EtD 37. Should routine fat supplementation vs. no supplementation be used in preterm infants receiving enteral feeds?

POPULATION:	Preterm infants receiving enteral feeds
INTERVENTION:	Routine fat supplementation
COMPARISON:	No fat supplementation
MAIN OUTCOMES:	**Critical outcomes** Faltering growth/body composition Necrotising enterocolitis Adverse effects (long term cardiometabolic health Time to full enteral feeds **Important but not critical** Neurodevelopmental impairment Duration of initial hospital stay Fully breastfed or breastmilk feeding at hospital discharge Sepsis: proven or suspected Mortality Bronchopulmonary dysplasia Retinopathy of prematurity 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 Growth/weight at day 30 Feeding intolerance Necrotising enterocolitis
SETTING:	Neonatal care
PERSPECTIVE:	Clinical recommendation
BACKGROUND:	Fat is a critical macronutrient for preterm infants, providing energy and essential fatty acids that are vital for growth, eye development and neurodevelopment. During fetal life, fat deposition accelerates in the third trimester, a process that is disrupted by preterm birth. As a result, preterm infants have limited fat and energy reserves and suboptimal levels of the essential fatty acids. Additional fat supplementation in enteral feeds is sometimes used to meet the high energy demands of preterm infants to promote weight gain and support neurodevelopmental outcomes. However, the benefits of fat supplementation must be balanced with potential risks, including feeding intolerance, gastrointestinal complications and altered body composition. Observational studies suggest associations between higher fat intake and improved growth outcomes, but excessive fat intake can reduce feeding tolerance or lead to fat malabsorption. Additionally, the type of fat used (e.g. medium-chain triglycerides vs. long chain fatty acids) may influence

	outcomes, with different formulations offering varying degrees of absorption and metabolic effects. It is important to determine whether the addition of fat supplements to breastmilk fed to preterm infants compared with no additional fat improves growth, brain development, body fat or obesity, without significant side effects especially for long term cardiometabolic health. This question relates to fat supplementation that is given in addition to, or instead of commercial breastmilk fortifier, to increase energy intake.
CONFLICT OF INTERESTS:	The following Amissah *et al* systematic review 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 a systematic review [1] includes one small trial (n=14) and one RCT [2]. **No faltering growth/body composition:** RCT: No significant increase in weight at the end of the study (MD 40 g higher; 258.62 lower to 338.62 higher) [Critical]. **No faltering growth/body composition:** RCT: No significant effect on weight gain (MD 0.6 g /kg/day higher; 2.36 lower to 3.56 higher); length gain (MD 0.10 cm/week higher; 0.08 lower to 0.28 higher); head circumference (MD 0.15 cm/week higher; 0.07 lower to 0.37 higher) [Critical]. **Time to full enteral feeds:** RCT: No effect on feeding intolerance (unable to calculate absolute effect due to minimal or no events). Less time to achieve full enteral feeding in fat supplement group 12.12±6.26 days vs. control group 20.18±13.54 days (p<0.001) [Important]. **Duration of hospital stay:** RCT: Shorter duration of hospital stay in fat supplement group 52.00±21.32 vs. control (n=48) 73.22±22.79 days (p<0.001). [Important] **Bronchopulmonary dysplasia:** RCT: Reduced number of infants with bronchopulmonary dysplasia with fat supplementation 5/48 (10.4%) vs. Control 16/48 (33.3%) (P=0.007). [Important] **Retinopathy of prematurity:** RCT: No significant difference in retinopathy of prematurity with fat supplementation 23/48 (47.9%) vs. Control 17/48 (35.4 %). [Important] **Desirable effects for Māori** No available evidence	We do not envisage that further trials of fat supplementation will be conducted, as energy is currently added to expressed breastmilk as a component of multi-nutrient fortification. **Population information for included evidence** The Swedish trial included in the systematic review [1] examined preterm infants <32 gestational weeks and of birthweight <1,500 grams. Turkey: RCT [2]: Very low birthweight infants. 0.5 mL of olive oil /30 mL milk was added to each feed for infants in the intervention group.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no supplementation	Risk difference with routine fat supplementation

Faltering growth/body composition: RCT assessed with: Weight gain (g/kg/day)	14 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	-	The mean faltering growth/body composition: RCT was **15.3 g/kg/day**	MD **0.6 higher** (2.36 lower to 3.56 higher)
Faltering growth/body composition: RCT assessed with: Weight at end of study (g)	14 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	-	The mean faltering growth/body composition: RCT was **2070 g**	MD **40 higher** (258.62 lower to 338.62 higher)
Faltering growth/body composition: RCT assessed with: Weight at discharge (g)	96 (1 RCT)	⨁◯◯◯ Very low[a,b,e]	-	Weight at discharge intervention group (n=48) 1924.16±124.00 g vs. control group (n=48) 1949.68±163.16 g (Not significant)	
Faltering growth/body composition: RCT assessed with: Length (cm/week)	14 (1 RCT)	⨁◯◯◯ Very low[a,b,c,]	-	The mean faltering growth/body composition: RCT was **0.83 cm/week**	MD **0.1 higher** (0.08 lower to 0.28 higher)
Faltering growth/body composition: RCT assessed with: Head circumference (cm/week)	14 (1 RCT)	⨁◯◯◯ Very low[a,b,c,]	-	The mean faltering growth/body composition: RCT was **0.94 cm/week**	MD **0.15 higher** (0.07 lower to 0.37 higher)
Necrotising enterocolitis - not measured	-	-	-	-	-
Adverse effects (long term cardiometabolic health) - not reported	-	-	-	-	-
Time to full enteral feeds: RCT assessed with: Days	96 (1 RCT)	⨁◯◯◯ Very low[a,b,e,]	-	Transition time to full enteral nutrition (days) Intervention group (n=48) 12.12±6.26 days vs. control group (n=48) 20.18±13.54 days (P <0.001)	
Time to full enteral feeds: RCT assessed with: Feeding intolerance	16 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	**RR 3.00** (0.14 to 64.26)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Neurodevelopmental impairment - not reported	-	-	-	-	-
Duration of initial hospital stay assessed with: Days	96 (1 RCT)	⨁◯◯◯ Very low[a,b,e]	-	Length of hospital stay (days) Intervention (n=48) 52.00±21.32 vs. control (n=48) 73.22±22.79 days (p<0.001)	
Fully breastfed or breastmilk feeding at hospital discharge - not measured	-	-	-	-	-
Sepsis: proven or suspected	96 (1 RCT)	⨁◯◯◯ Very low[a,b,e]	-	Intervention group 8/48 (16.7%) Control group 23/48 (47.9%) (P<0.001)	
Mortality - not measured	-	-	-	-	-
Bronchopulmonary dysplasia / chronic lung disease	96 (1 RCT)	⨁◯◯◯ Very low[a,b,e]	-	Intervention 5/48 (10.4%) Control 16/48 (33.3%) P=0.007	
Retinopathy of prematurity	96 (1 RCT)	⨁◯◯◯ Very low[a,b,e]	-	Intervention 23/48 (47.9%) Control 17/48 (35.4 %)	

				Not significant	
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	-	-	-	-	-

a. Downgraded one level risk of bias due to unclear reporting
b. Downgraded one level for indirectness as evidence is based on a single study
c. Downgraded one level for imprecision as there are wide confidence intervals that cross the line of no effect.
d. Downgraded one level for imprecision due to small sample size
e. Downgraded one level for indirectness as the population may not be generalisable as only included VLBW infants
f. Downgraded one level for imprecision with wide variation around the mean

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	The single included study in the systematic review did not report on any of the other outcomes associated with this clinical question. **Undesirable effects for Māori** No available evidence	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence is based on a single, small study of 14 infants in a Swedish study published in 1989. Very low certainty evidence overall. **Certainty of evidence for Māori** No available evidence	

Outcomes	Importance	Certainty of the evidence (GRADE)
Faltering growth/body composition: RCT assessed with: Weight gain (g/kg/day)	CRITICAL	⨁◯◯◯ Very low

Faltering growth/body composition: RCT assessed with: Weight at end of study (g)	CRITICAL	⨁◯◯◯ Very low
Faltering growth/body composition: RCT assessed with: Length (cm/week)	CRITICAL	⨁◯◯◯ Very low
Faltering growth/body composition: RCT assessed with: Head circumference (cm/week)	CRITICAL	⨁◯◯◯ Very low
Necrotising enterocolitis - not measured	CRITICAL	-
Adverse effects (long term cardiometabolic health) - not reported	CRITICAL	-
Time to full enteral feeds: RCT assessed with: Feeding intolerance	IMPORTANT	⨁◯◯◯ Very low
Neurodevelopmental impairment - not reported	IMPORTANT	-
Duration of initial hospital stay assessed with: Days	IMPORTANT	⨁◯◯◯ Very low
Fully breastfed or breastmilk feeding at hospital discharge - not measured	IMPORTANT	-
Sepsis: proven or suspected	IMPORTANT	⨁◯◯◯ Very low
Mortality - not measured	IMPORTANT	-
Bronchopulmonary dysplasia / chronic lung disease	IMPORTANT	⨁◯◯◯ Very low
Retinopathy of prematurity	IMPORTANT	⨁◯◯◯ Very low
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	-

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	Unlikely to be uncertainty or variability in the value place on the main outcomes.	

uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	**Values for Māori** No available evidence	

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 ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	**Fat supplementation compared with unsupplemented breastmilk - very low certainty of evidence** Reduction in time to full enteral feeds, duration of initial hospital stay, bronchopulmonary dysplasia Uncertain effect on feeding intolerance, weight, length and head circumference, retinopathy of prematurity **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	**Fat supplementation dose** 3.6 to 6.8 mL/kg/day Calogen 4 to 7 mL/kg/day Liquigen **Dose per baby per day** 5 to 10 mL Calogen (long-chain triglyceride emulsion) 5 to 10 mL Liquigen (medium chain triglyceride emulsion) **Cost per day** Calogen $0.40 to $0.80 Liquigen $2.15 to $4.30 **Cost per admission per infant (up to 100 days)** Calogen $40 to 80 Liquigen $215 to $430	Calogen is suitable for most infants (small cost).

	Resources required for Māori Similar - no additional data	

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 studies	The cost of fat supplements in Aotearoa New Zealand is known. **Certainty of evidence of required resources for Māori** No additional data	

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 fat supplementation compared with unsupplemented breastmilk, particularly in the context of preterm infants. **Cost effectiveness for Māori** No additional evidence available	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased	**Equity for Māori** Pēpi Māori, often born preterm or growth-restricted, may not consistently receive adequate nutrition due to variable hospital practices and limited regional resources. Culturally unsafe care and inadequate communication can prevent whānau Māori	

○ Increased ○ Varies ○ Don't know	from fully engaging in nutrition decisions. Equity requires national guidelines and culturally responsive care to ensure timely, appropriate supplementation if needed. **Equity for Pacific families** Pacific infants may experience inadequate nutrition due to systemic barriers, fragmented services and inconsistent clinician communication. Families may not be adequately supported to understand or advocate for nutritional needs. Equity demands standardised nutrition practices and culturally meaningful engagement to support optimal growth and reduce the length of hospital stay. **Equity for underrepresented groups** Infants from migrant, rural and lower-income families may experience barriers to adequate nutrition due to location, transport issues or lack of tailored health communication. These barriers can widen developmental disparities in preterm infants. Ensuring equitable nutrition requires clear national policies, accessible education and proactive outreach to support informed care across diverse communities.	

Acceptability

Is the intervention acceptable to key interest-holders?

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

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies	Fat supplementation is feasible in the Aotearoa New Zealand setting. **Feasibility for Māori** No available evidence	

○ Don't know		

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
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. Amissah, E.A.; Brown, J.; Harding, J.E. Fat supplementation of human milk for promoting growth in preterm infants. *Cochrane Database Syst. Rev.* **2020**, *8*, Cd000341, doi:10.1002/14651858.CD000341.pub3.
2. Aytemiz, S.; Sarı, M.; Yurttutan, S.; Çıkar, Y.; Topal, S.; Çaka, S.Y. Effects of enteral olive oil supplement on weight gain, length of hospital stay, and the development of some complications in preterm infants: A randomized controlled trial. *J Pediatr Res* **2024**, *11*, 95-102, doi:10.4274/jpr.galenos.2024.36937.

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