

Clinical Guideline: The routine supplementation of vitamins and iron and the management of zinc deficiency in preterm and small for gestational age infants

Authors: ODN’s Dietetic Group (NatNeoRD) and Affiliates.

[Adapted for the the EoE by Lynne Radbone, Lead Dietitian for the EOE ODN]

For use in: EoE Neonatal Units, Guidance specific to the care of neonatal patients.

Used by: Neonatal Pharmacists, neonatal dietitians, neonatal nursing staff and medics.

Key Words: preterm infant, iron, vitamins, zinc, supplementation.

Date of Ratification: December 2024

Review due: December 2027

Registration No: NEO-ODN-2024-2

Approved by:

Neonatal Clinical Oversight Group	
Clinical Lead Matthew James	Matthew James

Ratified by ODN Board:

Date of meeting	
------------------------	--

Audit Standards:

100% infants who meet the criteria for vitamin supplementation receive appropriate and timely supplements in line with the recommendations laid out in this guidance.

100% infants who meet the criteria for iron supplementation receive appropriate and timely supplements in line with the recommendations laid out in this guidance.

Contents

1.0 Routine Supplementation

- 1.1 Vitamin supplementation in preterm and small for gestational age infants
- 1.2 Iron supplementation in preterm and small for gestational age infants

2.0 Management of Deficiency

- 2.1 Zinc deficiency in preterm and small for gestational age infants

3.0 Supplementary Information

- 3.1 Using licensed medicines, unlicensed medicines and food supplements
- 3.2 Appendix 1: Evidence to Support Vitamin and Iron Recommendations
- 3.3 Appendix 2: Available Multivitamin Preparations
- 3.4 Appendix 3: Alternative Vitamin Supplementation
- 3.5 Appendix 4: Alternative Iron Supplementation
- 3.6 Appendix 5: Available term and specialist formulas
- 3.7 Appendix 6: Total vitamin A & D intakes by infant weight, milk choice and volume

4.0 Glossary

5.0 Authors

6.0 References

1.0 Routine supplementation

1.1 Vitamin supplementation in preterm and small for gestational age infants.

1.1.1 Introduction

Both fat- and water-soluble vitamins are essential nutrients for whole body function and homeostasis. Water-soluble vitamins are not stored in the body, so need to be provided continuously through dietary provision, whereas fat-soluble vitamins are stored in fatty tissue and the liver.

The third trimester of pregnancy is a period of rapid nutrient accretion and the time when fat-soluble vitamin stores are laid down. Premature birth interrupts this process, consequently preterm infants have lower stores of fat-soluble vitamins and potentially higher requirements for all vitamins than those born at term.

Although there is some limited evidence for a few key vitamins available from supplementation studies aimed at improving clinical outcomes, an overall lack of studies makes it difficult either to describe the metabolism of vitamins in preterm infants or to determine their vitamin requirements.

Current guidelines for preterm nutritional requirements (1, 2) recognise this lack of evidence and therefore base their recommendations for vitamin intakes on several factors:

- The vitamin dosages used from supplementation studies in preterm infants that demonstrated improvement in clinical outcomes.
- The recommendations of the European Food Safety Authority (EFSA) for term infants (<6 months). Theoretically, the EFSA daily recommendations may underestimate the increased requirements of the rapidly growing preterm infant. However, because of the weight difference between term and preterm infants the authors of these publications considered that daily, per kilogram, recommendations for term infants are likely to be adequate for preterm infants as they represent approximately a 3- to 5-fold higher intake per kilogram body weight per day.
- The EFSA best estimate of the vitamin content of mature mother's own milk, when fed at minimal recommended energy intake for a preterm infant of 115Kcal/Kg/day.
- The vitamin content of commercial preterm formulas when fed at a volume that provides 115Kcal/kg/day.

1.1.2 Scope & evidence

The recommendations in this document have been formulated through clinical consensus. They are based upon a thorough literature search, which includes 3 international publications (1-3) and a detailed quantitative analysis of milk, fortifier and vitamin formulations by gestation and weight, undertaken by the authors (4-12).

The dosing algorithm proposed for the East of England ODN is a pragmatic, single dosing approach that reflects current network practice, which to date has provided a simple to implement strategy with no evidence of harm.

It also ensures that baseline ESPGHAN requirements are met. In some smaller infants with a birth weight around 500g, this regimen will provide more than the ESPGHAN recommended daily vitamin A & D intakes (1) (see table 2 in Appendix 4) however the number of infants who will be in receipt of vitamin doses higher than ESPGHAN recommendations will be insufficient to justify a significant change in practice.

Some argue that concerns about potential vitamin A toxicity have led to caution in dosing regimens in preterm infants, however these arguments are largely unfounded (13). In one dose comparison study, intramuscular regimens of up to 8500 units/kg/day were administered and potential adverse effects were seen in less than 5% (14). ESPGHAN (1) currently acknowledge that there is insufficient data to change the existing recommendation for vitamin A in preterm infants.

This guideline is to be used as an adjunct to clinical decision making. Where infants are receiving volumes of milk considered outside the “normal” range of 150 -165 ml/kg/day advice should be sought from a suitably experienced neonatal dietitian.

1.1.3 Supply & alternatives

A limited range of suitable multivitamin preparations are available for use in the preterm population (Appendix 2). It is widely recognised that intermittent supply issues of first line vitamin preparations bring difficulties in provision to infants. A table of alternative multivitamin products suitable for use during these periods, or where a need for peanut and soya avoidance is required, can be found in Appendix 3.

DaliVit® is not recommended as a first line preparation as it has a much higher vitamin A content than other preparations. It is not a directly interchangeable product with others on the market (see Appendix 2)

1.1 4 Preterm vitamin requirements

Recommended enteral intakes for vitamins (ESPGHAN) (1)

	ESPGHAN (2022)
Thiamine (B1) (micrograms/kg/day)	140-290
Pantothenic acid (mg/kg/day)	0.6-2.2
Biotin (micrograms/kg/day)	3.5-15
Niacin (micrograms/kg/day)	1100-5700
Ascorbic acid (vitamin C) (mg/kg/day)	17-43
Riboflavin (B2) (micrograms/kg/day)	200-430
Pyridoxine (micrograms/kg/day)	70-290
Folic acid (micrograms/kg/day)	23-100
Cobalamin (B12) (micrograms/kg/day)	0.1-0.6
Vitamin A (units/kg/day)	1333-3300 (400-1000micrograms retinol ester/kg/d)
Vitamin D (units/kg/day)	400-700 IU/kg/day (<1000)
Vitamin E (mg/kg/day)	2.2 – 11
Vitamin K (micrograms/kg/day)	4.4 – 28

1.1.5 Who should receive vitamin supplementation?

The gestation below which additional vitamins are required is unclear, consequently supplementation practice has, in the past, varied across the UK.

Current guidelines provide recommendations for vitamin intakes in extremely low birth weight (ELBW) and very low birth weight (VLBW) infants (2) and for infants <1800g (1) but neither make any delineation by degree of prematurity.

The vitamin requirements of late and moderate preterm (LMPT) infants, defined as infants born 32+0 – 33+6 weeks gestation (moderate preterm) and 34+0 – 36+6 weeks gestation (late preterm), are likely to be higher than those for term infants, but again, there are insufficient data to inform intake levels for any except for vitamin D. Current recommendations are to provide all LMPT infants with a vitamin D supplement from birth and throughout early childhood (15 ,16).

Due to the lack of detailed guidance, a pragmatic approach needs to be taken as to the population this guideline applies to, however, available evidence would suggest some vitamin supplementation is required for all infants born <37 weeks gestation, and for all infants <37 weeks who are exclusively fed human milk to receive further vitamin K supplementation for at least the first 3 months post discharge. (36)

Single Dosing, Pragmatic Dosing Approach

All infants born <34 weeks <u>and/or</u> any infant born <1.8kg from 100mL/kg enteral feed	
Fortified Human milk (SMA or Nutriprem HMF)	Abidec® 0.6mL/day
Nutriprem 1® Hydrolysed Nutriprem 1 ® or SMA Gold Prem 1®	
Unfortified Human milk*	Folic Acid 50microgrammes/day (to term due date) and Abidec® 0.6 mL/day and Colecalciferol 300 units/day (NOT per kg)
On reaching 2.0kg <u>or</u> discharge	
Fortified Human milk, SMA Gold Prem or Nutriprem (including fortifier supplements at home). SMA Gold Prem 2® or Nutriprem 2® Term/specialist formula	Abidec® 0.6mL/day
Exclusive breastfeeding or where unfortified human milk provides more than 50% of total feed volume	Abidec® 0.6 mL/day <u>At discharge:</u> Stop Colecalciferol Consider 50 microgrammes/day vitamin K Continue folic acid to term
Any infant born 34-36+6 weeks <u>and</u> >1.8kg from 100ml/kg enteral feed	
Human milk or term /specialist formula	Abidec® 0.6 mL/day
On discharge	
Term /specialist formula	Abidec® 0.6 mL/day
Exclusive breastfeeding	Abidec 0.6mL/day Consider 50 microgrammes/day vitamin K

* ESPGHAN supports the routine use of breast/human milk in infants born <1.8Kg.

Without breast milk fortifier full nutritional requirements for electrolytes, vitamins, calcium, phosphate, other minerals and trace elements will not be met.

Consider continuing prescribed supplements to at least 6 months corrected (up to maximum of 1 year actual age), at which point national public health policy on childhood vitamin supplementation should be employed (43, 44).

Consider measuring serum 25-hydroxy vitamin D at 3-4 weeks of life and then every month until discharge (1).

1.2 Iron supplementation in preterm and small for gestational age infants

1.2.1 Introduction

Iron is an essential micro mineral, which is required for haem synthesis, oxygen transport, enzyme functions and brain development (2).

Preterm and low birth weight infants are at risk of deficiency due to low stores at birth, higher requirements secondary to rapid growth, losses caused by frequent blood sampling and the requirement for parenteral nutrition support for the smallest and sickest infants, which does not routinely contain iron (2). Freshly expressed human milk is recognised as the optimal feed for preterm infants (3). However, human milk does not meet the elevated iron requirements of preterm infants.

Iron deficiency anaemia should be avoided as it may adversely affect brain development (2). Excessive intakes of iron can also be detrimental to preterm infants and should be avoided, as there is no mechanism for excretion. Excess iron may increase oxidative stress and associated complications of prematurity (2).

Current guidelines for preterm nutritional requirements (1, 2) recommend intakes of iron that will not be met by human milk, nor by some commercial feeds used when human milk is unavailable. Iron supplementation is therefore recommended (1, 3). The iron supplement used in the United Kingdom is sodium ferredetate 27.5mg of iron per 5mL oral solution. The guidance in this document is based on this formulation.

1.2.2 Scope & evidence

These recommendations have been formulated through clinical consensus. They are based upon a thorough literature search, which includes 3 international publications (1-3) and a detailed quantitative analysis of milk, fortifier and iron supplement by gestation and weight, undertaken by the authors (4-12, 45).

A pragmatic approach has been taken to ensure that baseline requirements, as detailed by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) (1) are met, and that where intakes higher than the upper range are suggested, they do not exceed levels which could be considered harmful (e.g. toxicity).

This guideline is to be used as an adjunct to clinical decision making. Where infants are receiving volumes of milk considered outside the “normal” range of 150 -165 mL/kg/day advice should be sought from a suitably experienced neonatal dietitian.

1.2.3 Preterm and small for gestational age infant requirements

Current guidelines provide recommendations for iron intakes for any infants <1800g, preterm infants born at <1500g, 1500-2000g, 2000-2500g, <2500g, (1,15) and term infants born below 2.5kg (3). These guidelines vary in their recommendations for both iron dosing and for when to commence supplementation, with some proposing a staggered approach.

To meet these requirements exactly, using sodium ferredetate (27.5 mg of iron per 5mL oral solution) a supplementation strategy would involve multiple different doses based on gestation and weight.

The author group felt recommending a strategy that required multiple doses and different ages at which supplementation commenced would lead to reduced compliance, so a pragmatic approach to both dosing and timing has been taken in the construction of the recommendations.

In line with most recent guidelines, the group recommend that iron supplementation commences from 2 weeks' postnatal age.

The dose of iron given in combination feeding regimens should be informed by the predominant feed (that is the feed which comprises over 50% of intake).

The guidelines recommend iron supplementation continues until adequate iron intake from solids can be proven, however there is inadequate neonatal dietetic resource nationally to provide the individual assessment required to support this. In order to minimise the risk of anaemia in the ELBW and VLBW infants, the group recommend continuing iron supplementation to at least 6 months chronological age at 12 months actual/chronological age (or earlier if shown by dietetic assessment that iron requirement is being met from dietary sources). Clinical judgement should be employed where there is developmental delay or feeding difficulties.

A summary of guidance from the international guidelines and studies (1,2,15,3) focusing on iron supplementation is detailed the table below:

Guideline	Weight	Amount (expressed as elemental iron)	Start	End
ESPGHAN 2022 (1)	<1800g ≥1800g	2-3 mg/kg Not specified	2 weeks Not specified	6-12 months Not specified
Koletzko 2021 (2)	<1500g 1500 - 2000g 2000 - 2500g	2-3 mg/kg 2 mg/kg 1-2 mg/kg	2 weeks 2-4 weeks 4-6 weeks	6-12 months 6-12 months 6 months
BAPM 2023 – Late to moderate preterm infants (15)	<2000g >2500g	2-3 mg/kg 1-2 mg/kg	Not specified	At least 6 months
WHO 2022 – term infants (3)	<2500g	2-4 mg/kg	When enteral feeds are well established	Until baby receives iron from another source

1.2.4 Recommendations for iron supplementation

All infants born <34 weeks <u>and/or</u> any infant born <1.8kg from 2 weeks of age			
Feed type	Working weight (kg)	Sodium feredetate (27.5mg/5mL) dose (mL/day)	Ferrous Fumarate* (45mg/5mL) dose (mL/day)
Unfortified human milk or human milk fortified with Nutriprem Breast Milk Fortifier®	<1.5	0.5ml/day	0.3mL/day
	≥ 1.5	1.0ml/day	0.6mL/day
Standard, specialist or high calorie formula designed for term infants	≥ 1.0	0.5mL/day	0.3mL/day

The following feeds do not require iron supplementation for this cohort of infants:

Nutriprem 1® Hydrolysed Nutriprem 1® Nutriprem 2® SMA Gold Prem 1® SMA Gold Prem 2® human milk with SMA Gold Prem Breast Milk Fortifier®

Continue supplementation until 12 months actual age.

Clinical judgement should be exercised when discontinuing iron supplementation. Some infants, especially those born <2Kg, may require supplementation beyond this timeframe.

Infants born 34-36.6 weeks or >37 weeks with a birthweight 1.8kg - 2.5kg from 2 weeks of age		
Feed type	Sodium feredetate (27.5mg/5mL) dose (mL/day)	Ferrous Fumarate* (45mg/5mL) dose (mL/day)
Exclusive breastfeeding or where human milk provides more than 50% of total feed volume	0.5 mL/day	0.3mL/day

The following feeds do not require iron supplementation for this cohort of infants:

Standard, specialist or calorie dense formulas designed for term infants

Consider continuing supplementation until 6 months actual age (or earlier if dietetic assessment shows requirements are met from dietary sources)

* The Galfer® brand of ferrous fumarate has dosing recommendations for preterm neonates from 4 weeks of age. If using other ferrous fumarate products, assess the excipient content prior to use.

1.2.5 Monitoring supplementation

Ferritin is an acute phase protein and is used as a marker of iron status, with serum concentrations < 35-40 micrograms/L indicating deficiency and >300-350 micrograms/L signifying iron overload (1). Where inflammation or infection are evident, serum ferritin should not be used as a reliable marker as it will be elevated (1). Serum ferritin is also not a reliable marker where liver disease is present (1). It is recognised that the individual iron status of ELBW and VLBW infants will vary, subsequently repeated measurements of ferritin are recommended (1). Increasing iron dose to 3-4 mg/kg/day (in some cases 6 mg/kg/day) should be considered if ferritin < 35-70 micrograms/L, but an intake of >3 mg/kg/day for more than a few weeks should be avoided due to risk of adverse effects (1). Infants receiving erythropoietin treatment may require higher doses of iron, up to 6 mg/kg/day (1). If ferritin is > 300 micrograms/L iron supplementation should be stopped (1). For infants receiving human milk fortified with SMA Gold Prem 1 Breast milk fortifier® (a source of iron), this should be replaced with Nutriprem Breast Milk Fortifier® (which is not fortified with iron) until serum ferritin falls below this level.

1.2.6 Iron supplementation and blood transfusion

1.2.6.1 Iron supplementation following blood transfusion

There is currently limited guidance on whether iron supplementation should be withheld post blood transfusion. This is due to limited research conducted in this area. Iron supplementation should be withheld following blood transfusions in preterm babies where ferritin levels are >300 micrograms/L or for babies with haemolytic disorders as these may predispose the infant to iron overload. In cases where babies are transfused for the anaemia of phlebotomy losses or external haemorrhage, it may be appropriate to continue iron supplementation (3, 46).

1.2.6.2 Enteral feeding and transfusions

There is currently insufficient evidence from randomised controlled trials to guide whether feeds should be stopped during transfusion (47). Some studies suggest that feeding during transfusion increases morbidity and mortality (48), whilst others show no difference with or without feeds during transfusion (49).

The WHEAT trial (Withholding Enteral feeds Around packed red cell Transfusion) is an ongoing multi-centre randomised point of care trial aiming to find out whether withholding milk feeds before, during, and after blood transfusion in preterm infants reduces the risk of necrotising enterocolitis versus whether pausing feeds for 12 hours with each blood transfusion may have adverse effects in itself (50).

1.2.7 Considerations when administering iron supplements

In general, it is advised to give iron supplements on an empty stomach, and apart from food, to maximise absorption of iron. However, there is a historical consensus that the osmolality of enteral feeds should not exceed 450 mOsm/kg (58). The physiological response to hyperosmolar solutions is delayed gastric emptying (58). Sodium Ferredetate is known to have a high osmolar load, so it may be prudent to dilute iron supplements in milk feeds prior to administration (58). Srinivasan et al. (2009) recommend every 0.1 mL of Sodium Ferredetate needs a milk volume of 1.2 mL (59). Some centres choose to give the iron supplement just before a milk feed to ensure the full dose is taken and ensure the iron supplement is mixed with feed to maximise tolerance.

2.0 Management of zinc deficiency in preterm and small for gestational age infants

2.1 Introduction

Zinc is an essential trace element, meaning the body is unable to make or store it, requiring continuous dietary intake. Zinc is accrued during the third trimester of pregnancy. It is one of the most prevalent trace elements in the brain and contributes to its structure and function (60). It has an important role in gene transcription, immune defence (61), and growth due to its central role in the production of enzymes integral to the production of DNA and RNA (60) and tissue differentiation (2).

Preterm infants not only have lower reserves and reduced absorption of zinc but will have increased requirements during the postnatal period of rapid growth (63 64). Zinc deficiency is associated with poor growth, increased risk of infection, skin rash and possible poor neurodevelopment (2). Risk factors for poor zinc status include insufficient zinc intake either via parenteral or enteral routes, breastmilk with low zinc levels due to inadequate maternal zinc transfer, and excess gastrointestinal losses due to high enterostomy losses >20 mL/kg/day or persistent diarrhoea (1, 2). Genetic defects in zinc transporters located in the mammary gland can lead to breastmilk containing no zinc leading to cases of acrodermatitis enteropathica in the neonatal period secondary to zinc deficiency (64 66). Zinc excretion is also affected by renal immaturity (64), and concomitant use of certain medications such as diuretics and steroids.

Zinc does not have a pro-oxidant effect, and adverse effects of excess zinc intakes are rarely reported, although copper absorption may be impacted with high zinc intakes over a long period time i.e., >3 months (2).

2.2 Scope & evidence

These recommendations have been formulated through clinical consensus. They are based upon a thorough literature search, which includes international publications (1,2).

2.3 Preterm and small for gestational age infant requirements

Current guidelines recommend an enteral zinc intake of 2-3 mg/kg/day for preterm infants <1.8 kg (1, 2). There are no specific recommendations for small for gestational age or late to moderate preterm infants. However, there are recommended nutrient intakes for zinc for infants and children in general, which would include late preterm infants and small for gestational age infants (62).

Recommended nutrient intakes (RNI) for zinc have been established (Table 1). It should be noted the RNI should not be used to treat deficient states, as therapeutic supplementation will be required for a short period of time to treat a deficiency.

Guideline	Age range/weight	Recommended intake (Parenteral RNI)	Recommended intake (Enteral RNI)
ESPGHAN 2022 (1)	<1.8kg	400-500 micrograms/kg/day	2-3 mg/kg/day
Koletzko 2021 (2)	<1.8kg	400-500 micrograms/kg/day	2-3 mg/kg/day
Department of Health 1991 (50)	0-6 months post term		4 mg/day
Department of Health 1991 (50)	7-12 months post term		5 mg/day
ESPGHAN 2018 (53)	0-6 months post term	250 micrograms/kg/day	
ESPGHAN 2018 (53)	7-12 months post term	100 micrograms/kg/day	

Table 1: Recommended nutrient intake (RNI) for zinc in nutrition support

2.4 Optimising zinc intakes and treating deficiency

Zinc is an essential element for weight gain and linear growth. There are several contributing factors associated with low zinc levels, including enterostomy losses and use of certain medications (Table 2).

Zinc deficiency can be prevented by ensuring sufficient zinc is provided in nutrition support (parenteral nutrition and enteral) to meet recommended nutrient intakes. This is especially important where there is a high protein intake as more zinc will be required to support linear growth and muscle mass accretion (64). The NDIG working group and others (61 65) found

no evidence to support routine zinc supplementation over and above the recommended nutrient intake. Cases of zinc toxicity are rare but excessive prolonged zinc supplementation over months can also lead to copper and iron deficiency (62).

	Causes of abnormal biochemistry	action
PN >21 days	Limitation of zinc in PN	Where able, increase enteral intake to full fortified human milk
Unfortified human milk	Human milk does not contain adequate zinc	Infants <1.8kg at birth need fully fortified human milk or preterm formula
Enterostomy losses	High small bowel ostomy losses ≥ 20 mL/kg/day is associated with increased zinc losses	Review factors associated with ostomy losses, aim to control output ≤ 20 mL/kg/day
Systemic glucocorticoids	Reduce gut absorption of minerals including zinc which is essential for bone growth	Monitor growth and check zinc levels as per guideline
Proton Pump Inhibitors	Reduced gut absorption of zinc (neutralisation of stomach acid)	Refer to local reflux management guidelines
Diuretics	Increased urinary zinc losses	Encourage regular review of ongoing diuretic use and ensure lowest effective dose is used.

Table 2: Contributory factors in zinc insufficiency and recommended actions

2.5 Recommendations for Zinc Screening

ESPGHAN recommend serum zinc levels should be measured in infants on long term parenteral nutrition after 21 days and in the absence of any ongoing inflammatory response (such as NEC or sepsis). Serum zinc should be measured in infants with low alkaline phosphatase (ALP), poor linear growth or high ostomy or gastrointestinal losses to identify zinc deficiency and need for supplementation (1, 2).

Zinc levels should therefore be measured on or around day 21 of life in all babies with the following zinc deficiency risk factors:

- On PN at day 21 of life
- <1000g or <28 weeks at birth
- Acrodermatitis enteropathica
- Poor growth (length)
- ALP level below local reference range (or ≤ 61 units/L)
- Persistent GI fluid losses following enterostomy >20 mL/kg/day

Please note:

1. Check with local laboratory for unit-specific recommendations and blood tube guidance. **Note** the tube must *not* have an orange/ black rubber ring in the top (this contains zinc and will affect the accuracy of the reading).
2. When completing a serum zinc measurement, it is important that routine bloods of liver function tests (LFTs) and C-reactive protein are completed at the same time.
3. CRP levels reflect an acute inflammatory response. Serum zinc levels may be falsely low if CRP >10 mg/L.
4. Serum zinc measurements should therefore only be done when CRP <10 mg/L.

2.6 Recommendations for zinc management in cases of deficiency

Step One: Assess

If zinc levels <11.2 micromol/ L (or below local laboratory reference range) with a CRP <10 mg/L, zinc supplementation should be commenced at a dose of 2 mg/kg/day of elemental zinc for 4 weeks.

Step Two: Review

After 4 weeks do growth, skin or biochemical abnormalities still persist?

Yes

No

Step Three

Recheck zinc levels and continue zinc supplementation at 2mg/kg/day of elemental zinc for a further 4 weeks (total 8 weeks)

Step Three

Stop zinc supplementation and aim to provide age appropriate RNI for zinc

Step Four (Redress imbalances)

1. During this time ensure there is adequate nutritional intake (Table 1). Optimise enteral nutrition intake of zinc via fortified breastmilk and routine vitamin/ mineral supplement or age-appropriate alternative preterm infant formula in line with RNI.
2. Review medication and possible contributory factors as able (Table 2)

Things to consider:

- Low serum zinc levels (with normal CRP) will not be redressed through enteral feeds alone and zinc supplementation will be required for a restricted, supervised period of 4-8 weeks maximum.
- For infants with ileostomies, supplements should only be started once full feeds have been established, other electrolyte supplements have been commenced and tolerated.
- Zinc, iron, and copper compete for the same site of absorption, so when provided as individual mineral supplements, they should be administered at differing time points (51).
- Zinc has a low toxicity, but prolonged high dose supplementation will impair copper bioavailability
- Available zinc products/formulations: Solvazinc. Dilute 1 tablet (45mg elemental zinc) with 8.5mL water (noting 0.5mL displacement) to prepare a 5 mg elemental zinc/mL solution for administration (alternative dilutions can also be used – discuss with pharmacy).

2.7 Formulations of Zinc and dosage

There are three brands listed in the British National Formulary for Children (BNFc). These are Solvazinc[®], AadZinc[®] and Aactizinc[®]. Dosing in this guideline is based on Solvazinc[®] (67). The BNFc specifically states that 125 mg of zinc sulfate monohydrate is equivalent to 45 mg of elemental zinc in Solvazinc[®]. This product has gone through the licensing process and is a recognised “Pharmacy Only Medicine” (68). See “Things to consider” box on previous page for dilution information .

The group suggest a dose of 2 mg/kg/day for preterm babies (69, 70). This is higher than the BNFc dosage of 1mg/kg/day which just refers to neonates. Preterm babies will not have the stores of zinc that term babies are born with and have higher urinary losses (64). Therefore, if deficient, they will most likely need more zinc to correct this deficiency.

3.0 Supplementary Information

3.1 Using licensed medicines, unlicensed medicines and food supplements

Wherever possible, licensed medications should be used for treating patients. These medicines will have a product license (PL) number on the packaging indicating they undergone full evaluation by the MHRA (71).

Unlicensed medicines don't have a UK Marketing authorisation but meet the definition of a medicine in that they have properties for treating or preventing disease or are used for correcting, restoring or modifying a physiological, metabolic or immunological function. Pharmacists and prescribers must assure themselves of the quality, safety and efficacy of the unlicensed medicine they want to use (72).

Food supplements are defined as “a concentrated source of a vitamin or mineral or other substance with a nutritional or physiological effect, alone or in combination and is sold in dose form.” (73). Food supplements are made to different quality standards to medicines and are not evaluated by the MHRA. It is not possible to gain additional assurances from the manufacturers of food supplements.

Within this guidance there is reference to products that are considered to be food supplements such as certain brands of zinc, iron and phytomenadione. Where possible a licensed medication should be selected over a food supplement and a risk assessment should be completed if a food supplement is used over a licensed product.

Excipients

When choosing a product to use in children, do consider the products excipients. For further information see <https://nppg.org.uk/choosing-an-oral-liquid-for-a-child/> which contains information on assessing excipient content.

3.2 Appendix 1

Evidence to Support Vitamin Recommendations

Water Soluble Vitamins (including Folic Acid)

Water soluble vitamins are essential nutrients for whole body function and homeostasis. For most of the water-soluble vitamins there are very few data to provide evidence-based dietary recommendations for preterm infants. In the absence of robust evidence, recommendations are often inflated to ensure adequacy is well in excess. Current recommendations for water soluble vitamins predominantly reflect the amounts added from industry in preterm infant formulas. It is recommended to monitor nutrient status of preterm infants fed unfortified human breastmilk. Intakes above dietary recommendations are unlikely to be of benefit in improving patient outcomes (2).

Folate is essential to form normal red blood cells and certain amino acids. In one study folate intake has a positive association with weight and length gain in extreme preterm infants. (15) Plasma folate is lower in infants receiving only human breast milk rather than fortified human milk or preterm infant formula. Studies in infants receiving preterm formula or breast milk fortifiers have shown no evidence of folate deficiency, as indicated by serum concentrations or haematological profile results (16), or raised levels of homocysteine (17), a biomarker of folate deficiency, hence suggesting they all had adequate intake. Milk formulas and breast milk fortifiers usually contain much higher amounts of folate than is present in breast milk. Folic acid is not present in standard vitamin supplements (eg Abidec/Dalivit) so needs to be supplemented separately.

Fat Soluble Vitamins

Vitamin D

Vitamin D, a fat-soluble vitamin, is essential for the absorption of calcium and phosphorus and is therefore vital in bone formation. Supplementation is of no benefit to bone health if there are inadequate supplies of these two minerals, though its exact mechanism is unknown. Further study is needed to identify preterm vitamin D physiology and the status required to be most protective of bone and extra skeletal development (2).

Vitamin D is primarily transferred to the fetus in the third trimester of pregnancy and is also impacted by the mother's vitamin D status (2). Consequently, many preterm infants have low vitamin D levels at birth (18,19). There is no consensus regarding the definition of vitamin D deficiency in infants. ESPGHAN guidance pragmatically suggest that a serum 25-hydroxy vitamin D concentration >50 nmol/L be used to indicate sufficiency, but that concentrations > 120 nmol/L be avoided (1).

There are few adequately powered controlled trials on which to base firm recommendations for dosing and duration of vitamin D supplementation in preterm infants. ESPGHAN identified studies with dosage ranges of 200-300 units/kg/day to 400-670 units/kg/day that

sufficiently reduced vitamin D deficiency and suggest a dosing regimen of 400-700 units/kg/day (maximum dose of 1000 units/day) (1).

Several studies have also investigated the safety of vitamin D supplementation. They have identified toxicity in some, particularly very low birthweight infants, on a variety of standard dosing regimens (not calculated per kg bodyweight) and which were implemented without regular blood monitoring of vitamin D status (20 - 22). Supplementation with excess active vitamin D may cause calcium resorption of the bone and renal disease (e.g. nephrocalcinosis) and should only be considered where there is clear biochemical deficiency or poor absorption (e.g. significant cholestatic liver disease). ESPGHAN (1) recommends measuring serum 25-hydroxy vitamin D at 3-4 weeks of life and then every month until discharge for all preterm infants.

Vitamin A

Vitamin A is a fat-soluble vitamin that is essential for growth, body regulation and differentiation of cells, including the retina of the eye and lung maturation. Preterm infants are born with low plasma concentrations of retinol and retinol binding protein (RBP) (23). They are also susceptible to vitamin A deficiency due to low transplacental transport, poor enteral nutrition post birth and reduced gastrointestinal absorption (24).

A Cochrane review showed that additional vitamin A supplementation in premature infants may reduce the risk of mortality and chronic lung disease as well as lower the incidence of retinopathy of prematurity (25). However, those studies investigated intramuscular injections and their effect on bronchopulmonary dysplasia (BPD) and have been found to be painful, therefore it is not common practice. There is contradictory evidence of the beneficial effects of enteral vitamin A supplementation.

Recommended daily intake of vitamin A for premature infants on the neonatal unit is 400-1100 micrograms retinol ester/kg/day or 1330-3300 units/kg/day. However, according to the most recent ESPGHAN guidelines (2022), a higher vitamin A intake may be required for those infants with hepatic impairment, and lower intake for those with renal impairment (1).

Vitamin K

Vitamin K is a group of lipophilic, hydrophobic vitamins necessary for the synthesis of coagulation factors (factors II (prothrombin), VII, IX, and X, and the anticoagulation proteins C and S in the liver, as well as many other important functional proteins such as osteocalcin. Insufficient levels of vitamin K may lead to haematological complications, resulting in the impaired production of these active coagulation molecules (26 27) and a subsequent increased risk of vitamin K deficiency bleeding (VKDB), which may be devastating.

Vitamin K deficiency is far more common in neonates compared to adults due to immaturity of the coagulation system, inadequate colonisation with Vitamin K-producing bacteria in the intestines, limited maternal transfer of vitamin K across the placenta, and low concentrations of the vitamin in breast milk.(28) Exclusive human milk feeding is a risk factor for VKDB in otherwise-healthy preterm and term infants,(26 29 30 31) with a significant proportion of term infants showing evidence of subclinical Vitamin K deficiency at age 2-5 months related to breastfeeding duration (32 33 34)

All preterm infants are offered prophylactic Vitamin K at birth, and those exclusively fed human milk receive sufficient extra Vitamin K from multinutrient milk fortifiers if given during the NICU stay. However, a preterm infant on full exclusive unfortified breastmilk feeds (150 mL/kg/day) receives only a minimal proportion of their currently recommended Vitamin K intake of 4.4-28 micrograms/kg/day (1). A recent prospective observational study in exclusively-breastfed preterm infants who all received intramuscular prophylaxis at birth showed that some already had undetectable Vitamin K levels prior to discharge, and that the majority who remained exclusively breastfed post-discharge had developed biochemical evidence of functional subclinical Vitamin K deficiency by 2-3 months corrected age for both haematological and bone Vitamin K-dependant proteins.(35)

Nutritional guidelines for preterm infants do not offer recommendations for Vitamin K supplementation after discharge, however more recent publications suggest consideration should be given to the provision of a daily supplement of 50 micrograms/day for all preterm infants born <37 weeks gestation being discharged exclusively on unfortified human milk feeds. Where the decision is made offer this supplement, it should be taken for at least the first 3 months at home in order to improve intakes in early infancy and guard against subsequent deficiency.

Current multivitamin preparations used for preterm infants do not contain vitamin K, though there are a range of acceptable options for supplementation that can be implemented in line with unit preference and IntegratedCare Board product availability.(36) Options that would effectively deliver the equivalent of at least the minimum daily requirement of 50 micrograms could include:

- i) Konakion MM Paediatric® (phytomenadione 2mg in 0.2 mL; Neon Healthcare Ltd), 2 mg **given orally** once monthly
- ii) A single further Konakion MM Paediatric® 1mg intramuscular injection at discharge - this should protect for up to 3 months and would avoid compliance issues but may be far less acceptable to parents and babies.(36)
- iii) NeoKay oral drops® (Neoceuticals Ltd; 200 micrograms/mL VK₁) dose 50 micrograms(0.25 mL via dropper) once daily to provide daily VK₁ intake comparable to that from formula milks which are supplemented to meet current recommendations (VK₁ content typically 60-80 micrograms/L); 1 bottle at the recommended dose will last 3 months. This product is a food supplement.

Vitamin E

Vitamin E encompasses a group of biologically active tocopherols (1) This nutrient functions as an important antioxidant supporting the prevention of haemolytic anaemia, BPD and retinopathy of prematurity (ROP) (37). In addition, it may play a role in stimulating immunity (38) and protecting against intraventricular haemorrhage (IVH) however there is evidence that it may also increase the risk of sepsis. (39) Low circulating levels of vitamin E are noted in preterm infants at birth (40). Milk from mothers who delivered preterm however can contain a higher vitamin E content as does preterm formula in comparison to term formula. Studies of routine enteral vitamin E supplementation in this group suggest maintaining

plasma vitamin E concentrations of 10–35 mg/L (Minimum dose of 3.8 mg/kg/d) (1). No clinical benefits have been seen however, and the recommended daily intake of vitamin E in preterm infants is 2.2–11mg/kg/d. Additional higher supplementation should be considered for infants with cholestasis.

Evidence to Support Iron Recommendations

Iron supplementation versus no supplementation

A systematic review of 8 trials, conducted in 7 countries and including 1093 infants (birth weight <1.5kg and <32 weeks' gestation), was conducted by the World Health Organization to examine the impact of iron supplementation on morbidity, growth, neurodevelopment and anaemia (3). Most trials involved comparing supplementation of 1-7mg/kg/day iron with a placebo or no iron supplementation (3). One trial compared a multivitamin and iron preparation with multivitamins alone (3). Iron supplementation was reported to have little or no effect on sepsis, necrotising enterocolitis, cognitive development or feed intolerance (very low certainty evidence) (3). It was associated with increased weight (very low certainty evidence) and length (moderate certainty evidence) (3). Iron supplementation was found to decrease prevalence of anaemia and increased haemoglobin (moderate certainty evidence) (3).

Low birth weight infants

There is evidence to show that babies with birth weights of 2000-2500g (regardless of gestation) who are given iron supplements (1-2 mg/kg/day) from 6 weeks to 6 months of age have a decreased risk of iron deficiency (36% vs 4%) and iron deficiency anaemia (10% vs 0%) at 6 months (49). In addition, the risk of iron deficiency at 12 months of age is also reduced (44). The follow up to this randomised controlled trial (RCT) showed that at 3 ½ years of age, those supplemented with iron had a significantly lower prevalence of behavioural problems than those in the placebo group (3% vs 13%) (50) and they had significantly lower scores in aggressive and rule-breaking (externalising-type) behaviours and in thought problems at 7 years of age (51). It is recommended to give iron supplements to babies with birth weights of 2000-2500g regardless of gestational age, at a dose of 1–2 mg/kg/day up to 6 months of age (2).

Starting iron supplementation

ESPGHAN updated their recommendation to start iron supplementation at 2 weeks of age, compared with their previous advice of starting at 2-4 weeks, following a meta-analysis conducted by Jin et al (52). This found starting iron supplementation at ~2-3 weeks vs later ~4-8 weeks of age is associated with less of a decrease in serum ferritin and haemoglobin levels and consequently a lower need for blood transfusions in preterm

babies. Koletzko et al (2) also recommend initiation of iron at 2 weeks, following findings of improved haematological parameters with early initiation in babies born <1300g (53).

Discontinuing iron supplementation

ESPGHAN recommended that iron supplements are continued in preterm infants until 6–12 months of age (depending on diet) and that haemoglobin and serum ferritin should be monitored at follow-up visits (1).

Preterm and term infant should receive iron rich complementary foods (1, 54). It is acknowledged iron fortified foods and iron supplements may be needed to meet requirements during the introduction of complementary foods (54). The source of dietary iron will impact on absorption with approximately 25% of animal or haem sources of iron absorbed (54). Non haem sources of iron are less well absorbed, and absorption is affected by other dietary factors which can facilitated and inhibit absorption (54).

Excess iron

ESPGHAN warns against prolonged intake of high doses of iron as there are no mechanisms for excretion of iron from the human body and therefore excess iron may have potential for adverse effects. Such effects may cause oxidative injury in preterm babies which could exacerbate conditions such as necrotising enterocolitis and ROP (2, 53). This guideline advises against prolonged dietary iron intakes of >4 mg/kg/day. However, some babies may require high doses of iron for short periods (e.g. babies on erythropoietin may require supplementation up to 6 mg/kg/day) (1).

3.3 Appendix 2: Available Multivitamin Preparations

Vitamin D where prescribed singularly, is as colecalciferol. Preparations can vary by IU/ml.

Vitamin	Abidec® 0.3 ml	Abidec® 0.6 ml	DaliVit® 0.3 ml	DaliVit® 0.6 ml	Healthy Start 5 drops	Units
A	667 (200)	1333 (400)	2500 (750)	5000 (1500)	777 (233)	international units (micrograms)
D	200 (5)	400 (10)	200 (5)	400 (10)	400 (10)	international units (micrograms)
B1 (thiamine)	0.2	0.4	0.5	1	0	milligrams
B2 (riboflavin)	400	800	200	400	0	micrograms
B3 (nicotinamide/niacin)	4	8	2.5	5	0	milligrams
B6 (pyridoxine)	400	800	250	500	0	micrograms
C (ascorbic acid)	20	40	25	50	20	milligrams

3.4 Appendix 3: Alternative Vitamin Supplementation

Born <34weeks <u>and/or</u> <1.8kg	
Fortified breastmilk OR Nutriprem 1®, Hydrolysed Nutriprem 1®, SMA Gold Prem 1®	Colecalciferol (400 units/day)
Unfortified breastmilk	Folic Acid 50 micrograms/day (to term) and DaliVit® 0.3 mL/day and Colecalciferol (400 units/day)
On reaching 1.8kg – 2.0 kg <u>or</u> at discharge (if sooner) ** dependent upon local policy for change to nutrient enriched post discharge formulas	
Fortified Breastmilk OR Breastfeeding with Breastmilk Fortifier at home OR SMA Gold Prem 2, Nutriprem 2 OR Term/Specialist/High Calorie Term Formula	Healthy Start® (5 drops) OR Colecalciferol (400 units/day)
Unfortified breastmilk and/or breastfeeding	DaliVit® 0.6 mL/day Stop Colecalciferol Continue folic acid to term
Born 34-37weeks <u>and</u> >1.8kg	
Breast milk or Term Formula	Healthy Start® (5 drops) OR Colecalciferol (400 units/day Vitamin D - NOT per kg)

3.5 Appendix 4: Alternative Iron Supplementation

Sodium feredetate contains 27.5 mg of elemental iron in 5 mL and is widely the most acceptable oral solution used in neonatal units.

If sodium feredetate oral solution is not available, ferrous fumarate oral liquid can be considered (53). Ferrous fumarate contains 45 mg of elemental iron in 5 mL.

Equivalent dosing	
Sodium feredetate 27.5mg in 5ml	Ferrous fumarate 45mg in 5mL
0.5mL	0.3mL
1mL	0.6mL

3.6 Appendix 5: Available preterm, term and specialist formulas

Specialist formulas used for preterm infants need manipulation and should only be used under the direction of a neonatal dietitian

Formula	Indication for use	Nutrient modification	Suitable for preterm infants?
Preterm Formulas			
Nutriprem 1 SMA gold Prem 1 Hydrolysed Nutriprem	Nutritionally complete breastmilk substitutes, suitable as a sole source of nutrition for preterm and low birthweight infants weighing <1800g		Yes
Post discharge Formulas			
Nutriprem 2 SMA Gold Prem 2	Nutritionally complete breastmilk substitutes, suitable as a sole source of nutrition for preterm and low birthweight infants post discharge.		Yes
Term Standard Formulas			
Cow and Gate First infant milk Aptamil 1 First Infant milk Aptamil Advanced Aptamil Organic first Infant milk SMA Pro first Infant milk SMA Advanced Kendamil First infant milk Hipp Organic 1 First Infant milk Mamia First infant milk	Nutritionally complete breastmilk substitutes, suitable as a sole source of nutrition for infants born at term to 6 months of age.		No – formulated to meet requirements of term infants. Protein:energy ratio not suitable for preterm infants.
Specialist formulas			
Aptamil Pepti Junior	Malabsorption/post GI surgery	Hydrolysed protein/clinically lactose free/MCT fat	No – requires concentration and supplementation to meet preterm requirements.
Aptamil Pepti 1	Cow's milk intolerance	Extensively hydrolysed protein. Contains lactose, so not suitable if malabsorption suspected	No – requires concentration and supplementation to meet preterm requirements.
Nutramigen LGG	Cow's milk intolerance	Extensively hydrolysed protein. Clinically lactose free. Contains probiotics.	No – requires concentration and supplementation to meet preterm requirements. Needs making up with boiling water to denature probiotics.

Neocate Alfamino Puramino	Severe malabsorption –use only after failure with an extensively hydrolysed formula	Amino acids. Neocate does not contain MCT Clinically lactose free High osmolality	No - requires concentration and supplementation to meet preterm requirements.
Monogen	Chylothorax	Whole protein 80% fat as MCT	No – requires concentration and supplementation to meet preterm requirements.
Nutrient dense term formulas			
Similac High Energy Infatrini SMA High Energy	Infants >37 weeks (>2kg) with increased nutritional requirements/fluid restrictions	Nutrient dense. SMA High Energy contains partially hydrolysed protein	No – formulated to meet requirements of term infants. Protein:energy ratio not suitable for preterm infants.
Infatrini Peptisorb	Infants >37 weeks (>2kg) with increased requirements/fluid restrictions AND Malabsorption	Nutrient dense with extensively hydrolysed protein	No – formulated to meet requirements of term infants. Protein:energy ratio not suitable for preterm infants.

3.7 Appendix 6: Total vitamin A & D intakes by infant weight, milk choice

	Nutriprem 1 & Abidec 0.3ml OD						Nutriprem 1 & Abidec 0.6ml OD							
	500g		750g		1000g		1001g		1200g		1500g		1800g	
ml/kg	150	165	150	165	150	165	150	165	150	165	150	165	150	165
Vitamin A (ug/kg/d)	947	1000	814	871	748	803	948	1003	881	936	815	870	770	825
Vitamin D (IU/kg/d)	586	605	452	470	386	404	585	604	520	537	452	470	408	426
	SMA Gold Prem 1 & Abidec 0.3ml OD						SMA Gold Prem 1 & Abidec 0.6ml OD							
	500g		750g		1000g		1001g		1200g		1500g		1800g	
ml/kg	150	165	150	165	150	165	150	165	150	165	150	165	150	165
Vitamin A (ug/kg/d)	893	942	760	809	694	743	894	943	827	877	761	811	716	767
Vitamin D (IU/kg/d)	604	624	470	490	404	424	604	624	537	557	470	490	426	446
	Fortified Breastmilk (Cow and Gate) & Abidec 0.3ml OD						Fortified Breastmilk (Cow and Gate) & Abidec 0.6ml OD							
	500g		750g		1000g		1001g		1200g		1500g		1800g	
ml/kg	150	165	150	165	150	165	150	165	150	165	150	165	150	165
Vitamin A (ug/kg/d)	833	877	700	744	634	678	834	878	767	811	701	745	656	700
Vitamin D (IU/kg/d)	730 (104%)	763 (109%)	596	629	530	563	730 (104%)	763 (109%)	663	696	596	629	552	585
	Fortified Breastmilk (SMA) & Abidec 0.3ml OD						Fortified Breastmilk (SMA) & Abidec 0.6ml OD							
	500g		750g		1000g		1001g		1200g		1500g		1800g	
ml/kg	150	165	150	165	150	165	150	165	150	165	150	165	150	165
Vitamin A (ug/kg/d)	1055 (106%)	1120 (112%)	922	987	856	921	1057 (106%)	1122 (112%)	989	1054 (105%)	923	988	879	943
Vitamin D (IU/kg/d)	643	667	509	533	443	467	643	667	576	600	509	533	465	489

Table 1: Total daily vitamin A (ug/kg/day) & vitamin D (IU/kg/day) intakes with dose banding by infant weight (Option 1) for infants ≤1.8kg



Nutriprem 1 & Abidec 0.6ml OD												
	500g		750g		1000g		1200g		1500g		1800g	
ml/kg	150	165	150	165	150	165	150	165	150	165	150	165
Vitamin A (ug/kg/d)	1349 (135%)	1404 (140%)	1082 (108%)	1137 (114%)	949	1004	881	936	815	870	770	825
Vitamin D (IU/kg/d)	986 (141%)	1004 (143%)	719 (103%)	737 (105%)	586	604	520	537	452	470	408	426
SMA Gold Prem 1 & Abidec 0.6ml OD												
	500g		750g		1000g		1200g		1500g		1800g	
ml/kg	150	165	150	165	150	165	150	165	150	165	150	165
Vitamin A (ug/kg/d)	1295 (130%)	1344 (134%)	1028 (103%)	1077 (108%)	895	944	827	877	761	811	716	767
Vitamin D (IU/kg/d)	1004 (143%)	1024 (146%)	737 (105%)	757 (108%)	604	624	537	557	470	490	426	446
Fortified Breastmilk (Cow and Gate) & Abidec 0.6ml OD												
	500g		750g		1000g		1200g		1500g		1800g	
ml/kg	150	165	150	165	150	165	150	165	150	165	150	165
Vitamin A (ug/kg/d)	1235 (124%)	1279 (128%)	968	1012 (101%)	835	879	767	811	701	745	656	700
Vitamin D (IU/kg/d)	1130 (161%)	1163 (166%)	863 (123%)	896 (128%)	730 (104%)	763 (109%)	663	696	596	629	552	585
Fortified Breastmilk (SMA) & Abidec 0.6ml OD												
	500g		750g		1000g		1200g		1500g		1800g	
ml/kg	150	165	150	165	150	165	150	165	150	165	150	165
Vitamin A (ug/kg/d)	1457 (146%)	1522 (152%)	1190 (119%)	1255 (126%)	1057 (106%)	1122 (112%)	989	1054 (105%)	923	988	879	943
Vitamin D (IU/kg/d)	1043 (149%)	1067 (152%)	776 (111%)	800 (114%)	643	667	576	600	509	533	465	489

Table 2: Total daily vitamin A (ug/kg/day) & vitamin D (IU/kg/day) intakes with a pragmatic approach (Option 2) for infants ≤1.8kg

Vitamin,

Lynne Radbone

Version 2: November 2024

Glossary

Term	Definition
EFSA	European Food Safety Agency
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
ELBW	Extremely Low Birth Weight
VLBW	Very Low Birth Weight
LMPT	Late to Moderate Preterm
WHEAT	Withholding Enteral Feeds Around Packed Red Cell Transfusion
RBP	Retinol Binding Protein
BPD	Bronchopulmonary Dysplasia
IVH	Intraventricular Haemorrhage
ROP	Retinopathy of Prematurity
RCT	Randomized Controlled Trial

This guideline is based on a national resource produced by the British Dietetic Association Neonatal Dietitian’s Interest Group - **“The routine supplementation of vitamins and iron and the management of zinc deficiency in preterm and small for gestational age infants”** Jan 2024

Vitamin supplementation in preterm and small for gestational age infants

Katie Hay RD, Lead Neonatal Dietitian East Midlands ODN
Lynne Radbone RD MBE, Lead Neonatal Dietitian East of England ODN
Lynette Forsythe RD, Lead Neonatal Dietitian North West ODN
Dilyana Kraveva RD, Neonatal Dietitian Nottingham University Hospitals NHS Foundation Trust
Rachael Rodley RD, Neonatal Dietitian, Jessop Wing, Sheffield Teaching Hospitals
Hester Blair RD, Advanced Dietetic Practitioner (Neonates), Simpsons Centre for Reproductive Health, NHS Lothian
Suzannah Hibberd, Neonatal Pharmacist, University Hospital Southampton

Iron supplementation in preterm and small for gestational age infants

Louisa Whitfield-Brown RD, Lead Neonatal Dietitian Northern ODN
Stephanie Tagani RD, Clinical Lead Dietitian: Neonates, Imperial College Healthcare NHS Trust
Rachel Fox RD, Senior Specialist Dietitian, University Hospitals of Leicester NHS Trust
Carol Fudge RD, Childrens Dietitian, Poole General Hospital
William Williams RD, Neonatal lead Dietitian. Betsi Cadwaladr University Health Board
Sara Clarke RD, Lead Neonatal Dietitian West Midlands ODN and Chair of Neonatal Dietitians Interest Group
Melody Chan, Neonatal Pharmacist, University Hospital Southampton

Management of zinc deficiency in preterm and small for gestational age infants

Luise Marino, RD PhD, Clinical Academic Paediatric Dietitian, Paediatric Intensive Care Unit, Neonates and Paediatric Cardiology, Southampton Children’s Hospital, University Hospital Southampton Foundation Trust, and Honorary Associate Professor, University Southampton
Nikki Lyttle RD, Neonatal Dietitian, Royal Belfast Hospital for Sick Children/Royal Jubilee Maternity Hospital, Belfast
Grace Allmark RD, Paediatric Dietetic Lead, Hampshire Hospitals Foundation Trust
Tracey Elks RD, Neonatal Dietitian, Tunbridge Wells Hospital

All sections were peer reviewed by other section authors.

References

1. Enteral Nutrition in Preterm Infants (2022): A Position Paper from the ESPGHAN Committee on Nutrition and Invited Experts J Pediatr Gastroenterol Nutr 2023 Feb 1; 76(2):248-268. doi: 10.1097/MPG.0000000000003642.
2. Koletzko B et al (2021) Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines. Word Rev Nutrition and Dietetics, Karger, Vol 122
3. WHO recommendations for care of the preterm or low birth weight infant. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.
4. ESPGHAN Committee of Nutrition Position Paper on Enteral Nutrition (Feb 2022) Human Milk Nutrient Composition: Evidence Base and Justification. Available at: 1.7 Human Milk Reference revised.pdf
5. SMA Nutrition (Feb 2022) Databcard SMA Gold Prem Breast Milk Fortifier. Available at: SMA80250 SMA PRO GP2 databcard FA2 (smahcp.co.uk)
6. Nutricia (March 2023) Databcard Cow and Gate Nutriprem Human Milk Fortifier. Available at: Cow & Gate nutriprem Human milk Fortifier (nutricia.co.uk)
7. Nutricia (April 2023) Databcard Cow and Gate Nutriprem 1. Available at: Cow & Gate nutriprem 1 (nutricia.co.uk)
8. Nutricia (July 2023) Databcard Cow and Gate Nutriprem 2 Post Discharge Liquid 90ml. Available at: Cow & Gate nutriprem 2 Preterm & Low Weight Nutricia UK
9. Nutricia (August 2021) Databcard Cow and Gate Nutriprem 2 Post Discharge Powder. Available at: Cow & Gate nutriprem 2 Post-Discharge Powder (nutricia.co.uk)
10. SMA Nutrition (December 2019) Databcard SMA Gold Prem 1. Available at: SMA40250 SMA Gold PRO Prem Milk databcard lo1b (smahcp.co.uk) .
11. SMA Nutrition (April 2023) Databcard SMA Gold Prem 2 Powder. Available at: SMA80250 SMA PRO GP2 databcard FA2 (smahcp.co.uk)
12. SMA Nutrition (May 2023) Databcard SMA Gold Prem 2 Liquid. Available at: SMA80250 SMA PRO GP2 databcard FA2 (smahcp.co.uk)
13. Mactier, H and Weaver, L.T (2005) Vitamin A and preterm infants: what we know, what we don't know, and what we need to know. Archives of Disease in Childhood - Fetal Neonatal Ed;90:F103–F108.
14. Ambalavanan, N., Wu, T-J, Tyson, J.E., Kennedy, K.A., Roane, C., and Carlo, W. (2003) A comparison of three vitamin A dosing regimens in extremely low birthweight infants. The Journal of Pediatrics. 142: 656-661.
15. Feeding the Late and Moderately preterm infant: A position paper of the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr (2019) Aug; 69(2):259-270. doi: 10.1097/MPG.0000000000002397
16. Early Postnatal Care of the Moderate-Late Preterm Infant – A Framework for Practice (2023) British Association of Perinatal Medicine. Available from: https://www.bapm.org/resources/framework-early-postnatal-care-of-the-moderate-late-preterm-infant
17. Sjöström ES, Ohlund I, Ahlsson F, Domellof M. (2016) Intakes of micronutrients are associated with early growth in extremely preterm infants. Journal of Pediatric Gastroenterology and Nutrition, 62:885–92. 24
18. Oncel MY, Calisici E, Ozdemir R, Yurttutan S, Erdeve O, Karahan S, et al. (2014) Is folic acid supplementation really necessary in preterm infants \leq 32 weeks of gestation? Journal of Pediatric Gastroenterology and Nutrition, 58(2):188-192
19. Jyothi S, Misra I, Morris G, Benton A, Griffin D, Allen S. (2007) Red cell folate and plasma homocysteine in preterm infants. Neonatology, 92:264–8
20. Burris HH, Van Marter LJ, McElrath TF, Tabatabai P, Litonjua AA, Weiss ST, Christou H. (2014) Vitamin D status among preterm and full-term infants at birth. Pediatric Research.75:75–80.

<p>21. Monangi N, Slaughter JL, Dawodu A, Smith C, Akinbi HT. (2014) Vitamin D status of early preterm infants and the effects of vitamin D intake during hospital stay. <i>Archives of Disease in Childhood - Fetal and Neonatal Edition</i>. 99:F166–F168.</p>
<p>22. Kołodziejczyk-Nowotarska, A., Bokinić, R., and Seliga-Siwecka, J (2021) Monitored Supplementation of Vitamin D in Preterm Infants: A Randomized Controlled Trial. <i>Nutrients</i>. 13: 3442.</p>
<p>23. Adnan, M., Wu, S-Y., Khilfeh, M., and Davis, V. (2022) Vitamin D status in very low birth weight infants and response to vitamin D intake during their NICU stays: a prospective cohort study. <i>Journal of Perinatology</i>. 42, 209-216.</p>
<p>24. Mauras, M., Butin, M., Roy, P., Plaisant, F., Laborie, S., Bacchetta, J. (2022) Local protocol helped to deliver vitamin D levels more accurately in preterm infants. <i>Acta Paediatrica</i>. 111. 76-85.</p>
<p>25. Tammela, O., Aitola, M., & Ikonen, S. (1999). Cord blood concentrations of vitamin A in preterm infants. <i>Early human development</i>, 56(1), 39–47. https://doi.org/10.1016/s0378-3782(99)00032-8</p>
<p>26. Shearer MJ. Vitamin K deficiency bleeding (VKDB) in early infancy. <i>Blood Rev</i>. 2009;23(2):49-59. doi:10.1016/j.blre.2008.06.001</p>
<p>27. Lippi G, Franchini M. Vitamin K in neonates: facts and myths. <i>Blood Transfus</i>. 2011;9(1):4-9.</p>
<p>28. Haroon Y, Shearer MJ, Rahim S, Gunn WG, McEnery G, Barkhan P. The content of phylloquinone (vitamin K1) in human milk, cows' milk and infant formula foods determined by high-performance liquid chromatography. <i>J Nutr</i>. 1982;112(6):1105-1117.</p>
<p>29. Shearer MJ, Clarke P. Vitamin K metabolism in the fetus and neonate. In: Polin R, Abman S, Rowitch D, Benitz W, eds. <i>Fetal and Neonatal Physiology</i>. 6th ed. Elsevier; 2021:303-310.</p>
<p>30. Sutor AH, Dagres N, Niederhoff H. Late form of vitamin K deficiency bleeding in Germany. <i>Klin Padiatr</i>. 1995;207:89-97. doi:10.1055/s-2008-1046519</p>
<p>31. Busfield A, Samuel R, McNinch A, Tripp JH. Vitamin K deficiency bleeding after NICE guidance and withdrawal of Konakion neonatal: British Paediatric Surveillance Unit study, 2006-2008. <i>Arch Dis Child</i>. 2013;98:41-47. doi:10.1136/archdischild-2011-301029</p>
<p>32. Shearer M, Harvey J, Hodges S, Savidge G. Raised undercarboxylated prothrombin (PIVKA-II) in healthy 2-5 month-old infants shows evidence of subclinical vitamin K deficiency which is related to duration of breast feeding. [abstract]. <i>Blood</i>. 2001;98:530a.</p>
<p>33. Jain G, Adhikari KM, Vasnik GK, Singh D, Somasundaram V, Gupta R, et al. Prevalence of subclinical vitamin K deficiency in early infancy in exclusively breast-fed term infants. <i>Journal of Marine Medical Society</i> 2023;25(Suppl 1):S55-S57. DOI: 10.4103/jmms.jmms_75_22. Available at: https://journals.lww.com/jmsc/fulltext/2023/25011/prevalence_of_subclinical_vitamin_k_deficiency_in.10.aspx</p>
<p>34. Perrone S, De Bernardo G, Lembo C, et al. Vitamin K insufficiency and the prophylaxis strategy in term healthy infants: A multicentre study. <i>Eur J Clin Invest</i>. 2023;Dec 9:e14141. doi: 10.1111/eci.14141. Epub ahead of print. Available: https://onlinelibrary.wiley.com/doi/10.1111/eci.14141</p>
<p>35. Clarke P, Shearer MJ, Card DJ, et al. Exclusively breastmilk-fed preterm infants are at high risk of developing subclinical vitamin K deficiency despite intramuscular prophylaxis at birth. <i>J Thromb Haemost</i>. 2022;20:2773-85. doi: 10.1111/jth.15874. Epub 2022 Oct 3. Available: https://www.jthjournal.org/article/S1538-7836(22)18363-7/fulltext</p>

36. Clarke P, Embleton ND, Fewtrell M, Harrington DJ, Kelly AM, Moris N, Patto A, Ponnusamy V, Vasu V, Shearer MJ. Vitamin K: missed at peril—the case for extra supplementation to prevent deficiency in breastfed preterm infants. <i>Archives of Disease in Childhood Fetal & Neonatal Edition</i> . 2024: In press. http://dx.doi.org/10.1136/archdischild-2023-326737
37. Sun, H., Cheng, R., & Wang, Z. (2020). Early Vitamin A Supplementation Improves The Outcome Of Retinopathy Of Prematurity In Extremely Preterm Infants. <i>Retina (Philadelphia, Pa.)</i> , 40(6), 1176–1184. https://doi.org/10.1097/IAE.0000000000002543
38. Darlow, B. A., & Graham, P. J. (2007). Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. The Cochrane database of systematic reviews. https://doi.org/10.1002/14651858.CD000501.pub2
39. Thibeault DW. The precarious antioxidant defenses of the preterm infant. <i>Am J Perinatol</i> . 2000;17:167-81
40. Brigelius-Flohé R, Kelly FJ, Salonen JT, et al. The European perspective on vitamin E: current knowledge and future research. <i>Am J Clin Nutr</i> . 2002; 76:703-16
41. Brion LP, Bell EF, Raghuvver TS. Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. <i>Cochrane Database Syst Rev</i> 2003;3:CD003665.
42. Kositamongkol S, Suthutvoravut U, Chongviriyaphan N, et al. Vitamin A and E status in very low birth weight infants. <i>J Perinatol</i> . 2011; 31:471-6.
43. Department of Health (2021) Vitamins for children - NHS (www.nhs.uk)
44. Scottish Government (2023) Vitamin D: advice for parents - gov.scot (www.gov.scot)
45. Summary of Product Characteristics. (Sytron 27.5mg iron per 5ml Oral Solution). Accessed via https://www.medicines.org.uk/emc/product/8791 (27/09/2023)
46. MacQueen BC, Baer VL, Scott DM, Ling CY, O'Brien EA, Boyer C, Henry E, Fleming RE, Christensen RD. Iron Supplements for Infants at Risk for Iron Deficiency. <i>Glob Pediatr Health</i> . 2017 Apr 25;4:2333794X17703836. doi: 10.1177/2333794X17703836. PMID: 28491927; PMCID: PMC5405879.
47. Yeo KT, Kong JY, Sasi A, Tan K, Lai NM, Schindler T. Stopping enteral feeds for prevention of transfusion-associated necrotising enterocolitis in preterm infants. <i>Cochrane Database of Systematic Reviews</i> 2019, Issue 10. Art. No.: CD012888. DOI: 10.1002/14651858.CD012888.pub2. Accessed 18 September 2023.
48. Christensen RD, Lambert, DK, Henry, E, Wiedmeier, SE, Snow, GL, Baer, VL, Gerday, E., Ilstrup, S, Pysher TJ (2010) Is “transfusion-associated necrotizing enterocolitis” an authentic pathogenic entity? <i>Transfusion</i> , 50 (5): 1106-1112 DOI: 10.1111/j.1537-2995.2009.02542.x
49. Bajaj, M., Lulic-Botica, M., Hanson, A, Natarajan, G (2019) Feeding during transfusion and the risk of necrotizing enterocolitis in preterm infants. <i>Journal of Perinatology</i> 39: 540–546
50. Gale C, Modi N, Jawad, S. (2019) The WHEAT pilot trial—WithHolding Enteral feeds Around packed red cell Transfusion to prevent necrotising enterocolitis in preterm neonates: a multicentre, electronic patient record (EPR), randomised controlled point-of-care pilot trial. <i>BMJ Open</i> ;9:e033543. doi: 10.1136/bmjopen-2019-033543
51. Berglund S, Westrup B, Domellöf M. Iron supplements reduce the risk of iron deficiency anemia in marginally low birth weight infants. <i>Pediatrics</i> . 2010 Oct;126(4):e874-83. doi: 10.1542/peds.2009-3624. Epub 2010 Sep 6. PMID: 20819898.
52. Berglund SK, Westrup B, Hägglöf B, Hernell O, Domellöf M. Effects of iron supplementation of LBW infants on cognition and behavior at 3 years. <i>Pediatrics</i> . 2013 Jan;131(1):47-55. doi: 10.1542/peds.2012-0989. Epub 2012 Dec 10. PMID: 23230066.
53. Berglund SK, Chmielewska A, Starnberg J, Westrup B, Hägglöf B, Norman M, Domellöf M. Effects of iron supplementation of low-birth-weight infants on cognition and behavior at 7 years: a randomized controlled trial. <i>Pediatr Res</i> . 2018 Jan;83(1-1):111-118. doi: 10.1038/pr.2017.235. Epub 2017 Oct 25. PMID: 28953856.

54. Jin HX, Wang RS, Chen SJ, Wang AP, Liu XY. Early and late Iron supplementation for low birth weight infants: a meta-analysis. <i>Journal of Pediatrics</i> (2015) 41:16
55. Mills RJ, Davies MW. Enteral iron supplementation in preterm and low birth weight infants. <i>Cochrane Database Syst Rev.</i> 2012 Mar 14;(3):CD005095. doi: 10.1002/14651858.CD005095.pub2. PMID: 22419305.
56. Fewtrell M, Bronsky J, Campoy C, Domellöf M, Embleton N, Fidler Mis N, Hojsak I, Hulst JM, Indrio F, Lapillonne A, Molgaard C. Complementary Feeding: A Position Paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition. <i>J Pediatr Gastroenterol Nutr.</i> 2017 Jan;64(1):119-132. doi: 10.1097/MPG.0000000000001454. PMID: 28027215.
57. Summary of Product Characteristics. (Ferrous fumarate 140mg/5ml Syrup). Accessed via https://www.medicines.org.uk/emc/product/8791 (27/09/2023)
58. Pearson F, Johnson MJ, Leaf A. Milk osmolality: does it matter? <i>Archives of Disease in Childhood - Fetal and Neonatal Edition</i> 2013;98:F166-F169
59. Srinivasan L, Bokinić R, King C, Weaver G, Edwards AD. Increased osmolality of breast milk with therapeutic additives. <i>Arch Dis Child Fetal Neonatal Ed.</i> 2004 Nov;89(6):F514-7. doi: 10.1136/adc.2003.037192. PMID: 15499144; PMCID: PMC1721783
60. Black MM. Zinc deficiency and child development. <i>Am J Clin Nutr.</i> 1998 Aug;68(2 Suppl):464S-469S. doi: 10.1093/ajcn/68.2.464S. PMID: 9701161; PMCID: PMC3137936.
61. Staub E, Evers K, Askie LM. Enteral zinc supplementation for prevention of morbidity and mortality in preterm neonates. <i>Cochrane Database of Systematic Reviews</i> 2021, Issue 3. Art. No.: CD012797. DOI: 10.1002/14651858.CD012797.pub2. Accessed 16 November 2023.
62. Department of Health, Dietary Reference Values for Food Energy and Nutrients for the United Kingdom, HMSO, 1991.
63. Terrin G, Boscarino G, Di Chiara M, Iacobelli S, Faccioli F, Greco C, Onestà E, Sabatini G, Pietravalle A, Oliva S, Conti MG, Natale F, De Curtis M. Nutritional Intake Influences Zinc Levels in Preterm Newborns: An Observational Study. <i>Nutrients.</i> 2020 Feb 19;12(2):529. doi: 10.3390/nu12020529. PMID: 32093077; PMCID: PMC7071515.
64. Terrin G, Berni Canani R, Di Chiara M, Pietravalle A, Aleandri V, Conte F, De Curtis M. Zinc in Early Life: A Key Element in the Fetus and Preterm Neonate. <i>Nutrients.</i> 2015 Dec 11;7(12):10427-46. doi: 10.3390/nu7125542. PMID: 26690476; PMCID: PMC4690094.
65. Domellöf M, Szitanyi P, Simchowicz V, Franz A, Mimouni F; ESPGHAN/ESPEN/ESPR/CSPEN working group on pediatric parenteral nutrition. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Iron and trace minerals. <i>Clin Nutr.</i> 2018 Dec;37(6 Pt B):2354-2359. doi: 10.1016/j.clnu.2018.06.949. Epub 2018 Jun 18. PMID: 30078716.
66. Willoughby JL, Bowen CN. Zinc deficiency and toxicity in pediatric practice. <i>Curr Opin Pediatr.</i> 2014 Oct;26(5):579-84. doi: 10.1097/MOP.000000000000132. PMID: 25029226.
67. Summary of Product Characteristics. (Solvazinc 45mg effervescent tablets). Accessed via https://www.medicines.org.uk/emc/product/4930/smpc#about-medicine (15/1/2024)
68. Joint Formulary Committee. <i>British National Formulary</i> (12/2023). London: British Medical Association and Royal Pharmaceutical Society. Electronic edition. Accessed via http://www.medicinescomplete.com/mc/bnf/current/ (12/1/2024)
69. Zaladonis CA, Safeer LZ, Hanson DC, Erickson-Parsons L and Krakowski AC (2022) Zinc Deficiency in a Preterm Infant. <i>The Journal of Pediatrics.</i> 240: 304-306. DOI: https://doi.org/10.1016/j.jpeds.2021.08.020 Accessed via https://www.jpeds.com/article/S0022-3476(21)00781-2/fulltext (18/1/24)
70. Starship (2018) Zinc deficiency in the newborn. Accessed via https://starship.org.nz/guidelines/zinc-deficiency-in-the-newborn/ (18/1/2024)

71 Specialist Pharmacy Service https://www.sps.nhs.uk/articles/explaining-the-licensed-status-of-medicines/ . Accessed 30th August 2024.
72 Specialist Pharmacy Service https://www.sps.nhs.uk/articles/understanding-unlicensed-medicines/ Accessed 30th August 2024.
73 Food Standards Agency https://www.food.gov.uk/business-guidance/food-supplements Accessed 30th August 2024.

Exceptional Circumstances Form

Form to be completed in the **exceptional** circumstances that the Trust is not able to follow ODN approved guidelines.

Details of person completing the form:	
Title:	Organisation:
First name:	Email contact address:
Surname:	Telephone contact number:
Title of document to be excepted from:	
Rationale why Trust is unable to adhere to the document:	
Signature of speciality Clinical Lead:	Signature of Trust Nursing / Medical Director:
Date:	Date:
Hard Copy Received by ODN (date and sign):	Date acknowledgement receipt sent out:

--	--

Please return completed form to kelly.hart5@nhs.net requesting receipt.

Send hard signed copy to:

Kelly Hart, EOE ODN Office Manager

Box 402

Rosie Hospital

Robinson Way

Cambridge University Hospital

Hills Road

Cambridge CB2 0SW

All Rights Reserved. The East of England Neonatal ODN withholds all rights to the maximum extent allowable under law. Any unauthorised broadcasting, public performance, copying or re-recording will constitute infringement of copyright. Any reproduction must be authorised and consulted with by the holding organisation (East of England Neonatal ODN).

The organisation is open to share the document for supporting or reference purposes but appropriate authorisation and discussion must take place to ensure any clinical risk is mitigated. The document must not incur alteration that may pose patients at potential risk. The East of England Neonatal ODN accepts no legal responsibility against any unlawful reproduction. The document only applies to the East of England region with due process followed in agreeing the content.