,500 -15,000 mcg (100,000 – 600,000 IU) to treat vitamin D deficiency.
- In a retrospective study of case reports over a 5-year period, 38 patients aged 0.3-4 years presented with vitamin D intoxication (vomiting, loss of appetite and constipation) and hypercalcemia (mean calcium

levels were 3.75 ± 0.5 mmol/L) after consumption of either a prescribed vitamin D3 vial for stoss therapy, non-prescribed vitamin D3 vials or incorrectly produced fish oil.

  - 9 patients using the vials without prescription were exposed to 15,000-45,000 mcg (600,000-2,400,00 IU).
  - 23 patients prescribed vials for stoss therapy were exposed to between 15,000-60,000 mcg (600,000-I,800,000 IU).
  - Patients who had consumed improperly produced fish oil supplements were exposed to 25,000-50,000 mcg (1,000,000 – 2,000,000 IU) – duration of consumption unclear.
  - The researchers determined that the minimum dose causing vitamin D intoxication was 15,000 mcg (600,000 IU) and at the time of admission serum 25(OH)D levels were 990 ± 275 nmol/L (396 ± 110 ng/mL).

- In other studies of stoss therapy using lower doses of vitamin D, there were no reports of vitamin D-related adverse effects such as hypercalcemia or hyperphosphatemia.
- SACN (2016) reported that a number of cases of intoxication occurring as a result of high medicinal doses or excessive or mis-formulated supplement use were associated with serum 25(OH)D levels of as low as 300 nmol/L, but often exceeding 1000 nmol/L. The doses in these cases ranged from 750-1,500,000 mcg (30,000-60,000,000 IU) and the duration of consumption ranged from 4 days to 10 years.
- However, some have cited evidence in humans based on anecdotal case reports of acute accidental vitamin D intoxication resulting in plasma 25(OH)D concentrations of 710-1587 nmol/L, that the threshold for toxic effects is around 750 nmol/L 25(OH)D.
- A threshold for toxicity was not proposed by SACN or COT as the case reports provided only limited information for risk assessment purposes as the doses consumed, where known, varied in amount and duration.
- Vitamin D toxicity is not thought to occur following UV exposure.

Pregnancy

- Data on the effects of high levels of vitamin D intakes during pregnancy or lactation are limited.
- No adverse effects were observed in 2 studies (Wagner et al., 2006; Hollis et al., 2011) which supplemented pregnant women with vitamin D doses ≥ 100 mcg/day (4000 IU).
- Noted that serum calcium has not always been measured in studies and where it was done, hypercalcaemia was not observed.
- There is potential for hypercalcemia to occur during pregnancy in individuals with mutations of genes involved in vitamin D metabolism (eg, loss of function CYP24A1 mutations).
- Excessive vitamin D intake during pregnancy can also result in risk of fetal hypercalcemia (Larquè et al., 2018), and hypercalcemia during pregnancy may be associated with increased risk of fetal and neonatal morbidity (Sato, 2008); the assertion in Sato, 2008 appears to be based on case reports, but limited details are provided.
- Neonatal hypercalcemia has been evident in neonates born to mothers with an excess maternal vitamin D intake.
- In a case reported by Reynolds et al. (2017), a female baby was diagnosed with hypercalcemia with a 25(OH)D level of 73 nmol/L, which was at the upper end of the reference range (50-75 nmol/L). The baby had a total serum calcium level of 3.09 mmol/L, which was outside the reference range of 1.9-2.6 mmol/L. The mother took two supplements with a total dose of 4,000 IU daily and had elevated 25(OH)D of 127 nmol/L, which was slightly outside the reference range (> 125 nmol/L) and total serum calcium of 2.38 mmol/L which was within the reference range of 2.1-2.66 nmol/L.

Risk characterisation

- Most supplements aimed at non-pregnant adults do not exceed the TUL of 100 mcg/day (4,000 IU).
- Consumption of high dose supplements (>100 mcg/day) may may increase the risk of hypercalcemia and hypercalciuria in women attempting conception, pregnant and lactating women.
- Doses of 7500 mcg (300,000 IU) at intervals of 3 months or longer would not be expected to cause adverse effects in adults (not specific to pregnant women). There is greater uncertainty about the effects of larger doses.

Conclusion

- Consumption of higher strength vitamin D supplements, either alone or in combination with dietary intake, may result in exposure levels that exceed the TUL and would therefore be of potential health concern.
- Consumption of lower strength supplements aimed at pregnant and breast-feeding women, either alone or in combination with dietary intake, is very unlikely to result in excessive exposure to vitamin D.

3.1.2 Specialist Pharmacy Service (United Kingdom): Vitamin D deficiency – treatment during pregnancy (2025) [5]

This guidance notes that management of vitamin D deficiency in pregnancy is based on specialist consensus opinion rather than specific guidance and recommends following local guidance.

Treatment options

Use oral vitamin D (either as colecalciferol or ergocalciferol) to treat vitamin D deficiency during pregnancy. Some products are licensed for use in pregnancy. Seek specialist advice in complex cases such as a history of rickets in a previous pregnancy. Do not prescribe vitamin D injections in pregnancy.

Dose

Consider a daily dose between 1,000 units to 2,000 units to manage vitamin D deficiency during pregnancy. When selecting a dose within this range, consider factors such as:

- the extent of deficiency
- whether there are symptoms of deficiency
- advice of the specialist
- the amount of vitamin D in supplements being taken.

It may be appropriate to consider a daily dose of up to 4,000 units in some cases of severe vitamin D deficiency that is symptomatic.

Duration

There is no guidance on duration. A cumulative dose of 300,000 units is sufficient to correct vitamin D deficiency in adults. Using the dosing range above, it could take several months to correct deficiency. For example, in a patient taking 2,000 units daily, it may take five months to correct the deficiency. After correction, provide advice on preventing recurrence of vitamin D deficiency.

Preventing recurrence

All pregnant women should take a 10 micrograms (400 units) vitamin D supplement daily from October to March. Women with dark skin or those who cover their skin may need supplements year-round. Most pregnancy supplements contain 400 units of vitamin D.

Monitoring

Use of vitamin D at any stage in pregnancy is not regarded as grounds for additional fetal monitoring.

There is no specific guidance for monitoring vitamin D levels during pregnancy. The monitoring requirements would be the same as for non-pregnant patients.

Routine monitoring of vitamin D levels is generally unnecessary but may be appropriate in patients with symptomatic deficiency, malabsorption or where poor compliance is suspected. Vitamin D levels can be checked around 3 to 6 months after starting treatment when steady state levels are likely to have been attained.

Check adjusted plasma calcium levels 1 month after starting vitamin D in case primary hyperparathyroidism has been unmasked.

Neonatal calcium and vitamin D levels may be checked at delivery if there are concerns about these.

3.1.1 Health New Zealand: Companion statement on vitamin d and sun exposure in pregnancy and infancy in New Zealand (2024) [1]

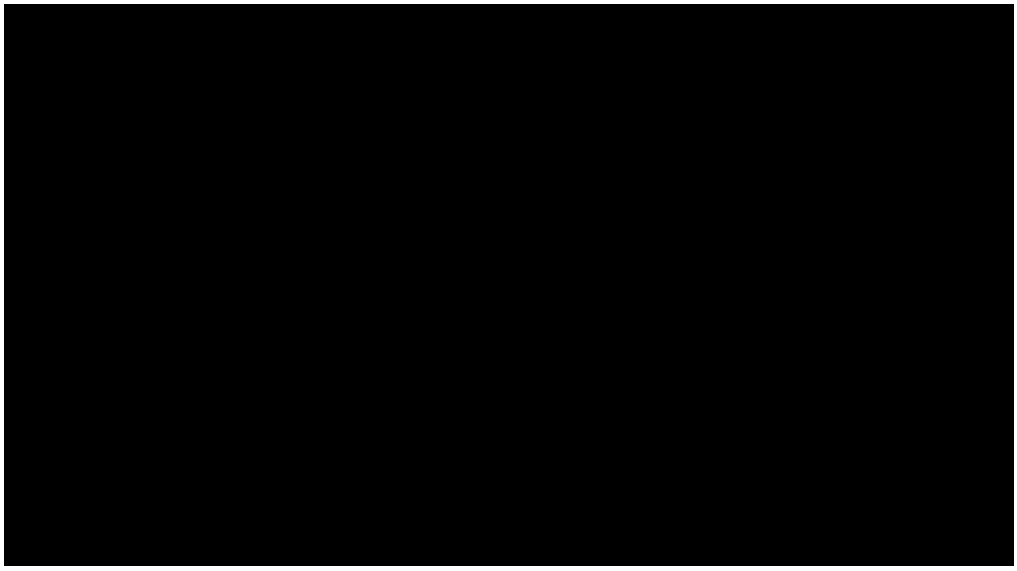
This statement provides information about vitamin D and sun exposure in pregnancy and infancy. Key information from the statement is summarised below.

Recommended vitamin D intake

Vitamin D supplementation is not universally recommended in the general adult population, but the National Health and Medical Research Council (2006) recommends a supplement of 400 International Units per day (10 micrograms per day) in pregnancy or when breastfeeding if there is little exposure to daily sunlight.

Table 3 shows the recommended intakes across different countries and organisations.

Table 3: Recommended dietary intakes of vitamin D



Source: Health New Zealand. 2024. Companion statement on vitamin d and sun exposure in pregnancy and infancy in New Zealand 7 June 2024. URL: https://www.tewhatuora.govt.nz/publications/companion-statement-on-vitamin-d-and-sun-exposure-in-pregnancy-and-infancy-in-new-zealand (accessed 24 September 2025).

Vitamin D status during pregnancy and infancy in New Zealand

Risks for vitamin D deficiency include sun avoidance, living south of Nelson/Marlborough, winter and spring season, and darker skin tone. Adults are more likely to be vitamin D insufficient in late winter and early spring (August to October). In NZ, seasonal differences in UV are larger in the south than in the north.

A 2015 Aotearoa New Zealand prospective surveillance study (Wheeler et al, 2015 [38]) investigated incidence and characteristics of vitamin D deficiency in Aotearoa New Zealand among 58 children with confirmed

vitamin D deficiency rickets. The median age was 1.4 years old from an observed range of 0.3 to 11 years. Key risk factors for developing vitamin D deficiency rickets were darker skin pigment, Indian and African ethnicity, age less than 3 years, exclusive breastfeeding and southern latitude, particularly when combined with season (winter/spring).

An NZ study (Ekeroma et al, 2015 [7]) involving 259 ethnically diverse pregnant women (grouped into European, Māori, Pacific, and other ethnic groups) reported that vitamin D insufficiency (serum 25(OH)D < 50 nm/L) was present in 42 percent of study participants. Vitamin D deficiency (serum 25(OH)D < 25 nm/L) was present in 11 percent of study participants.

Enrolment season ($p<0.001$) and ethnicity (Māori, Pacific, and other ethnic groups all at increased risk compared with those of European ethnicity) ($p=0.003$) were independently associated with the likelihood of vitamin D insufficiency, but sunlight exposure or dietary vitamin D intake were not associated with deficiency. Of those enrolled in winter and spring, vitamin D deficiency was present in 80 percent of Pacific women, 67 percent of wāhine Māori, 59 percent of women of other ethnic groups, and 43 percent of European women.

Testing for vitamin D insufficiency/deficiency

Testing asymptomatic pregnant people and infants for vitamin D insufficiency is not recommended.

Vitamin D testing may be appropriate if symptoms of unexplained bone pain, atypical osteoporosis, or seizures where hypocalcaemia is implicated are present. This includes testing during pregnancy when there is evidence of:

- unexplained raised serum alkaline phosphatase, or low calcium or phosphate
- atypical osteoporosis
- unexplained bone pain, unusual fractures, or other evidence suggesting metabolic bone disease (consider specialist advice).

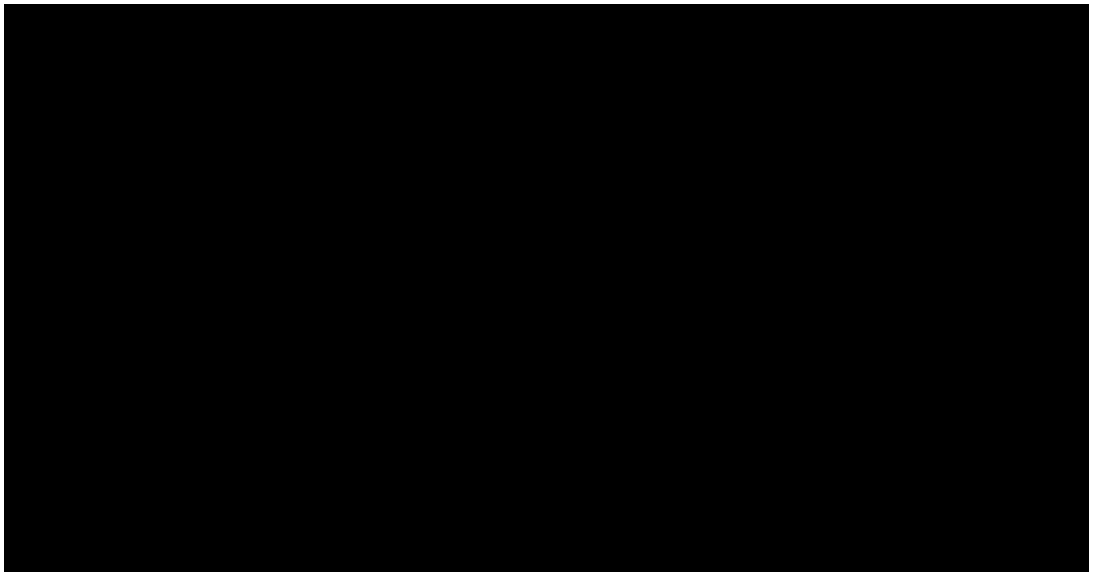
Vitamin D deficiency may be associated with adverse maternal and infant health outcomes

There is convincing evidence that vitamin D deficiency (25(OH)D <25 or <30 nmol/L) is associated with vitamin D deficiency rickets. The risk of rickets increases below a serum 25(OH)D level of 30 nmol/L and is minimal when serum 25(OH)D levels are between 30 and 50 nmol/L (when calcium intakes are also adequate).

Vitamin D dietary reference values for bone health are shown in table 4 below.

There is currently insufficient evidence that vitamin D status is a causative factor for gestational diabetes mellitus (GDM) or pre-eclampsia. However, evidence is increasing. Observational evidence suggests maternal vitamin D deficiency in pregnancy is associated with an increased risk of low birth weight. There is insufficient evidence that vitamin D insufficiency/deficiency is associated with dental caries or acute respiratory illness.

Table 4: Vitamin D dietary reference intakes (IOM, 2011)



Source: Health New Zealand. 2024. Companion statement on vitamin d and sun exposure in pregnancy and infancy in New Zealand 7 June 2024. URL: https://www.tewhatuora.govt.nz/publications/companion-statement-on-vitamin-d-and-sun-exposure-in-pregnancy-and-infancy-in-new-zealand (accessed 24 September 2025).

Supplementation during pregnancy

The main aim of vitamin D supplementation in pregnancy is to ensure that the fetus has sufficient vitamin D and that the infant is not born vitamin D deficient. Sufficient vitamin D *in utero* may allow for bone health and prevention of rickets in infants. Vitamin D supplementation during pregnancy is likely to increase maternal and infant vitamin D status.

People at lower risk of vitamin D deficiency during pregnancy may benefit (and are unlikely to suffer harm) from vitamin D supplementation of between 400 IU per day (10 mcg/day) and 800 IU per day (20 mcg/day) throughout pregnancy, particularly in the third trimester.

Vitamin D supplementation should be offered to people at risk of vitamin D deficiency:

- naturally darker skin pigmentation and/or are of South Asian, African or Middle Eastern heritage.
- live south of Nelson/Marlborough during winter or spring.
- are sun avoidant and/or spend limited time outdoors for religious, personal or medical reasons.

Prescribe 400 to 800 IU (1 to 2 drops) colecalciferol oral liquid (7,500 IU/mL) vitamin D drops per day for prevention.

Individuals with all three risk factors in pregnancy may be at higher risk of vitamin D deficiency and blood testing may be considered. Where vitamin D insufficiency or deficiency is confirmed through testing, follow the advice from New Zealand Formulary.

3.1.2 American College of Obstetricians and Gynaecologists committee opinion: Vitamin D – screening and supplementation during pregnancy (2011) [39]

- Recent evidence suggests that vitamin D deficiency is common during pregnancy especially among high-risk groups, including vegetarians, women with limited sun exposure (eg, those who live in cold climates, reside in northern latitudes, or wear sun and winter protective clothing) and ethnic minorities, especially those with darker skin.
- Newborn vitamin D levels are largely dependent on maternal vitamin D status. Consequently, infants of mothers with or at high risk of vitamin D deficiency are also at risk of vitamin D deficiency.

- For the individual pregnant woman thought to be at increased risk of vitamin D deficiency, the serum concentration of 25(OH)D can be used as an indicator of nutritional vitamin D status. Although there is no consensus on an optimal level to maintain overall health, most agree that a serum level of at least 20 ng/mL (50 nmol/L) is needed to avoid bone problems.
- Based on observations of biomarkers of vitamin D activity, such as parathyroid hormone, calcium absorption, and bone mineral density, some experts have suggested that vitamin D deficiency should be defined as circulating 25(OH)D levels less than 32 ng/mL (80 nmol/L). An optimal serum level during pregnancy has not been determined and remains an area of active research.
- In 2010, the Food and Nutrition Board at the Institute of Medicine of the National Academies established that an adequate intake of vitamin D during pregnancy and lactation was 600 international units per day. Most prenatal vitamins typically contain 400 international units of vitamin D per tablet.
- Summarising recent observational and interventional studies, the authors of a recent clinical report from the Committee on Nutrition of the American Academy of Paediatrics suggested that a daily intake higher than that recommended by the Food and Nutrition Board may be needed to maintain maternal vitamin D sufficiency.
- Although data on the safety of higher doses are lacking, most experts agree that supplemental vitamin D is safe in dosages up to 4,000 international units per day during pregnancy or lactation.
- At this time there is insufficient evidence to support a recommendation for screening all pregnant women for vitamin D deficiency. For pregnant women thought to be at increased risk of vitamin D deficiency, measuring maternal serum 25(OH)D levels can be considered and should be interpreted in the context of the individual clinical circumstance.
- When vitamin D deficiency is identified during pregnancy, most experts agree that 1,000–2,000 international units per day of vitamin D is safe. Higher dose regimens used for the treatment of vitamin D deficiency have not been studied during pregnancy.
- Recommendations concerning routine vitamin D supplementation during pregnancy beyond that contained in a prenatal vitamin should await the completion of ongoing randomized clinical trials. At this time, there is insufficient evidence to recommend vitamin D supplementation for the prevention of preterm birth or preeclampsia.

3.1.3 WHO antenatal care recommendations for a positive pregnancy experience. Nutritional interventions update: Vitamin D supplements during pregnancy (2020) [40]

In the context of routine antenatal care, oral vitamin D supplementation is not recommended for all pregnant women to improve maternal and perinatal outcomes.

Pregnant women should be encouraged to receive adequate nutrition – which is best achieved through consumption of a healthy, balanced diet – and to refer to guidelines on healthy eating. Pregnant women should be advised that sunlight is the most important source of vitamin D. The amount of time needed in the sun is not known and depends on many variables, such as the amount of skin exposed, the time of day, latitude and season, skin pigmentation (darker skin pigments synthesize less vitamin D than lighter pigments) and sunscreen use.

For pregnant women with suspected vitamin D deficiency, vitamin D supplements may be given at the current recommended nutrient intake of 200 IU (5 µg) per day. This may include women in populations where direct sun exposure is limited.

3.2 Cochrane review of vitamin D supplementation for women during pregnancy

A 2024 Cochrane review has examined whether vitamin D supplementation given to women during pregnancy can safely improve certain maternal and neonatal outcomes. The review found uncertain evidence on the outcomes of pre-eclampsia, gestational diabetes, preterm birth, nephritic syndrome, severe postpartum haemorrhage and low birth weight. [41]

There were ten randomised trials included in the review, which evaluated the effect of supplementation with vitamin D alone (8 trials) or in combination with calcium (one trial) or with calcium and other micronutrients (one trial) for women during pregnancy in comparison to placebo or no intervention (Table 5).

The review excluded 117 studies, mainly because all pregnant women received vitamin D either as different regimens, or as standard care, without placebo or no treatment control. There were also 34 studies awaiting assessment. Some studies were excluded or awaiting assessment due to unresolved trustworthiness red flags and are not discussed in this report.

The 10 studies included in the review were conducted in Australia (1), Bangladesh (2), Brazil (1), India (1), Iran (1), NZ (1), Pakistan (1) and the UK (2) across various seasons. The sample size ranged from 78 to 1,560 participants. The review noted that pre-gestational BMI, an important determinant of vitamin D status, was only reported in two studies. No studies used the Fitzpatrick skin tone, but several studies reported the ethnicity of participants. Four studies started supplementation before week 20 of gestation and six studies started supplementation at 20 weeks of gestation or later.

The doses of vitamin D varied widely across the studies, and included daily weekly, monthly and single bolus doses. Daily doses ranged from 200 IU daily to 4,000 IU daily, weekly doses ranged from 4,200 IU to 35,000 IU, monthly doses ranged from 60,000 IU to 120,000 IU and there was a study that used a single bolus dose of 200,000 IU (ergocalciferol). The cumulative vitamin D dose during pregnancy was <56,000 IU in 5 studies, 56,000 to 200,000 IU in four studies and >200,000 IU in four studies.

There were four trials investigating higher/intermittent doses, ranging from 4,200 IU weekly to 200,000 IU as a single bolus (Roth 2013, Roth 2018, Sablok 2015 and Yu 2009). [42-45]

The studies are summarised in the table below. A small number of elevated serum calcium measurements were seen that were mostly normal on repeat testing and had no associated adverse events. Roth 2018 found increasing rates of elevated urinary ca:cr measurements with increasing dose, without associated adverse events. There were no adverse safety findings in the studies, however the studies were not powered to detect differences in infrequent adverse maternal or infant outcomes. Sablok 2015 did not monitor for hypercalcaemia during the course of treatment and did not report calcium levels at delivery.

Table 5: Summary of randomised trials included in the 2024 Cochrane review

Publication	Methods	Results
Rodda 2015 [46] ACTRN12609000142235 Australia	Participants: 78 pregnant women, 14-18 weeks gestation at risk (dark skinned or veiled with untreated vitamin D deficiency). Interventions: 2,000 IU colecalciferol daily (increased to 4,000 at 28 weeks gestation if still deficient) OR no treatment. Following delivery, women and their infants in the no treatment arm were offered a bolus dose of a vitamin D to make sure everyone was treated. Outcomes: Maternal vitamin D level, infant vitamin D level.	Cord serum 25(OH)D level at delivery was significantly higher in neonates of treatment group compared with neonates of control group. Treatment group: 18/22 neonates analysed were vitamin D sufficient. Controls: 5/23 neonates analysed were vitamin D sufficient. No documented adverse effects. No further safety information reported.
Khan 2016, Khan 2017 [47, 48] NCT01422122 Pakistan	Participants: 86 pregnant women, 12-16 weeks gestation. Intervention: 4,000 IU colecalciferol daily OR placebo. Outcomes: Maternal periodontal probing depth, salivary cytokine levels.	No difference in birth weight, periodontal health measures or salivary cytokines. No safety/infant outcomes reported.
Diogenes 2013 [49] NCT01732328 Brazil	Participants: 84 pregnant adolescents, 23-29 weeks gestation Intervention: 200 IU colecalciferol + 600 mg calcium daily OR placebo. Outcomes: Maternal postpartum serum 25(OH)D, PTH, IGF-I, lumbar spine PA, bone mineral content, serum prolactin, and oestradiol.	Vitamin D supplementation during pregnancy of adolescents with low calcium intake resulted in higher lumbar spine bone mass and a reduced rate of femoral neck bone loss during lactation. No adverse effects reported. No further safety/infant information reported.
Grant 2014 (New Zealand) [50] ACTRN12610000483055 New Zealand	Participants: 260 pregnant women, 26-30 weeks gestation. Intervention: 1,000 IU colecalciferol daily OR 2,000 IU colecalciferol daily OR placebo. Outcomes: Maternal and infant serum 25(OH)D concentration. Infants were supplemented from birth.	Vitamin D supplementation during pregnancy and infancy increased the proportion of infants with 25(OH)D ≥20 ng/mL. No hypercalcaemia occurred. No other safety outcomes reported.

Publication	Methods	Results
Cooper 2016 [51] ISRCTN82927713 United Kingdom	Participants: 1,200 pregnant women, less than 17 weeks gestation with 25(OH)D level at nuchal fold/dating scan (10-17 weeks gestation). Intervention: 1,000 IU colecalciferol daily OR placebo (from 14 weeks gestation). Outcome: Infant bone mineral/density outcomes.	Vitamin D supplementation did not increase offspring whole-body BMC but most pregnant women were vitamin-D replete. Rates of individual adverse events were similar between groups. No events deemed treatment related. Fewer cases of severe PPH in treatment group (65 [11.5%] vs 96 [16.9%]; p=0.01). Congenital abnormalities: 5 (0.9%) placebo vs 8 (1.4%); p=0.4. Intrauterine death: 3 (0.5%) placebo vs 1 (0.2%); p=0.32. A post hoc analysis found that maternal gestational colecalciferol supplementation was associated with a smaller gestational increase in bone resorption markers compared to placebo. Late-pregnancy CTX was inversely associated with postpartum measures of maternal bone from DXA. The authors considered the findings consistent with a protective effect of gestational vitamin D supplementation on maternal bone health. [52]
Roth 2013 [42] NCT01126528 Bangladesh	Participants: 160 pregnant women Inclusion: 18-35 years, 26 to <30 weeks gestation, residing in Dhaka with plans to deliver at study centre. Exclusion: use of vitamin D supplements, anticonvulsants, antimycobacterial medicine, severe anaemia, hypertension, proteinuria, glycosuria, complicated medical or obstetric history, previous birth with MCA, birth asphyxia or perinatal death. Intervention: **Colecalciferol 35,000 IU per week** OR placebo. Outcomes: Maternal serum 25(OH)D, serum calcium, urine Ca:Cr ratio. Infant immune function, infant growth, postnatal vitamin D status, albumin adjusted serum calcium. Weekly symptom checklist for pregnancy complications and hypo-/hypercalcaemia. Random spot urine samples at baseline, 2 weeks post-enrolment and delivery. Blood samples taken at baseline and once between gestational weeks 30 and 37 (immediately before vitamin D dose) and at delivery.	13 participants lost to follow up. Maternal and cord blood serum specimens at delivery were available for 80% of participants. Median 11 doses taken. Most participants in both groups were vitamin D insufficient by the IOM threshold (25(OH)D <50 nmol/L) at baseline. 100% of mothers and 95% of neonates attained 25(OH)D >50 nmol/L at delivery, compared to 21% and 19% of mothers and neonates in the placebo group. The highest 25(OH)D value was 200 nmol/L (vitamin D group at delivery) with concurrent normal adj-Ca and urine ca:cr. In the placebo group, mean 25(OH)D was 44.0 ± 20.9 nmol/L at baseline and 38.4 ± 18.1 at delivery. In the treatment group, mean 25(OH)D was 45.4 ± 18.4 nmol/L at baseline and 134.4 ± 30.7 nmol/L at delivery. There was substantial interindividual variation in maternal 25(OH)D and cord-to-maternal ratio. Mean maternal adj-Ca concentration rose over time within the reference range, and the increase was slightly greater in the vitamin D group. No cases of confirmed hypercalcaemia. One participant had an isolated adj-Ca value of 2.62 nmol/L in the context of acute diarrhoeal illness (25(OH)D ranged from 22 to 118 nmol/L). Normal on repeat measurements. One case of hypercalciuria with no hypercalcaemia or nephrocalcinosis. There were 3 cases of transient hypercalciuria in the placebo group and 4 in the vitamin D group. There was one stillbirth in each group, and 3 neonatal deaths in the placebo group and 1 in the vitamin D group. Rates of neonatal serious adverse events were similar between the groups. *Evaluator comment: Blood sampling was immediately prior to dosing. Dosing was weekly, limiting the interval between dosing and sampling. Blood samples were taken at delivery regardless of timing of the previous dose.*

Publication	Methods	Results
Roth 2018 [43] NCT01924013 Bangladesh	Participants: 1,300 pregnant women 17-24 weeks gestation. Intervention: 4,200 IU colecalciferol weekly OR **16,800 IU colecalciferol weekly** OR **28,000 IU colecalciferol weekly** OR **28,000 IU colecalciferol weekly**, **continuing to 26 weeks postpartum** OR placebo All participants received a supplement containing calcium 500 mg, iron 66 mg, folic acid 350 mcg. Outcomes: Maternal serum 25(OH)D, serum calcium, urinary calcium excretion, PTH. Infant length-for-age, birth outcomes, morbidity, serum 25(OH)D, serum calcium, urinary calcium excretion. Weekly assessments during pregnancy to administer standardised questionnaires. Blood specimens collected at baseline, 30 weeks of gestation, delivery and 3 and 6 months postpartum. Urine specimens collected at baseline, delivery and 6 months post-partum.	Of the 1,300 participants, 64% had vitamin D deficiency. Mean maternal 25(OH)D at delivery was 23.8 ± 13.9 nmol/L in the placebo group and ranged from 69.7 ± 19.5 nmol/L to 113.6 ± 25.7 nmol/L across the intervention groups. Mean cord blood 25(OH)D was 12.9 ± 7.9 nmol/L in the placebo group, and ranged from 40.5 ± 11.4 to 82.1 ± 18.5 nmol/L across the intervention groups. No episodes of 'confirmed hypercalcaemia' (ie, two subsequent elevated measurements) during pregnancy. Eight asymptomatic cases (0.7%) in post-partum women (5 in 28,000 IU pre/post-partum group) and 6 infants (0.6%) across the vitamin D groups. Two asymptomatic cases of maternal confirmed hypercalciuria, one each in the placebo group and the prenatal/postpartum 28,000 IU group. 60 mothers across the groups had 'possible hypercalciuria' (ie, 1 elevated ca:cr measurement). The proportion with 'possible hypercalciuria' was lowest in the placebo group and increased with increasing dose. One infant (4,200 IU group) had confirmed hypercalciuria, and 9 infants across the groups had 'possible hypercalciuria'. No serious AEs related to confirmed hypercalcaemia or hypercalciuria. Rates of congenital malformations: 16 (6.5%) in placebo group, 16 (2.4%) in 4,200 IU group, 5 (2.0%) in 16,800 IU group, 8 (3.2%) in 28,000 IU group and 7 (2.8%) in the 28,000 IU group that continued post-partum. Rates not significantly different in adjusted analysis. Infant 1-year follow-up completed for 94% of infants alive. No effect of supplementation of infant length or other anthropometric measures. No differences seen in pregnancy/neonatal outcomes. Four infants with rickets (3 in placebo group and 1 in 4,200 IU group). Not powered to detect differences in infrequent adverse outcomes. A secondary analysis of biochemical rickets screening at 6 and 12 months found that overall, 39/790 (4.9%) infants had biochemical rickets. Prevalence was highest in the placebo group (7.8%), and the risk was significantly lower among infants whose mothers received combined prenatal and postpartum vitamin D at 28 000 IU/week (1.3%; RR, 0.16; 95% CI, 0.03–0.72). Risks among infants whose mothers received only prenatal supplementation (4200 IU, 16 800 IU, 28 000 IU weekly) were not significantly different from placebo. [53] Another follow-up study found that antenatal vitamin D supplementation did not improve child BMC, aBMD, or grip strength at 4 years of age. [54] Other follow-up studies found no impact on pneumococcal acquisition or carriage, nor risk of respiratory tract infection for infants up to 6 months of age. [55, 56]

Publication	Methods	Results
Sablok 2015 [44] (CT ID not stated) India	Participants: 180 pregnant women, 14-20 weeks gestation Exclusion criteria: pre-existing osteomalacia, known hyperparathyroidism, renal, liver dysfunction, tuberculosis, sarcoidosis. Intervention: Bolus colecalciferol dose(s) (**monthly**) starting at 20 weeks Randomised to two groups. Group A: no intervention (n=60). Group B: patients with 25(OH)D >50 nmol/L received **1 dose of 60,000 IU**; patients with 25(OH)D >25 nmol/L received **2 doses of 120,000 IU**; patients with 25(OH)D <25 nmol/L received **4 doses of 120,000 IU** (n=120). Outcomes: Maternal: preterm labour, pre-eclampsia, gestational diabetes, serum 25(OH)-D concentration, serum calcium, phosphorus, and serum ALP levels. Infant: Apgar score, birthweight, LBW, cord blood 25(OH)D, SGA, appropriate for gestational age. All assessed at time of delivery.	Three patients in group A and twelve patients in group B were lost to follow up. In the no intervention group (group A), median maternal 25(OH)D at delivery was 24 nmol/L. No baseline measurement was available for this group. In the intervention group (group B), the subset of patients with 25(OH)D <25 nmol/L who received a total of 480,000 IU had a median 25(OH)D of 38 nmol/L at baseline and 65 nmol/L at birth. At birth, cord blood 25(OH)D levels were >50 nmol/L in 14.0% of group A and 46.2% of group B. Pre-term labour occurred in 21.1% of group A and 8.3% of group B. Gestational hypertension or pre-eclampsia occurred in 21.1% of group A and 11.1% of group B. Incidence of GDM was low and similar between groups. 19.2% of infants in group A and 8% of infants in group B were SGA. *Evaluator comment: The publication does not describe the characteristics of participants and whether the groups were similar. The pre- and post-supplementation maternal 25(OH)D levels by dose are not clearly reported, making interpretation difficult. There is no discussion of safety parameters, such as hypercalcaemia or adverse events and it does not appear that these were monitored during the course of treatment. Calcium levels at delivery were measured but not reported. Treatment allocation appears to be unblinded.*
Vafaei 2019 [57] IRCT20140317017034N6 Iran	Participants: 140 pregnant women aged 20-35 years Intervention: 1,000 IU vitamin D daily OR placebo from 2 weeks after absent period. Outcomes: TM1: Crown-rump length (CRL) and femur length (FL) TM2/3: humerus and femur lengths and their proximal metaphyseal diameter (PMD), midshaft diameter (MSD), and distal metaphyseal diameter (DMD)	The study found that supplementation increased femur and humerus length in second and third trimesters. No safety findings reported. *Evaluator comment: The publication doesn't state whether the intervention was vitamin D2 (ergocalciferol) or vitamin D3 (colecalciferol).*

Publication	Methods	Results
Yu 2009 [45] EUCTR2006-006080-23-GB United Kingdom	Participants: 180 pregnant women (Indian Asian, Middle Eastern, Black and Caucasian) at 27 weeks gestation. Intervention: 800 IU ergocalciferol daily for 13 weeks OR **single dose of 200,000 IU of calciferol** OR no treatment Outcomes: Maternal and cord 25(OH)-D at delivery, PTH corrected calcium at delivery, adverse events. Infant: 25(OH)D, SGA, wheezing, bronchodilator use, rhinitis, asthma, eczema, allergies, and others.	The final maternal 25-hydroxyvitamin D levels were significantly higher in the supplemented group, but only a fraction of women (30%) and babies (8%) were vitamin D sufficient. All ethnic groups had normal calcium levels at 27 weeks (baseline) and at delivery. There were significantly fewer women with secondary hyperparathyroidism in the supplemented group compared to no treatment group. No significant difference in the gestational age at delivery, birth weights or number of infants with birth weight <10th percentile. There was one unexplained stillbirth and one neonatal death, both in the no treatment group. One woman developed nephritic syndrome and stopped vitamin D treatment. *Evaluator comment: The publication doesn't state whether the stat dose of 'calciferol' was ergocalciferol or colecalciferol (vitamin D3). Ergocalciferol may be less potent in increasing 25(OH)D than colecalciferol. Blood specimens were taken only at baseline (27 weeks) and delivery.*

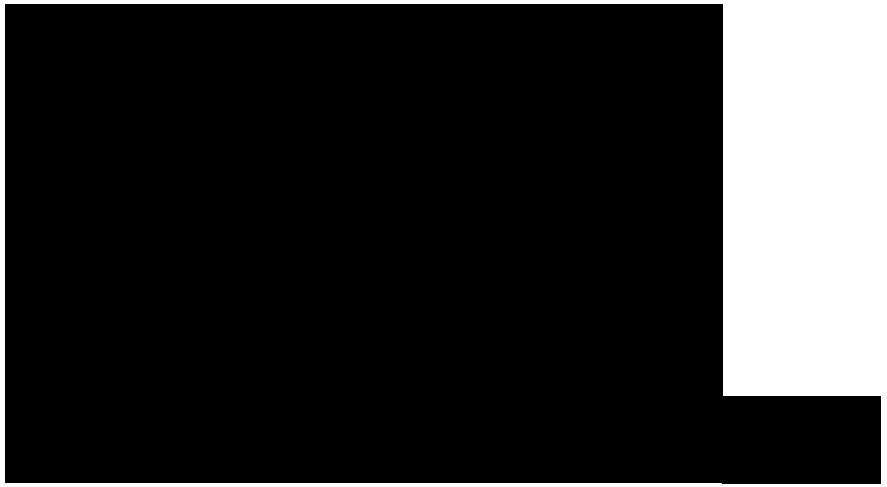
3.3 Other clinical trials

Other publications describing trials of high, intermittent doses are summarised below in table 6. Trials that were noted in the Cochrane review as having trustworthiness red flags were not reviewed.

Trials in women with gestational diabetes mellitus (GDM) or investigating GDM as a primary outcome are presented separately in Table 7. Many of these publications have issues affecting interpretation, such as insufficient description of methods.

Table 6: Other publications describing clinical trials of high intermittent doses (eg, weekly or monthly) of vitamin D in pregnancy

Publication	Methods	Results
Aggarwal 2022 [58] (India) CTRI/2013/10/004056	Participants: Pregnant women at 12-16 weeks' gestation. Intervention: 30,000 IU colecalciferol twice daily for 5 days at 18 weeks' gestation OR placebo. Outcomes: Prevalence of vitamin D deficiency, maternal outcomes and neonatal outcomes.	Of the 304 eligible women, 92% had vitamin D deficiency and 65% had severe deficiency. 297 women were randomised to intervention or placebo and 16 women were lost to follow up. There was no significant difference in incidence of preeclampsia, gestational diabetes mellitus, and gestational age at delivery between the intervention and placebo groups. The median weight-for-gestational age, head circumference, crown-heel length, Apgar score, and admission to NICU were not significantly different between the two groups. Fetal malformations were observed in three newborns in the intervention group and in two newborns in the placebo group. There was one stillbirth and two abortions in the placebo group. *Evaluator comment: 25(OH)D and calcium levels not measured following the intervention.*

Publication	Methods	Results
Bimson 2017 (poster abstract) [59]	Participants: 67 pregnant women <20 weeks' gestation with vitamin D deficiency. Intervention: 50,000 IU colecalciferol weekly for 8 weeks plus usual care (prenatal vitamin containing 400 IU vitamin D) OR placebo plus usual care. Outcome: 25(OH)D levels.	Nine patients were lost to follow-up. After 8 weeks of treatment, 25(OH)D levels were 48.1 ± 19.6 ng/mL and 21.1 ± 5.9 ng/mL with 84.4% and 3.9% achieving vitamin D sufficiency (>30 ng/mL) in the treatment group and placebo group, respectively. At delivery, 25(OH)D levels were 28.8 ± 9.8 ng/mL and 20.5 ± 8.9 ng/mL in the treatment group and placebo group, respectively, with 30.8% and 24% achieving vitamin D sufficiency in the treatment group and placebo group, respectively. There were no statistically significant differences in delivery outcomes, or in antepartum, maternal, or fetal complications. *Evaluator comment: This is a poster abstract and therefore contains limited information. Safety data were not presented.*
Bhowmik 2021 [60] (Bangladesh) NCT01924013	Participants: 748 pregnant women at 6–14 weeks with vitamin D and/or B12 deficiency Inclusion criteria: 18–28 years, singleton pregnancy, conceiving without fertility treatment. Exclusion criteria: diabetes, history of congenital malformations, supplement intolerance, history of hypercalcaemia or renal stones, serum calcium >2.65 mmol/L, CKD, liver disease, thyroid disease, active sarcoidosis, tuberculosis, or malignancy, certain medicines, planned home delivery. Intervention: vitamin D3 and/or B12 (B complex tablet). 25(OH)D <30 nmol/L = **200,000 IU every 60 days** 25(OH)D 30-70 nmol/L = **200,000 IU every 90 days** B12 tablet given every 14 days (B12 200 mcg, pyridoxine HCl 200 mg, thiamine nitrate 200 mg). Control: Dietary instruction plus standard care. Observational arm consisted of non-deficient participants. Outcomes: Vitamin D and B12 repletion, serum calcium. Study visits at baseline, 24-28 weeks and delivery.	Approximately 25% of participants were lost to follow up. Mean 25(OH)D levels rose in both the intervention and control groups, and were similar between the two groups at all three visits (figure 6). **Figure 6: Mean values of vitamin D (nmol/L)**  Adverse events of hypercalcaemia (corrected serum calcium >2.65 mmol/L) occurred in 9/306 (2.9%) participants treated with vitamin D only, 1/14 (7.1%) treated with vitamin B complex only, 2/64 (3.1%) treated with both vitamin D and B vitamin B complex, 2/364 (0.5%) of the dietary advice arm and 2/113 (1.8%) of the observational arm. There were 4 neonatal deaths and 21 miscarriages in the intervention group, and 3 neonatal deaths and 19 miscarriages in the control group.

Publication	Methods	Results
		Evaluator comment: The publication has limited detail on methods and results which limits interpretation. For example, it does not state how many vitamin D doses were administered to participants, the frequency or timing of serum calcium measurements in relation to dosing, or how many participants had maternal blood samples available. There is no discussion of the safety findings, including whether hypercalcaemia was confirmed on repeat testing, symptomatic/associated with adverse events or attributable to vitamin D treatment based on clinical context (eg, elevated 25(OH)D, intercurrent illness, other causes). Hypercalcaemia appears to be defined by a single elevated serum calcium measurement (laboratory finding vs adverse event). The stated rates do not account for loss to follow up/number of patients with blood samples available.
Das 2009 (abstract) [61] India CT ID not stated	Participants: 150 pregnant women in 2nd trimester from 6 villages in North India. Intervention: No treatment OR 60,000 IU colecalciferol OR 240,000 IU colecalciferol. All participants were educated on sunshine exposure and were given 1 g calcium carbonate daily. Outcome: 25(OH)D levels measured at baseline and delivery.	Delivery samples available for 84/150 participants. At baseline, 74% of participants had 25(OH)D <50 nmol/L and 32% had 25(OH)D <25 nmol/L. There was a significant rise of 25(OH)D from baseline to delivery (p = 0.001) only in the group that received 240,000 IU colecalciferol. *Evaluator comment: This is a poster abstract and therefore contains limited information.*
Etemadifar 2015 [62] (Iran)	Participants: 15 pregnant women with multiple sclerosis (MS) and low 25(OH)D (<20 ng/mL) at 12 to 16 weeks' gestation. Intervention: 50,000 IU colecalciferol weekly until delivery OR routine care. Outcomes: Mean change in serum 25(OH)D, expanded disability status scale (EDSS) score, MS relapse events. Vital signs, safety labs, ECG, and adverse reactions.	Mean serum 25(OH)D level at 6 months following delivery in vitamin D3 supplemented group increased from baseline and was higher than routine care group (33.7 ng/mL vs. 14.6 ng/ml). There were no adverse events, urinary dysfunction, symptomatic nephrolithiasis or abnormal ECG results reported. *Evaluator comment: The publication doesn't say whether there was postpartum supplementation.*
Goldring 2013 [63] (United Kingdom) ISRCTN68645785	Participants: 180 pregnant women at 27 weeks gestation. Intervention: 800 IU ergocalciferol daily until delivery OR single oral bolus of 200,000 IU cholecalciferol. Primary outcomes: child history of wheeze at 3 years. Secondary outcomes: eczema, atopy.	158 of 180 (88%) offspring evaluated for primary outcome. There was no significant difference in the outcomes of 'wheeze ever', eczema or atopy between treatment groups. Sensitivity analyses found that dropouts did not influence the results, and that there was no significant difference in 25(OH)D levels between offspring with and without the studied outcomes. There were 4 deaths, all in the control group. No adverse events related to treatment were reported in the offspring.

Publication	Methods	Results
Hashemipour 2014 [64] (Iran) NCT02021864 / IRCT201205119491N2	Participants: 130 pregnant women (24-26 weeks gestation) with vitamin D deficiency or insufficiency. Control: 200 mg calcium plus a multivitamin (containing 400 IU colecalciferol) daily Intervention: 200 mg calcium plus a multivitamin (as above) AND 50,000 IU colecalciferol weekly for 8 weeks. Outcomes: Maternal and cord blood 25(OH)D levels, maternal weight gain, fetal growth indices.	19 participants were lost to follow up. At delivery, maternal serum vitamin D level was significantly higher in the intervention group compared with the control group. In the control group, mean 25(OH)D was 17.5 ± 4.8 ng/mL at baseline and 15.9 ± 6.6 ng/mL at delivery. In the intervention group, mean 25(OH)D was 15.8 ± 5.6 ng/mL at baseline and 47.8 ± 11.1 ng/mL at delivery. 100% and 3% of the intervention and control groups achieved 25(OH)D >30 ng/mL, respectively. Mean cord blood 25(OH)D was 10.9 ± 4.4 ng/mL in the control group and 27.7 ± 5.2 ng/mL in the intervention group. 33% and 0% of the intervention and control groups achieved cord blood 25(OH)D >30 ng/mL, respectively. Mean neonatal length was 0.8 cm greater in the intervention group compared with the control group (p = 0.01), and mean neonatal head circumference was also higher in the intervention group (p = 0.001). Mean birth weight was 170.2 g heavier in the intervention group (p = 0.01). Maternal weight gain was higher in the intervention group (p = 0.001). Maternal vitamin D level was significantly independently correlated with neonatal length, weight and head circumference. No cases of neonatal death or congenital malformations occurred in either group. One neonate in the control group was small for gestational age, and all neonates in the intervention group were of normal weight. *Evaluator comment: 25(OH)D only measured at baseline and at delivery. Serum/urine calcium levels were not measured.*
Kabuyanga 2024 [52] (DR Congo) [65] ISRCTN46539495	Participants: 1,300 pregnant women 12-16 weeks gestation Inclusion criteria: primigravida, singleton pregnancy, planning delivery at same facility). Exclusion criteria: pre-eclampsia, pathology associated with impact on fetal growth, vit D/calcium supplements, liver or renal disease, diabetes. Intervention: 60,000 IU colecalciferol monthly for 6 months OR no supplementation. Outcomes: Serum 25(OH)D and calcium (baseline and 34 weeks). Primary: pre-eclampsia. Secondary: preterm delivery, birth weight and height, mode of delivery, and APGAR score.	156 participants were lost to follow-up: 73 in the control group and 68 in the vitamin D supplementation group. In the intervention group, mean 25(OH)D was 34.20 ± 11.9 ng/mL at baseline and 37.25 ± 9.4 ng/mL at 34 weeks. The proportion of participants with vitamin D sufficiency (≥30 ng/mL [75 nmol/L]) was 59% at baseline and 80% at 34 weeks. In the control group, mean 25(OH)D was 35.61 ± 12.7 ng/mL at baseline and 41.47 ± 20.3 ng/mL at 34 weeks. The proportion of participants with vitamin D sufficiency was 70% at baseline and 72% at 34 weeks. The incidences of preeclampsia, preterm delivery and LBW were significantly lower in the supplemented group than in the control group (table 7 and table 8).

Publication	Methods	Results
		Table 7: Vitamin D, ionised calcium, type of delivery and gestational outcomes  *Evaluator comment: This study is described as single-blinded as the comparator was no treatment rather than placebo. Blood samples were taken at 34 weeks irrespective of when supplementation was started. The timing of sampling in relation to dosing is not described.* *The results are difficult to interpret as relative 25(OH)D increase from baseline is not presented. The mean 25(OH)D at 34 weeks is higher in the control group but the proportion with vitamin D sufficiency is slightly lower (72% vs 80%). Based on this, it is difficult to understand the plausibility of a relationship with the observed drastically lower rates of pre-eclampsia, preterm birth and LBW.* *Information relevant to safety is not presented (eg, adverse events, range of observed 25(OH)D and calcium levels, out-of-range results).*

Publication	Methods	Results
Kalra 2012 [66] (India) CTRI/2010/091/000499	Participants: 299 pregnant women 12 to 24 weeks' gestation. 43 non-supplemented (usual care) mothers in the third trimester were used as controls. Intervention: 60,000 IU colecalciferol at induction OR 120,000 IU at induction and at 28 weeks' gestation. All prescribed 1g calcium daily. Outcomes: Maternal 25(OH)D at term, cord blood (CB) alkaline phosphatase (ALP), neonatal serum Ca and anthropometry at birth, 3 6 and 9 months.	97/299 women supplemented with vitamin delivered at the study centre hospital. Women who returned for follow-up were slightly older, had higher BMI and higher calcium intake. The maternal characteristics were similar across the groups included in the analysis. Median maternal serum 25(OH)D at delivery was significantly higher in the 120,000 IU group (58.7 nmol/L; IQR 38.4-89.4) compared with the 60,000 IU group (26.2 nmol/L; IQR 17.7-57.7) and the usual care group (39.2 nmol/L; IQR 21.2-73.4). More women had 25(OH)D >50 nmol/L at delivery in the 120,000 IU group (62.5%) compared with the 60,000 IU group (27%) and the usual care group (44.2%). Median CB 25(OH)D, as well as the proportion of CB samples with 25(OH)D >25 or >50 nmol/L, did not differ significantly between the three groups. Median CB ALP and the proportion with elevated CB ALP were higher in the usual care group. Neonatal Ca, prevalence of hypocalcaemia and LRTI episodes were similar across the groups. The anthropometry studies found significantly higher birth weight, length and head circumference, and smaller anterior fontanelle in both supplemented groups compared to usual care, which persisted from birth to 9 months. The frequency of pregnancy-related complications, including intra-uterine death, pregnancy-induced hypertension, cephalopelvic disproportion, non-progression of labour, caesarean section and placenta praevia, did not differ among the three groups (data not presented). *Evaluator comment: The usual care group was not allocated randomly. There was a massive loss to follow up. Baseline 25(OH)D not presented for usual care group. Comparison of 25(OH)D and other parameters between baseline and delivery is not discussed. For the 60,000 IU group, median serum 25(OH)D appears lower at delivery compared to baseline and is lower than the usual care group at delivery. Reasons for these findings are not addressed in the publication. There is limited safety data presented and there was no follow-up between treatment and delivery.*

Publication	Methods	Results
Marya 1981 [67] (India)	Participants: 120 women in third trimester of pregnancy. Exclusion criteria: preeclampsia, antepartum haemorrhage, twins. Interventions: No supplements (n = 75) 1,200 IU vitamin D daily (low dose) throughout third trimester (n- 25) 600,000 IU in 7th and 8th month of pregnancy (n = 25). Outcomes: Maternal and cord blood calcium, serum proteins, heat-labile alkaline phosphatase (HLAP), inorganic phosphate levels at delivery.	Maternal serum calcium (mg%) at delivery was 8.80 ± 0.72 in the non-supplemented group, 9.05 ± 0.70 in the low daily dose group and 9.24 ± 0.48 in the high monthly dose group. Maternal serum Inorganic phosphate (mg%) at delivery was 3.95 ± 0.63 72 in the non-supplemented group, 3.36 ± 0.61 in the low daily dose group and 9.41 ± 6.08 in the high monthly dose group. Cord blood serum calcium (mg%) at delivery was 10.06 ± 0.93 in the non-supplemented group, 10.20 ± 0.67 in the low daily dose group and 10.68 ± 0.48 in the high monthly dose group. Cord blood serum inorganic phosphate (mg%) at delivery was 5.51 ± 2.65 in the non-supplemented group, 5.48 ± 1.91 in the low daily dose group and 6.41 ± 1.63 in the high monthly dose group. The publication reports that infant birth weight was greater in women who received vitamin D supplements and was higher in the high dose group. None of the patients in the high dose group showed maternal or neonatal hypercalcaemia. *Evaluator comments: It is not stated whether the daily dose group received colecalciferol or ergocalciferol. HLAP results are not discussed above as heat inactivation is considered an imprecise method for differentiating ALP fractions originating from liver and bone. It is unclear what 'serum proteins' are. Safety outcomes such as hypercalcaemia were not monitored during pregnancy.*
Prabhakar 2024 [68] (India) CTRI/2017/12/010850	Participants: 100 women in third trimester of pregnancy Maternal inclusion criteria: 19-35 years, spontaneous conception, height >145 cm, pre-pregnancy weight >45 kg, Hb >9g/dL, BP <140/90 mmHg, urine dipstick negative for proteins, planning to exclusively breastfeed. Women with chronic diseases or prior vitamin D supplementation excluded. Infant inclusion criteria: born at 37 to 41 weeks gestation, APGAR score >7, no gross congenital anomalies. Neonates who developed seizures, sepsis, birth asphyxia or required exchange transfusion, or those who received vitamin D in infancy were excluded. Intervention: 60,000 IU colecalciferol weekly for 5 weeks (total 300,000 IU) during third trimester OR placebo. All mothers counselled on infant sun exposure and asked to record this in a diary.	Out of 100 pregnant mothers enrolled in the study, 72 mother-infant pairs (37 infants in the vitamin D group and 35 infants in the placebo group) were followed-up for 6 months. At baseline, 90% of mothers had 25(OH)D <20 ng/mL (<50 nmol/L) and 60% had 25(OH)D <11 ng/mL (<27.5 nmol/L). At delivery, the mean cord blood 25(OH)D concentration was significantly higher in the intervention group (42 ± 17.1 ng/mL vs 12.7 ± 6.3 ng/mL) and this remained higher in infants at 6 months of age (31.8 ± 10.9 ng/mL vs 12.5 ± 5.7 ng/mL) (table 9) even after adjustment for birth weight, maternal and cord blood 25(OH)D and sunlight exposure (analysis not presented). Three infants developed biochemical rickets and two infants suffered from radiological rickets in the placebo group compared to none in the intervention group. There was no clinical evidence of hypervitaminosis D in infants during follow-up. *Evaluator comment: The proportion of infants with vitamin D insufficiency/deficiency at 6 months of age was much lower in the maternal supplementation group. It isn't clear whether the authors accounted for maternal use of supplements during breastfeeding. There is limited information reported on safety.*

Publication	Methods	Results
	Outcomes: Vitamin D status of breastfed infant at 6 months of age. Serum 25(OH)D, calcium, phosphorus and alkaline phosphatase measured at recruitment, in cord blood at delivery and in infant at 6 months of age.	**Table 9: Biochemical profile of neonates at birth and 6 months of age.** [redacted]

Publication	Methods	Results
Rostami 2018 [69] (Iran) IRCT20141025196 60N1	Participants: Pregnant women with moderate or severe vitamin D deficiency at <14 weeks' gestation. Interventions: Moderate deficiency: I1: 50,000 IU colecalciferol weekly for 6 weeks I2: 50,000 IU weekly for 6 weeks then monthly until delivery I3: 300,000 IU IM stat I4: 300,000 IU IM stat then 50,000 IU monthly until delivery Severe deficiency: I5: 50,000 IU weekly for 12 weeks I6: 50,000 IU weekly for 12 weeks then monthly until delivery I7: 300,000 IU IM – 2 doses every 6 weeks I8: 300,000 IU IM - 2 doses every 6 weeks then 50,000 IU monthly until delivery A no intervention group from a different site was used for comparison. Primary outcome: 25(OH)D at delivery. Secondary outcomes: pregnancy outcomes.	53% of participants across the vitamin D intervention groups achieved 25(OH)D >20 ng/mL at delivery. The odds of achieving >20 ng/mL in moderate deficiency were highest for I4 (300,000 IU IM stat then 50,000 IU monthly until delivery). The odds of achieving >20 ng/mL in severe deficiency were highest for I6 (50,000 IU weekly for 12 weeks then monthly until delivery). Numbers of adverse pregnancy outcomes were compared between participants receiving any vitamin D intervention and participants at another site with no screening/intervention. The odds of pre-eclampsia, GDM and preterm delivery were significantly lower in patients receiving vitamin D interventions. *Evaluator comment: The magnitude of the observed significantly reduced ORs (0.3 to 0.6) for some adverse pregnancy outcomes in the vitamin D intervention groups seem implausible, especially given the small sample size and may reflect confounding. The use of eight different interventions limits interpretation of the findings. It is difficult to tell whether some comparisons are being made against only vitamin D deficient patients at the non-screening/intervention site or all patients at the site regardless of vitamin D status.*
Roth 2012 and **Roth 2013** [70, 71] (Bangladesh) NCT00938600	Participants: 28 pregnant women 27 to <31 weeks' gestation and 16 non-pregnant women. Interventions: High dose: single dose of **70,000 IU** colecalciferol **followed by 35,000 IU** weekly until delivery (PH group) or for 10 weeks in non-pregnant participants (NH group). OR low dose: 14,000 IU weekly until delivery (PL group). Outcomes: 25(OH)D. Safety parameters monitored included maternal and cord serum calcium, urine ca:cr, clinical adverse events and birth outcome.	This was primarily a PK study that also reported on safety. Mean 25(OH)D rose in all groups and was higher in the high dose group at week 10. 19/20 pregnant participants with 25(OH)D levels at week 10 achieved vitamin D sufficiency (≥50 nmol/L). 23/23 cord blood samples showed 25(OH)D ≥50 nmol/L. There were no episodes of confirmed maternal hypercalcaemia or persistent hypercalciuria. Pregnancy and newborn clinical outcomes were as expected for the study population. See section 3.4 for further details and pharmacokinetic results.

Publication	Methods	Results
Sahoo 2017 [72] (India)	Participants: 300 pregnant women (n = 300) at 14–20 weeks gestation Interventions: Colecalciferol **60,000 IU** 4 weekly (group 1), 8 weekly (group 2), or placebo (group 3). All received 1 g calcium daily (groups 1 and 2 without, and group 3 with 400 units vitamin D). Outcomes: Maternal and cord blood 25(OH)D, measured at baseline and term. Bone mineral content (BMC), bone, mineral density (BMD), body composition, infection rates in offspring.	At term, there was substantial improvement in maternal serum 25(OH)D levels in group 1 and 2, but not in group 3. Groups 1 and 2 had higher cord blood 25(OH)D (47.8 ± 13.8 and 31.0 ± 14.0 nmol/L) versus group 3 (17.8 ± 13.5 nmol/L, p < 0.001). Babies in group 3 (placebo) had higher BMC (250.8 ± 42.5 gm) and BMD (0.335 ± 0.033 gm/cm2) compared to group 1 (213.1 ± 46.2 gm and 0.295 ± 0.041 gm/cm2) and group 2 (202.9 ± 29.9 gm and 0.287 ± 0.023 gm/cm2) (p = 0.006 and 0.001, respectively). Parameters of body composition were comparable among the groups. Neonatal serum calcium levels were similar across the groups. None of the mothers or children had hypercalcemia or serum 25(OH)D level >250 nmol/L. Vitamin D supplementation to pregnant women with severe deficiency in doses that improved cord blood 25(OH)D did not result in improved bone health or body composition in offspring at 12–16 months. BMC and BMD were influenced only by age, and BMC was age-appropriate in all three groups. No difference in infections. No child had biochemical or radiological rickets nor signs of vitamin deficiency. *Evaluator comments: Measurements of 25(OH)D and calcium taken at baseline and delivery only.*
Shakiba 2023 [73] (Iran)	Participants: 51 pregnant women in 2nd trimester of pregnancy. Interventions: A: 50,000 IU colecalciferol monthly B: 50,000 IU every 2 weeks C: 50,000 IU weekly for 4 weeks, the 50,000 IU monthly (vitamin D deficient patients – not randomised). Outcomes: Maternal 25(OH)D and calcium, cord blood 25(OH)D at delivery, neonatal birth weight and length.	All but 4 participants in group A achieved cord blood 25(OH)D ≥20 ng/mL. Mean cord blood 25(OH)D was higher in group B compared to group A (32 ± 12 vs 25 ± 7 ng/mL; p=0.003). Calcium levels were normal for all participants at delivery. No significant differences in neonatal birth weight or length. There was 1 premature birth. *Evaluator comments: No placebo group – all participants received vitamin D. Measurements of 25(OH)D and calcium taken at delivery only.*
Singh 2021 [74] (India)	Participants: 127 pregnant women (≥16 weeks' gestation) with vitamin D deficiency. Screening women who were vitamin D sufficient (n=15) were used as controls. Interventions: 60,000 IU cholecalciferol (oral) weekly OR 60,000 IU (IM) fortnightly for 8 weeks. Outcomes: 25(OH)D after 12 weeks, maternal and neonatal outcomes.	3 participants discontinued the study. Age, parity and length of gestation at the start of the study were similar between the groups. 15 patients were >34 weeks pregnant and could not complete the vitamin D regimen due to delivery. After 12 weeks, mean 25(OH)D was significantly higher in the IM group than the oral group (29.3 ± 2.08 vs 22.8 ± 2.1 ng/mL; p<0.0001), despite receiving a lower cumulative dose. *Evaluator comments: No placebo group and controls were vitamin D sufficient. Comparison of maternal and neonatal outcomes was limited.*

Publication	Methods	Results
Soheilykhah 2013 [75] (Iran)	Participants: 120 pregnant women. Interventions from 12 weeks of pregnancy until delivery: Group A: 200 IU vitamin D (calciferol) daily Group B: 50 000 IU vitamin D monthly Group C: 50 000 IU vitamin D every 2 weeks. Outcomes: Fasting blood sugar (FBS), insulin, calcium, 25(OH)D, HOMA-IR at end of pregnancy.	7 participants did not complete the study. The mean 25(OH)D level increased in all treatment groups, with greater increase in the higher dose groups. Group A increased from 8.3±7.8 to 17.7±9.3 ng/ml. Group B increased from 7.3±5.3 to 27.23±10.7 ng/ml. Group C increased from 7.3±5.9 to 34.1±11.5 ng/ml. In Group C, 64% of participants achieved 25(OH)D >30 ng/mL. Change in mean serum calcium was not different between the groups. There was a smaller increase in HOMA-IR in group C compared to group A. No events of hypercalcaemia. *Medsafe: Doesn't state whether intervention was ergocalciferol or colecalciferol. Proportion of women achieving vitamin D sufficiency across groups not reported. Serum calcium measured only at end of pregnancy.*

Table 10: Publications describing clinical trials of vitamin D interventions in pregnant women with GDM or investigating GDM-related outcomes.

Publication	Methods	Results
Bhavya 2020 [76] (India)	Participants: 99 pregnant women with gestational diabetes. Intervention: 60,000 IU colecalciferol monthly until delivery (if deficient) OR no treatment. Outcomes: Metformin and insulin requirements, adverse events.	40 of 50 women randomised to treatment arm were vitamin D deficient and received treatment. 39 of 49 women randomised to the no treatment arm were vitamin D deficient and were included in the control group for analysis. At delivery, there were no differences in mean metformin or insulin requirements between the treatment and control groups. The incidence of NICU admissions and LBW were numerically lower in the treatment group. The were no adverse events related to supplementation. *Evaluator comment: Length of gestation at enrolment not presented. 25(OH)D and calcium levels not measured following the intervention. No safety data presented.*
Huang 2021 [77] (China)	Participants: 150 pregnant women with gestational diabetes. Intervention: 40,000 IU vitamin D and 8,000 mg omega fatty acids twice daily OR placebo. Outcomes: Markers of blood glucose and lipid metabolism.	After taking 40,000 IU vitamin D and 8,000 mg omega fatty acids twice daily for 6 weeks, the treatment group had significantly decreased fasting blood glucose, insulin, HOMA-IR, triglycerides, total cholesterol, low-density lipoprotein, and very-low-density lipoprotein, and improved HOMA-beta compared to the placebo group. No safety data is presented. *Evaluator comment: The publication doesn't state whether the intervention was vitamin D2 (ergocalciferol) or vitamin D3 (colecalciferol). The vitamin D intervention does not appear to be randomly allocated as study states 'The patients were divided into test and control groups according to whether they took vitamin D and omega-3 fatty acids'. No information on the length of gestation of participants. Large effect sizes raise concerns around plausibility.*

Publication	Methods	Results
Kumari 2025 [78] (India) CTRI/2019/01/017185	Participants: 76 pregnant women with GDM and vitamin D deficiency. Interventions: vitamin D 500 IU/day OR 60,000 IU every 2 weeks, up to a maximum cumulative dose of 600,000 IU. Outcomes: Birth weight, changes in FBS, PPBS, insulin requirement, and various maternal/neonatal outcomes.	7 patients did not complete the study. Mean birth weight was 2.97 ± 0.37 kg in the 60,000 IU group and 2.52 ± 0.45 kg in the 500 IU group (p<0.001). There was a lower incidence of LBW, neonatal hypoglycaemia and hyperbilirubinaemia in the 60,000 IU group. *Evaluator comment: The publication doesn't state whether the intervention was vitamin D2 (ergocalciferol) or vitamin D3 (colecalciferol). Gestational age of participants and cumulative doses received not reported. Impact of intervention on vitamin D status or serum calcium not assessed.*
Mojibian 2015 [79] (Iran) IRCT20110723 7097N1	Participants: 500 pregnant women at 12 to 16 weeks' gestation and serum 25(OH)D <30 ng/ml. Interventions: 400 IU colecalciferol daily OR 50,000 IU weekly until delivery. Primary outcome: Diagnosis of GDM. Secondary outcomes: obstetric outcomes, vitamin D status at term and neonatal outcomes.	The authors considered that participant baseline characteristics were similar between the groups. 246 subjects from group A (400 IU) and 224 pregnant women from group B (50,000 IU) completed participation for assessment of primary outcome. The mean (± SD) level of fasting plasma glucose, 1-h, 2-h and 3-h blood glucose at OGTT were significantly lower in group B than group A. The occurrence of GDM in group B was significantly lower than group A (6.7% vs 13.4%; OR: 0.46 [95% CI: 0.24-0.87]). In this study, 203 subjects from group A and 186 pregnant women from group B completed participation for assessment of secondary outcomes. Mean 25(OH)D at delivery was significantly higher in group B (37.9 ± 19.8 ng/mL vs 27.2 ± 18.8 ng/mL). A higher proportion of maternal and cord blood levels were >30 ng/mL in group B (51.9% and 56.3% vs 29.5 and 26.4%). There was no difference in maternal, obstetric or neonatal outcomes. No hypervitaminosis D observed at delivery. The publication refers to their previous study (Soheilykhah 2013) regarding safety of the high dose regimen, in which no hypercalcemia or hypervitaminosis D was observed. *Evaluator comment: Although not statistically significant, there were a higher number of patients with history of GDM (2.7% vs 0.8%) and family history of diabetes (58.3% vs 50.8%) in the low dose group. Mean pre-pregnancy BMI was higher in the low dose group (26.8 ± 4 vs 25.9 ± 4.8). Most patients lost to follow up for the primary outcome were in the high dose group. FBG/glucose tolerance were not assessed at baseline, so we don't know if the observed differences between the groups were due to baseline differences or the intervention. This trial did not investigate safety and may not have been powered to detect differences in secondary outcomes.*

Publication	Methods	Results
Razavi 2017 [80] (Iran) IRCT20170130 5623N106	Participants: 120 women with GDM at 24–28 weeks' gestation. Interventions (for 6 weeks): 1) 1000 mg omega-3 fatty acids twice a day + placebo 2) 50,000 IU vitamin D every 2 weeks + placebo 3) 50,000 IU vitamin D every 2 weeks + 1000 mg omega-3 fatty acids twice a day 4) placebo + placebo Primary outcome: biomarkers of inflammation. Secondary outcomes: oxidative stress, pregnancy/newborn outcomes.	After 6 weeks of the intervention, mean serum 25(OH)D increased by 18.1 ± 4.4 ng/mL in the vitamin D group and 19.5 ± 3.2 ng/mL in the vitamin D + omega-3 group. Mean hs-CRP and MDA were significantly decreased, and TAC and GSH were significantly increased in the vitamin D + omega-3 group compared to placebo. These findings did not change after adjustment for baseline values of biochemical parameters, age and baseline BMI. Differences in pregnancy/newborn outcomes did not reach statistical significance, other than newborn hyperbilirubinaemia and hospitalisations, which were lower in the intervention groups. No side effects reported. No other safety findings presented. *Evaluator comment: The publication doesn't state whether the intervention was vitamin D2 (ergocalciferol) or vitamin D3 (colecalciferol).*
Sedighi 2020 (preprint) [81] (Iran) IRCT20150607 022585N3	Participants: 50 pregnant women with GDM. Intervention: 100,000 IU colecalciferol at baseline and day 21, plus 1,000 mg calcium daily OR placebo + calcium. Outcomes: FBG, lipid profile, insulin, 25(OH)D, calcium phosphorous, HOMA-AR at 6 weeks.	Mean length of gestation at the start of the study was 22.6 weeks in the vitamin D group and 21.5 weeks in the placebo group. After adjustment for baseline values, 25(OH)D was significantly increased in the vitamin D group compared to the placebo group (increase of 12.12 ± 1.81 vs 0.71 ± 0.82 ng/mL). Calcium and phosphorous levels did not change significantly and remained within the reference range. FPG, insulin, HOMA-IR and TGs were significantly decreased in the vitamin D group compared to the placebo group, while other components of the lipid profile were unchanged. No side effects were observed.
Valizadeh 2016 [82] (Iran) IRCT20121016 11144N1	Participants: 96 pregnant women with gestational diabetes at 12-32 weeks' gestation. Intervention: 200,000 IU colecalciferol daily for two days, then 50,000 IU weekly (or 100,000 IU weekly in patients at ≥28 weeks' gestation) up to a cumulative dose of 700,000 IU OR no treatment. Outcomes: Fasting plasma glucose, insulin, 2-hPLG, HOMA-IR, HbA1C, 25(OH)D 6-12 weeks after delivery. Maternal and neonatal outcomes. Urine ca:cr performed as a safety measure.	Six participants with baseline vitamin D sufficiency were not treated and/or were excluded from the analysis (2 in the treatment group and 4 in the control group). Insulin requirements and markers of glycaemic control at end of pregnancy were not significantly different between the treatment and control groups. There were no cases of maternal hypercalcaemia. Maternal and neonatal outcomes were not significantly different between the groups. At 6-12 weeks post parturition, the mean maternal serum 25(OH)D in the treatment group (32.4±14.4 ng/mL) was significantly higher than that in the control group C 19.3±9.6 ng/mL, P<0.001). 20% of participants in the treatment group were vitamin D deficient (<20 ng/mL) compared to 58% in the control group. Mean cord blood 25(OH)D was significantly higher in the treatment group (37.7±5.3 ng/mL) compared to the control group (15.0±6.8 ng/mL). *Evaluator comment: The study was not blinded. Urine ca:cr was only measured once and other safety parameters were not monitored. The sample size was too small to detect differences in maternal and neonatal outcomes.*

Publication	Methods	Results
Yadzchi 2016 [83] (Iran) IRCT20130625 3140N11	Participants: 76 pregnant women with gestational diabetes at 24-28 weeks' gestation. Intervention: 50,000 IU colecalciferol every 2 weeks for 2 months OR placebo. Outcomes: Metabolic indices, CRP, 25(OH)D.	72 of 76 participants completed the study. No adverse effects of supplementation were reported. Two months after supplementation, there was a greater increase in mean 25(OH)D from baseline in the vitamin D group compared to the placebo group (19.15 [IQR 14.15-29.12] vs. -0.40 [IQR -0.82-0.30] ng/mL; P <0.01). At baseline, 66 patients (93.1%) had 25(OH)D levels <20 ng/mL. At the end of the study, 100% of the patients in the vitamin D group had serum 25(OH)D levels >20 ng/ml compared with 3 patients (8.3%) in the placebo group. No patient had 25(OH)D >50 ng/mL. The vitamin D group had significantly decreased fasting plasma glucose and HbA1c compared to placebo. Lipids were not significantly decreased in the treatment group. *Evaluator comment: Participants were not monitored for hypercalcaemia. The study did not investigate birth outcomes.*
Zhang 2016 [84] (China)	Participants: 283 pregnant women with a new diagnosis of GDM. Intervention: Low dose (200 IU calciferol daily), medium dose (50,000 IU monthly), high dose (50,000 IU every 2 weeks), or placebo, starting at 24-28 weeks of pregnancy and continuing until delivery. Outcomes: FPG, insulin, HOMA-IR, hs-CRP, lipid profile, 25(OH)D and calcium at end of pregnancy.	Vitamin D and calcium levels are not presented. Mean FPG and TGs were not significantly different between the groups. Mean insulin, HOMA-IR and total cholesterol change were significantly lower in the medium and high dose groups, compared to placebo. Mean hs-CRP was not significantly different across the groups. TAC and GSH were significantly increased in the low, medium and high dose groups, compared to placebo. *Evaluator comment: The publication doesn't state whether the intervention was vitamin D2 (ergocalciferol) or vitamin D3 (colecalciferol). Clinical trial registration ID not provided in publication. Baseline values for the outcomes of interest, including vitamin D status, are not presented. No vitamin D or calcium results are presented. The large effect sizes, for example on insulin, raise concerns around plausibility.*

3.4 Pharmacokinetic studies

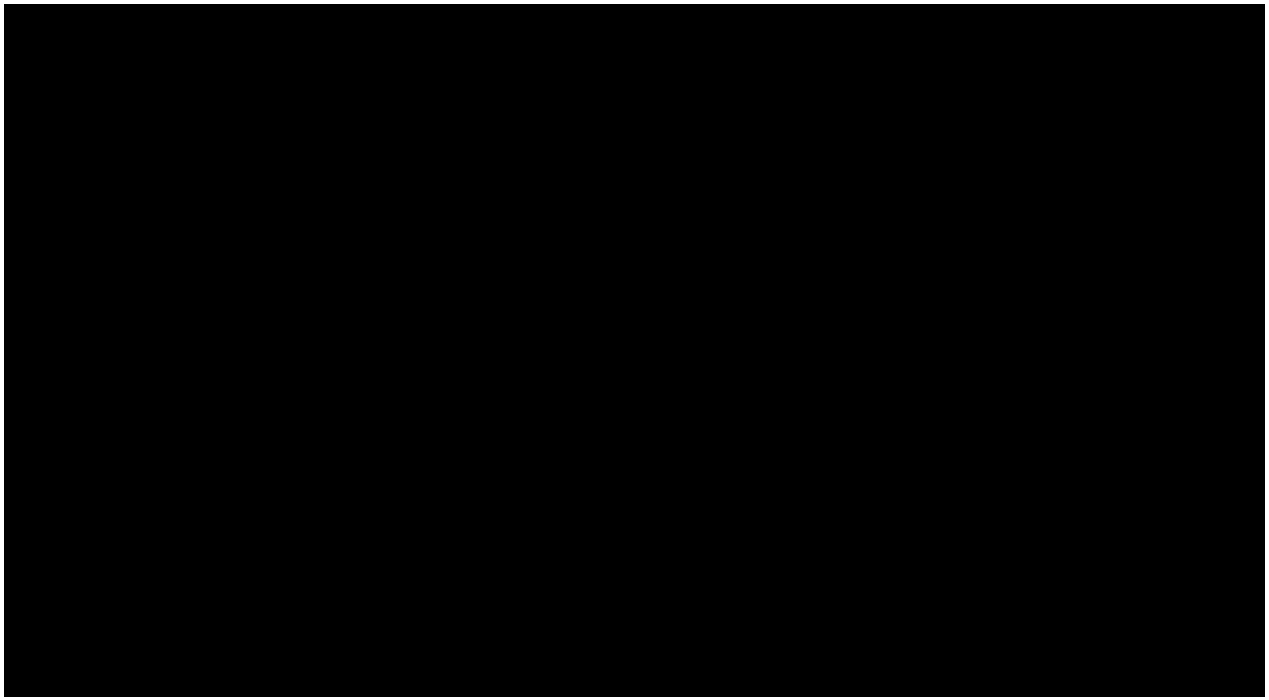
A number of studies were identified that describe the pharmacokinetics of high doses of vitamin D (35,000 to 150,000 IU) when given as a single dose or as weekly to monthly repeated doses. Studies in pregnant participants are described in table 11 and studies in non-pregnant participants are described in table 12.

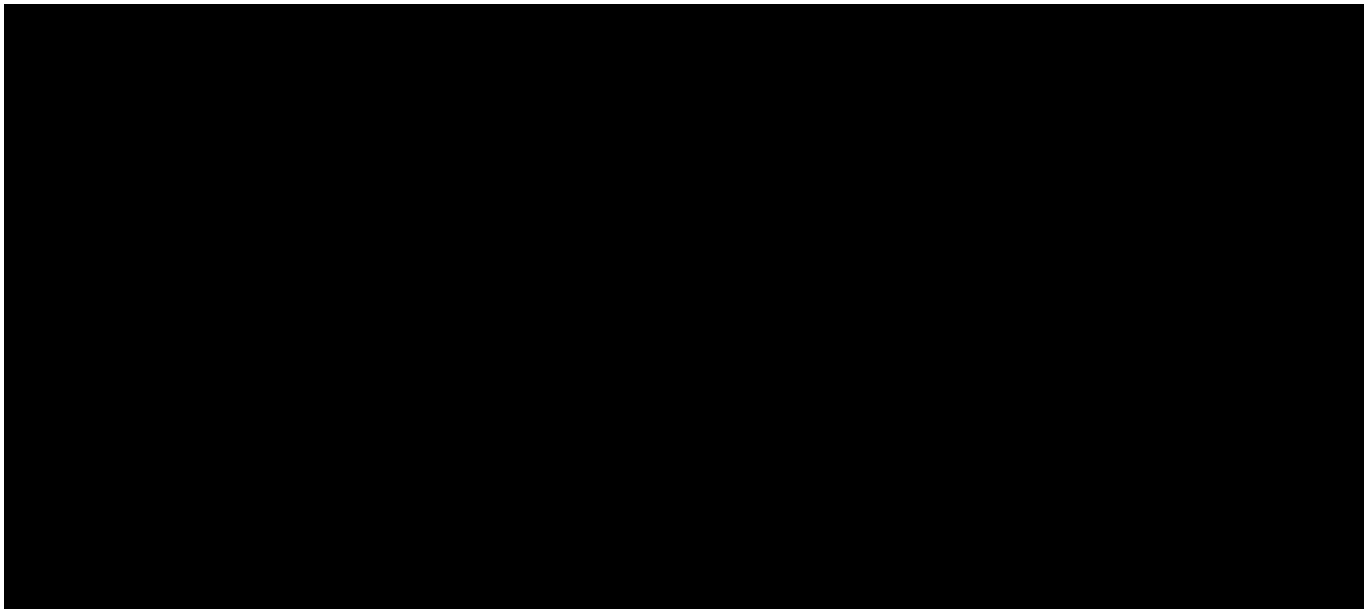
Table 11: Publications describing pharmacokinetics of high doses of vitamin D in pregnant participants

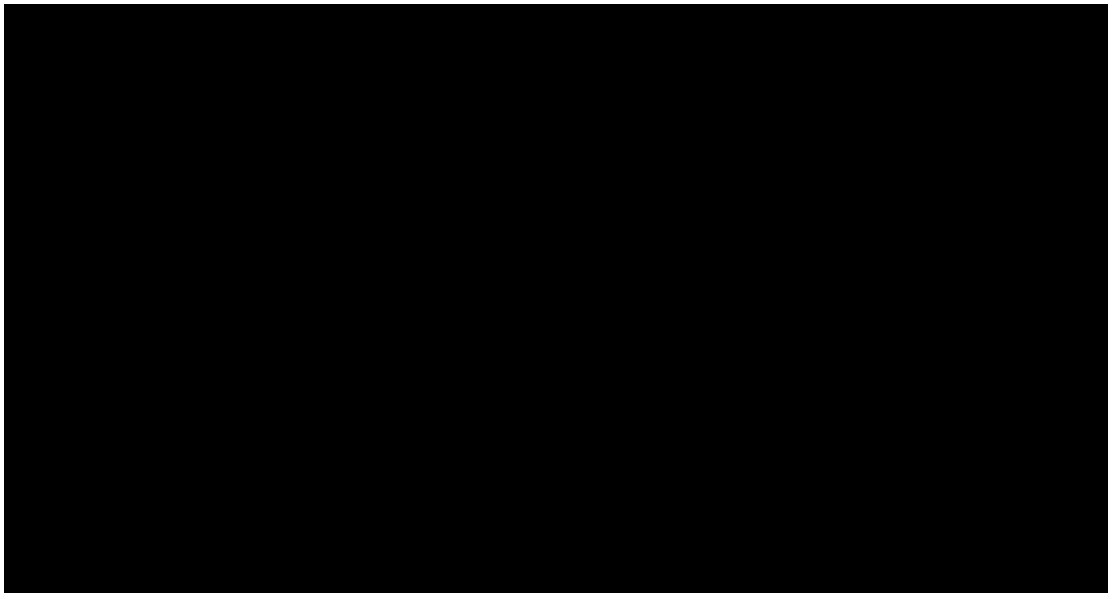
Publication	Methods	Results
Roth 2012 [71] Bangladesh NCT00938600	Participants: 34 non-pregnant and 27 pregnant women (27 to 30 weeks gestation) enrolled in Dhaka, Bangladesh between July 2009 and February 2010. Included: age 18 to <34 years, residence in Dhaka. Excluded: use of vitamin D supplements, anticonvulsants, antimycobacterials, severe anaemia, hypertension, risk factors for preterm delivery, pregnancy complications, prior delivery with congenital anomaly or perinatal death. Intervention: **Single dose of colecalciferol 70,000 IU.** Follow-up: Blood and urine samples taken at days 0, 2, 4, 7 days and weekly thereafter. Measured 25(OH)D, serum calcium and urinary calcium to creatinine ratio (ca:cr). Weekly checklist of symptoms of hypo- and hypercalcemia, blood pressure measurement, and confirmation of fetal viability.	Mean baseline 25(OH)D was 54 nmol/L (95% CI: 47-52) in non-pregnant participants and 39 nmol/L (95% CI: 34-45) in pregnant participants. The difference is at least partly due to differing seasons of enrolment. There was substantial inter-individual variation in 25(OH)D responses. The population-average pattern consisted of an abrupt increase in 25(OH)D in the first week, followed by a peak within the first three weeks, and then a gradual return to baseline over the ensuing two months (figure 7). The highest 25(OH)D in non-pregnant and pregnant participants was 164 nmol/L and 116 nmol/L, respectively. Overall, ΔCmax and AUC were similar in pregnant and non-pregnant women. 25(OH)D was an average of 19 nmol/L (95% CI, 14 to 25) higher than baseline during the first month after supplementation. Mean cord blood 25(OH)D (n=12) was 50 nmol/L (95% CI: 40-62; range: 29-80). **Figure 7: Serum 25(OH)D in non-pregnant (A) and pregnant (B) participants following a single dose of colecalciferol 70,000 IU.**  Mean serum Ca and urinary ca:cr were increased from baseline during follow-up. No episodes of confirmed maternal hypercalcemia, persistent hypercalciuria or neonatal hypercalcaemia. Pregnancy and birth outcome metrics were as expected for the study population. There was a stillbirth and neonatal death that were caused by placental abruption and respiratory failure, respectively. There was no evidence that either was related to the vitamin D supplementation.

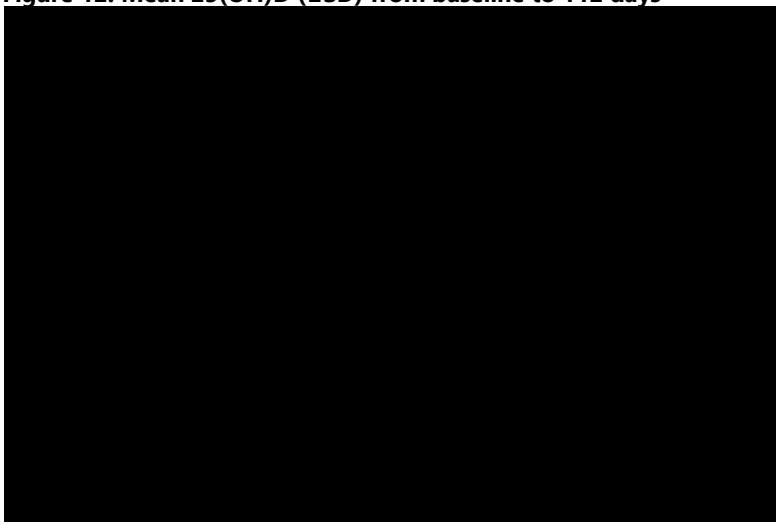
Publication	Methods	Results
Roth 2013 [70] Bangladesh NCT00938600	Participants: 28 pregnant women 27 to <31 weeks' gestation and 16 non-pregnant women enrolled between August 2009 and February 2010. Interventions: High dose: single dose of **70,000 IU colecalciferol followed by 35,000 IU weekly** until delivery (PH group) or for 10 weeks in non-pregnant participants (NH group). Low dose: 14,000 IU weekly until delivery (PL group). Follow-up: Participants provided blood and urine samples according to schedules A and B (high dose) and C (low dose). Measured 25(OH)D, albumin-adjusted serum calcium and urinary calcium to creatinine ratio (ca:cr), plus symptom checklist and blood pressure measurement. [redacted]	Baseline 25(OH)D (95% CI) was 57 nmol/L (47-69) in NH, 35 nmol/L (30-42) in PH and 31 nmol/L (26-38) in PL. Higher 25(OH)D in non-pregnant participants was at least partly due to differing seasons of enrolment. Mean 25(OH)D rose gradually in all groups (figure 8). Almost all (19/20) pregnant participants with levels at week 10 had 25(OH)D ≥50 nmol/L. All cord blood samples (n=23) showed 25(OH)D ≥50 nmol/L. Δ25(OH)D was higher in PH compared with PL (98 [89-109] vs 76 [61-95] nmol/L) and lower in PH compared with NH (98 [89-109] vs 139 [121-160] nmol/L) but these findings were not statistically significant. There was substantial inter-subject variability in response. Among PH/NH, there was a 7-fold difference between the lowest and highest Δ25(OH)D at week 10. Three NH participants had 25(OH)D >200 nmol/L, but the highest 25(OH)D in any pregnant participant was 153 nmol/L. **Figure 8: Changes in serum 25-hydroxyvitamin D concentration from baseline to day 70** [redacted] No episodes of confirmed maternal hypercalcaemia. One measurement of adj-Ca 2.61 mmol/L (PH group) – normal on same-day testing. 5 episodes of elevated ca:cr (3 in NH group and 2 in PL group). One PL participant had two consecutive elevated ca:cr measurements but serum Ca and subsequent ca:cr measurements were normal. No supplement-related clinical AEs. In PL and PH respectively, 3/12 (25%) and 1/12 (8%) of infants were preterm, 8/12 (67%) and 9/12 (75%) were SGA, and 4/12 (33%) and 2/12 (17%) had LBW. Clinical outcomes were as expected for the study population.

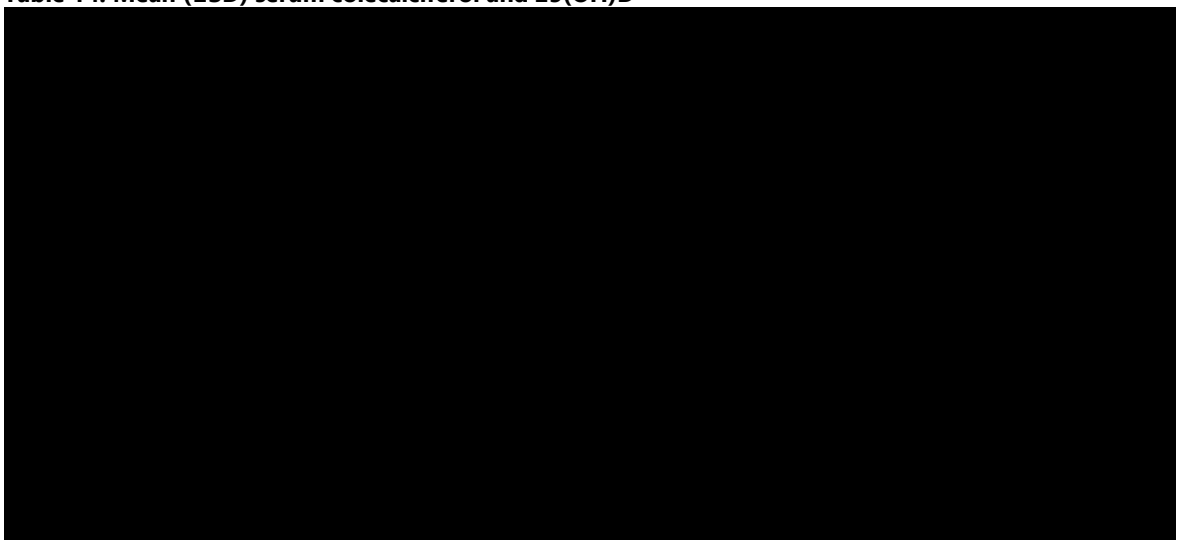
Table 12: Publications describing pharmacokinetics of high doses of vitamin D in non-pregnant participants

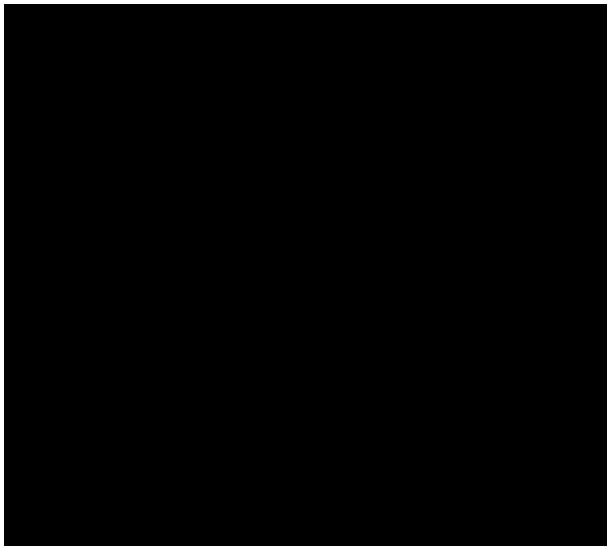
Publication	Methods	Results
De Niet 2018 [85] Belgium	Participants: 60 healthy Caucasian participants with vitamin D insufficiency in Belgium. Interventions: **2,000 IU daily OR 50,000 IU every 25 days** for 75 days. Cumulative dose 150,000 IU. Follow-up: Blood samples at screening and days 1, 2, 4, 7, 14, 25, 50, 75 and 105.	Serum 25(OH)D3 increased more rapidly in the monthly dosing group compared to the daily dosing group, and were significantly different between the groups at days 5, 10 and 15 (figure 9). The AUC D1–D75 of 25(OH)D was not significantly different between the groups. The maximum 25(OH)D level observed was 87.5 nmol/L in the monthly group and 105 nmol/L in the daily group at day 75. Increases in serum 1,25(OH)2D3 from baseline were significantly different between the treatment groups at day 2, 4, and 7 (figure 10). All participants achieved 25(OH)D3 >50 nmol/L. The authors concluded that daily and monthly dosing were similarly effective to increase 25(OH)D, but daily dosing takes two weeks longer to reach sufficiency. There were no treatment-related adverse effects or significant differences in laboratory parameters measured at baseline and the end of the study. **Figure 9: Mean change of 25(OH)D serum concentrations over time.** 

Publication	Methods	Results
		Figure 10: Mean change of 1,25(OH)2D3 serum concentrations over time. 

Fassio 2020 [86] Italy	Participants: 75 healthy Caucasian participants with 25(OH)D <20 ng/mL (<50 nmol/L) Interventions: Group A: 10,000 IU/day for eight weeks followed by 1000 IU/day for four weeks; Group B: 50,000 IU/week for 12 weeks, Group C: 100,000 IU/every other week for 12 weeks. Total cumulative doses were 588,000 IU, 600,000 IU and 600,000 IU, respectively. Follow-up: Blood samples for PK analysis were collected pre-dose on each of days 1, 7, 14, 21, 28, 35, 42, 49, 56, 63, 77, 84 during the treatment period and on each of days 85, 87, 89, 96, 103, and 112 of the follow-up period. Blood samples for calcium, albumin, and phosphate were collected pre-dose on day 1, 28, 56, 84 and 112.	There were 73 participants who completed the study. Mean 25(OH) levels increased from a baseline of 13.5 ± 3.7 ng/mL to peak values of 81.0 ± 15.0 ng/mL in Group A, 63.6 ± 7.9 ng/mL in Group B and 59.4 ± 12 ng/mL in Group C (figure 11). The maximum 25(OH)D observed was 113.6 ng/mL (284 nmol/L) in a participant in group A. The highest observed value seen in group B was 76.8 ng/mL (192 nmol/L). Systemic exposure was higher in group A compared to groups B and C (table 12). Absolute increase from baseline was also highest in Group A. Most participants achieved vitamin D repletion by day 14. At day 112, 98.5% of participants had 25(OH)D >30 ng/mL. There were no cases of hypercalcaemia. There were 118 AEs reported of which none were severe or serious. One event of mild constipation was considered related to treatment. **Figure 11: Mean 25(OH)D levels**  **Table 13: Pharmacokinetic parameters** 

Publication	Methods	Results
Mentaverri 2019 [87] France	Participants: 53 healthy adults in France. Interventions: A single oral dose using Kipos soft capsule (Group 1) OR Uvedose oral solution in ampoule (Group 2) of colecalciferol 100,000 IU. Follow-up: 25(OH)D measured on days 1, 3, 7, 14, 28, 45, 90 and 112. Serum calcium was measured on Days 0, 45, 90, 112 and PTH on days 0 and 112.	Serum 25(OH)D level in Group 1 was higher than in Group 2 at all time-points (figure 12). For group 1, mean serum 25(OH)D levels were between 20 and 30 ng/mL during the four months following administration of the soft capsule. Mean Cmax was 28.5 ± 5.0 ng/mL and Tmax was reached within 14 days for more than half of participants. The highest 25(OH)D concentration observed was 25.44 ng/mL on Day 7. Serum calcium remained stable during the study (2.3 mmol/L) in both groups. There were 12 participants with AEs – none were severe or related to treatment. **Figure 12: Mean 25(OH)D (±SD) from baseline to 112 days** 
Ilahi 2008 [88] USA	Participants: 30 healthy participants. Intervention: A single oral dose of **colecalciferol 100,000 IU**. Follow-up: Blood samples were taken on days 0, 1, 3, 5, 7, 14, 21, 28, 42, 56, 70, 84, 96, and 112. Serum calcium measured on days 0, 1, 3, 5, and 112. PTH measured on days 0 and 112.	Serum 25(OH)D rose from a mean baseline of 27.1 ± 7.7 ng/mL to a Cmax of 42.0 ± 9.1 ng/mL (figure 13). Median Tmax was 7 days. Mean values were similar to baseline by 84 days. Serum calcium did not rise at any time point and there were no cases of hypercalcaemia. **Figure 13: Time course of mean 25(OH)D (±SEM) from baseline to 112 days** 

Publication	Methods	Results
Meekins 2014 [89] USA	Participants: 39 healthy, non-pregnant, non-lactating females aged 18-40 years. Intervention: **Colecalciferol 5,000 IU daily for 28 days OR a single dose of 150,000 IU** Follow-up: Serum colecalciferol, 25(OH)D, calcium, and phosphorus were measured on days 0, 1, 3, 7, 14, and 28.	In the 150,000 IU group, the mean (±SD) serum colecalciferol peaked on day 1 at 236.5 ± 58.3 nmol/L, dropped sharply by day 3, and continued to fall on day 7. On days 14 and 28, colecalciferol was not detectable in 13 and 17 of 20 subjects, respectively. In the daily group, serum colecalciferol peaked at 27.9 nmol/L by day 14. There was no difference in serum cholecalciferol AUC28 between the two treatment groups (table 14). The 150,000 IU group showed a rapid rise in 25(OH)D concentration on day 1, which reached a peak value of 139.0 ± 26.0 nmol/L at day 7, and slowly declined thereafter but remained significantly higher than baseline values at days 14 and 28. The daily group had a gradual, almost linear increase in 25(OH)D concentrations, with no evidence of plateau at day 28. The 150,000 IU group had a significantly greater mean 25(OH)D AUC28 compared with the daily group. On days 3 and 7, serum calcium concentrations were higher than baseline in the 150,000 IU group but remained within the normal reference range. The highest observed serum calcium was 2.6 mmol/L in both treatment groups. **Table 14: Mean (±SD) serum colecalciferol and 25(OH)D** 

Publication	Methods	Results
Armas 2004 [90] USA	Participants: 30 healthy men Interventions: 50,000 IU ergocalciferol or 50,000 IU colecalciferol as a single dose, or no supplement. Follow-up: Blood samples were taken at 0 and 28 days in the control group, and at 0, 1, 3, 5–7, 14, and 28 days.	Blood ergocalciferol (D_2) and colecalciferol (D_3) levels peaked after 1 day and were similar between groups, indicating similar extent of absorption. Mean change in 25(OH)D was greater in the colecalciferol group. The values in figure 14 were corrected for the change measured in the control population. Absolute values of 25(OH)D are not presented, including at baseline. AUC28 was 60.2 ± 23.4 ng.d/ml (150.5 ± 58.5 nmol.d/L) for D2 and 204.7 ± 32.4 ng.d/ml (511.8 ± 80.9 nmol.dl) for D3 (P < 0.002). Serum calcium was not measured. **Figure 14: Mean (±SEM) serum 25(OH)D** 

3.5 Literature case reports

Case reports describing infant hypercalcaemia following maternal intake of vitamin D are summarised in table 15 below. No case reports describing teratogenesis or congenital malformations were identified. Case reports of disordered vitamin metabolism in pregnancy due to loss of function CYP24A1 mutations are not included.

Table 15: Literature case reports

Author, year	Maternal dose	Summary
Altunhan et al, 2013 [91]	300,000 IU weekly for last 40 days of pregnancy	**A severe neonatal hypercalcemia case due to maternal high dose vitamin D usage** A 9-day-old baby boy was admitted with fever, diminished suction, vomiting and weight loss and was found to have severe hypercalcaemia (total calcium 19.2 mg/dl [9-10.6]) and nephrocalcinosis. His 25(OH) vitamin D level was 480 ng/ml (10-80). The mother had a serum total calcium of 13.6 mg/dL and a 25(OH) vitamin D level of 430 ng/ml (20-80). A history revealed that she had been taking 300,000 IU vitamin D orally weekly for last 40 days of pregnancy. The baby's hypercalcaemia was attributed to excessive vitamin D intake via breastmilk.
Küçükali et al, 2021 [92]	1,500,000 IU every other day for the last 5 weeks of gestation	**Perinatal outcomes of high-dose vitamin D administration in the last trimester** A baby boy was born prematurely by caesarean section due to bradycardia, which required positive pressure ventilation followed by NICU admission. On the postnatal fifth day, serum calcium level was 10.8 (N: 8.9-10.8) mg/dL, ionized calcium: 1.44 (N: 1-1.3) mg/dL which increased to 12 mg/dL and 1.57 mg/dL, respectively. Enquiry revealed that the mother had taken 1,500,000 IU vitamin D orally every other day during the last five weeks of gestation due to a medication error. The intended dose was 150,000 IU. The maternal 25-OH-vitamin D was 142 ng/mL and she was found to have nephrocalcinosis. The infant's 25-hydroxyvitamin D levels gradually decreased. However, hypercalcemia persisted for 3.5 months and troponin I elevation, hypoxic-ischemic encephalopathy (HIE) and platelet elevation were also observed.
Marx et al, 1980 [93]	17-36 mcg 1,25(OH)D daily	**Normal intrauterine development of the fetus of a woman receiving extraordinarily high doses of 1,25-dihydroxyvitamin D3** A 28-yr-old patient with hereditary insensitivity to 1,25(OH)2D received 17-36 mcg 1,25(OH)D daily. Serum concentrations of 1,25(OH)2D were very high throughout gestation. At parturition, the calcium concentration was 9.6 mg/dl in maternal serum and 10.2 mg/dl in cord serum. The concentration of total 1,25-(OH)2D in cord serum was high (470 pg/ml). The child manifested mild hypercalcemia in the first 2 days of life but was otherwise healthy.

Reynolds et al, 2017 [94]	4,000 IU daily throughout pregnancy	**Transient neonatal hypercalcaemia secondary to excess maternal vitamin D intake: too much of a good thing** A baby girl was incidentally found to have hypercalcaemia at 5 on day 5 of life. Her total serum calcium was 3.09 mmol/L (1.9-2.6), with an ionised calcium level of 1.47 mmol/L (1-1.5). Her 25-hydroxyvitamin D concentration was at the upper end of the normal range (73 nmol/L) (50-75). Her parathyroid hormone level was appropriately suppressed (5 ng/L). Subsequent enquiry revealed a history of excessive maternal vitamin D intake. From several months prior to conception, the patient's mother had been taking two supplements: one multivitamin capsule containing 1000 IU vitamin D3 three times per day and one 1000 IU vitamin D3 oral spray once per day. The total daily vitamin D3 intake was 4000 IU. While the mother's own total serum calcium (2.38 mmol/L) concentration was normal, her 25-OH vitamin D was very elevated (127 nmol/L) and her parathyroid hormone (PTH) level was appropriately suppressed (13 ng/L). Despite the elevated total serum calcium, the baby remained clinically well. Renal ultrasound showed no evidence of nephrocalcinosis. Routine vitamin D supplementation was withheld. The infant continued to breast feed exclusively. The total serum calcium level was monitored and found to be elevated on several more occasions, but dropped to the normal range within 2 weeks.

4 DISCUSSION AND CONCLUSIONS

Medsafe was requested by New Zealand Formulary to review the contraindication to use in pregnancy for colecalciferol 50,000 IU capsules.

Most international product information documents for colecalciferol 50,000 IU capsule presentations recommend against use in pregnancy and state that a lower strength formulation should be used. Some products in the UK and Ireland list a contraindication to use in pregnancy. Product information generally states that teratogenicity was observed in animal studies at doses much higher than those used therapeutically in humans. Some product information notes that prolonged maternal hypercalcaemia during pregnancy may pose risks of congenital disorders and neonatal hypoparathyroidism.

Position statements and guidance generally recommend daily doses of 400 to 800 IU colecalciferol for the prevention of vitamin D deficiency in pregnant women, or 1,000 to 2,000 IU daily for the treatment of identified deficiency. Doses up to 4,000 IU daily are considered safe. New Zealand Formulary states that a dose of 50,000 IU monthly can be used for documented deficiency in pregnancy. However, no other guidance was located that recommends the use of monthly bolus doses in pregnancy. [1, 5, 39, 95]

It is noted that the daily doses recommended in guidance for correction of deficiency (ie, up to 4,000 IU) can be achieved by using the funded liquid colecalciferol supplement (ie, up to 10 drops daily).

There is limited data from clinical studies to support the safety or efficacy of a dosage regimen of 50,000 IU colecalciferol monthly in pregnancy. Many studies investigating similar bolus doses report safety parameters at baseline and delivery only. In studies where calcium was measured periodically during pregnancy, cases of hypercalcaemia were not identified. For example, a pharmacokinetic study in a small number of pregnant women who received 70,000 IU as a single dose or followed by 35,000 IU weekly measured vitamin D levels and calcium during the first days and weeks of treatment and periodically thereafter and did not identify cases of hypercalcaemia. [70, 71] Overall, the available clinical data do not highlight adverse pregnancy or neonatal outcomes following treatment with bolus doses but are insufficient to draw conclusions on safety.

The clinical and pharmacokinetic studies highlight substantial interindividual variation in vitamin D levels seen during the course of treatment. For example, the same study mentioned above found a 7-fold difference between the lowest and highest increase in 25(OH)D after 10 weeks of treatment. The data suggest that a proportion of individuals may achieve vitamin D levels significantly higher than necessary for bone health following a single dose of 70,000 IU. However, the study population included individuals who were vitamin D sufficient at baseline.

Pharmacokinetic data in non-pregnant individuals comparing a cumulative dose of colecalciferol 300,000 IU administered as 2,000 IU daily or 50,000 IU every 25 days found a similar AUC for 25(OH)D between the two regimens. There was a significantly higher level of 1,25(OH)D3 during the week following a dose of 50,000 IU, compared to an equivalent daily dose. [85] The safety implications of this are not known. 1,25(OH)D3 is not thought to cross the placenta. Other pharmacokinetic studies of colecalciferol 100,000 IU as a single dose and 5,000 IU daily for 28 days versus 150,000 IU as a single dose did not identify cases of hypercalcemia.

Hypercalcaemia is the recognised safety concern associated with vitamin D treatment. Based on the experiences of women with primary hyperparathyroidism, prolonged maternal hypercalcaemia has been associated with substantial fetal morbidity. It is unknown whether transiently elevated maternal vitamin D, 1,25(OH)D or serum calcium pose a risk to the fetus or whether fetal calcium metabolism can be altered in the absence of maternal changes. Three case reports were identified in the literature of neonatal hypercalcaemia following maternal vitamin D intake of 300,000 IU weekly, 1,500,000 IU every other day and 4,000 IU daily, respectively. No case reports of teratogenicity/congenital malformations were identified in the literature.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether any changes to the colecalciferol data sheet information on use in pregnancy are recommended based on the available clinical data.

6 ANNEXES

None.

7 REFERENCES

1. Health New Zealand. 2024. *Companion statement on vitamin d and sun exposure in pregnancy and infancy in New Zealand* 7 June 2024. URL: https://www.tewhatuora.govt.nz/publications/companion-statement-on-vitamin-d-and-sun-exposure-in-pregnancy-and-infancy-in-new-zealand (accessed 24 September 2025).
2. Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. 2011. Vitamin D upper levels: intake-response assessment and specification of upper levels. In: A. Catharine Ross, Christine L Taylor, Ann L Yaktine, et al. (Eds). *Dietary Reference Intakes for Calcium and Vitamin D*. Washington (DC): National Academies Press.
3. Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. 2011. Vitamin D: dietary reference intakes for adequacy. In: A. Catharine Ross, Christine L Taylor, Ann L Yaktine, et al. (Eds). *Dietary Reference Intakes for Calcium and Vitamin D*. Washington (DC): National Academies Press.
4. Ministry of Health and Cancer Society of New Zealand. 2012. *Ministry of Health and Cancer Society of New Zealand. 2012. Consensus Statement on Vitamin D and Sun Exposure in New Zealand* 14 March 2012. URL: https://www.health.govt.nz/publications/consensus-statement-on-vitamin-d-and-sun-exposure-in-new-zealand (accessed 22 April 2026).
5. Specialist Pharmacy Service. 2025. *Vitamin D deficiency: treatment during pregnancy* 5 March 2025. URL: https://www.sps.nhs.uk/articles/vitamin-d-deficiency-treatment-during-pregnancy/ (accessed 23 September 2025).

6. Mason K, Templeton R and Weerasekera D. 2012. *Vitamin D status of New Zealand adults: Findings from the 2008/09 New Zealand adult nutrition survey.* Ministry of Health.
7. Ekeroma AJ, Camargo CA, Jr., Scragg R, et al. 2015. Predictors of vitamin D status in pregnant women in New Zealand. *N Z Med J* 128(1422): 24-34. (accessed 6 May 2026).
8. Wheeler BJ, Taylor BJ, De Lange M, et al. 2018. A Longitudinal Study of 25-Hydroxy Vitamin D and Parathyroid Hormone Status throughout Pregnancy and Exclusive Lactation in New Zealand Mothers and Their Infants at 45° S. *Nutrients* 10(1): 86. URL: https://www.mdpi.com/2072-6643/10/1/86 (accessed 6 May 2026).
9. DeLuca HF. 2004. Overview of general physiologic features and functions of vitamin D. *The American Journal of Clinical Nutrition* 80(6): 1689S-1696S. DOI: 10.1093/ajcn/80.6.1689S (accessed 6 May 2026).
10. Park CY and Han SN. 2021. The Role of Vitamin D in Adipose Tissue Biology: Adipocyte Differentiation, Energy Metabolism, and Inflammation. *J Lipid Atheroscler* 10(2): 130-144. DOI: 10.12997/jla.2021.10.2.130 (accessed 22 April 2026).
11. Wamberg L, Christiansen T, Paulsen SK, et al. 2013. Expression of vitamin D-metabolizing enzymes in human adipose tissue—the effect of obesity and diet-induced weight loss. *International Journal of Obesity* 37(5): 651-657. DOI: 10.1038/ijo.2012.112 (accessed 22 April 2026).
12. Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. 2011. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington (DC): National Academies Press.
13. Kovacs CS. 2016. Maternal Mineral and Bone Metabolism During Pregnancy, Lactation, and Post-Weaning Recovery. *Physiological Reviews* 96(2): 449-547. DOI: 10.1152/physrev.00027.2015 (accessed 1 May 2026).
14. J L Lewis III. 2025. *Hypercalcaemia* June 2025. URL: https://www.msdmanuals.com/professional/nephrology/electrolyte-disorders/hypercalcemia (accessed 24 April 2026).
15. Committee on Toxicity. 2022. *Statement on the potential effects of excess vitamin D intake during preconception, pregnancy and lactation* 17 November 2022. URL: https://cot.food.gov.uk/2022-statementsandpositionpapers (accessed 29 September 2025).
16. Roth DE. 2011. Vitamin D supplementation during pregnancy: Safety considerations in the design and interpretation of clinical trials. *Journal of Perinatology* 31(7): 449-459. DOI: 10.1038/jp.2010.203
17. Galior K, Grebe S and Singh R. 2018. Development of Vitamin D Toxicity from Overcorrection of Vitamin D Deficiency: A Review of Case Reports. *Nutrients* 10(8): DOI: 10.3390/nu10080953 (accessed 13 April 2026).
18. Lee JP, Tansey M, Jetton JG, et al. 2018. Vitamin D Toxicity: A 16-Year Retrospective Study at an Academic Medical Center. *Lab Med* 49(2): 123-129. DOI: 10.1093/labmed/lmx077 (accessed 13 April 2026).
19. Laubenthal F, Reichenberger M and Reinwein D. 1975. Vitamin-D-Intoxikation mit tödlichem Ausgang. *Dtsch Med Wochenschr* 100(09): 412-415. DOI: 10.1055/s-0028-1106229 (accessed 15 April 2026).
20. Bauer J and Freyberg R. 1946. Vitamin D intoxication with metastatic calcification. *Journal of the American Medical Association* 130: 1208–1215. (accessed 15 April 2026).
21. Narsaria P, Sankar J and Lodha R. 2016. Fatal Outcome of Accidental Vitamin D Overdose. *The Indian Journal of Pediatrics* 83(9): 1040-1040. DOI: 10.1007/s12098-016-2109-z (accessed 15 April 2026).
22. Hoegberg LCG and Boegevig S. 2018. Pediatric vitamin D poisoning: A review of the literature. *Clinical Toxicology* 56(6): 551-552. DOI: 10.1080/15563650.2018.1457818 (accessed 15 April 2026).
23. Taylor PN and Davies JS. 2018. A review of the growing risk of vitamin D toxicity from inappropriate practice. *Br J Clin Pharmacol* 84(6): 1121-1127. DOI: 10.1111/bcp.13573 (accessed 13 April 2026).
24. Burt LA, Billington EO, Rose MS, et al. 2019. Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength: A Randomized Clinical Trial. *JAMA* 322(8): 736-745. DOI: 10.1001/jama.2019.11889 (accessed 28 April 2026).
25. McCarthy A, Howarth S, Khoo S, et al. 2019. Management of primary hyperparathyroidism in pregnancy: a case series. *Endocrinology, Diabetes & Metabolism Case Reports* 2019: 19-0039. DOI: 10.1530/edm-19-0039 (accessed 17 April 2026).

26. Multichem NZ Limited. 2025. *Vit.D3 New Zealand data sheet* 6 May 2025. URL: https://www.medsafe.govt.nz/profs/Datasheet/v/VitD3cap.pdf (accessed 18 May 2026).
27. Health New Zealand. 2025. *Pharmaceutical data web tool* 14 August 2025. URL: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 6 May 2026).
28. Key Pharmaceuticals Pty Ltd. 2024. *Ostevit-D One-A-Week Australian product information* 9 July 2024. URL: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2024-PI-02237-1&d=20260518172310101 (accessed 18 May 2026).
29. Crescent Pharma Limited. 2025. *Colecalciferol 50,000 IU summary of product characteristics* 14 April 2025. URL: https://mhraproducts4853.blob.core.windows.net/docs/0e78f6a7313b0790b4001b2d3a7510494c91c076 (accessed 18 May 2025).
30. IBSA Farmaceutici Italia S.r.l. 2024. *Ditralia 50 000 IU summary of product characteristics* 27 September 2024. URL: https://mhraproducts4853.blob.core.windows.net/docs/9a113a2e36bd080bde1c354f7e6dd4f518216608 (accessed 18 May 2026).
31. Galen Limited. 2024. *Deltius 50,000 IU summary of product characteristics* 27 June 2024. URL: https://mhraproducts4853.blob.core.windows.net/docs/753c3febe57e53d2336b8f6057c331ed2e98df72 (accessed 18 May 2026).
32. Osgen Pharmaceuticals Limited. 2022. *Choli-D3 50,000 IU summary of product characteristics* 22 December 2022. URL: https://mhraproducts4853.blob.core.windows.net/docs/f86296623bbbb24c1d24ab7cf0df45bca1d9170c (accessed 18 May 2026).
33. Consilient Health Limited. 2016. *InVita D3 50,000 IU summary of product characteristics* 21 July 2016. URL: https://mhraproducts4853.blob.core.windows.net/docs/7d0911bc4b489db329f664e74f2d48ecb8c0d003 (accessed 18 May 2026).
34. Consilient Health Limited. 2024. *altavitaD3 50,000 IU summary of product characteristics* February 2024. URL: https://assets.hpra.ie/products/Human/29643/Licence_PA1876-004-004_08022024131905.pdf (accessed 18 May 2026).
35. Euro-Pharm International Canada Inc. 2023. *Euro-D 50 000 IU* 10 November 2023. URL: https://pdf.hres.ca/dpd_pm/00073525.PDF (accessed 18 May 2026).
36. JAMP Pharma Corporation. 2023. *JAMP-Vitamin D prescribing information* 30 October 2023. URL: https://pdf.hres.ca/dpd_pm/00073300.PDF (accessed 18 May 2026).
37. Pharmin USA L. 2017. *Decalcitrol prescribing information* 28 December 2017. URL: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c5475e39-3d34-40f9-abf9-cb1af73c4c6c (accessed 18 May 2026).
38. Wheeler BJ, Dickson NP, Houghton LA, et al. 2015. Incidence and characteristics of vitamin D deficiency rickets in New Zealand children: a New Zealand Paediatric Surveillance Unit study. *Australian and New Zealand Journal of Public Health* 39(4): 380-383. DOI: https://doi.org/10.1111/1753-6405.12390 (accessed 14 May 2026).
39. American College of Obstetricians and Gynaecologists. 2011. *Vitamin D: Screening and supplementation during pregnancy* July 2011. URL: www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2011/07/vitamin-d-screening-and-supplementation-during-pregnancy (accessed 24 September 2025).
40. World Health Organization. 2020. *WHO antenatal care recommendations for a positive pregnancy experience. Nutritional interventions update: Vitamin D supplements during pregnancy.* URL: https://www.who.int/publications/i/item/9789240008120 (accessed 18 May 2026).
41. Palacios C, Kostiuk LL, Cuthbert A, et al. 2024. Vitamin D supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews* URL:https://doi.org//10.1002/14651858.CD008873.pub5, DOI:10.1002/14651858.CD008873.pub5(7): DOI: 10.1002/14651858.CD008873.pub5 (accessed 1 October 2025).

42. Roth DE, Al Mahmud A, Raqib R, et al. 2013. Randomized placebo-controlled trial of high-dose prenatal third-trimester vitamin D3 supplementation in Bangladesh: the AViDD trial. *Nutrition Journal* 12(1): 47. DOI: 10.1186/1475-2891-12-47 (accessed 2 October 2025).
43. Roth DE, Morris SK, Zlotkin S, et al. 2018. Vitamin D Supplementation in Pregnancy and Lactation and Infant Growth. *New England Journal of Medicine* 379(6): 535-546. DOI: doi:10.1056/NEJMoa1800927 (accessed 14 October 2025).
44. Sablok A, Batra A, Thariani K, et al. 2015. Supplementation of vitamin D in pregnancy and its correlation with feto-maternal outcome. *Clinical Endocrinology* 83(4): 536-541. DOI: https://doi.org/10.1111/cen.12751 (accessed 14 October 2025).
45. Yu CKH, Sykes L, Sethi M, et al. 2009. Vitamin D deficiency and supplementation during pregnancy. *Clinical Endocrinology* 70(5): 685-690. DOI: https://doi.org/10.1111/j.1365-2265.2008.03403.x (accessed 14 October 2025).
46. Rodda CP, Benson JE, Vincent AJ, et al. 2015. Maternal vitamin D supplementation during pregnancy prevents vitamin D deficiency in the newborn: an open-label randomized controlled trial. *Clinical Endocrinology* 83(3): 363-368. DOI: https://doi.org/10.1111/cen.12762 (accessed 1 October 2025).
47. Khan FR, Ahmad T, Hussain R, et al. 2016. A Randomized Controlled Trial of Oral Vitamin D Supplementation in Pregnancy to Improve Maternal Periodontal Health and Birth Weight. *Journal of International Oral Health* 8(6): 657-665. DOI: 10.2047/jioh-08-06-03 (accessed 2 October 2025).
48. Khan FR, Iqbal NT, Ahmed K, et al. 2017. Effect of Vitamin D Supplementation on the Salivary Cytokines of Pregnant Women: A Randomized Placebo-Controlled Trial. *J Int Acad Periodontol* 19(4): 118-125. (accessed 2 October 2025).
49. Diogenes ME, Bezerra FF, Rezende EP, et al. 2013. Effect of calcium plus vitamin D supplementation during pregnancy in Brazilian adolescent mothers: a randomized, placebo-controlled trial. *Am J Clin Nutr* 98(1): 82-91. DOI: 10.3945/ajcn.112.056275 (accessed 2 October 2025).
50. Grant CC, Stewart AW, Scragg R, et al. 2014. Vitamin D During Pregnancy and Infancy and Infant Serum 25-Hydroxyvitamin D Concentration. *Pediatrics* 133(1): e143-e153. DOI: 10.1542/peds.2013-2602 (accessed 2 October 2025).
51. Cooper C, Harvey NC, Bishop NJ, et al. 2016. Maternal gestational vitamin D supplementation and offspring bone health (MAVIDOS): a multicentre, double-blind, randomised placebo-controlled trial. *The Lancet Diabetes & Endocrinology* 4(5): 393-402. DOI: 10.1016/S2213-8587(16)00044-9 (accessed 2 October 2025).
52. Curtis EM, Parsons C, Maslin K, et al. 2021. Bone turnover in pregnancy, measured by urinary CTX, is influenced by vitamin D supplementation and is associated with maternal bone health: findings from the Maternal Vitamin D Osteoporosis Study (MAVIDOS) trial. *Am J Clin Nutr* 114(5): 1600-1611. DOI: 10.1093/ajcn/nqab264 (accessed 25 March 2026).
53. Lautatzis M-E, Keya FK, Al Mahmud A, et al. 2024. Maternal Vitamin D Supplementation and Infantile Rickets: Secondary Analysis of a Randomized Trial. *Pediatrics* 153(6): DOI: 10.1542/peds.2023-063263 (accessed 25 March 2026).
54. O'Callaghan KM, Shanta SS, Fariha F, et al. 2022. Effect of maternal prenatal and postpartum vitamin D supplementation on offspring bone mass and muscle strength in early childhood: follow-up of a randomized controlled trial. *Am J Clin Nutr* 115(3): 770-780. DOI: 10.1093/ajcn/nqab396 (accessed 25 March 2026).
55. Taghivand M, Pell LG, Rahman MZ, et al. 2022. Effect of maternal vitamin D supplementation on nasal pneumococcal acquisition, carriage dynamics and carriage density in infants in Dhaka, Bangladesh. *BMC Infect Dis* 22(1): 52. DOI: 10.1186/s12879-022-07032-y (accessed 25 March 2026).
56. Morris SK, Pell LG, Rahman MZ, et al. 2021. Effects of Maternal Vitamin D Supplementation During Pregnancy and Lactation on Infant Acute Respiratory Infections: Follow-up of a Randomized Trial in Bangladesh. *J Pediatric Infect Dis Soc* 10(9): 901-909. DOI: 10.1093/jpids/piab032 (accessed 25 March 2026).

57. Vafaei H, Asadi N, Kasraeian M, et al. 2019. Positive effect of low dose vitamin D supplementation on growth of fetal bones: A randomized prospective study. *Bone* 122: 136-142. DOI: https://doi.org/10.1016/j.bone.2019.02.022 (accessed 14 October 2025).
58. Aggarwal N, Singla R, Dutta U, et al. 2022. Prevalence of Vitamin D deficiency among pregnant women and effect of Vitamin D supplementation on maternal and fetal outcomes: A double-blind randomized placebo controlled trial. *Asian Journal of Medical Sciences* 13(2): 95-101. DOI: 10.3126/ajms.v13i2.40639 (accessed 17 February 2026).
59. Bimson B, Brustman L, Al Ibraheemi Z, et al. 2017. 647: Can weekly vitamin d dosing adequately treat vitamin d deficiency in pregnancy? *American Journal of Obstetrics & Gynecology* 216(1): S380-S381. DOI: 10.1016/j.ajog.2016.11.381 (accessed 17 February 2026).
60. Bhowmik B, Siddiquee T, Mdala I, et al. 2021. Vitamin D3 and B12 supplementation in pregnancy. *Diabetes Research and Clinical Practice* 174: 108728. DOI: https://doi.org/10.1016/j.diabres.2021.108728 (accessed 25 March 2026).
61. Das V, Agarwal A, Bhatia V, et al. 2009. O205 Evaluation of Vit D status and need for supplementation in pregnant women of a rural area of North India. *International Journal of Gynecology & Obstetrics* 107(S2): S151-S151. DOI: https://doi.org/10.1016/S0020-7292(09)60577-4 (accessed 2026/02/16).
62. Etemadifar M and Janghorbani M. 2015. Efficacy of high-dose vitamin D3 supplementation in vitamin D deficient pregnant women with multiple sclerosis: Preliminary findings of a randomized-controlled trial. *Iran J Neurol* 14(2): 67-73. (accessed 26 Febuary 2026).
63. Goldring ST, Griffiths CJ, Martineau AR, et al. 2013. Prenatal vitamin d supplementation and child respiratory health: a randomised controlled trial. *PLoS One* 8(6): e66627. DOI: 10.1371/journal.pone.0066627 (accessed 18 March 2026).
64. Hashemipour S, Ziaee A, Javadi A, et al. 2014. Effect of treatment of vitamin D deficiency and insufficiency during pregnancy on fetal growth indices and maternal weight gain: a randomized clinical trial. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 172: 15-19. DOI: https://doi.org/10.1016/j.ejogrb.2013.10.010
65. Kabuyanga RK, Tugirimana PL, Sifa B, et al. 2024. Effect of early vitamin D supplementation on the incidence of preeclampsia in primigravid women: a randomised clinical trial in Eastern Democratic Republic of the Congo. *BMC Pregnancy and Childbirth* 24(1): 107. DOI: 10.1186/s12884-024-06277-6 (accessed 18 May 2026).
66. Kalra P, Das V, Agarwal A, et al. 2012. Effect of vitamin D supplementation during pregnancy on neonatal mineral homeostasis and anthropometry of the newborn and infant. *Br J Nutr* 108(6): 1052-8. DOI: 10.1017/s0007114511006246 (accessed 17 February 2026).
67. Marya RK, Rathee S, Lata V, et al. 1981. Effects of vitamin D supplementation in pregnancy. *Gynecol Obstet Invest* 12(3): 155-61. DOI: 10.1159/000299597
68. Prabhakar P, Faridi MMA, Aggarwal A, et al. 2024. Effect of Antenatal Oral Vitamin D Supplementation on Serum 25(OH)D Concentration in Exclusively Breastfed Infants at 6 Months of age - A Randomized Double-Blind Placebo-Controlled Trial. *Indian Pediatr* 61(6): 533-539. (accessed 25 March 2026).
69. Rostami M, Tehrani FR, Simbar M, et al. 2018. Effectiveness of Prenatal Vitamin D Deficiency Screening and Treatment Program: A Stratified Randomized Field Trial. *The Journal of Clinical Endocrinology & Metabolism* 103(8): 2936-2948. DOI: 10.1210/jc.2018-00109 (accessed 19 February 2026).
70. Roth DE, Mahmud AA, Raqib R, et al. 2013. Pharmacokinetics of High-Dose Weekly Oral Vitamin D3 Supplementation during the Third Trimester of Pregnancy in Dhaka, Bangladesh. *Nutrients* 5(3): 788-810. DOI: https://doi.org/10.3390/nu5030788 (accessed 16 February 2026).
71. Roth DE, Al Mahmud A, Raqib R, et al. 2012. Pharmacokinetics of a single oral dose of vitamin D3 (70,000 IU) in pregnant and non-pregnant women. *Nutr J* 11: 114. DOI: 10.1186/1475-2891-11-114 (accessed 10 February 2026).
72. Sahoo SK, Katam KK, Das V, et al. 2017. Maternal vitamin D supplementation in pregnancy and offspring outcomes: a double-blind randomized placebo-controlled trial. *Journal of Bone and Mineral Metabolism* 35(4): 464-471. DOI: 10.1007/s00774-016-0777-4

73. Shakiba M and Iranmanesh MR. 2013. Vitamin D requirement in pregnancy to prevent deficiency in neonates: a randomised trial. *Singapore Med J* 54(5): 285-8. DOI: 10.11622/smedj.2013110 (accessed 19 February 2026).
74. Singh S, Garg R, Meena A, et al. 2021. Perinatal outcome in vitamin D deficiency and effect of oral and intramuscular vitamin D3 supplementation in antenatal women on pregnancy outcomes. *Journal of SAFOG (South Asian Federation of Obstetrics and Gynaecology)* 13(3): 86–89. DOI: 10.5005/jp-journals-10006-1888 (accessed 19 February 2026).
75. Soheilykhah S, Mojibian M, Moghadam MJ, et al. 2013. The effect of different doses of vitamin D supplementation on insulin resistance during pregnancy. *Gynecol Endocrinol* 29(4): 396-9. DOI: 10.3109/09513590.2012.752456
76. Bhavya Swetha RV, Samal R and George CE. 2020. The Effect of Vitamin D Supplementation on Improving Glycaemic Control in Diabetic Vitamin D-Deficient Pregnant Women: A Single-Blinded Randomized Control Trial. *J Obstet Gynaecol India* 70(2): 119-125. DOI: 10.1007/s13224-019-01289-1 (accessed 17 February 2026).
77. Huang S, Fu J, Zhao R, et al. 2021. The effect of combined supplementation with vitamin D and omega-3 fatty acids on blood glucose and blood lipid levels in patients with gestational diabetes. *Annals of Palliative Medicine* 10(5): 5652-5658. URL: https://apm.amegroups.org/article/view/70427 (accessed 18 February 2026).
78. Kumari S, Jena SK, Singh S, et al. 2025. Effect of Vitamin D Supplementation on Glycemic Control and Perinatal Outcomes Among Women with Gestational Diabetes Mellitus Having Vitamin D Deficiency: A Randomized Controlled Trial. *The Journal of Obstetrics and Gynecology of India* URL:https://doi.org/10.1007/s13224-025-02290-7, DOI:10.1007/s13224-025-02290-7: DOI: 10.1007/s13224-025-02290-7
79. Mojibian M, Soheilykhah S, Fallah Zadeh MA, et al. 2015. The effects of vitamin D supplementation on maternal and neonatal outcome: A randomized clinical trial. *Iran J Reprod Med* 13(11): 687-96. (accessed 19 February 2026).
80. Razavi M, Jamilian M, Samimi M, et al. 2017. The effects of vitamin D and omega-3 fatty acids co-supplementation on biomarkers of inflammation, oxidative stress and pregnancy outcomes in patients with gestational diabetes. *Nutr Metab (Lond)* 14: 80. DOI: 10.1186/s12986-017-0236-9 (accessed 19 February 2017).
81. Sedighi K, Shahbazi R, Boushehri E, et al. 2020. Effect of Vitamin D3 Supplementation on Fasting Plasma Glucose, Insulin Resistance and Lipid Profile in Women with Gestational Diabetes Mellitus: A Double-blind Randomized Controlled Clinical Trial. (accessed 19 February 2026).
82. Valizadeh M, Piri Z, Mohammadian F, et al. 2016. The Impact of Vitamin D Supplementation on Post-Partum Glucose Tolerance and Insulin Resistance in Gestational Diabetes: A Randomized Controlled Trial. *Int J Endocrinol Metab* 14(2): e34312. DOI: 10.5812/ijem.34312 (accessed 18 February 2026).
83. Yazdchi R, Gargari BP, Asghari-Jafarabadi M, et al. 2016. Effects of vitamin D supplementation on metabolic indices and hs-CRP levels in gestational diabetes mellitus patients: a randomized, double-blinded, placebo-controlled clinical trial. *Nutr Res Pract* 10(3): 328-35. DOI: 10.4162/nrp.2016.10.3.328 (accessed 18 February 2026).
84. Zhang Q, Cheng Y, He M, et al. 2016. Effect of various doses of vitamin D supplementation on pregnant women with gestational diabetes mellitus: A randomized controlled trial. *Exp Ther Med* 12(3): 1889-1895. DOI: 10.3892/etm.2016.3515 (accessed 19 February 2026).
85. De Niet S, Coffiner M, Da Silva S, et al. 2018. A Randomized Study to Compare a Monthly to a Daily Administration of Vitamin D_3 Supplementation. *Nutrients* 10(6): DOI: 10.3390/nu10060659 (accessed 10 February 2026).
86. Fassio A AG, Rossini M, Giollo A, Caimmi C, Bixio R, Viapiana O, Milleri S, Gatti M, Gatti D. 2020. Pharmacokinetics of Oral Cholecalciferol in Healthy Subjects with Vitamin D Deficiency: A Randomized Open-Label Study. *Nutrients* 12(6): 1553. DOI: https://doi.org/10.3390/nu12061553 (accessed 10 February 2026).

87. Mentaverri R, Souberbielle JC, Brami G, et al. 2019. Pharmacokinetics of a New Pharmaceutical Form of Vitamin D3 100,000 IU in Soft Capsule. *Nutrients* 11(3): DOI: 10.3390/nu11030703 (accessed 13 April 2026).
88. Ilahi M, Armas LA and Heaney RP. 2008. Pharmacokinetics of a single, large dose of cholecalciferol. *Am J Clin Nutr* 87(3): 688-91. DOI: 10.1093/ajcn/87.3.688 (accessed 13 April 2026).
89. Meekins ME, Oberhelman SS, Lee BR, et al. 2014. Pharmacokinetics of daily versus monthly vitamin D3 supplementation in non-lactating women. *Eur J Clin Nutr* 68(5): 632-4. DOI: 10.1038/ejcn.2013.278 (accessed 13 April 2026).
90. Armas LAG, Hollis BW and Heaney RP. 2004. Vitamin D2 Is Much Less Effective than Vitamin D3 in Humans. *The Journal of Clinical Endocrinology & Metabolism* 89(11): 5387-5391. DOI: 10.1210/jc.2004-0360 (accessed 14 April 2026).
91. Altunhan H, Annagur A, Konak M, et al. 2013. A severe neonatal hypercalcemia case due to maternal high dose vitamin D usage. *Acta Medica Anatolia* 1(1): 33-34. URL: https://www.ingentaconnect.com/content/doaj/21482357 (accessed 2 February 2026).
92. Karacan Küçükali G, Keskin M, Savaş Erdeve Ş, et al. 2021. Perinatal outcomes of high-dose vitamin D administration in the last trimester. *Turk J Obstet Gynecol* 18(2): 159-162. DOI: 10.4274/tjod.galenos.2021.90023 (accessed 5 February 2026).
93. Marx SJ, Swart EG, Jr., Hamstra AJ, et al. 1980. Normal intrauterine development of the fetus of a woman receiving extraordinarily high doses of 1,25-dihydroxyvitamin D3. *J Clin Endocrinol Metab* 51(5): 1138-42. DOI: 10.1210/jcem-51-5-1138 (accessed 24 March 2025).
94. Reynolds A, O'Connell SM, Kenny LC, et al. 2017. Transient neonatal hypercalcaemia secondary to excess maternal Vitamin D intake: Too much of a good thing. *BMJ Case Reports* 2017: DOI: 10.1136/bcr-2016-219043 (accessed 5 February 2026).
95. New Zealand Formulary (NZF). 2025. *Nutritional supplements in pregnancy and breast-feeding* 1 September 2025. URL: https://nzf.org.nz/nzf_70053 (accessed 30 September 2025).