EtD 5. Should routine iodine vs. no additional iodine supplementation be used for preterm infants?

POPULATION:	Preterm infants
INTERVENTION:	Routine Iodine
COMPARISON:	No additional iodine supplementation
MAIN OUTCOMES:	**Critical outcomes** Mortality Neurodevelopmental impairment Adverse effects (prevention of unnecessary blood tests) **Important but not critical** Faltering growth/body composition Retinopathy of prematurity Bronchopulmonary dysplasia Fully breastfed or breastmilk feeding at hospital discharge Time to full enteral feeds Duration of initial hospital stay Sepsis: proven or suspected Necrotising enterocolitis Anaemia of prematurity Cost: cost of intervention, cost of neonatal care and life-long cost **Less important for decision making** Time to full sucking feeds
SETTING:	Neonatal care
PERSPECTIVE:	Clinical recommendation: population perspective
BACKGROUND:	Iodine is a critical micronutrient required for thyroid hormone synthesis, which supports growth, neurodevelopment and metabolic regulation. Preterm infants are particularly vulnerable to iodine deficiency due to limited in utero iodine accumulation, reduced postnatal stores and reliance on parenteral nutrition. This vulnerability is compounded by maternal iodine deficiency, which is prevalent in Aotearoa New Zealand due to low environmental iodine content. Congenital hypothyroidism, the most common preventable cause of intellectual disability worldwide, has a significantly higher incidence among preterm infants (1:100–150) compared to term infants (1:2000). While often transient in preterm infants, congenital hypothyroidism can have severe biochemical presentations (thyroid stimulating hormone >50 milli-International units per litre (mIU/L) that if untreated may impact neurodevelopment. Factors such as the immaturity of the hypothalamic-pituitary-thyroid axis, iodine deficiency and illnesses like respiratory distress syndrome are believed to contribute to this condition. Maternal iodine supplementation during pregnancy and breastfeeding is recommended to reduce the risk of iodine deficiency in newborns. However, studies show that up to 30% of women of reproductive age in Aotearoa New Zealand may remain iodine deficient despite supplementation guidelines. For preterm infants, the iodine content of parenteral nutrition is critical. Previous parenteral iodine recommendations (1

	µg/kg/day) were set intentionally low due to the use of iodine-containing antiseptics. However, practices have since changed, and more recent guidelines have increased parenteral iodine intake to 1–10 µg/kg/day, though this remains below the recommended enteral intake of 10–55 µg/kg/day. Research indicates that even 3 µg/kg/day IV iodine may lead to a negative iodine balance in preterm infants, highlighting the need for updated and evidence-based intake recommendations.
CONFLICT OF INTERESTS:	The following 2019 Cochrane systematic review (Walsh *et al*) co-author wrote this Evidence to Decision document: Julie Brown

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Evidence from one Cochrane review [1] and the ESPGHAN/ESPEN/ESPR/CSPEN guidelines [2].** **Parenteral Nutrition guidelines ESPGHAN/ESPEN/ESPR/CSPEN (2018) [2]** Iodine should be provided with parenteral nutrition at a daily dose of 1–10 µg/kg/day in preterm infants (strong recommendation, strong consensus). Patients on long-term parenteral nutrition should be regularly monitored for iodine status by measuring at least thyroid hormone concentrations (conditional recommendation, strong consensus). **Enteral Nutrition guidelines ESPGHAN (2022) [3]** recommends enteral iodine should be provided at 11–55 µg/kg/day **Mortality:** RCT: No significant effect of additional iodine supplementation compared with no additional iodine supplementation on the incidence of death before hospital discharge (1 more per 1,000; 24 fewer to 37 more). [Critical] **Neurodevelopment impairment:** RCT: No significant effect of additional iodine supplementation compared with no additional iodine supplementation on Bayley-III Cognitive composite score: 2 years of age corrected for prematurity (MD 0.3 points lower; 2.44 lower to 1.84 higher); Bayley-III Motor composite at 2 years of age corrected for prematurity (MD 0.2 points higher; 2.15 lower to 2.55 higher); Bayley-III Language composite score at 2 years of age corrected for prematurity (MD 0.1 points lower; 2.5 lower to 2.3 higher); auditory impairment (1 more per 1,000; 13 fewer to 30 more). No significant effect for a low score (neurodevelopmental impairment) in any main Bayley domain (<85) or death (25 more per 1,000; 29 fewer to 83 more) and visual impairment (10 fewer per 1,000; 19 fewer to 12 more). [Critical].	**Population information for included evidence** 2 RCTs in the Cochrane review [1]: One RCT (n=1273) from the United Kingdom iodine given at 30 µg/kg/day either parenterally or enterally until 34 weeks postmenstrual age. One RCT (n= 121) from United Kingdom iodine supplemented "preterm" formula milk (272 µg/L, approx 40 to 49 µg/kg/day) versus unsupplemented with iodine concentration (68 µg/L, approx 10 to 12 µg/kg/day)

	Retinopathy of prematurity: RCT: No significant effect in retinopathy of prematurity for additional iodine supplementation compared with no additional iodine supplementation (2 fewer per 1,000; 23 fewer to 31 more). [Important] **Desirable effects for Māori** No additional data	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo/no supplementation	Risk difference with routine Iodine
Mortality: RCT assessed with: Mortality before hospital discharge	1380 (2 RCTs)	⨁⨁◯◯ Low[a,b]	**RR 1.01** (0.72 to 1.42)	Study population	
				87 per 1,000	**1 more per 1,000** (24 fewer to 37 more)
Neurodevelopmental impairment: RCT assessed with: Bayley-III Cognitive composite score: 2 years of age corrected for prematurity Scale from: 1 to 100	1259 (1 RCT)	⨁◯◯◯ Very low[a,c]	-	The mean Neurodevelopmental impairment: RCT was **89.2 points**	MD **0.3 lower** (2.44 lower to 1.84 higher)
Neurodevelopmental impairment: RCT assessed with: Bayley-III Motor composite at 2 years of age corrected for prematurity Scale from: 1 to 100	1259 (1 RCT)	⨁◯◯◯ Very low[a,c]	-	The mean neurodevelopmental impairment: RCT was **88.0 points**	MD **0.2 higher** (2.15 lower to 2.55 higher)
Neurodevelopmental impairment: RCT assessed with: Bayley-III Language composite score at 2 years of age corrected for prematurity Scale from: 1 to 100	1259 (1 RCT)	⨁◯◯◯ Very low[a,c]	-	The mean neurodevelopmental impairment: RCT was **85.2 points**	MD **0.1 lower** (2.5 lower to 2.3 higher)
Neurodevelopmental impairment: RCT assessed with: Low score in any main Bayley domain (< 85) or death	1259 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 1.05** (0.94 to 1.17)	Study population	
				490 per 1,000	**25 more per 1,000** (29 fewer to 83 more)
Neurodevelopmental impairment: RCT assessed with: Visual impairment	1092 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 0.63** (0.28 to 1.45)	Study population	
				26 per 1,000	**10 fewer per 1,000** (19 fewer to 12 more)
Neurodevelopmental impairment: RCT assessed with: Auditory impairment	1093 (1 RCT)	⨁⨁◯◯ Low[a,b]	**RR 1.05** (0.51 to 2.16)	Study population	
				26 per 1,000	**1 more per 1,000** (13 fewer to 30 more)
Faltering growth/body composition - not measured	-	-	-	-	-
Adverse effects - not measured	-	-	-	-	-

Retinopathy of prematurity	1257 (1 RCT)	⨁⨁⨁◯ Moderate[a]	**RR 0.97** (0.64 to 1.49)	Study population	
				64 per 1,000	**2 fewer per 1,000** (23 fewer to 31 more)
Bronchopulmonary dysplasia / assessed with: Bronchopulmonary dysplasia in surviving infants (supplemental oxygen requirement at 36 weeks' postmenstrual age)	1377 (1 RCT)	⨁⨁◯◯ Low[a,d]	**RR 1.07** (0.94 to 1.22)	Study population	
				377 per 1,000	**26 more per 1,000** (23 fewer to 83 more)
Fully breastfed or breastmilk feeding at hospital discharge - not measured	-	-	-	-	-
Time to full enteral feeds - not measured	-	-	-	-	-
Duration of initial hospital stay - not measured	-	-	-	-	-
Sepsis: proven or suspected - not measured	-	-	-	-	-
Necrotising enterocolitis: RCT	1259 (1 RCT)	⨁⨁⨁◯ Moderate[a]	**RR 1.24** (0.98 to 1.56)	Study population	
				164 per 1,000	**39 more per 1,000** (3 fewer to 92 more)
Anaemia of prematurity - not measured	-	-	-	-	-
Cost: cost of intervention, cost of neonatal care and life-long cost - not measured	-	-	-	-	-
Time to full sucking feeds - not measured	-	-	-	-	-
Total plasma thyroxine: RCT assessed with: (nmol/L) at 34–36 weeks' postmenstrual age.	1121 (2 RCTs)	⨁⨁⨁◯ Moderate[c]	-	The mean Total plasma thyroxine: RCT was **83.45 nmol/L**	MD **0.29 higher** (1.51 lower to 2.09 higher)
Thyroid-stimulating hormone: RCT assessed with: (mU/L) at 34–36 weeks' postmenstrual age.	1119 (2 RCTs)	⨁⨁⨁◯ Moderate[c]	-	The mean thyroid-stimulating hormone: RCT was **1.8 mU/L**	MD **0.05 higher** (0.09 lower to 0.18 higher)

a. Downgraded one level as reports on outcomes of iodine supplementation but does not compare relevant doses
b. Downgraded one level for imprecision with confidence intervals crossing the line of no effect
c. Downgraded two levels for imprecision with very wide confidence intervals that cross the line of no effect.
d. Downgraded one level for inconsistency as I2 is between 50 and 80%

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Necrotising enterocolitis:** RCT: No significant increase in necrotising enterocolitis for additional iodine supplementation compared with no additional iodine supplementation (39 more per 1,000; 3 fewer to 92 more). **Bronchopulmonary dysplasia:** RCT: No significant increase in bronchopulmonary dysplasia for additional iodine supplementation compared with no additional iodine supplementation (26 more per 1,000; 23 fewer to 83 more) [Important]. **Thyroid function at 34-36 weeks' post-menstrual age**: RCT: No significant effect of iodine on thyroid function for additional iodine supplementation compared with no additional iodine supplementation for thyroid-stimulating hormone: MD 0.05 mU/L higher; 0.09 lower to 0.18 higher) or total plasma thyroxine (MD 0.29 nmol/L higher; 1.51 lower to 2.09 higher) [Not important]. **Undesirable effects for Māori -** No additional data	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High	Moderate to very low certainty evidence overall	Evidence is primarily based on one large, well-designed study. However, there is only one study conducted in the United Kingdom and the critical outcomes have large treatment effects with wide

○ No included studies		confidence intervals crossing the line of no effect.

Outcomes	Importance	Certainty of the evidence (GRADE)
Mortality: RCT assessed with: Mortality before hospital discharge	CRITICAL	⨁⨁◯◯ Low
Neurodevelopmental impairment: RCT assessed with: Bayley-III Cognitive composite score: 2 years of age corrected for prematurity Scale from: 1 to 100	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT assessed with: Bayley-III Motor composite at 2 years of age corrected for prematurity Scale from: 1 to 100	CRITICAL	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT assessed with: Bayley-III Language composite score at 2 years of age corrected for prematurity Scale from: 1 to 100	IMPORTANT	⨁◯◯◯ Very low
Neurodevelopmental impairment: RCT assessed with: Low score in any main Bayley domain (< 85) or death	CRITICAL	⨁⨁◯◯ Low
Neurodevelopmental impairment: RCT assessed with: Visual impairment	CRITICAL	⨁⨁◯◯ Low
Neurodevelopmental impairment: RCT assessed with: Auditory impairment	CRITICAL	⨁⨁◯◯ Low
Faltering growth/body composition - not measured	CRITICAL	-
Adverse effects - not measured	CRITICAL	-
Retinopathy of prematurity	IMPORTANT	⨁⨁⨁◯ Moderate
Bronchopulmonary dysplasia assessed with: Chronic lungdisease in surviving infants (supplemental oxygen requirement at 36 weeks' postmenstrual age)	IMPORTANT	⨁⨁◯◯ Low
Fully breastfed or breastmilk feeding at hospital discharge - not measured	IMPORTANT	-
Time to full enteral feeds - not measured	IMPORTANT	-
Duration of initial hospital stay - not measured	IMPORTANT	-
Sepsis: proven or suspected - not measured	IMPORTANT	-
Necrotising enterocolitis: RCT	IMPORTANT	-

Anaemia of prematurity - not measured	IMPORTANT	-
Cost: cost of intervention, cost of neonatal care and life-long cost - not measured	IMPORTANT	-
Time to full sucking feeds - not measured	NOT IMPORTANT	-
Total plasma thyroxine: RCT assessed with: (nmol/L) at 34–36 weeks' postmenstrual age.	NOT IMPORTANT	⨁⨁⨁◯ Moderate
Thyroid-stimulating hormone: RCT assessed with: (mU/L) at 34–36 weeks' postmenstrual age.	NOT IMPORTANT	⨁⨁⨁◯ Moderate

Certainty of evidence for Māori
No additional data

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Probably no important uncertainty or variability. **Values for Māori** No additional data	

Balance of effects
Does the balance between desirable and undesirable effects favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison	**Iodine versus no iodine - moderate certainty evidence** Little or no difference in thyroid function	

○ Probably favours the comparison ● Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Uncertain effect on necrotising enterocolitis, retinopathy of prematurity **Iodine versus no iodine - low certainty evidence** Uncertain effect on mortality, bronchopulmonary dysplasia, neurodevelopmental impairment (auditory and visual impairment; Low score in any main Bayley domain (<85) or death **Iodine versus no iodine - very low certainty evidence** Uncertain effect on neurodevelopmental impairment (Bayley III cognitive, motor, language) **Balance of effects for Māori** No additional data	

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Dose approx. 50 µg iodine per day. Potassium iodate 253 µg tablet (equivalent to 150 µg iodine) - $0.07 per tab The cost of iodine supplementation is negligible, $0.07 per day	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included	The cost of iodine supplementation is minimal and certain. **Certainty of evidence of required resources for Māori** No additional data	

studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	There are no studies that assess the specific cost-effectiveness of iodine supplementation compared with no iodine supplementation, particularly in the context of preterm infants. **Cost effectiveness for Māori** No additional data	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	**Equity for Māori** In 2008/09, 44% of wāhine Māori had moderate iodine deficiency, with urinary iodine concentrations below 50 µg/L, and 80% had levels below 100 µg/L, indicating mild deficiency. While the overall proportion of women with iodine levels below 100 µg/L was similar between Māori and non-Māori, wāhine Māori were significantly more likely to have moderate deficiency, even after adjusting for age (Ministry of Health, 2012). To address the re-emergence of iodine deficiency, mandatory use of iodised salt in bread-making was introduced in late 2009. By 2014/15, urinary iodine levels had nearly doubled across all age, gender, and ethnic groups. Iodine status was considered adequate for Māori, Pacific, and Asian women, while European/other women continued to show mild deficiency (NZ Health Survey, 2014/15). Since	

	2010, a subsidised iodine-only tablet (150 µg) has been available in Aotearoa New Zealand, and the Ministry of Health recommends daily supplementation for all pregnant and breastfeeding women. However, access to this supplement requires awareness of the pregnancy and access to a prescriber or maternity carer, which may present barriers for some. **Equity for Pacific families** There is likely inequity in iodine status for Pacific Island infants and some other ethnicities, although data specifically focused on ethnic differences in infant iodine levels in Aotearoa New Zealand is limited. Pacific Is women are less likely to receive timely antenatal care, be prescribed iodine supplements and be given clear information about iodine's importance in pregnancy and breastfeeding. This leads to increased risk of iodine deficiency for their infants, especially if exclusively breastfed without maternal supplementation and there is limited consumption of iodine-rich foods (e.g. dairy, seafood, iodised salt). **Equity for other underrepresented groups** If iodine supplementation is overlooked or inconsistently applied in under-resourced settings, underrepresented infants may face preventable risks to growth and neurodevelopment. Clear national standards and equity-focused monitoring are needed to ensure all preterm infants receive essential micronutrients like iodine regardless of their location or family circumstances. Asian women (especially recent migrants) may also be at risk due to restrictive postnatal dietary practices (e.g. low dairy/iodised salt intake) or lack of health system navigation. Refugee and migrant communities may have low awareness and inconsistent access to supplementation.	

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Iodine supplementation is easy to administer and is likely to be acceptable to most stakeholders. **Acceptability for Māori**	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No	Iodine supplementation is feasible in neonatal care.	

○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Feasibility for Māori** No additional data available.	

Summary of judgements

	JUDGEMENT						
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	**Does not favour either the intervention or the comparison**	Probably favours the intervention	Favours the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know

	JUDGEMENT						
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

References

1. Walsh, V.; Brown, J.V.E.; McGuire, W. Iodine supplementation for the prevention of mortality and adverse neurodevelopmental outcomes in preterm infants. *Cochrane Database Syst. Rev.* **2019**, *2*, CD005253, doi:10.1002/14651858.CD005253.pub3.
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Back to question list