Does iodine deficiency cause congenital hypothyroidism in preterm babies?

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Research Summary

Hypothesis: Iodine deficiency is associated with an increase in rates of TSH elevation in very preterm infants (<32 weeks gestation and/or <1500g birth weight)

Study aim: To determine if very preterm infants (<32 weeks gestation and/or <1500g birth weight) with elevated screening TSH concentrations have lower urinary iodine concentrations than preterm infants with normal screening TSH concentrations.

Background

Over the past decade, a dramatic and more than 10-fold increase in congenital hypothyroidism has been noted in preterm infants in Aotearoa New Zealand. Congenital hypothyroidism is a condition where the infant's thyroid gland cannot make enough thyroid hormone. It is the most common disorder detected through newborn metabolic (Guthrie card) screening, and the most common cause of preventable brain damage worldwide. Congenital hypothyroidism affecting preterm infants is most often transient (temporary), suggesting that the cause is different to that in full term infants, but it can still cause permanent brain damage.

We suspect that hypothyroidism in preterm infants may be due in part, to iodine deficiency. Iodine is a mineral necessary for the body to produce thyroid hormone, and Aotearoa as a country has low levels in our locally sourced food. Universal supplementation of iodine is recommended and funded during pregnancy but many women do not receive this. At the moment, only very low and probably inadequate levels of iodine are provided in the specialised feeds given to preterm infants.

We need to confirm if preterm infants with congenital hypothyroidism have low iodine levels, so that we can provide better advice to pregnant mothers and better nutrition to preterm infants.

Design

Very preterm (<32 weeks gestational age) or very low birth weight (<1500g) infants and their childbearing parent who are participating in newborn metabolic screening within the Auckland region will be eligible for this observational study. 40 cases will be recruited with 80 matched controls over a two year period. Recruitment will be by local research nurses within the neonatal intensive care units in conjunction with the clinical teams. At recruitment, the childbearing parent will complete a questionnaire and have baseline thyroid function blood test, urinary iodine concentration and breast milk iodine concentration measured. The infant will have a baseline and a 36 week-corrected-gestational-age urinary iodine concentration and monitoring of their nutritional data throughout the study period.

We intend to recruit 40 cases and 80 controls over a two-year period from the greater Auckland region. We aim to determine if there is an association between elevated TSH screening and iodine deficiency in infants who are very preterm (<32 weeks gestational age) or very low birth weight (<1500g). The primary outcome measure is the infant's urinary iodine concentration (random) at the time of initial elevated newborn screening result.

Significance

This research will have near immediate impact as it will inform the production of new national neonatal nutrition guidelines to increase iodine fortification and will be fed back to midwives involved in the care of pregnant women.

Background

Newborn Screening

Newborn screening involves the collection of a heel-prick sample onto a blood spot (Guthrie) card, usually between 24-72 hours after birth, which is then used to screen for over 20 life-threatening or serious conditions before severe symptoms or permanent damage occurs. Newborn screening undertakes a crucial role in improving childhood health, is available to all New Zealand infants with parental consent and has almost complete uptake (>98%).

Primary Congenital Hypothyroidism

Primary congenital hypothyroidism is the most common disorder detected on newborn screening and is the most common preventable cause of intellectual disability worldwide(1–3). The overall Aotearoa New Zealand and incidence of primary congenital hypothyroidism is 1:2000 births(2). However rates are significantly higher in very preterm infants at 1:100-150(4–8). Over the past decade many newborn screening programmes, including the New Zealand Newborn Screening Unit, have noted an increasing incidence of congenital hypothyroidism amongst preterm infants(9,10). Whilst congenital hypothyroidism in preterm babies is most often observed to be transient, it may be still be biochemically severe (TSH > 50mIU/L) and potentially affect future neurodevelopment if untreated(6). Interestingly, we have recently observed that Māori preterm infants have a higher rate of congenital hypothyroidism than European infants (New Zealand Newborn Metabolic Screening Programme, National Screening Unit, 2008-2018, unpublished screening data)”), which contrasts to lower overall rates in term Māori babies (7), this difference suggests the causes of preterm congenital hypothyroidism are not the same. The aetiology of the increased frequency of congenital hypothyroidism in preterm infants remains unclear but is hypothesised to be due to a number of factors including: immaturity of the hypothalamic-pituitary-thyroid axis, medications (steroids, dopamine), non-thyroidal illness (eg. respiratory distress syndrome) and iodine deficiency (5,8,11,12).

Iodine and maternal supplementation

Iodine is a critical component in thyroid hormone synthesis and iodine deficiency is associated with raised TSH levels and primary hypothyroidism. New Zealand has low environmental iodine content (13). Infants are at risk of iodine deficiency as they rely on maternal iodine levels, placental function and breastmilk for their iodine intake. To this end, maternal iodine supplementation is recommended during pregnancy and breastfeeding as the iodine requirement increases by 50%(14). While iodine supplementation and the prevalence of maternal iodine insufficiency across New Zealand are unknown, recent data from subfertile women of reproductive age in Auckland (n=196) indicated nearly 30% were iodine deficient despite supplementation recommendations from their fertility specialists(15) . This is in concordance with recent US data, suggesting maternal iodine deficiency may be more prevalent than previously believed(16) and may increase the risk of iodine deficiency in newborn infants.

Preterm infants and iodine

Preterm infants are at even greater risk of iodine deficiency as they have had less time *in utero* accumulating iodine stores, as well as reduced iodine exposure after birth. Preterm infants are often initiated on intravenous nutrition in neonatal units while oral feeding is initiated. Transition to full enteral feeds can take weeks for very preterm infants. Iodine content of intravenous nutrition varies across Australasia but is generally well below current recommended daily intakes. The previous European Society for Paediatric Gastroenterology Hepatology and Nutrition recommendation for preterm infants was 1mcg/kg/day iodine in intravenous nutrition(17), which was intentionally low to account for iodine contamination via intravenous contrast, topical iodine antiseptic preparations and medications(14). However, due to increased awareness and reduced use of iodine-containing preparations, this approach may no longer be valid.

In 2018, the European Society for Paediatric Gastroenterology Hepatology and Nutrition adjusted their recommendation to 1 – 10mcg/kg/day for intravenous iodine in preterm infants. While this is an increase, it is still low compared with their recommendation for enteral daily intake of 10 – 55 mcg/kg/day for the same population of infants, considering that there is high enteral absorption of iodine(18). Furthermore, a recent study provided evidence that the recommended level is likely to be insufficient, as preterm infants receiving intravenous nutrition with a mean daily intake of 3mcg/kg/day had negative iodine balance (19). The broad recommended daily intake ranges for both enteral and parenteral intake reflects a paucity of research in this area.

The higher iodine levels in intravenous nutrition allowed by the revised upper range have not yet been adopted across New Zealand neonatal intensive care units. To compound this concern, there are wide regional differences in preterm congenital hypothyroidism prevalence and in nutritional practices between neonatal intensive care units in New Zealand (New Zealand Newborn Metabolic Screening Programme, National Screening Unit, 2020-2022, unpublished screening data). It is possible that differences in iodine intake could contribute to the differences in the rate of delayed-onset congenital hypothyroidism seen across New Zealand.

In summary, preterm infants are at greater risk of iodine deficiency due to the compounding effects of low maternal iodine, prematurity-related reduction in iodine stores, and low concentrations of iodine in their intravenous nutrition. The high rate of delayed onset hypothyroidism observed amongst preterm infants is typically attributed to immaturity of the hypothalamic-pituitary-thyroid axis, but may be due to, or exacerbated by, low iodine stores at birth and progressive insufficiency developing over the first weeks of life.

Hypothesis: Iodine deficiency is associated with an increase in rates of TSH elevation in very preterm infants (<32 weeks gestation and/or <1500g birth weight)

Study aim: To determine if very preterm infants (<32 weeks gestation and/or <1500g birth weight) with elevated screening TSH concentrations have lower urinary iodine concentrations than preterm infants with normal screening TSH concentrations.

Outcomes

Primary outcome:

Urinary iodine concentration (random) within one week of elevated screening thyroid stimulating hormone result (cases) or within one week of recruitment (controls).

Secondary outcomes:

Serum thyroid function test results (cases)
Urinary iodine concentration at 36 weeks
Whole blood screening thyroid stimulating hormone at 36 weeks
Maternal urinary iodine concentration
Maternal serum thyroid function test results.
Expressed breast milk iodine concentration at recruitment.
Maternal iodine supplementation use
Iodine content of neonatal feeds/nutrition
Maternal demographics

Methodology

We plan to carry out a prospective matched case-control study. Preterm infants with elevated TSH on screening will be matched in a 1:2 ratio with preterm infants who did not have an elevated TSH on newborn screening. Infants will be matched by both gestational age at birth (± 7 days) and post-natal age at recruitment. Twins will be eligible for inclusion both as cases and controls.

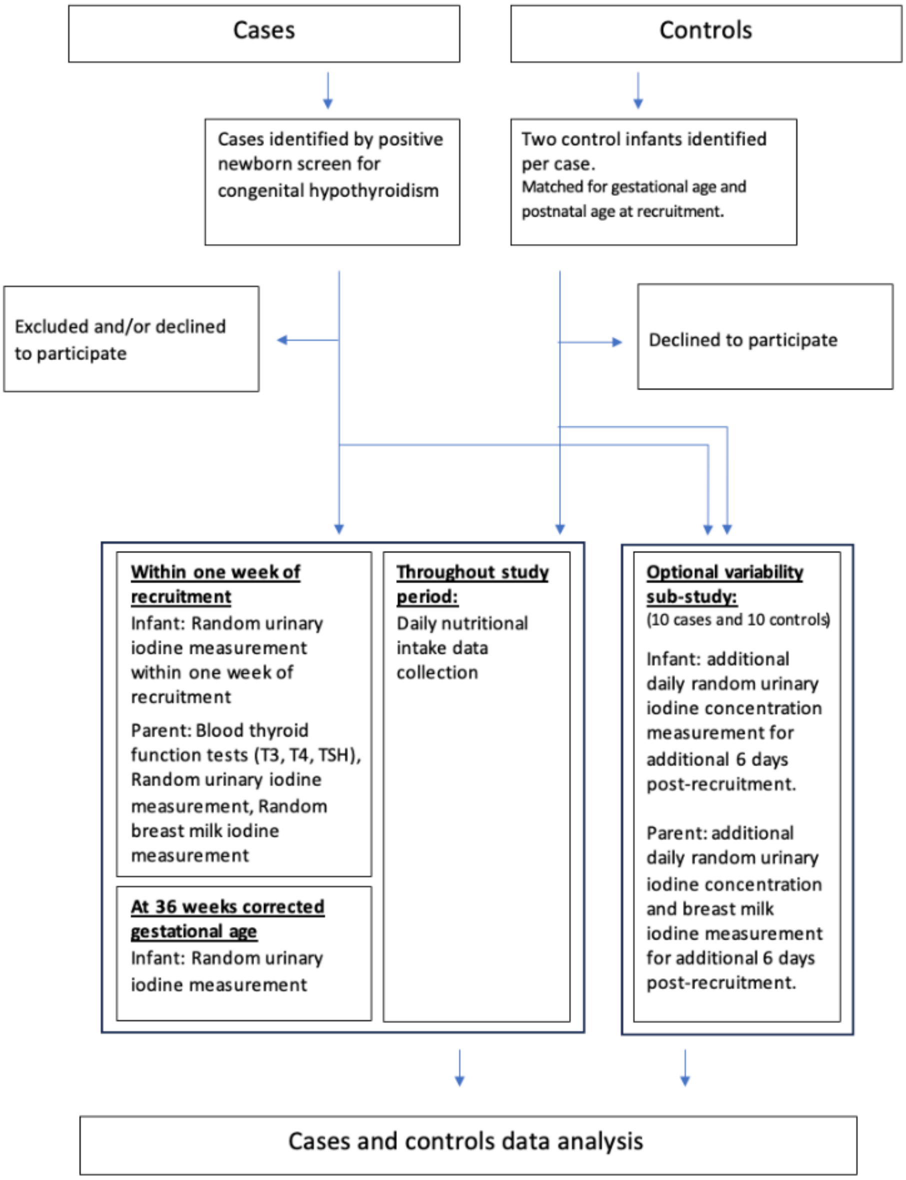
Participating infants will be screened as per the New Zealand Newborn Metabolic Screening Programme congenital hypothyroidism protocol, via the updated Preterm Metabolic Bloodspot Screening Protocol for infants with a birth weight of <1500g or <32 weeks gestational age. The initial screening sample for both protocols involves a whole blood heel prick blood spot onto a sample card taken between 24 and 72 hours of age, analysed for whole blood TSH concentration via GSP, Perkin Elmer analyser at the national testing laboratory at LabPlus, Auckland. Results are reported on the same or next working day after the sample is received. The Preterm protocol includes a second sample taken at 14 days of age if the infant's birth weight is <1500g or <32 weeks gestational age and a third sample at 28 days of age if the infant's birth weight is <1000g. All infants with a birth weight of <1500g or <32 weeks gestational age will also have a final sample taken at 36 weeks corrected gestational age or pre-discharge (whichever comes first, unless another sample has been collected within 2 weeks). For the 24-72 hour sample (at any birth weight or gestational age), a TSH ≥ 13mIU/L is considered elevated. For samples collected beyond a week of age (i.e. the second and third screening samples collected through the Low Birth Weight Protocol), a TSH ≥ 6mIU/L is considered elevated. Elevated results prompt referral to paediatrics or paediatric endocrinology for serum thyroid function tests. Note that blood spot TSH thresholds are given in whole blood units, to convert to serum units multiply by a conversion factor of 2.2.

Inclusion criteria:

- Singleton and twin infants born within the Auckland region,
- Birth weight <1500g and/or <32 weeks gestation,
- Participant in Newborn Metabolic Screening Programme,
- Born within time frame of study (anticipated to be August 2024-August 2026),
- Whole blood TSH above the screening threshold for recall (unless is a control) as stipulated above.

Exclusion criteria:

- Critically unwell infants or mothers/childbearing parents where it is unreasonable to gain consent,
- Infants with known or strongly suspected syndromes with known thyroid abnormalities, e.g. Trisomy 21,
- Maternal thyroid disease requiring treatment with thyroxine, carbimazole or propylthiouracil,
- Major congenital anomalies or receiving palliative care,
- Suspected or confirmed pituitary abnormalities,
- Triplets and higher order multiples.



Infant assessments:

Cases: recruited at first abnormal TSH screening result as per National Screening Guideline.

- Screening whole blood TSH concentrations at recruitment as per protocol.
- Spot urinary iodine (random) within 7 days of recruitment.
- Serum thyroid function tests (TSH, free T4, free T3) within 7 days of abnormal screening result (as part of standard clinical care in the instance of an abnormal screening result).
- Spot urinary iodine (random) 36 weeks corrected gestational age or discharge, whichever comes first.
- Nutritional variables: days on intravenous nutrition, mcg/kg/day iodine intake, days to full enteral feeds and enteral feeding method.

Controls:

- Screening TSH samples as per protocol.
- Spot urinary iodine (random) at recruitment.
- Random spot urinary iodine at 36 weeks corrected gestational age or discharge, whichever comes first.
- Nutritional variables: days on intravenous nutrition, mcg/kg/day iodine intake, days to full enteral feeds and enteral feeding method.

Parent assessments (cases and controls):

- Parental questionnaire: demographic details: NZ Individualised Deprivation score, ethnicity, maternal age and gestation at delivery, relevant medical and family history. Data on iodine supplementation, medications taken during pregnancy and antenatal care received, including fertility treatment.
- Maternal serum thyroid function tests
- Spot urinary iodine (random) within 7 days of detection of abnormal infant screening TSH concentration in cases or at recruitment for controls.
- Expressed breast milk iodine concentration within one week of recruitment.

Assessments in the iodine in preterm babies with congenital hypothyroidism study

	Recruitment†	Daily for 6 further days	Across the study period	36 weeks corrected gestational age
Mothers				
Urinary iodine	✓	(✓*)		
Serum thyroid tests	✓			
Breast milk iodine	✓	(✓*)		
Antenatal nutritional variables	✓			
Demographic data	✓			
Case babies				
TSH Screening test	✓			✓
Thyroid tests	✓			
Urinary iodine	✓	(✓*)		✓
Nutritional variables	✓		✓	✓
Control babies				
TSH Screening test	✓			✓
Urinary iodine	✓	(✓*)		✓
Nutritional variables	✓		✓	✓

†within 7 days of positive TSH result or recruitment of control

* for those 10 case and 10 control participants in the variability sub-study

Special consideration – Twins

Cases who are twins will be included in the study. Their unaffected twin will not be matched as a control as their in utero iodine exposure is the same and their mother/childbearing parent will only be included once in the study. We will collect the data for the unaffected twin of the case.

Controls who are twins will be included in the study. Each mother/childbearing parent of twins is considered a single control and data collected for both infants.

Special consideration – if a Control becomes a Case

If an infant has been enrolled in the study as a control but develops an elevated TSH, they will become a case and two new controls will be recruited for them. An additional control would be recruited for the original case to whom they were initially matched.

Sample size:

120 infants in total, with 40 infants enrolled as cases and 80 infants as matched controls. 40 infants with a birth weight <1500g and/or <32 weeks gestation recalled for an elevated newborn screening TSH concentration (and 80 control infants with normal TSH levels) will be recruited into this study in a 1:2 ratio. We will aim to recruit 20 cases and 40 controls/year from the Te Whatu Ora Te Toka Tumai Auckland and

Counties Manukau domicile regions. These regions encompass all neonatal intensive care units in the greater Auckland City Area. Given historical case numbers, recruitment is expected to be completed within two years.

Plan to ensure representative Māori and Pacific participation:

We recognise that congenital hypothyroidism in preterm babies is an important issue for Māori and Pasifika, who are over-represented compared with Pakeha. In Auckland 22% of preterm babies with a positive screen were Māori and 26% Pacific (New Zealand Newborn Metabolic Screening Programme, National Screening Unit, 2008-2018, unpublished screening data). We would expect similar proportions within our study. To achieve this we will focus on ensuring that the study is presented in a positive and culturally appropriate manner, and will take advice from our Māori health researcher on our team. We will produce translated information materials and make interpreters available if necessary. We will not recruit cases preferentially as there is a limited number of preterm babies with positive screens, and it is important that all whanau with a preterm baby with congenital hypothyroidism in Auckland are free to participate. However, there is a much wider pool of potential babies who could be recruited as controls increasing the risk that insufficient proportions of Māori and Pasifika are recruited in the control group.

We will review the ethnic proportions of participants in the study as each 10 cases and 20 controls are recruited (i.e. each quarter). If the pool of participants is deviating from expectations we will meet as a team, to identify factors contributing and make a plan to avert them. If, once 60 controls are recruited, Māori and Pasifika are significantly under-represented we will pause recruitment of non-Māori, non-Pasifika controls.

Variability sub-study:

Urinary Iodine is the accepted and commonly used measure of iodine sufficiency in clinical practice, so that it is the appropriate primary outcome measure for this study. However, urinary iodine is a dynamic measure, changing quickly when the dietary intake changes. The day to day variability of urinary iodine amongst neonates and mothers after delivery is not well understood. As the primary outcome of the study is a single timepoint measure of urinary iodine in the babies, and maternal iodine is also assessed with a single timepoint, it is important to determine how representative this is of daily levels. This will also have implications for the use of urinary iodine measures in assessment of neonates. Further, while breast milk iodine has been said to be a better measure than urinary iodine(20), its day to day variability is not known.

To find out, we will ask 10 cases and 10 controls (mothers and their babies) to participate in a more intensive sub-study. The mothers will be able to opt-in to this if they wish to. In addition to all aspects in the main study, we will collect a further six consecutive days of breast milk samples as well as urine samples from mother and baby. This will be used to assess variation across a week period for each case/control in this sub-study. We will determine the coefficient of variation as well as the range between highest and lowest values for each participant.

Laboratory Analysis:

All neonatal screening tests will be conducted by the Newborn Metabolic Screening Unit as part of their routine screening.
Routine serum thyroid function tests for infants will be analysed by Lab Plus (Te Toka Tumai) as part of their standard clinical care in the event of an abnormal screening test.
Infant and parent urinary samples will be analysed for iodine concentration by Lab Plus (Te Toka Tumai Auckland).
Breast milk iodine levels will be sent to Hills laboratory for analysis via mass spectrometry. Samples will be collected from the parent, split into three aliquots and labelled with de-identified study labels and put in

freezer within the neonatal intensive care unit. They will then be transported to the secure sample freezer at the Liggins Institute as soon as possible and stored at -80 degrees Celsius. They will be couriered frozen to Hill Laboratory in monthly batches for analysis.

Power Calculation:

Based on a standard deviation of 33 mcg/L(21)using an α of .05 and power 0.9, we require 28 infants with abnormally raised TSH and 56 matched control infants (with normal TSH concentrations) to detect a difference of urinary iodine of 25 mcg/L between groups. This represents a minimum detectable difference of 40% between groups, as the mean urinary iodine in the preterm population is 64 mcg/L(21). Differences smaller than this would be unlikely to affect thyroid function. Allowing for up to 20% drop out we expect to collect outcome data on a minimum of 32 cases and 64 controls and complete this study within 2 years.

Statistical Analysis:

The primary outcome of the study will be the between-group (case vs controls) difference in urinary iodine in babies at recruitment. Differences between groups will be assessed using logistic regression models. Models will potentially include gestational age, age at diagnosis and maternal age, but these variables will be removed if they do not improve the predictive ability of the model. The potential association between maternal urinary iodine and baby urinary iodine, and between maternal urinary iodine and breast milk iodine will be assessed using multivariable regression models.

The non-independence of control twins will be accounted for in the statistical analysis. If sufficient numbers of twins are recruited, an analysis of iodine concentrations for twins will be considered.

Data management

Identifiable health data will be collected to enable investigators to inform clinical care teams of any significant abnormal results. When the data is extracted from the database for analysis, it will be deidentified. Data will initially be stored within the secure ADHB and University of Auckland networks before being deidentified for further analysis. Identifiable data will only be accessed by those within the core research team e.g. named investigators, research nurses and study coordinator.

Ethics

Locality approvals will be sought from Te Whatu Ora Te Toka Tumai Auckland and Counties Manukau.
All urinary iodine results will be reported to the clinicians caring for the infants. The research team will not be directing management of the results and will only inform the clinical team. The clinical team can then decide independently if the result warrants action.

The primary ethical issue is that of coercion. The investigating team is made up of endocrinologists and a neonatologist who may well become involved in the clinical care of an infant within the study. Children with positive screening tests for congenital hypothyroidism are referred to the Paediatric Endocrine Team to provide advice on investigation and management, and follow up through childhood. The investigators Dr Albert, Dr Heather and Professor Hofman may be asked to provide some aspect of clinical care from this perspective. Dr Brown, is a Paediatric Endocrine fellow who could similarly be involved in care. A/Prof Alsweiler is a neonatologist who could also be involved in the care of preterm babies who are part of this study either as participants with congenital hypothyroidism or as controls.

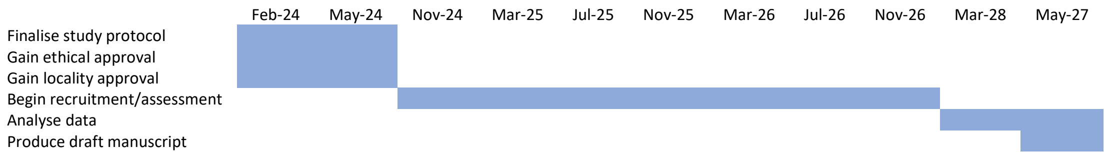
To mitigate this conflict, infant-parent pairs will be initially approached by a specialist research nurse who is not involved in clinical care of the infant. This nurse will also be the primary person gaining consent, and interacting with the participants during the study. If the infant's whanau wish to speak to a member of the investigating team, we would ensure it was a member of the team not involved in the infant's clinical care to avoid any risk of actual or perceived coercion to participate. Our research team is sufficiently large that this should always be possible. In addition, it will always be made clear that whether potential participants choose to participate in the study either as cases or controls, or discontinue participation, it will not affect the management of their endocrine or neonatal health conditions.

Participating Sites

Te Whatu Ora Te Toka Tumai Auckland and Counties Manukau – these two sites include all NICU locations in the greater Auckland region.

Timeline:

Ethics and locality approval applications will be produced and submitted in early 2024 so that approvals have been obtained in order to start recruitment in November 2024. This coincides with the updated preterm screening protocol for Newborn Metabolic Screening rolling out on 1st July 2024 so all infant participants will be screened under the same criteria. We will aim to have recruited all participants by November 2026, so that data analysis can be occur, and a draft manuscript produced by May 2027.



Research Team

Dr Ashleigh Brown is a paediatric endocrine fellow and PhD Candidate and will be the main researcher carrying out this study. It is the largest project of her PhD and she will have significant oversight and support from the experienced team of coinvestigators. This project will be a crucial part of her early development as a new clinical researcher. She is supported by an experienced team of coinvestigators and advisors who include Endocrinologists, a senior Neonatologist, experts in Newborn Screening and in Māori health. The long-established collaboration between the Newborn Metabolic Screening Programme, paediatric endocrinology and neonatology, along with the large number of preterm babies born in the Auckland region, makes Auckland the best setting to determine the cause of the rise in positive congenital hypothyroid screening tests in preterm babies.

Professor Paul Hofman is a Paediatric Endocrinologist at Starship Child Health and the Clinical Director of the Clinical Research Unit at the Liggins Institute at the University of Auckland. Dr Ben Albert is a Paediatric Endocrinologist and Senior Research Fellow at Liggins Institute and Starship Child Health. Dr Natasha Heather is a Paediatric Endocrinologist at Starship Child Health and the Clinical Lead at the Newborn Metabolic Screening Programme. Associate Professor Dr Jane Alsweiler is a Neonatologist at Starship Child Health and an associate professor within the department of paediatrics at the University of Auckland. Dr Dianne Webster is the Director of the Newborn Metabolic Screening Programme and an Honorary Professor at the Liggins Institute at University of Auckland. Dr Jade Tamatea is an endocrinologist at Te Whatu Ora Waikato and a Senior Lecturer and Māori Health Researcher at Te Kupenga Hauora Māori at the University of Auckland. Dr Barbara Cormack is a Senior Research Fellow at the Liggins Institute, University of Auckland and a Specialist Neonatal Dietitian and Clinical Lead for the Paediatric Dietitians at Starship Child Health.

Research nurses from the neonatal intensive care unit will assist with recruitment and collection of samples. To ensure this study is carried out efficiently over 2 sites a research coordinator will be employed at 0.1FTE, they will work closely with Dr Brown and Dr Ben Albert.

Research Impact

Preterm infants may currently be at risk of harm from unrecognised iodine insufficiency. There is little evidence to support current nutritional practices, which may lead to weeks of negative iodine balance for very preterm infants. If iodine deficiency were found to be a causative factor in the aetiology of delayed onset congenital hypothyroidism, this information would impact NICU nutritional practices across Australasia. It would also provide further evidence of the need to improve antenatal iodine supplementation. Preventative strategies would be anticipated to improve rates of iodine sufficiency amongst preterm infants and lead to fewer diagnoses of congenital hypothyroidism, reducing the medical burden and risk of neurodevelopmental harm in an already vulnerable patient population.

In addition, it is important to recognise the burden on families that positive newborn screening tests for congenital hypothyroidism impart. They lead to additional investigations including frequent blood tests and often treatment for years with ongoing frequent blood test monitoring and dose changes. This is a great burden to add to the parents of a child who has been born preterm. If this study can show that iodine deficiency is the cause of the frequent positive screening tests in preterm babies, then it is likely that better nutritional replacement will help to prevent positive tests. This will reduce burden for families, and also the substantial costs to the health system that follow a positive test.

References:

1. Ford G, LaFranchi SH. Screening for congenital hypothyroidism: a worldwide view of strategies. Best Pract Res Clin Endocrinol Metab. 2014 Mar;28(2):175–87.

2. Huynh T, Greaves R, Mawad N, Greed L, Wotton T, Wiley V, et al. Fifty years of newborn screening for congenital hypothyroidism: current status in Australasia and the case for harmonisation. Clin Chem Lab Med. 2022 Sep 1;60(10):1551–61.

3. National Screening Unit. Newborn Metabolic Screening Programme Annual Report 2021 [Internet]. Ministry of Health; 2023. Available from: https://www.nsu.govt.nz/system/files/page/nmsp_annual_report_-_2021_0_0.pdf

4. Woo HC, Lizarda A, Tucker R, Mitchell ML, Vohr B, Oh W, et al. Congenital hypothyroidism with a delayed thyroid-stimulating hormone elevation in very premature infants: incidence and growth and developmental outcomes. J Pediatr. 2011 Apr;158(4):538–42.

5. LaFranchi SH. Thyroid Function in Preterm/Low Birth Weight Infants: Impact on Diagnosis and Management of Thyroid Dysfunction. Front Endocrinol . 2021 Jun 15;12:666207.

6. McGrath N, Hawkes CP, Mayne P, Murphy NP. Optimal Timing of Repeat Newborn Screening for Congenital Hypothyroidism in Preterm Infants to Detect Delayed Thyroid-Stimulating Hormone Elevation. J Pediatr. 2019 Feb;205:77–82.

7. Albert BB, Cutfield WS, Webster D, Carll J, Derraik JGB, Jefferies C, et al. Etiology of increasing incidence of congenital hypothyroidism in New Zealand from 1993-2010. J Clin Endocrinol Metab. 2012 Sep;97(9):3155–60.

8. Bijarnia S, Wilcken B, Wiley VC. Newborn screening for congenital hypothyroidism in very-low-birth-weight babies: the need for a second test. J Inherit Metab Dis. 2011 Jun;34(3):827–33.

9. Kaluarachchi DC, Allen DB, Eickhoff JC, Dawe SJ, Baker MW. Increased Congenital Hypothyroidism Detection in Preterm Infants with Serial Newborn Screening. J Pediatr. 2019 Apr;207:220–5.

10. Odenwald B, Fischer A, Röschinger W, Liebl B. Long-term course of hypothyroidism detected through neonatal TSH screening in a population-based cohort of very preterm infants born at less than 32 weeks of gestation. International Journal of [Internet]. 2021; Available from: https://www.mdpi.com/2409-515X/7/4/65

11. Raymond J, LaFranchi SH. Fetal and neonatal thyroid function: review and summary of significant new findings. Curr Opin Endocrinol Diabetes Obes. 2010 Feb;17(1):1–7.

12. Ares S, Saenz-Rico B, Arnaez J, Diez-Sebastian J, Omeñaca F, Bernal J. Effects of oral iodine supplementation in very low birth weight preterm infants for the prevention of thyroid function alterations during the neonatal period: results of a randomised assessor-blinded pilot trial and neurodevelopmental outcomes at 24 months. Eur J Pediatr. 2022 Mar;181(3):959–72.

13. Thomson CD. Selenium and iodine intakes and status in New Zealand and Australia. British Journal of Nutrition. 2004;91(5):661–72.

14. Kanike N, Groh-Wargo S, Thomas M, Chien EK, Mhanna M, Kumar D, et al. Risk of Iodine Deficiency in Extremely Low Gestational Age Newborns on Parenteral Nutrition. Nutrients [Internet]. 2020 Jun 1;12(6). Available from: http://dx.doi.org/10.3390/nu12061636

15. Mathews DM, Peart JM, Sim RG, Johnson NP, O'Sullivan S, Derraik JGB, et al. The SELFI Study: Iodine Excess and Thyroid Dysfunction in Women Undergoing Oil-Soluble Contrast Hysterosalpingography. J Clin Endocrinol Metab. 2022 Nov 25;107(12):3252–60.

16. Mills JL, Buck Louis GM, Kannan K, Weck J, Wan Y, Maisog J, et al. Delayed conception in women with low-urinary iodine concentrations: a population-based prospective cohort study. Hum Reprod. 2018 Mar 1;33(3):426–33.

17. Cicalese MP, Bruzzese E, Guarino A, Spagnuolo MI. Requesting iodine supplementation in children on parenteral nutrition. Clin Nutr. 2009 Jun;28(3):256–9.

18. Domellöf M, Szitanyi P, Simchowitz V, Franz A, Mimouni F, ESPGHAN/ESPEN/ESPR/CSPEN working group on pediatric parenteral nutrition. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Iron and trace minerals. Clin Nutr. 2018 Dec;37(6 Pt B):2354–9.

19. Ibrahim M, de Escobar GM, Visser TJ, Durán S, van Toor H, Strachan J, et al. Iodine deficiency associated with parenteral nutrition in extreme preterm infants. Arch Dis Child Fetal Neonatal Ed. 2003 Jan;88(1):F56-7.

20. Dold S, Zimmermann MB, Aboussad A, Cherkaoui M, Jia Q, Jukic T, et al. Breast Milk Iodine Concentration Is a More Accurate Biomarker of Iodine Status Than Urinary Iodine Concentration in Exclusively Breastfeeding Women. J Nutr. 2017 Apr;147(4):528–37.

21. Nazeri P, Akbarzadeh M, Pearce EN, Hedayati M, Dalili H. Iodine Status of Preterm Infants Born in an Area of Iodine Sufficiency: Are They at Risk of Iodine Deficiency? Endocr Pract. 2022 Sep;28(9):835–41.