Published Title: **Using record linkage to investigate perinatal factors and neonatal thyroid-stimulating hormone.**

Record-linkage is a feasible method for investigating the relationship between perinatal factors, maternal and neonatal thyroid stimulating hormone

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Abstract

Context: Studies examining the relationship between maternal and infant thyroid parameters have shown conflicting results. Record-linkage provides an opportunity to examine the association between maternal and infant thyroid stimulating hormone (TSH) levels.

Objective: To demonstrate the feasibility of record-linkage of newborn screening, laboratory, and birth databases for research by investigating the association between maternal and newborn TSH levels.

Design: Record-linkage cohort study

Setting and Participants: The records of 2,802 women with first trimester serum TSH concentrations were linked with population-based birth data and newborn screening data (NBS) containing infant TSH levels. Association between moderately high neonatal TSH levels (>5mlU/L) and maternal and infant characteristics were evaluated. The correlation and association between maternal and infant TSH levels were assessed using Pearson's correlation coefficient and multivariable linear regression, respectively.

Results: 99.3% of maternal and birth records linked with a NBS record. Mother's country of birth, gestational age (>41 weeks) and lower birth weight were associated with neonatal TSH levels >5mlU/L. Neonatal and maternal first-trimester TSH levels were not correlated, although statistically significant (r=0.05, P=0.008). The association between neonatal TSH and maternal TSH, after adjusting for maternal age, gestational age and age at NBS testing, was also small (β=0.039, P=0.009).

Conclusions: Record-linkage is a feasible and cost-efficient way to investigate the association between maternal factors and neonatal hormone levels. First trimester maternal thyroid levels are not correlated with neonatal TSH levels. This method of outcome assessment can be used for future research examining long term outcomes for infants with different newborn screening results.

Introduction:

Record linkage is the 'bringing together of records from different sources but relating to the same individual'[1] which enables individuals' health records to be followed both cross-sectionally and longitudinally, and in the case of perinatal research allows records to be linked from a mother to her infant. Record linkage of routinely collected population health data to newborn screening and pathology data is a new approach for examining the relationship between perinatal factors and infant outcomes. Record linkage is potentially more efficient and efficacious than other study methods, such as the collection and testing of blood samples from a prospective cohort.

Maternal thyroid dysfunction is demonstrated to be associated with adverse reproductive outcomes including miscarriage, preterm delivery, and growth restriction[2-6]. During the 1st trimester, the fetus is entirely dependent on maternal thyroid hormones[7]. Fetal thyroid function begins at 12-14 weeks gestation, however maternal transfer of thyroid hormones continues until term and presents an important source of thyroid hormone to the fetus[8]. Adequate maternal thyroid hormone levels in early pregnancy are important for correct maturation of the central nervous system of the fetus[9] with untreated hypothyroidism in mothers associated with impaired neurodevelopment in infants[10, 11].

Little is known about how maternal thyroid function influences neonatal thyroid function. Recent studies examining the relationship between maternal and neonatal thyroid function have shown conflicting results[12-14]. However loss to follow up has been a major concern of these studies. Other studies have measured neonatal thyroid parameters from cord blood[15, 16] which may be effected by maternal lifestyle factors (such as alcohol intake)[17], or a long labour[18]. An alternate source of neonatal thyroid hormone measurement is newborn screening for congenital hypothyroidism. Elevated levels of thyroid stimulating hormone (TSH) identify infants who require further testing for diagnosis and treatment. Internationally, the initial TSH level in dried blood spots to trigger further testing ranges from 10mIU/L [19] to 20mIU/L [20], however there has been debate about the optimal cut-off value with some suggesting cut-offs as low as 5mIU/L[21]. Lowering the

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threshold has been shown to identify more infants with abnormalities of thyroid function, but greatly increases the number of false positive cases [22].

In a prior study, we have used record linkage to link first trimester maternal screening data to routinely collected birth data to evaluate the association between high maternal serum TSH concentrations and adverse pregnancy outcomes[6]. Extending this linkage to newborn screening data would provide an opportunity to evaluate the relationship between maternal and neonatal TSH levels. The aims of this study were to demonstrate the feasibility of record-linkage of the newborn screening database to a laboratory database and routinely-collected birth data, by investigating the association between maternal and newborn TSH levels.

Methods:

Data sources and study population

The study population was based on all infants born to women with TSH measured in early pregnancy between July and October 2006, as outlined in a previous study examining maternal TSH levels.[6] These women were identified from the Pacific Laboratory Medicine Services (PaLMs) first trimester screening database. PaLMs is a pathology screening service in NSW that receives maternal blood samples taken between 10 and 14 weeks gestation as part of first trimester screening for chromosomal anomalies. Information from the PaLMs database was then linked to the Perinatal Data Collection (PDC) and the Newborn Screening database (NBS) to obtain data on maternal and infant birth outcomes and neonatal TSH levels, respectively. The PDC is a legislated population-based surveillance system of all births in NSW of $\geq$ 20 weeks gestation or a baby $\geq$ 400 grams birth weight and includes maternal information on pregnancy, labour and delivery and infant outcomes. The NBS laboratory is a state-wide reference laboratory for newborn screening services of metabolic disorders for all babies born in NSW and ACT. In NSW, Australia's largest state, 99.9 % of parents consent for newborn screening for approximately 100,000 neonates each year[23]. A neonatal blood sample is collected via a heel-prick requested to be taken 48 to 72 hours after birth and tested for a number of

metabolic disorders, including congenital hypothyroidism. The NBS database includes the following information; maternal first and family name, infant's date of birth, date and time of sample, hospital of birth and clinician, TSH level (mIU/L whole blood), and details of subsequent testing.

Record linkage

The record linkage was performed at the NSW Centre for Health Record Linkage (CHeReL)[24]. Australia does not have unique individual identifying numbers therefore records must be linked probabilistically. CHeReL uses a range of personal identifying information to link maternal and infant records such as maternal first and family name, infant gender, infant date of birth and hospital of birth. Probabilistic linkage usually involves an iterative process based on the calculation of weighted scores which reflect the likelihood of a pair of records belonging to the same person. The false-positive linkage rate reported from CHeReL was 3/1000 (0.3%).

 Once records are linked, a unique identifier is created, and this identifier and the clinical information is provided to the researcher. This ensures that the researcher does not have access to any personal identifying information. Ethics for data linkage and this study has been granted by the NSW Population and Health Services Research ethics committee.

Analysis

Descriptive statistics for continuous measurements of neonatal TSH concentrations were calculated and dichotomised to identify infants with moderately elevated TSH, using a cut-point of >5mlU/L. Maternal and infant characteristics were compared for the infant TSH cut-points. Differences between groups were examined using contingency analysis (χ^2) and associated relative risks and 95% confidence intervals were calculated.

Association between maternal and neonatal TSH concentrations was also assessed. Given maternal TSH concentrations differ by gestational week, maternal TSH levels were standardized using multiple of medians (MoM) for the corresponding gestational week[25]. Distribution of maternal MoM and

neonatal blood TSH levels were then assessed and log-transformed to normalise each distribution. Pearson's correlation coefficient (r) was used to measure correlation, and multivariate linear regression applied to evaluate the association between the log maternal TSH MoM and log neonatal TSH measurements, adjusted for maternal age, gestational week of maternal TSH testing, gestational age of birth and infant age at NBS testing. Association between maternal and neonatal TSH levels was further examined using relevant cut-points, and contingency analysis (χ^2) to assess whether moderately elevated neonatal TSH levels (>5mlU/L) were associated with reduced (<2.5[th] percentile) or elevated ($\geq$97.5[th] percentile) maternal TSH. All analyses were conducted using SAS v9.3 and P-value <0.05 was considered statistically significant.

Results:

There were 3,090 maternal first trimester screening (PaLMS) records available for linkage (Figure 1). Ninety five per cent of these records linked to a PDC record. The NBS was then linked to this PaLMS-PDC dataset, resulting in a linkage rate of 99.3% (n=2,808) for infants born within the study dates. There was one stillbirth and one infant death on the first day of life that did not link to a NBS record. Once these infants were excluded, the unlinked records did not differ from the linked records on a range of characteristics; maternal age, maternal smoking, gestational age, birthweight, 1 and 5 minute Apgar scores. There were 5 stillbirths and one other PDC record that did link to the NBS but did not have a TSH measurement recorded, and were subsequently excluded from the analysis, leaving 2,802 linked PaLMS-PDC-NBS records available for analysis (Figure 1).

The median neonatal TSH value was 1.34mIU/L (inter-quartile range, 0.70-2.13) and 2.0% (n=56) of the infants had a moderately high level of TSH (>5mIU/L). Of the 56 infants with TSH >5mIU/L, two infants had a TSH measurement between 10mIU/L and 20mIU/L and two infants had a TSH measurement greater than 20mIU/L. Ninety eight per cent of infants had the blood sample for TSH testing taken on days 2 to 4, with the majority (63.5%) tested on day 3. Table one presents the maternal and infant characteristics stratified by TSH $\leq$5mIU/L and >5mIU/L. Moderately high TSH levels were associated with mother's country of birth (South East Asia, Southern Asia, New Zealand

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and Oceania), gestational age (>41 weeks) and lower birthweight (Table 1), however some results were imprecise due to small cell size.

Although statistically significant, no correlation was found between neonatal and maternal TSH levels (r=0.05, P=0.008, Figure 2). The univariate association between neonatal TSH and maternal TSH levels from the linear regression model was also small, but significant (β =0.039, P=0.008). This association did not change when adjusted for maternal age, gestational age and age at NBS testing. There was no significant association between either reduced (<2.5th percentile equated to <0.017 MoM, P=0.61) or elevated (≥97.5th percentile equated to ≥3.01 MoM, P=0.16) maternal TSH and moderately elevated neonatal TSH levels.

Discussion:

The results of this study have shown that it is feasible to link a state-wide newborn screening database to laboratory data and routinely collected perinatal datasets. The NBS database had a high proportion of linked records with the other databases and the significant association between elevated levels of neonatal TSH and maternal country of birth, gestational age and birthweight, consistent with previous literature [26-28], demonstrates that these linkages have high face validity. This study has also shown that maternal and neonatal are not correlated. To our knowledge, this is the largest study to examine the association between maternal TSH and neonatal TSH levels collected 2 to 5 days after birth.

The linkage of 99.3% of perinatal records to newborn screening records is a very high linkage rate. This is an increase in successful linkages of 4% compared to the linkage of mother's laboratory data to the perinatal database[29]. The addition of one more piece of personal information, hospital of birth, available on NBS data led to this increase in linkage rates. The processes of record linkage and data analysis are separated, therefore researchers only have access to de-identified data and study participants' privacy is ensured. As a consequence, the risk to personal privacy for women and infants involved in the study is also reduced by using record linkage to attain outcome data, and loss to follow up is minimised. Women participating in the study do not need to be contacted again

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minimising the risk of harm to participants, especially those that have experienced a negative outcome such as a stillbirth or neonatal loss.

We found that moderately elevated TSH levels in neonates were significantly associated with increased gestational age, lower birthweight and South East or Southern Asian maternal country of birth. Gestational age greater than 40 weeks is a reported risk factor for congenital hypothyroidism[26, 27], although data from California have shown a significantly higher prevalence of infants with congenital hypothyroidism in both the low birthweight (<2500g) and high birthweight (>4500g) categories[28]. Our data have not shown the same association amongst the large infants, however numbers are very small. The same data from California found a greater prevalence of congenital hypothyroidism amongst infants that were Chinese, Vietnamese, Asian Indian, Middle Eastern and Hispanic compared to White infants[28]. Our data showed a significant association with raised neonatal TSH levels for infants of South East Asian and Southern Asian (Indian) mothers. While infants with a mother born in the Middle East, or Central and South America had a non-significant association with raised neonatal TSH levels, the numbers were small, once again. The association between elevated TSH levels and known risk factors in our study provide additional evidence and face validity that linkage between the NBS and the PDC are correct linkages.

A number of studies assessing the relationship between maternal and neonatal thyroid function have been published recently[13, 14, 16, 30, 31], however findings were inconclusive. These studies, conducted in iodine-replete populations, experienced large loss to follow up with 17%[13] to 49%[14] of the cohorts missing neonatal thyroid measurements, which can lead to biased results. However a number of these studies presented correlation coefficients between maternal and neonatal thyroid measurements below one, signifying no correlation, results very similar to our study. A cohort study from Belgium of 5,393 pregnant women collected the cord serum TSH concentrations of 3,036 (56%) of the cohort's newborns, and found no correlation between maternal and cord TSH levels (r=0.08, P<0.001)[16]. Our study had TSH levels on a similar number of mother-infant pairs (n=2,802), and also carried out in an iodine-replete setting, however we had neonatal data on 99% of our study

population. The lack of correlation and small effect size we found between maternal and neonatal TSH (r=0.05, P=0.008), although statistically significant, has no clinical significance. Small sub-group analyses within two larger studies showed significant associations between maternal and neonatal TSH levels collected after 48 hours[12] and on day 5[30]. While a study from the UK found no correlation between maternal and cord TSH in over 600 babies (r=0.004, P=0.92), and no correlation between maternal TSH and another neonatal thyroid hormone, free thyroxine (r= -0.08. P=0.04)[31].

The strengths of this study include the large proportion of linked records with less than 1% of maternal and hospital records unable to link with a newborn screening record. Validation studies comparing routinely collected birth datasets to medical records have shown that gestational age and birthweight are accurately reported[32], while reporting of maternal country of birth in the PDC had a 96.4% agreement with medical records[33]. The main limitation of this study is the small number of infants with a clinically elevated level of TSH (>10mIU/L). However future research linking the NBS database to larger population datasets will increase the number of infants in this group, and allow for greater examination of these infants.

Routinely collected data have been used to address key issues in health. The population coverage and accessibility of administrative health data make it an attractive and inexpensive resource for research allowing description of the total burden of disease in the population, assessment of risk factors[34] and investigation of rare outcomes[35]. We have shown that linking newborn screening data to other routinely collected datasets is a feasible way to investigate the association between maternal characteristic and neonatal hormone levels or other screening results. This method of outcome assessment can be used for future research examining long term outcomes for infants with different newborn screening results.

Acknowledgements

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Figure 1: Study population via record-linkage of NSW PaLMs, PDC and NBS datasets, 2007
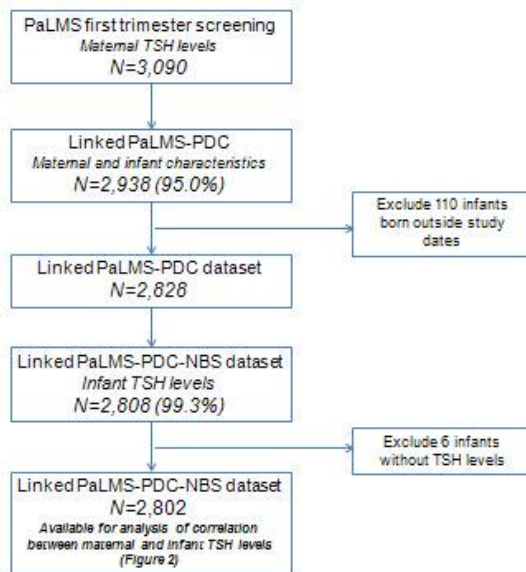
PaLMs – Pacific Laboratory Medicine Services (PaLMs) first trimester screening database, PDC – Perinatal Data collection,

NBS – Newborn screening data

Table 1: Association between maternal and infant characteristics from the Perinatal Data Collection and newborn screening TSH levels from the Newborn Screening database

	≤5 mU/l (n=2,742)	>5 mU/l (n=56)	Relative risk (95% CI)
Maternal/delivery characteristics			
Maternal age			
≤ 25 years	167 (98.8)	2 (1.2)	0.60 (0.15-2.45)
25-39 years	2454 (98.0)	49 (2.0)	referent
≥ 40 years	138 (96.5)	5 (3.5)	1.81 (0.73-4.48)
Previous pregnancy			
No	1236 (98.2)	23 (1.8)	referent
Yes	1506 (97.8)	33 (2.2)	1.18 (0.69-1.99)
Maternal smoking			
No	2589 (97.9)	56 (2.1)	referent
Yes	153 (100)	0 (0)	-
Not stated	17 (100)	0 (0)	-
Country of birth**			
Australia	1837 (98.6)	26 (1.4)	referent
New Zealand and Oceania	85 (94.4)	5 (5.6)	4.15 (1.63-10.56)
UK, Ireland, Europe, Nth America & others	330 (98.5)	5 (1.5)	1.07 (0.41-2.77)
Middle East	53 (96.4)	2 (3.6)	2.66 (0.65-10.94)
Africa	55 (98.2)	1 (1.8)	1.28 (0.18-9.30)
South East Asia (e.g. Vietnam)	142 (95.3)	7 (4.7)	3.48 (1.54-7.88)
Southern Asia (e.g. India)	85 (93.4)	6 (6.7)	4.98 (2.11-11.79)
North East Asia (e.g China)	192 (98.5)	3 (1.5)	1.10 (0.34-3.61)

Central and South America	31 (96.9)	1 (3.1)	2.28 (0.32-16.27)
Infant characteristics			
Gender			
Male	1386 (97.7)	33 (2.3)	referent
Female	1373 (98.4)	23 (1.6)	0.70 (0.41-1.19)
Plurality			
Singleton	2714 (97.9)	56 (2.0)	referent
Twin/Triplet	45 (100)	0 (0)	-
Gestational age*			
Preterm	135 (97.1)	4 (2.9)	1.56 (0.57-4.27)
Term	2586 (98.1)	49 (1.9)	referent
Postdates	38 (92.7)	3 (7.3)	4.16 (1.36-12.78)
Birthweight*			
$\leq$2500g	97 (95.1)	5 (4.9)	2.54 (1.03-6.24)
2501-4000g	2365 (98.0)	48 (2.0)	referent
>4000g	297 (99.0)	3 (1.0)	0.50 (0.16-1.59)

*χ^2 test: $p<0.05$, **χ^2 test $p<0.001$

Figure 2: Correlation between the log maternal TSH MoMs and log neonatal TSH measurements