A.10d Vitamin A supplementation

Recommendation and remarks

RECOMMENDATION A.10d (UPDATED)

Enteral vitamin A supplementation may be considered for human milk-fed very preterm (< 32 weeks' gestation) or very-low-birth-weight (< 1.5 kg) infants who are not receiving vitamin A from another source. *(Conditional recommendation, low-certainty evidence)*

Remarks

- 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.
- There were no trials in infants born ≥ 32 weeks' gestation or ≥ 1.5 kg birth weight, so the GDG did not make a recommendation for those infants.
- 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 1000–5000 IU may be initiated when enteral feeds are well established, and may be continued until the infant receives vitamin A from another source.

Background and definitions

Vitamin A regulates cellular growth and helps to maintain the integrity of the mucosa and epithelium of the respiratory and gastrointestinal tracts *(116,117)*. Vitamin A may also boost immune function *(118,119)*. Preterm infants are born with low cord blood and liver storage of vitamin A *(117)*. Supplementation with vitamin A has been reported to reduce bronchopulmonary dysplasia in studies of very preterm infants (born before 32 weeks' gestation) *(116,120,121)*.

Summary of the evidence

OVERVIEW	A.10d Vitamin A supplementation
PICO	**Population** – Preterm or LBW infants who are fed mother's own milk or donor human milk **Intervention** – Vitamin A supplementation **Comparator** – No vitamin A 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 A supplementation versus no vitamin A supplementation

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of RCTs of "low" daily dose (< 10 000 IU/day) enteral vitamin A supplementation for preterm and/or LBW infants, which included four trials and 800 participants from three countries (China, India and the United Kingdom) *(122)*. All infants in the included trials had gestational age below 32 weeks or birth weight below 1.5 kg and most were born before 28 weeks' gestation (extremely preterm) or with birth weight below 1.0 kg (extremely LBW). Doses ranged from 1500 to 10 000 IU/day and initiation of supplementation was between 1 and 4 days of age in the trials. Two trials provided supplementation until 28 days after birth while the other two trials continued until 34–36 weeks PMA.

Critical outcomes

For vitamin A supplementation compared with no vitamin A supplementation, four trials reported all-cause mortality, five reported morbidity (4 reported bronchopulmonary dysplasia, 1 pneumothorax, 1 pulmonary haemorrhage, 4 retinopathy

of prematurity, 2 patent ductus arteriosis, 1 periventricular leukomalacia, 3 sepsis, 1 seizures, 3 necrotizing enterocolitis, 2 intraventricular haemorrhage) and one reported growth (weight gain). No trials reported neurodevelopment. (Full details are provided in GRADE Table A.10d, in the Web Supplement.)

- **Mortality:** Moderate-certainty evidence from four trials totalling 800 participants suggests a decrease in all-cause mortality at latest follow-up (mean 10.3 weeks) (RR 0.74, 95% CI 0.53 to 1.02).
- **Morbidity:** Low-certainty evidence from four trials totalling 746 participants suggests a decrease in bronchopulmonary dysplasia at latest follow-up (mean 11.75 weeks) (RR 0.77, 95% CI 0.50 to 1.16). Low-certainty evidence from one trial with 154 participants suggests a decrease in pneumothorax at latest follow-up (10 weeks) (RR 0.75, 95% CI 0.46 to 1.21). Low-certainty evidence from one trial with 154 participants suggests a decrease in pulmonary haemorrhage at latest follow-up (10 weeks) (RR 0.60, 95% CI 0.30 to 1.21). Low-certainty evidence from four trials totalling 742 participants suggests a decrease in retinopathy of prematurity at latest follow-up (mean 11.75 weeks) (RR 0.69, 95% CI 0.37 to 1.30). Low-certainty evidence from two trials totalling 350 participants suggests a decrease in patent ductus arteriosus at latest follow-up (mean 7 weeks) (RR 0.66, 95% CI 0.21 to 2.06). Low-certainty evidence from one trial with 262 participants suggests a decrease in periventricular leukomalacia at latest follow-up (17 weeks) (RR 0.66, 95% CI 0.38 to 1.14). Low-certainty evidence from three trials totalling 646 participants suggests little to no effect on sepsis at latest follow-up (mean 12.3 weeks) (RR 0.87, 95% CI 0.64 to 1.19). Low-certainty evidence from one trial with 154 participants suggests little to no effect on seizures at latest follow-up (10 weeks) (RR 0.82, 95% CI 0.54 to 1.25). Very-low-certainty evidence from three trials totalling 604 participants suggests little to no effect on necrotizing enterocolitis at latest follow-up (mean 12.3 weeks) (RR 1.05, 95% CI 0.71 to 1.51). Very-low-certainty evidence from two trials totalling 450 participants suggests little to no effect on intraventricular haemorrhage at latest follow-up (mean 13.5 weeks) (RR 1.00, 95% CI 0.46 to 2.17).
- **Growth:** Low-certainty evidence from one trial with 188 participants suggests little to no effect on weight gain at latest follow-up (by hospital discharge or 16 weeks) (MD 0.02, 95% CI -0.2 to 0.24).

Other outcomes

There was a decrease in length of hospital stay (mean 6.3 weeks) (MD -8.76, 95% CI -32.1 to 14.58; 2 trials, 450 participants) and an increase in serum retinol concentration (measured in µg/ml) at latest follow-up (mean 8 weeks) (MD 4.7, 95% CI 1.2 to 8.2; 1 trial, 36 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 A 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 A for preterm and LBW infants include infant multivitamin formulations (e.g. vitamins D, A, C, B group) in 30–50 ml bottles. Many formulations contain 1000–5000 IU vitamin A 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 available about the feasibility and equity of providing vitamin A supplements to preterm or LBW babies.

Summary of judgements

Comparison: Vitamin A supplementation vs no vitamin A supplementation (A.10d)	
Justification	In trials where most participants are very preterm (< 32 weeks' gestation) or VLBW (< 1.5 kg): • Evidence of small benefit: decreased mortality *(moderate-certainty evidence)*, decreased bronchopulmonary dysplasia, pneumothorax, pulmonary haemorrhage, retinopathy of prematurity, patent ductus arteriosis and periventricular leukomalacia *(low-certainty evidence)* • No evidence of harm • Evidence of little or no effect on sepsis, seizures, weight *(low-certainty evidence)* and on necrotizing enterocolitis and intraventricular haemorrhage *(very-low-certainty evidence)* • No evidence on other critical outcomes
Evidence-to-Decision summary	
Benefits	Small or trivial to none
Harms	Trivial or none
Certainty	Low
Balance	Probably favours vitamin A supplementation
Values	Uncertainty or variability about outcomes
Acceptability	Probably acceptable
Resources	Low to moderate
Feasibility	Feasible
Equity	Probably equitable