A.10c Vitamin D supplementation

Recommendation and remarks

RECOMMENDATION A.10c (UPDATED)

Enteral vitamin D supplementation may be considered for human milk-fed preterm or low-birth-weight infants who are not receiving vitamin D from another source. *(Conditional recommendation, low-certainty evidence)*

Remarks

- The GDG noted that the evidence on harms (increased mortality) was uncertain due to low-certainty evidence and imprecision.
- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- The GDG also noted improvements in vitamin D deficiency and alkaline phosphatase levels but there were no data on other markers of bone health such as osteopenia or rickets.
- The GDG noted that there were limited data on the dose, timing of initiation and duration of supplementation. Based on most trials included in the evidence review, the GDG suggests a daily dose of 400–800 IU may be initiated when enteral feeds are well established, and may be continued until the infant receives vitamin D from another source.

Background and definitions

Vitamin D increases intestinal absorption of calcium and phosphorus, and enhances bone mineralization *(42)*. Low vitamin D levels are associated with seizures, irritability, rickets (swollen, deformed, painful joints and bones), bone fractures, osteopenia (radiological evidence of thin bones) and metabolic bone disease (radiological evidence of widened or deformed bones) *(109-111)*. Vitamin D deficiency has also been associated with increased risk of respiratory and diarrhoeal disease. Human milk may not be able to meet the nutritional requirements of preterm or LBW infants because of their low vitamin D stores and catch-up growth *(56)*. Babies born to darker-skinned mothers are at higher risk of vitamin D deficiency, especially those born in higher latitudes and in the winter months *(112)*. In 2011, WHO recommended that VLBW infants with birth weight below 1.5 kg should be given vitamin D supplements (400–1000 IU per day) until 6 months of age *(19)*. A systematic review published in 2020 reported improvements in vitamin D biomarkers (vitamin D levels, calcium levels, parathyroid hormone) after vitamin D supplementation was provided to all preterm infants *(113)*.

Summary of the evidence

OVERVIEW	A.10c Vitamin D supplementation
PICO	**Population** – Preterm or LBW infants who are fed mother's own milk or donor human milk **Intervention** – Vitamin D supplementation **Comparator** – No vitamin D supplementation **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)

Effectiveness: Comparison – Vitamin D supplementation versus no vitamin D supplementation

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of three RCTs totalling 2479 preterm or LBW infants from two countries (India and the USA) *(114)*. One trial in India enrolled 2079 (84%) of these infants. Most had a birth weight of at least 1.5 kg or were born at 32 weeks' gestation or later. The trials used a dose of vitamin D supplementation ranging from 200 IU to 800 IU per day. Two trials compared vitamin D with placebo, while the third trial compared vitamin D plus multivitamins with multivitamins alone. Vitamin D supplementation began between birth and 7 days chronological age in all trials. The mean duration of supplementation was 19 (SD 19) days and the median duration was 26 (IQR 4 to 26) days.

Critical outcomes

For vitamin D supplementation compared with no vitamin D supplementation, two trials reported all-cause mortality, five reported morbidity (1 reported bronchopulmonary dysplasia, 1 reported "at least one serious morbidity"), two reported growth (2 reported WAZ, 2 LAZ/HAZ, 1 head circumference z scores) and two reported neurodevelopment (cognitive development and neurodevelopmental impairment). (Full details are provided in GRADE Table A.10c, in the Web Supplement.)

- **Mortality**: Low-certainty evidence from two trials totalling 2179 participants suggests an increase in all-cause mortality at latest follow-up (RR 1.81, 95% CI 0.92 to 3.56).
- **Morbidity:** Very-low-certainty evidence from one trial with 100 participants suggests a decrease in bronchopulmonary dysplasia at 8 weeks of age (RR 0.77, 95% CI 0.47 to 1.27). Very-low-certainty evidence from two trials totalling 2179 participants suggests little or no effect on any (at least one) serious morbidity at latest follow-up (median 17 [IQR 8–26] weeks) (RR 0.94, 95% CI 0.72 to 1.24). "At least one serious morbidity" is defined as any (at least one) serious morbidity assessed with: any severe morbidity (hospital admission, or outpatient visits with diagnoses selected based on clinical judgement that represented severe illness: pneumonia, persistent diarrhoea, dysentery, severe fever, severe protein energy malnutrition, ear infections, meningitis and septicaemia), RDS, early-onset sepsis (≤ 72 hours), late-onset sepsis (> 72 hours) and culture-positive meningitis *(115)*.
- **Growth:** Moderate-certainty evidence from one trial with 1273 participants suggests an increase in WAZ at 6 months (MD 0.12, 95% CI 0.01 to 0.23). Low-certainty evidence from one trial with 912 participants suggests little or no effect on WAZ scores between 3 and 6 years of age (MD -0.07, 95% CI -0.18 to 0.04). Moderate-certainty evidence from one trial with 1258 participants suggests an increase in LAZ at 6 months (MD 0.12, 95% CI 0.03 to 0.21). Low-certainty evidence from one trial with 912 participants suggests little or no effect on height-for-age z scores (HAZ) between 3 and 6 years of age (MD 0.07, 95% CI -0.05 to 0.19). Low-certainty of evidence from one trial with 1259 participants suggests little or no effect on head circumference z scores at 6 months (MD -0.08, 95% CI -0.17 to 0.01).
- **Neurodevelopment:** Very-low-certainty evidence from one trial with 70 participants suggests little or no effect on cognitive scores assessed at 104 weeks (RR 0.85, 95% CI 0.45 to 1.59). Very-low-certainty evidence from one trial with 71 participants suggests a decrease in neurodevelopmental impairment assessed at 104 weeks (RR 0.69, 95% CI 0.41 to 1.17).

Other outcomes

There was little or no effect on hospitalization (at least one hospitalization) at latest follow-up (6 months) (RR 0.84, 95% CI 0.42 to 1.66; 2 trials, 1468 participants). There was a decrease in serum alkaline phosphatase (ALP) (measured in IU per litre) (note: ALP should be ≥ 500 IU/L) at 6 months follow-up (RR 0.37, 95% CI 0.10 to 1.36; 1 trial, 265 participants). There was a decrease in vitamin D deficiency (< 20 µg/ml) at latest follow-up (6 months) (RR 0.58, 95% CI 0.49 to 0.68; 2 trials, 504 participants).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials reporting on any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting nutrition, and want to take an active role in deciding what interventions are given to infants, including

what and how they are fed *(14)*. There was no specific evidence available about whether families value vitamin D supplements for their preterm or LBW baby or whether they find them acceptable.

Resources required and implementation considerations

Organization of care

The supplements can be provided in the health-care facility or at home. The family needs accurate information on the dose and how to administer the supplement. National or local guidance for health-care facilities should be used.

Infrastructure, equipment and supplies

Common methods of providing enteral vitamin D for preterm and LBW infants include infant multivitamin formulations (e.g. vitamins D, A, C, B group). Many formulations contain 400 IU vitamin D per 0.45–0.6 ml. Droppers or syringes can be used to administer the supplement to the infant. National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can support mothers and families. Standardized packages are needed for training, supervision and monitoring. Dispensing needs to be documented in clinical records.

Feasibility and equity

There was no specific evidence on the feasibility and equity of providing vitamin D supplements to preterm or LBW babies.

Summary of judgements

Comparison: Vitamin D supplementation vs no vitamin D supplementation (A.10c)	
Justification	• Evidence of small benefit: decreased bronchopulmonary dysplasia *(very-low-certainty evidence)*, increased weight and length *(moderate-certainty evidence)* and decreased neurodevelopmental impairment *(very-low-certainty evidence)* • Evidence on harms uncertain: mortality *(low-certainty evidence)* • Evidence of little or no effect on infections *(moderate-certainty evidence)*, hospital admissions *(very-low-certainty evidence)*, head circumference *(low-certainty evidence)*, weight *(low-certainty evidence)* and length *(moderate-certainty evidence)*

Evidence-to-Decision framework	
Benefits	Moderate
Harms	Unknown
Certainty	Moderate
Balance	Probably favours vitamin D supplementation
Values	No uncertainty or variability about outcomes
Acceptability	Varies
Resources	Low to moderate
Feasibility	Varies
Equity	Varies