National Institute for Health and Care Excellence

Final

Neonatal parenteral nutrition

[D5] Iron

NICE guideline NG154

Evidence reviews

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Final

These evidence reviews were developed by the National Guideline Alliance which is part of the Royal College of Obstetricians and Gynaecologists

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Contents

Individual constituents in parental nutrition for preterm and term babies: intravenous iron

Review question

What is the most effective and safe iron supplementation compared to no iron or different dosage/formulations in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Introduction

Iron is important for growth and development. Iron stores are accumulated during the third trimester of pregnancy, and therefore iron deficiency is particularly relevant for premature infants who typically have low iron stores at birth and have excessive demands due to a rapid rate of growth. Iron deficiency can have serious negative effects including anaemia, and may adversely affect neurodevelopment, such as deficits of cognition, hearing, memory and behaviour. Iron itself is not an innocuous substance, due to concerns regarding iron overload and potential exposure to free radicals. The need for iron supplementation in newborn babies on parenteral nutrition (PN) is therefore an important matter for consideration.

Summary of the protocol

Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	• Babies born preterm, up to 28 days after their due birth date (preterm babies) • Babies born at term, up to 28 days after their birth (term babies)
Intervention	Iron (any dosage)
Comparison	• No iron • Different dosages • Different formulations

Outcomes	**Critical**
	• Adverse effects of iron administration:
	  ○ Iron overload (serum ferritin)
	  ○ Infection (including sepsis)
	• Neurodevelopmental outcomes (general cognitive abilities at two years corrected age as measured by a validated scale)
	Important
	• Growth/Anthropometric measures:
	  ○ Weight gain (g/kg/d)
	  ○ Linear growth
	  ○ Head circumference (mm)
	• Mortality
	• Haemoglobin concentration and haematocrit
	• Serum iron

	• Total iron binding capacity

For further details see the review protocol in appendix A.

Clinical evidence

Included studies

Two randomised controlled trials (RCTs) were included in the review (Friel 1995, Qiao 2017). Both studies compared a PN formulation with added iron supplement to a PN formulation without iron. No meta-analysis was undertaken as the two studies included different outcomes.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B, study selection flow chart in appendix C, evidence tables in appendix D, and GRADE tables in appendix F.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes	Comments
Friel 1995 RCT Canada	N=26 VLBW infants <u>Mean GA (weeks)</u> Iron group: 28 (SD 2.3) No Iron group: 29 (SD 2.2) <u>Mean birth weight (g)</u> Iron group: 963 (SD 285) No Iron group: 1054 (SD 326)	Iron group (n=14) Total PN (with iron already in PN as manufacturing contaminant, concentration not reported) plus iron supplementation (200 to 250 µg/kg/day as dextran iron) Mean days on full (>75% energy intake) total PN: 15.5 (SD 8.0) Mean days on partial (<75% energy intake) total PN: 3.6 (SD 2.7)	No Iron group (n=12) Total PN (with iron already in PN as manufacturing contaminant, concentration not reported)	• Adverse effect of iron: ○ Infection (sepsis) (positive blood or cerebral fluid culture, or local lesions)	At week 1, 100% of newborns in both groups received PN, this declined over time with enteral feeding being provided.

Study	Population	Intervention	Comparison	Outcomes	Comments
Qiao 2017 RCT China	N=96 preterm infants N included = 61 <u>Mean GA (weeks)</u> Iron group: 30.4 (SD 1.7) Control group: 30.3 (SD 2.1) <u>Mean birth weight (g)</u> Iron group: 1525 (SD 502) Control group: 1486 (SD 392)	Iron group (n=31) Standard PN: (all in one solution containing 20% lipids, 6% amino acids, glucose, trace elements, minerals, and vitamins, +0.9 mg of iron per 100 mL from standard preterm formula) Plus IV iron 200µg/kg/day	Control group (n=30) Standard PN: (all in one solution containing 20% lipids, 6% amino acids, glucose, trace elements, minerals, and vitamins +0.9 mg of iron per 100 mL from standard preterm formula)	• Iron overload (serum ferritin) • Mortality • Haemoglobin concentration • Haematocrit • Serum iron • Total iron binding capacity	All infants received PN from the second day of birth until they could receive 120 mL/kg per day of enteral feedings. Three treatment groups were included in the study; a group supplemented with iron combined with EPO (400 U/kg twice a week) is not included in the analysis

EPO: erythropoietin; GA: Gestational age; IV: intravenous; NICU: neonatal intensive care unit; PN: parenteral nutrition; RCT: randomised controlled trial; SD: standard deviation; VLBW: very low birth weight

See appendix D for full evidence tables.

Quality assessment of clinical outcomes included in the evidence review

GRADE was conducted to assess the quality of outcomes. Evidence was identified for critical and important outcomes. The clinical evidence profiles can be found in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question. A single economic search was undertaken for all topics included in the scope of this guideline. Please see supplementary material D for details.

Excluded studies

No studies were identified which were applicable to this review question.

Summary of studies included in the economic evidence review

No economic evidence was identified which was applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Clinical evidence statements

Iron overload (serum ferritin) (<32 weeks' gestation age)

- Low quality evidence from 1 RCT (n=61) showed no clinically important difference in serum ferritin concentration levels in babies receiving IV iron started at 2-3 days of life compared to those not receiving IV iron at 2 weeks after birth. However, there was uncertainty around the effect: Mean difference (MD) 30.20 (95% CI 11.94, 72.34).

Infection (sepsis) (<32 weeks' gestational age)

- Very low quality evidence from 1 RCT (n=26) showed no clinically important difference in rates of infection (sepsis) at 4 weeks after birth in babies receiving IV iron compared to those not receiving IV iron. However, there was high uncertainty around the effect: Relative risk (RR) 1.10 (95% CI 0.59, 2.04).

Mortality (<32 weeks' gestational age)

- Very low quality evidence from 1 RCT (n=61) showed a clinically important difference in mortality at 2 weeks after birth in babies receiving IV iron compared to those not receiving IV iron, favouring babies not receiving IV iron. However, there was uncertainty around the effect: Peto odds ratio (POR) 7.15 (95% CI 0.14, 360.75).

Haemoglobin (<32 weeks' gestational age)

- Low quality evidence from 1 RCT showed no clinically important difference in haemoglobin concentration at 2 weeks after birth in babies receiving IV iron compared to those not receiving IV iron. However, there was uncertainty around the effect: MD -2.00 (95% CI -13.87, 9.87; n=61).

Haematocrit (<32 weeks' gestational age)

- Low quality evidence from 1 RCT (n=61) showed no clinically important difference in haematocrit percentage at 2 weeks after birth in babies receiving IV iron compared to those not receiving IV iron. However, there was uncertainty around the effect: MD -0.70 (95% CI -4.66, 3.26).

Serum iron (<32 weeks' gestational age)

- Low quality evidence from 1 RCT showed no clinically important difference in serum iron concentration at 2 weeks after birth in babies receiving IV iron compared to those not receiving IV iron. However, there was uncertainty around the effect: MD -0.60 (95% CI -2.82, 1.62; n=61).

Total iron binding capacity (<32 weeks' gestational age)

- Low quality evidence from 1 RCT (n=61) showed a clinically important difference in total iron binding capacity at 2 weeks after birth in babies receiving IV iron compared to those not receiving IV iron, favouring babies receiving IV iron. However, there was uncertainty around the effect: MD -4.90 (95% CI -7.37, -2.43).

Economic evidence statements

No economic evidence was identified which was applicable to this review question.

Recommendations

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee prioritised adverse events and neurodevelopmental outcomes as critical for this review. Iron overload which can be the cause of organ damage is directly influenced by the provision of iron (measured as serum ferritin). Iron overload and iron deficiency influences the number of red blood cells in the body which has an effect on the amount of oxygen that the cells in the body receive. This could also impact on neurodevelopment because the cells do not receive the optimal amount of oxygen to support their function. Iron in PN may also increase the risk of sepsis, and therefore this was also considered critical. Growth outcomes and mortality were considered important outcomes as they may be influenced by a range of factors, not specifically iron in the PN. The other important outcomes, haemoglobin and haematocrit, serum iron, and total iron binding capacity were selected as although related to iron provision, they are markers for iron levels but may not be directly harmful to the baby.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE methodology. All evidence was rated as either very low or low, indicating high uncertainty in the reliability of the data. The committee noted that it was unclear in one of the studies (Friel 1995) whether or not the control group received iron. The intervention group was described as having iron as an "unintentional manufacturing contaminant", and while this may have been in trace amounts, the concentration of the iron was not reported. In addition, the babies received enteral preterm formula that contained iron and it was not clear how much iron was received in total. Therefore, the committee was uncertain how this could be interpreted. Both studies were too small to record relevant adverse events with much certainty and therefore the evidence was downgraded due to imprecision related to the effect size. Overall, the committee had a low level of confidence in the evidence available.

Benefits and harms

The committee considered the evidence presented, and used their clinical knowledge and experience to write the recommendations by informal consensus. The evidence showed that there were no differences between the babies receiving iron and those who did not receive iron in relation to serum ferritin concentration (there was no evidence of iron overload as indicated by serum ferritin levels), and serum iron. The evidence suggested a potential clinical importance relation to total iron binding capacity, which seemed to support improved iron status early on in the group of babies receiving iron supplementation. However, the data was imprecise and true clinical benefit is uncertain. In addition, the data showed increased mortality in babies receiving iron, but again data was imprecise, and therefore uncertain.

The committee had limited confidence in the evidence; however, they noted mortality was greater in babies who received iron in their PN, although there was high uncertainty in the data. The committee agreed that the evidence was insufficient to recommend the use of iron in preterm or term babies who are younger than 28 days PN. Iron therapy has inherent risks such as iron overload and oxidative effects. The committee also agreed, based on their experience and expertise, that the requirement for a blood transfusion is rarely associated with iron deficiency per se, but rather due to iatrogenic blood-letting and immature haematopoiesis.

The committee agreed, based on their knowledge, that newborn babies' haematocrit values are high at birth, providing an initial iron store as red blood cells are broken down in the early weeks of life in both preterm and term babies, releasing iron stores. The committee acknowledge that there are many different sources that influence the iron status of preterm babies. For instance preterm babies in particular may have frequent blood sampling and may have blood transfusions (which would decrease or increase iron levels). The committee noted that there was a further variable, timing of cord clamping, affects iron levels. However, the committee noted that this is outside the scope of this guideline; but they were aware that this was covered in the Intrapartum care for healthy women and babies (CG190) NICE guideline. Readers could consult this if they would like further information. Another consideration is the fact that many babies on PN are also receiving some EN, which may include iron supplement. On that basis, the committee agreed that supplementation is not necessary in the early weeks, but if the preterm baby is on longer term parenteral nutrition (i.e. longer than 28 days) the babies' haematocrit levels would no longer be as replete and it would then be advisable to monitor for iron deficiency and provide iron supplements if needed.

For term babies who are 28 days or older, the committee could not make a recommendation on intravenous supplementation of iron in PN, because these babies were not included in the scope of the guideline. However, they noted that term babies continuing on long-term PN may need iron supplementation, and this would then have to be considered on a case-by-case basis.

The committee agreed that their recommendation was consistent with common current practice in the UK to administer PN without iron supplementation in babies. Given the lack of evidence and the committee's agreement that risks could well outweigh the possible benefits of early supplementation it was agreed by informal consensus that a strong recommendation should be made against its use.

Cost effectiveness and resource use

No economic studies were identified which were applicable to this review question.

The committee considered that the cost of iron supplementation is low, but that the costs associated with the potential harms would be higher and therefore the overall iron supplementation would be a cost effective option.

Since this is already current practice, the recommendation reaffirms this and therefore there is no associated resource impact.

References

Friel 1995

Friel, J. K., Andrews, W. L., Hall, M. S., Rodway, M. S., Keith, M., McCloy, U. C., Matthew, J. D., Long, D. R., Intravenous iron administration to very-low-birth-weight newborns receiving total and partial parenteral nutrition, JPEN. Journal of parenteral and enteral nutrition, 19, 114-8, 1995

Qiao 2017

Qiao, Linxia, Tang, Qingya, Zhu, Wenying, Zhang, Haiyan, Zhu, Yuefang, Wang, Hua, Effects of early parenteral iron combined erythropoietin in preterm infants: A randomized controlled trial, Medicine, 96, e5795, 2017

Wyllie 2015

Wyllie J., Ainsworth, S., Tinnion, R., Resuscitation and support of transition of babies at birth: https://www.resus.org.uk/resuscitation-guidelines/resuscitation-and-support-of-transition-of-babies-at-birth/

Appendices

Appendix A – Review protocols

Review protocol for review question: What is the most effective and safe iron supplementation compared to no iron or different dosage/formulations in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Table 3: Review protocol for intravenous iron

Field (based on PRISMA-P)	Content
Review question	What is the most effective and safe iron supplementation compared to no iron or different dosage/formulations in preterm and term babies who are receiving parenteral nutrition and neonatal care?
Type of review question	Intervention review
Objective of the review	Iron deficiency can have serious negative effect including potentially anaemia and may adversely affect neurodevelopment. The need for iron supplementation in newborn babies on PN was therefore an important matter for consideration.
Eligibility criteria – population/disease/condition/issue/domain	• Babies born preterm, up to 28 days after their due birth date (preterm babies) • Babies born at term, up to 28 days after their birth (term babies)
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Iron (any dosage)
Eligibility criteria – comparator(s)/control or reference (gold) standard	• No iron • Different dosages • Different formulations
Outcomes and prioritisation	**Critical** • Adverse effects of iron administration: • Iron overload (serum ferritin) • Infection (including sepsis) • Neurodevelopmental outcomes (general cognitive abilities at two years corrected age as measured by a validated scale) **Important** • Growth/Anthropometric measures: • Weight gain (g/kg/d)

Field (based on PRISMA-P)	Content
	• Linear growth • Head circumference (mm) • Mortality • Haemoglobin concentration and haematocrit • Serum iron • Total iron binding capacity
Eligibility criteria – study design	Only published full text papers- Systematic reviews of RCTs RCTs Comparative cohort studies (only if RCTs unavailable or limited data to inform decision making) Non-comparative studies (only if no evidence from RCTs or comparative cohort studies, limited data on critical outcomes to inform decision making) No date restriction needed Participant numbers (no restrictions for observational studies). For neurodevelopmental outcomes, studies with sample size of minimum 50 participants will be considered. Conference abstracts of RCTs will only be considered if no evidence is available from full published RCTs (if no evidence from RCTs or comparative cohort studies available and are recent i.e., in the last 2 years-authors will be contacted for further information)
Other inclusion exclusion criteria	Clinical settings that provide neonatal care or specialist paediatric care. UK and non-UK studies. (Non-UK studies from high and middle income countries according to WHO/World Bank criteria). Low income countries will be downgraded for indirectness
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analysis: Babies born preterm, up to 28 days after their due birth date (preterm babies) Babies born at term, up to 28 days after their birth (term babies) Iron started from less than 3 weeks and more than 3 weeks of age Subgroup analysis: The following groups will be considered for subgroup analysis: Population subgroups: Age of baby

Field (based on PRISMA-P)	Content
	Preterm (extremely preterm <28 weeks' GA; very preterm 28-31 weeks' GA; moderately preterm 32-36 weeks' GA) Birthweight: Low birth weight (< 2500g); very low birth weight (< 1500g) and extremely low birth weight (< 1000g) Critically ill babies or those requiring surgery (for example infants requiring inotropic support, receiving therapeutic hypothermia, fluid restriction) Intervention subgroups: Time of commencement (different times for commencing PN) Route of delivery Confounders: Important confounders (when comparative observational studies are included for interventional reviews) Age of baby Preterm (Very early <28 weeks GA; 28-31 weeks GA; 32-36 weeks GA) Birthweight: Low birth weight (< 2500g); very low birth weight (< 1500g) and extremely low birth weight (< 1000g) Sex of baby Number of blood transfusions Oral iron Erythropoietin Actual dose received For neurodevelopmental outcomes the following important confounders also include: Biological (sex, small for gestational age, ethnicity) Neonatal (PVL, IVH, infarct, sepsis, ROP, NEC, antenatal/postnatal steroids, BPD at 36 weeks) Social (SES, substance abuse, alcohol abuse, multiple pregnancy, chorioamnionitis, neglect, maternal age, maternal mental health disorder) Postnatal (epilepsy, age of establishing feeding)
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. A random sample of the references identified in the search will be sifted by a second reviewer. This sample size will be 10% of the total, or 100 studies if the search identified fewer than 1000 studies. All disagreements will be resolved by discussion between the two reviewers. The senior systematic reviewer or guideline lead will act as arbiter where necessary.
Data management (software)	Pairwise meta-analyses, if possible, will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. Low income countries will be downgraded for indirectness.

Field (based on PRISMA-P)	Content
	NGA STAR software will be used for generating bibliographies/citations, study sifting, data extraction and recording quality assessment using checklists (ROBIS (systematic reviews and meta-analyses); Cochrane risk of bias tool (RCTs or comparative cohort studies); Cochrane risk of bias tool (Non-randomised studies).
Information sources – databases and dates	A search strategy will be developed to include medical subject headings and free text terms based on the eligibility criteria. Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase databases will be searched. The search will be limited to human studies and those conducted in the English language. See appendix B for full strategies
Identify if an update	This is not an update.
Author contacts	Developer: The National Guideline Alliance https://www.nice.org.uk/guidance/indevelopment/gid-ng10037
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014.
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see appendix B.
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual 2014. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/.
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual 2014.
Methods for analysis – combining studies and exploring (in)consistency	For details of the methods please see supplementary material C.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014.
Rationale/context – current management	For details please see the introduction to the evidence review.

Field (based on PRISMA-P)	Content
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Alliance (NGA) and chaired by Dr Joe Fawke (Consultant Neonatologist and Honorary Senior Lecturer, University Hospitals Leicester NHS Trust), in line with section 3 of Developing NICE guidelines: the manual 2014. Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details of the methods please see supplementary material C.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds the NGA to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	This review is not registered with PROSPERO.

BPD: bronchopulmonary dysplasia; CDSR: Cochrane Database of Systematic Reviews; CCTR: Cochrane Controlled Trials Register; DARE: Database of Abstracts of Reviews of Effects; GA: gestational age; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; IVH: intraventricular haemorrhage; MID: minimally important difference; NEC: necrotising enterocolitis; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; PN: Parenteral nutrition; PRISMA-P: preferred reporting items for systematic review and meta-analysis protocols; PROSPERO: International prospective register of systematic reviews; PVL: periventricular leukomalacia; RCT: randomised controlled trial; RoB: risk of bias; ROBIS: risk of bias in systematic reviews; ROP: retinopathy of prematurity; SD: standard deviation; SES: socioeconomic status; UK: United Kingdom; WHO: World Health Organisation.

Appendix B – Literature search strategies

Literature search strategies for review question: What is the most effective and safe iron supplementation compared to no iron or different dosage/formulations in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

#	Searches
1	INFANT, NEWBORN/
2	(neonat$ or newborn$ or new-born$ or baby or babies).ti,ab.
3	PREMATURE BIRTH/
4	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 (birth? or born)).ab,ti.
5	exp INFANT, PREMATURE/
6	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 infan$).ti,ab.
7	(pre#mie? or premie or premies).ti,ab.
8	exp INFANT, LOW BIRTH WEIGHT/
9	(low adj3 birth adj3 weigh$ adj5 infan$).ti,ab.
10	((LBW or VLBW) adj5 infan$).ti,ab.
11	INTENSIVE CARE, NEONATAL/
12	INTENSIVE CARE UNITS, NEONATAL/
13	NICU?.ti,ab.
14	or/1-13
15	PARENTERAL NUTRITION/
16	PARENTERAL NUTRITION, TOTAL/
17	PARENTERAL NUTRITION SOLUTIONS/
18	ADMINISTRATION, INTRAVENOUS/
19	INFUSIONS, INTRAVENOUS/
20	CATHETERIZATION, CENTRAL VENOUS/
21	exp CATHETERIZATION, PERIPHERAL/
22	(parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?).ti,ab.
23	((peripheral$ or central$) adj3 (line? or catheter$)).ti,ab.
24	drip?.ti,ab.
25	or/15-24
26	IRON/
27	IRON, DIETARY/
28	IRON COMPOUNDS/
29	IRON-DEXTRAN COMPLEX/
30	FERRIC COMPOUNDS/
31	FERROUS COMPOUNDS/
32	FERROSOFERRIC OXIDE/
33	(iron or ferro$ or ferri$).mp.
34	or/26-33
35	TRACE ELEMENTS/
36	(trace adj3 (element? or mineral? or metal?)).ti,ab.
37	(Biometal? or Bio-metal?).ti,ab.
38	(micromineral? or micro-mineral?).ti,ab.
39	or/35-38
40	14 and 25 and 34
41	14 and 25 and 39
42	or/40-41
43	limit 42 to english language
44	LETTER/
45	EDITORIAL/
46	NEWS/
47	exp HISTORICAL ARTICLE/
48	ANECDOTES AS TOPIC/
49	COMMENT/
50	CASE REPORT/
51	(letter or comment*).ti.
52	or/44-51
53	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
54	52 not 53

#	Searches
55	ANIMALS/ not HUMANS/
56	exp ANIMALS, LABORATORY/
57	exp ANIMAL EXPERIMENTATION/
58	exp MODELS, ANIMAL/
59	exp RODENTIA/
60	(rat or rats or mouse or mice).ti.
61	or/54-60
62	43 not 61

Databases: Embase; and Embase Classic

#	Searches
1	NEWBORN/
2	(neonat$ or newborn$ or new-born$ or baby or babies).ti,ab.
3	PREMATURITY/
4	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 (birth? or born)).ab,ti.
5	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 infan$).ti,ab.
6	(pre#mie? or premie or premies).ti,ab.
7	exp LOW BIRTH WEIGHT/
8	(low adj3 birth adj3 weigh$ adj5 infan$).ti,ab.
9	((LBW or VLBW) adj5 infan$).ti,ab.
10	NEWBORN INTENSIVE CARE/
11	NEONATAL INTENSIVE CARE UNIT/
12	NICU?.ti,ab.
13	or/1-12
14	PARENTERAL NUTRITION/
15	TOTAL PARENTERAL NUTRITION/
16	PERIPHERAL PARENTERAL NUTRITION/
17	PARENTERAL SOLUTIONS/
18	INTRAVENOUS FEEDING/
19	INTRAVENOUS DRUG ADMINISTRATION/
20	exp INTRAVENOUS CATHETER/
21	(parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?).ti,ab.
22	((peripheral$ or central$) adj3 (line? or catheter$)).ti,ab.
23	drip?.ti,ab.
24	or/14-23
25	IRON/
26	IRON INTAKE/
27	IRON DERIVATIVE/
28	IRON DEXTRAN/
29	FERRIC ION/
30	FERROUS ION/
31	MAGNETITE/
32	(iron or ferro$ or ferri$).mp.
33	or/25-32
34	TRACE ELEMENT/
35	TRACE METAL/
36	(trace adj3 (element? or mineral? or metal?)).ti,ab.
37	(Biometal? or Bio-metal?).ti,ab.
38	(micromineral? or micro-mineral?).ti,ab.
39	or/34-38
40	13 and 24 and 33
41	13 and 24 and 39
42	or/40-41
43	limit 42 to english language
44	letter.pt. or LETTER/
45	note.pt.
46	editorial.pt.
47	CASE REPORT/ or CASE STUDY/
48	(letter or comment*).ti.
49	or/44-48
50	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
51	49 not 50
52	ANIMAL/ not HUMAN/
53	NONHUMAN/
54	exp ANIMAL EXPERIMENT/

#	Searches
55	exp EXPERIMENTAL ANIMAL/
56	ANIMAL MODEL/
57	exp RODENT/
58	(rat or rats or mouse or mice).ti.
59	or/51-58
60	43 not 59

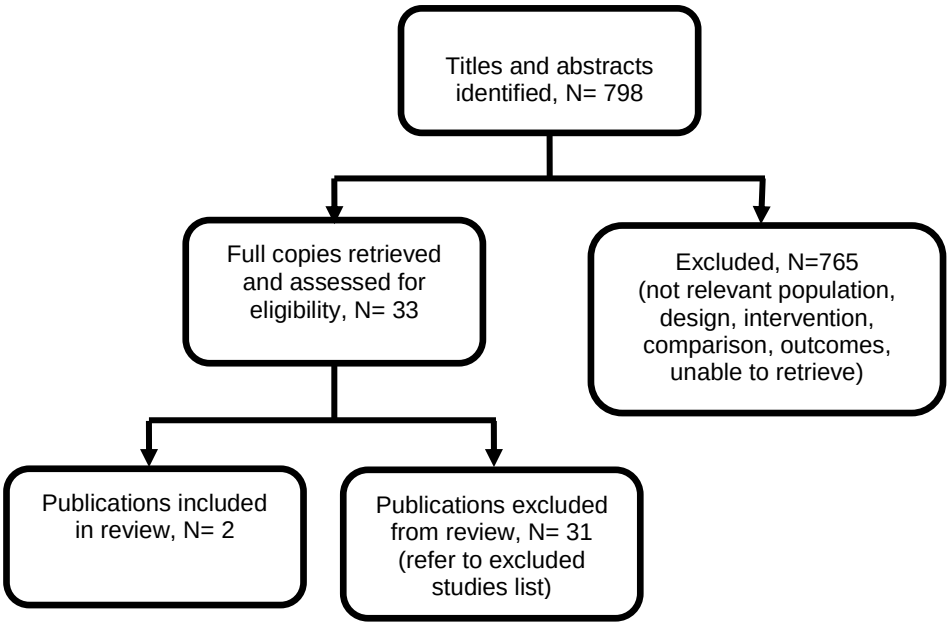
Databases: Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; and Health Technology Assessment

#	Searches
1	MeSH descriptor: [INFANT, NEWBORN] this term only
2	(neonat* or newborn* or new-born* or baby or babies).ti,ab.
3	MeSH descriptor: [PREMATURE BIRTH] this term only
4	((preterm* or pre-term* or prematur* or pre-matur*) near/5 (birth* or born)).ab,ti.
5	MeSH descriptor: [INFANT, PREMATURE] explode all trees
6	((preterm* or pre-term* or prematur* or pre-matur*) near/5 infan*).ti,ab.
7	(pre#mie? or premie or premies).ti,ab.
8	MeSH descriptor: [INFANT, LOW BIRTH WEIGHT] explode all trees
9	(low near/3 birth near/3 weigh* near/5 infan*).ti,ab.
10	((LBW or VLBW) near/5 infan*).ti,ab.
11	MeSH descriptor: [INTENSIVE CARE, NEONATAL] this term only
12	MeSH descriptor: [INTENSIVE CARE UNITS, NEONATAL] this term only
13	NICU?.ti,ab.
14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
15	MeSH descriptor: [PARENTERAL NUTRITION] this term only
16	MeSH descriptor: [PARENTERAL NUTRITION, TOTAL] this term only
17	MeSH descriptor: [PARENTERAL NUTRITION SOLUTIONS] this term only
18	MeSH descriptor: [ADMINISTRATION, INTRAVENOUS] this term only
19	MeSH descriptor: [INFUSIONS, INTRAVENOUS] this term only
20	MeSH descriptor: [CATHETERIZATION, CENTRAL VENOUS] this term only
21	MeSH descriptor: [CATHETERIZATION, PERIPHERAL] explode all trees
22	(parenteral* or intravenous* or intra-venous* or IV or venous* or infusion*).ti,ab.
23	((peripheral* or central*) near/3 (line? or catheter*)).ti,ab.
24	drip?.ti,ab.
25	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26	MeSH descriptor: [IRON] this term only
27	MeSH descriptor: [IRON, DIETARY] this term only
28	MeSH descriptor: [IRON COMPOUNDS] this term only
29	MeSH descriptor: [IRON-DEXTRAN COMPLEX] this term only
30	MeSH descriptor: [FERRIC COMPOUNDS] this term only
31	MeSH descriptor: [FERROUS COMPOUNDS] this term only
32	MeSH descriptor: [FERROSOFERRIC OXIDE] this term only
33	(iron or ferro* or ferri*).ti,ab.
34	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
35	MeSH descriptor: [TRACE ELEMENTS] this term only
36	(trace near/3 (element? or mineral? or metal?)).ti,ab.
37	(Biometal? or Bio-metal?).ti,ab.
38	(micromineral? or micro-mineral?).ti,ab.
39	#35 or #36 or #37 or #38
40	#14 and #25 and #34
41	#14 and #25 and #39
42	#40 or #41

Appendix C – Clinical evidence study selection

Clinical study selection for: What is the most effective and safe iron supplementation compared to no iron or different dosage/formulations in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Figure 1: PRISMA Flow chart of clinical article selection for review question on most effective and safe iron supplementation in preterm and term babies.



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is the most effective and safe iron supplementation compared to no iron or different dosage/formulations in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Table 4: Clinical evidence table for included studies

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Friel, J. K., Andrews, W. L., Hall, M. S., Rodway, M. S., Keith, M., McCloy, U. C., Matthew, J. D., Long, D. R., Intravenous iron administration to very-low-birth-weight newborns receiving total and partial parenteral nutrition, JPEN. Journal of parenteral and enteral nutrition, 19, 114-8, 1995 Ref Id 606385 Country/ies where the study was carried out Canada Study type	Sample size N=26 Iron: n=14 No Iron: n=12 Characteristics Gestational age (weeks) - mean ±SD Iron: 28 (2.3) No Iron: 29 (2.2) Birth weight (g) - mean ±SD Iron: 963 (285) No Iron: 1054 (326) Transfusion volume (mL) - mean ±SD Iron: 28 (22) No Iron: 26 (23)	Interventions Iron: Iron dextran 200 to 250µg/kg/day in addition to iron normally present as a contaminant. No iron: Only iron already present as an unintentional manufacturing contaminant.	Details Neonates were administered TPN (including amino acids, vitamins, and lipids). Measurements were recorded and samples (blood, urine and faecal loss, and gastric aspirates) were taken at baseline (0 to 3 days), and then during weekly 3-day periods during 4 weeks for a total of five collection periods. A final blood sample was collected on day 56. At week 1, 100% of newborns in both treatment groups received PN. This declined over time with enteral feeding being provided. Power analysis	Results At 4 weeks after birth Infection* (reported as sepsis) - n/N Iron: 9/14 No Iron: 7/12	Limitations Risk of bias assessed with Cochrane risk of bias tool for randomised trials Selection bias: Methods used to generate or conceal the allocation sequence were not described (high risk of bias). Performance bias: The authors did not report on blinding of personnel; participants were neonates and blinding was therefore not applicable (unclear risk of bias). Detection bias: The authors did not report on blinding of outcome assessors (unclear risk of bias).

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Randomised controlled trial Aim of the study To assess the safety of parenteral iron supplementation (200 to 250 µg/kg/d) and the effect on very low birth weight (VLBW) neonates. Study dates Not reported. Source of funding Supported by the Medical Research Council of Canada.	<u>Transfusions (N) - mean ±SD</u> Iron: 2.3 (1.7) No Iron: 2.3 (2.1) <u>Days on full total parenteral nutrition (TPN) - mean ±SD</u> Iron: 15.5 (8.0) No Iron: 16.0 (10.0) <u>Days on partial TPN - mean ±SD</u> Iron: 3.6 (2.7) No Iron: 4.7 (7.5) None of the neonates had a draining enterostomy, diarrhoea, or clinical evidence of liver or kidney disease. Inclusion criteria • VLBW neonates in the neonatal intensive care unit; • Receiving full (>75% of energy intake) or partial		Not reported. Statistical analysis Repeated measures analysis of variance and Student's t test were used to analyse data at each collection period. Intention-to-treat (ITT) analysis Not reported.		Attrition bias: The authors reported that 1 infant died and 2 infants were withdrawn from the study by parents/guardians (approximately 11% of participants) (low risk of bias). Reporting bias: The authors stated that anthropometric, biochemical, and haematologic measurements were taken, but data were not presented (high risk of bias). Other bias: Insufficient information to assess whether an important risk of bias exists (unclear risk of bias). Other information *Infection was defined as the presence of positive blood or cerebrospinal fluid culture, or local lesions.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	(<75% of energy intake) TPN. Exclusion criteria Not reported.				
Full citation Qiao, Linxia, Tang, Qingya, Zhu, Wenying, Zhang, Haiyan, Zhu, Yuefang, Wang, Hua, Effects of early parenteral iron combined erythropoietin in preterm infants: A randomized controlled trial, Medicine, 96, e5795, 2017 Ref Id 681800 Country/ies where the study was carried out China Study type Randomised controlled trial Aim of the study To assess whether anaemia improved in	Sample size N=96 (n=91 analysed) Iron supplemented (IS group): n=31 No iron (control group): n=30 Iron supplemented plus EPO (IS+EPO group)*: n=30 Characteristics Sex (male/female) - N IS: 19/12 Control: 17/13 Gestational age (weeks) - mean ±SD IS: 30.4 (1.7) Control: 30.3 (2.1) Birth weight (g) - mean ±SD IS: 1525 (502)	Interventions IS: Standard PN plus iron supplement (given every day with PN at 200 µg/kg per day, with the dose continuing until 2 weeks after birth). Control: Standard PN The neonates were treated for 2 weeks, or as long as they received PN. PN was given to all neonates from the second day of birth until they could receive 120mL/kg per day of enteral feedings)	Details Preterm neonates were treated for two weeks or as long as they required PN. All neonates received standard PN (all in one solution containing lipids (20%), amino acids (6%), glucose, minerals, trace elements, and vitamins) as well as standard preterm formula containing 0.9mg/100mL iron, starting at 10mL/kg/day followed by incremental dose of 10mL/kg/day until a maximum of 150mL/kg/day was reached. Outcomes were measured at 2 weeks after birth, 1 month corrected age and 3 months corrected age, by radio-immunoassay method, chemical	Results At 2 weeks after birth (unless otherwise stated) Serum ferritin (µg/L) - mean ±SD IS: 295.1 (84.2) Control: 264.9 (83.7) Mortality (reported during study) - n/N IS: 1/31 Control: 0/30 Haemoglobin concentration (g/L) - mean ±SD IS: 136.2 (20.7) Control: 138.2 (26.2) Haematocrit (%) - mean ±SD IS: 40.4 (6.7) Control: 41.1 (8.9)	Limitations Risk of bias assessed with Cochrane risk of bias tool for randomised trials Selection bias: Infants were randomly assigned to treatment groups using cards with a unique randomisation code which were placed in sequentially numbered opaque envelopes (low risk of bias). Performance bias: All physicians and nurses were blind to participant treatment assignment (only the pharmacist who supervised the quality of iron sucrose and the PN preparation was aware of treatment assignment); participants were neonates and blinding was therefore not

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
preterm infants administered parenteral iron combined with erythropoietin (EPO). Study dates February 2014 to June 2014. Source of funding None.	Control: 1486 (392) Haemoglobin (g/L) - mean ±SD IS: 161.8 (23.6) Control: 163.1 (31.6) Haematocrit (%) - mean ±SD IS: 50.3 (6.7) Control: 52.3 (8.3) Serum iron (µmol/L) - mean ±SD IS: 15.6 (7.4) Control: 13.3 (4.6) Serum ferritin (µg/L) - mean ±SD IS: 212.0 (63.4) Control: 219.8 (78.5) Total iron binding capacity (µmol/L) - mean ±SD IS: 43.9 (12.5) Control: 45.3 (8.4) Inclusion criteria		method or by an automatic biochemical analyser. Power analysis 21 participants per treatment group were required to achieve 80% power. Statistical analysis Outcome data were reported as means and standard deviations (SDs) or medians and interquartile range (IQR). Differences in rates were analysed using the chi-squared test. Intention-to-treat (ITT) analysis Not reported.	Serum iron (µmol/L) - mean ±SD IS: 17.0 (5.0) Control: 17.6 (3.8) Total iron binding capacity (µmol/L) - mean ±SD IS: 36.7 (4.6) Control: 41.6 (5.2)	applicable (low risk of bias). Detection bias: The authors stated that all investigators were blind to treatment assignment (low risk of bias). Attrition bias: The authors reported that 5 infants (approximately 5%) did not complete the study (1 infant died; 4 infants were discharged as treatments were discontinued by their parents) (low risk of bias). Reporting bias: (low risk of bias). Other bias: No other bias detected (low risk of bias). Other information *IS+EPO group outcome data not included.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	• Preterm infants with gestational age between 28 and 34 weeks treated in the neonatal intensive care unit (NICU) of a university hospital. Exclusion criteria • Neonates with liver and kidney dysfunction; • Haemolytic disease of newborns; • Haemorrhage (gastrointestinal, pulmonary, and intracranial haemorrhage grade III–IV, 24h decline in Hb> 2g/L; • Neonates receiving blood transfusion; • Neonates with major or life-				

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	threatening malformations.				

EPO: erythropoietin; IQR: interquartile range; IS: iron supplementation; ITT: intention-to-treat; N: number; NICU: neonatal intensive care unit; PN: parenteral nutrition; SD: standard deviation; TPN: total parenteral nutrition; VLBW: very low birthweight.

Appendix E – Forest plots

Forest plots for review question: What is the most effective and safe iron supplementation compared to no iron or different dosage/formulations in preterm and term babies who are receiving parenteral nutrition and neonatal care?

No meta-analysis was conducted for this review; therefore there are no forest plots.

Appendix F – GRADE tables

GRADE tables for review question: What is the most effective and safe iron supplementation compared to no iron or different dosage/formulations in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Table 5: Evidence profile for outcomes related to the comparison of intravenous iron versus no iron in babies receiving PN

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Iron group	No iron group	Relative (95% CI)	Absolute	Quality	Importance
Iron overload (Serum ferritin) (follow-up 2 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	31	30	-	MD 30.2 higher (11.94 lower to 72.34 higher)	⊕⊕OO LOW	CRITICAL
Infection (follow-up 4 weeks)												
1	randomised trials	very serious [3]	no serious inconsistency	serious[4]	very serious[5]	none	9/14 (64.3%)	7/12 (58.3%)	RR 1.1 (0.59 to 2.04)	58 more per 1000 (from 239 fewer to 607 more)	⊕OOO VERY LOW	CRITICAL
Mortality (follow-up 2 weeks)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[6]	none	1/31 (3.2%)	0/30 (0%)	Peto OR 7.15 (0.14 to 360.75)	-	⊕⊕OO LOW	IMPORTANT
Haemoglobin concentration (follow-up 2 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[7]	none	31	30	-	MD 2 lower (13.87 lower to 9.87 higher)	⊕⊕OO LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Iron group	No iron group	Relative (95% CI)	Absolute	Quality	Importance
Haematocrit (follow-up 2 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[8]	none	31	30	-	MD 0.7 lower (4.66 lower to 3.26 higher)	⊕⊕OO LOW	IMPORTANT
Serum iron (follow-up 2 weeks; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[9]	none	31	30	-	MD 0.6 lower (2.82 lower to 1.62 higher)	⊕⊕OO LOW	IMPORTANT
Total iron binding capacity (follow-up 2 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[10]	none	31	30	-	MD 4.9 lower (7.37 to 2.43 lower)	⊕⊕OO LOW	IMPORTANT

CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio.

[1] Evidence was downgraded by 1 as babies in the no iron group received 0.9 mg of iron per 100 mL from standard preterm formula.
[2] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (41.85).
[3] Evidence was downgraded by 2 due to high risk of bias for methods of randomisation and reporting of outcomes; unclear risk of bias for allocation concealment, blinding of personnel and assessors, and other bias.
[4] Evidence was downgraded by 1 as babies in the no iron group received an unknown concentration of iron, described by the authors as "unintentional manufacturing contamination".
[5] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MID for dichotomous outcomes (0.80 and 1.25).
[6]Evidence was downgraded for risk of imprecision due to low event rate).
[7] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-13.1).
[8] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-4.45).
[9] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at

baseline (-1.9).
[10] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 s SD control at baseline (-2.6).

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the most effective and safe iron supplementation compared to no iron or different dosage/formulations in preterm and term babies who are receiving parenteral nutrition and neonatal care?

One global search was conducted for all review questions. See supplementary material D for further information.

Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the most effective and safe iron supplementation compared to no iron or different dosage/formulations in preterm and term babies who are receiving parenteral nutrition and neonatal care?

No evidence was identified which was applicable to this review question.

Appendix I – Health economic evidence profiles

Economic evidence profiles for review question: What is the most effective and safe iron supplementation compared to no iron or different dosage/formulations in preterm and term babies who are receiving parenteral nutrition and neonatal care?

No evidence was identified which was applicable to this review question.

Appendix J – Health economic analysis

Economic analysis for review question: What is the most effective and safe iron supplementation compared to no iron or different dosage/formulations in preterm and term babies who are receiving parenteral nutrition and neonatal care?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: What is the most effective and safe iron supplementation compared to no iron or different dosage/formulations in preterm and term babies who are receiving parenteral nutrition and neonatal care?

Clinical studies

Table 6: Excluded studies and reasons for their exclusion

Study	Reasons for exclusion
A. S. P. E. N. Clinical Practice Committee Shortage Subcommittee, Plogsted S, Brooks G. DiBaise J. Fuhrman T. Ybarra J. Holcombe B. Andris D. A. Houston D. R. Plogsted S. W., A.S.P.E.N. parenteral nutrition trace element product shortage considerations, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 29, 249-51, 2014	Guideline.
Andrews, W. L., Nutrition and development in premature infants: Overview, Nutrition, 10, 62, 1994	No references in document to support needs for iron in preterm neonates.
Anonymous,, Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients, Journal of Parenteral and Enteral Nutrition, 26, 1SA-138SA, 2002	Checked reference for iron. One reference is to iron fortification in milk, the other study is lab-based study looking at precipitation of iron in PN mixtures.
Ball, P. A., Iron in pediatric parenteral nutrition: are we getting rusty?, Nutrition (Burbank, Los Angeles County, Calif.), 15, 815-6, 1999	Checked individual studies, one study included in our database.
Candy, D. C. A., Parenteral nutrition in paediatric practice: A review, Journal of Human Nutrition, 34, 287-296, 1980	No relevant studies regarding IV iron.
Cantwell, R. J., Iron deficiency anemia of infancy: some clinical principles illustrated by the response of Maori infants to neonatal parenteral iron administration, Clinical pediatrics, 11, 443-9, 1972	Outcomes were measured at 2 months after birth.
Carnielli, V. P., Da Riol, R., Montini, G., Iron supplementation enhances response to high doses of recombinant human erythropoietin in preterm infants, Archives of disease in childhood. Fetal and neonatal edition, 79, F44-8, 1998	Wrong comparison, all groups were given standard formula which contained iron.
Challa, A., Vantziou, S., Cholevas, V., Giapros, V., Andronikou, S., Growth factors of premature infants in relation to parenteral nutrition during the first month of life, Nutrition Research, 21, 1089-1097, 2001	Outcomes were not relevant to PICO.
Cockburn, F., Giles, M., Harvie, A., Jorge, S. K., Logan, R. W., Sim, F., Nutrition of the preterm newborn infant, Progress in clinical and biological research, 77, 661-70, 1981	Checked individual studies, No relevant studies regarding IV iron.

Study	Reasons for exclusion
Domellof, Magnus, Nutritional care of premature infants: microminerals, World review of nutrition and dietetics, 110, 121-39, 2014	Checked included studies in article for IV iron, relevant studies already included in our search.
Finch, Carolyn Weiglein, Review of trace mineral requirements for preterm infants: what are the current recommendations for clinical practice?, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 30, 44-58, 2015	This guideline recommended further research for addition of iron to PN formula.
Friel, J. K., Penney, S., Reid, D. W., Andrews, W. L., Zinc, copper, manganese, and iron balance of parenterally fed very low birth weight preterm infants receiving a trace element supplement, JPEN. Journal of parenteral and enteral nutrition, 12, 382-6, 1988	Non-comparative study; outcomes of ferritin, Hb, HCT are reported in included RCT.
Griffin, I., Cooke, R. J., Iron retention in preterm infants fed low iron intakes: a metabolic balance study, Early Hum Dev, 86 Suppl 1, 49-53, 2010	The same population received two different PN formulations, not a comparison between two separate treatment groups.
Haiden, Nadja, Schwindt, Jens, Cardona, Francesco, Berger, Angelika, Klebermass, Katrin, Wald, Martin, Kohlhauser-Vollmuth, Christina, Jilma, Bernd, Pollak, Arnold, Effects of a combined therapy of erythropoietin, iron, folate, and vitamin B12 on the transfusion requirements of extremely low birth weight infants, Pediatrics, 118, 2004-13, 2006	The comparator group received no EPO, iron was given 15 days later in the comparator group, variation of other components in the intervention group that the comparator group did not receive.
Johnson, Patricia J., Review of micronutrients in parenteral nutrition for the NICU population, Neonatal network : NN, 33, 155-61, 2014	No relevant information regarding IV iron.
Kon, Noriko, Tanaka, Kyoko, Sekigawa, Mariko, Negishi, Yoshie, Yoshikawa, Naomi, Hisata, Ken, Shoji, Hiromichi, Shimizu, Toshiaki, Association between iron status and neurodevelopmental outcomes among VLBW infants, Brain & development, 32, 849-54, 2010	Study aim was to identify a link between iron status and neurodevelopment, not via parenteral nutrition.
Kumpf, V. J., Parenteral iron supplementation, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 11, 139-46, 1996	Checked individual studies. PN/IV iron study was based on adults.
Lobo, Bianca W., da Veiga, Venicio F., Cabral, Lucio M., Michel, Ricardo C., Volpato, Nadia M., de Sousa, Valeria P., Influence of the relative composition of trace elements and vitamins in physicochemical stability of total parenteral nutrition formulations for neonatal use, Nutrition journal, 11, 26, 2012	Not a comparative study; more to do with stability of 3 different PN solutions.
Lorenz, L., Franz, A. R., Enteral iron supplementation in preterm infants has no adverse effect on growth: Evidence from randomized trials, Journal of Pediatric Gastroenterology and Nutrition, 64, e26, 2017	Enteral; editors comment of a retrospective study.
Mayhew, S. L., Quick, M. W., Compatibility of iron dextran with neonatal parenteral nutrient solutions, American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists, 54, 570-1, 1997	The comparison is not relevant to the comparison defined in our PICO.

Study	Reasons for exclusion
Ohls, R. K., Ehrenkranz, R. A., Wright, L. L., Lemons, J. A., Korones, S. B., Stoll, B. J., Stark, A. R., Shankaran, S., Donovan, E. F., Close, N. C., Das, A., Effects of early erythropoietin therapy on the transfusion requirements of preterm infants below 1250 grams birth weight: a multicenter, randomized, controlled trial, Pediatrics, 108, 934-42, 2001	The comparator group did not receive EPO, but received iron, wrong comparator.
Ohls, R. K., Harcum, J., Schibler, K. R., Christensen, R. D., The effect of erythropoietin on the transfusion requirements of preterm infants weighing 750 grams or less: a randomized, double-blind, placebo-controlled study, The Journal of pediatrics, 131, 661-5, 1997	Study is about EPO, no information about IV iron.
Qingqing, W., Wang, W., Tang, Q., Efficacy and safety of iron-containing parenteral nutrition for anemia in preterm infants: A randomized, double-blind and controlled study, Journal of Pediatric Gastroenterology and Nutrition, 64, 956, 2017	Conference abstract.
Robinson, S., Iron deficiency, anaemia and mortality-focus on high-income countries, Transfusion Medicine, 27, 21, 2017	Conference abstract.
Sachdev, Hps, Gera, Tarun, Nestel, Penelope, Effect of iron supplementation on mental and motor development in children: systematic review of randomised controlled trials, Public health nutrition, 8, 117-32, 2005	Individual studies checked for inclusion, none met the protocol criteria (age and intervention).
Tang, Q., Lin, J., Cai, W., The study of nutrient intake from enteral and parenteral nutrition among preterm infants in Shanghai, Journal of Pediatric Gastroenterology and Nutrition, 63, S111, 2016	Conference abstract.
Wang, Bo, Zhan, Siyan, Gong, Ting, Lee, Liming, Iron therapy for improving psychomotor development and cognitive function in children under the age of three with iron deficiency anaemia, Cochrane Database of Systematic Reviews, 2013	Individual studies checked, population did not match protocol criteria, not PN.
Wilson, D. C., Cairns, P., Halliday, H. L., Reid, M., McClure, G., Dodge, J. A., Randomised controlled trial of an aggressive nutritional regimen in sick very low birthweight infants, Archives of disease in childhood. Fetal and neonatal edition, 77, F4-11, 1997	Does not mention iron specifically
Wong, Theodoric, Parenteral trace elements in children: clinical aspects and dosage recommendations, Current opinion in clinical nutrition and metabolic care, 15, 649-56, 2012	References checked for iron, one study included was ESPGHAN, and other study looked at iron/brain development.
Zlotkin, S. H., Atkinson, S., Lockitch, G., Trace elements in nutrition for premature infants, Clinics in perinatology 22 (1), 223-40, 1995	No relevant studies found in the review.
Zlotkin, S. H., Lay, D. M., Kjarsgaard, J., Longley, T., Determination of iron absorption using erythrocyte iron incorporation of two stable isotopes of iron (57Fe and 58Fe) in very low	Not a comparative study.

Study	Reasons for exclusion
birthweight premature infants, Journal of Pediatric Gastroenterology and Nutrition, 21, 190-9, 1995	

Economic studies

No economic evidence was identified for this review. See supplementary material D for further information.

Appendix L – Research recommendations

Research recommendations for review question: What is the most effective and safe iron supplementation compared to no iron or different dosage/formulations in preterm and term babies who are receiving parenteral nutrition and neonatal care?

No research recommendations were made for this review.