NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM IN EARLY DISCHARGED INFANTS

Carmelita Fagela-Domingo[1], Carmencita D Padilla[2]

[1]Sections of Endocrinology and [2]Genetics, Department of Pediatrics, College of Medicine and Philippine General Hospital, University of the Philippines Manila

Abstract. A study of newborn thyroid stimulating hormone (TSH) levels was undertaken to determine whether a quantitative relationship exists between TSH values obtained between the 12th to 24th hours of life and the 48th to 72nd hours of life. The study was designed to: (a) measure TSH levels in full term newborns between the 12th – 24th hours of life, (b) measure TSH levels in the same set of newborns at 48 – 72 hours of life, (c) correlate TSH values obtained during the two time periods of specimen collection, (d) determine whether TSH results at 12 to 24 hours are predictive of TSH levels at 8 to 72 hours, and (e) determine the effects of other factors on $TSH_{48\text{-}72}$. One thousand three hundred seventy full term normal infants delivered at the Philippine General Hospital and at the Rizal Medical Center from August 1999 to March 2001 participated in the study. Eighty-three percent were from Metro Manila and the rest from the provinces. Although there was a significant association between $TSH_{12\text{-}24}$ and $TSH_{48\text{-}72}$, the magnitude of association could not account for all of the variance in the $TSH_{48\text{-}72}$ values. By itself, $TSH_{12\text{-}24}$ cannot clinically predict 48-72 hour TSH levels. Multiple regression analysis showed that sex and mode of delivery by cesarean section were significant factors affecting TSH levels at 48-72 hours.

INTRODUCTION

The thyroid stimulating hormone (TSH) is known to exhibit a physiologic surge at birth, which peaks at 30 minutes and subsides by 48 to 72 hours (Fisher and Klein, 1981; De Zegher *et al*, 1994). This is the main reason for the recommendation that blood specimens for newborn thyroid screening be collected on the 2nd to the 8th day of life (Amar, 1997). The trend towards early discharge (Therrell, 1995; Coody *et al*, 1993) is a concern since newborn screening programs recommend specimen collection prior to hospital discharge and early specimen collection can produce specimens with falsely elevated TSH values resulting from the newborn TSH surge. This study was undertaken to determine the quantitative relationship between TSH values obtained on the 12th to 24th hour of life with those obtained on the 48th to the 72nd hour in the same set of normal full term infants. A specific objective was to determine whether 12 to 24 hour levels could be predictive of 48 to 72 hour levels.

MATERIALS AND METHODS

The participants of the study consisted of 1,370 full term normal infants delivered either at the Philippine General Hospital or at the Rizal Medical Center from August 1999 to March 2001. After informed consent was obtained, blood samples were collected by heel prick onto the prescribed filter paper collection card for newborn screening at 12 to 24 hours and again at 48 to 72 hours on the enrolled infants. Thyroid stimulating hormone (TSH) was determined by fluoroimmunoassay using the AutoDelfia procedures (Wallac Oy, Turku, Finland).

DATA ANALYSIS

Data analysis was carried out using descriptive methods, Pearson correlation and regression analysis. Analysis of residuals and tests for omitted variables and for heteroscedasticity were performed.

RESULTS

Of the 1,370 study participants, 730 (53.3%) were males and 640 (46.7%) were females. Mean birth weight was 3013.46 gm (SD=351.07) and mean birth length was 48.93 cm. (SD=2.09). The majority (57.0%) were delivered by cesarean section (CS), 37.4% were by normal vaginal delivery and 5.5% were by outlet forceps extraction. Eighty-three percent (83%) of the study population came from Metro Manila while 16.2% came from the provinces.

Mean number of hours at time of specimen collection for the first sample was 17.61 hours (SD=4.29) and 65.85 hours (SD=18.63) for the second. Mean TSH results on

the first and second samples were 5.12μIU/ml (SD=2.89) and 2.60μIU/ml (SD=1.85) respectively. The correlation coefficient between TSH_{12-24} and TSH_{48-72} showed a value of 0.326 which was highly significant. However, scattergrams using raw data as well as transformed values for TSH did not show any definite pattern of correlation. Simple regression of TSH on other factors including sex, birth weight, birth length and body mass index showed that sex and birth weight were significant ($p = <0.05$) (Table 1).

Multiple regression analysis was performed to determine factors that are associated with TSH_{48-72}. Birth weight and birth length were used instead of BMI as a measure of size. Regression coefficient for sex and mode of delivery by cesarean section (MODCS) were significant ($p = < 0.05$) (Table 2).

A test for interaction between birth weight and mode of delivery showed that birth weight and CS had significant interaction while birth weight and outlet forceps extraction (OFE) did not. Separate models using transformed values for the selected predictors, such as log TSH_{12-24}, the square of TSH_{12-24} and the cube of TSH_{12-24}, plus all the other variables in the full model did not improve correlation. A test for residuals with variables in the regression model showed a pattern of variation suggesting heteroscedasticity or variance non-homogeneity. Ramsey RESET test for omitted variables and Cook-Weisberg test for heteroscedasticity using fitted values of TSH_{48-72} showed a probability > $F = 0.1800$ and probability > $chi^2 = 0.0000$ indicating no omitted variables and that the data are heteroscedastic.

Table 1. Simple regression analysis of TSH_{48-72} on other variables.

Predictor	Regression coefficient	95% Confidence intervals	Standard error	p - value
TSH_{12-24}	0.2080	0.176, 0.240	0.016	0.000
Sex	0.2270	0.031, 0.423	0.100	0.023
Birth weight	-0.0003	-0.001, 0.000	0.000	0.022
Birth length	-0.0326	-0.080, 0.014	0.024	0.173
BMI	-0.0621	-0.139, 0.015	0.039	0.113
MODCS	0.1870	-0.018, 0.393	0.105	0.074
MODOFE	0.4640	0.019, 0.909	0.227	0.041

MODCS = mode of delivery by cesarean section
MODOFE = mode of delivery by outlet forceps extraction

Table 2. Full model of multiple linear regression analysis.

Predictor	Regression coefficient	95% Confidence intervals	Standard error	p - value
TSH_{12-24}	0.2050	0.173, 0.237	0.016	0.000
Sex	0.1950	0.008, 0.382	0.095	0.041
Birth weight	-0.0002	-0.001, 0.000	0.000	0.142
Birth length	-0.0158	-0.068, 0.037	0.027	0.554
MODCS	0.2260	0.030, 0.421	0.100	0.024
MODOFE	0.3470	-0.073, 0.768	0.214	0.106
Constant	2.7820	0.560, 5.004	1.133	0.014

MODCS = mode of delivery by cesarian section
MODOFE = mode of delivery by outlet forceps extraction

The final model, which was obtained by using Ordinary Least Squares Regression (OLS), showed overall result significance although the model can explain only 10% of variation in TSH_{48-72} (Table 3).

DISCUSSION

The American Academy of Pediatrics defines early discharge and very early discharge as hospital stays of 48 hours, and 24 hours or less, respectively following an uncomplicated vaginal delivery. As early as 1995, in the Western US, stays of 12 to 24 hours or less following an uncomplicated vaginal delivery and 48 to 72 hours following an uncomplicated cesarean delivery were standard practices. Among the reasons cited for early discharge was the emergence of third party payers who required that newborn babies must be discharged in less than 24 hours (Braveman *et al*, 1995). Other reasons included money saved by cutting the duration of hospitalization, convenience of continuing maternal recovery in the comfort of home and family, and the possibility of an equally good follow-up as an outpatient.

A previous study (Toublanc, 1999) showed that in the case of early discharge, sampling for sensitive TSH assays within the first 24 hours did not increase the recall rate and that cord sampling using TSH assay was also possible. Moreover, studies of newborn screening results in New Jersey between 1993 and 1994 (Saslow *et al*, 1996) showed that no infant with CH would have been missed even in samples obtained at 12 to 24 hours as long as the infants who were screened weighed 2,500 g or more.

A cost benefit analysis of the Philippine screening procedure (Dans *et al*, 2003) suggests that the costs of screening may outweigh the benefits in hospitalized patients mainly because of an added day to the hospital stay of both the mother and the infant. Performing newborn screening within the first day of life and decreasing costs by shortening hospital confinement reduces the costs of the hospital stay associated with screening. Previous studies, however, demonstrated a greater number of false positive results especially when screening is done during the first 3 to 6 hours of life (Foley and Torresani, 1995) and this would require increased follow-up contributing to an increased cost of screening.

Although the results of our study showed that mean TSH_{48-72} was approximately half of mean TSH_{12-24}, statistical analysis of our findings does not appear to provide us with enough evidence to conclude that TSH levels at 12 to 24 hours when used alone are clinically predictive of levels at 48 to 72 hours. Testing for the contribution of other factors (BW, BL, BMI, MODCS or MODOFE) did not improve correlation results significantly. The finding of Auger *et al* (1997) on sex as a factor is not in agreement with our results. Using other methods of data analysis, including simple linear regression, gave significant regression coefficients with BW and MODOFE, and multivariate analysis by backward regression resulted in significant regression coefficients with BW and MODCS. Nonetheless, regression coefficients in the full model, which increased significantly, could not fully account for the rest of the variance in the values of TSH_{48-72}. In addition, tests for heteroscedasticity showed non-hemogeneity of our data.

One possible solution to screening problems related to early discharge is the collection of a second

Table 3. Final regression model [number of observations = 1370, F (7, 1362)= 21.32, Prob > F = 0.0000, R^2 = 0.0987, adjusted R^2 = 0.0941, Root MSE = 1.6692].

TSH_{48-72}	Coefficient	Standard error	p- value
TSH_{12-24}	0.1989699	0.0175859	0.000
Sex	0.1515302	0.0909861	0.096
BW	0.0000434	0.0002224	0.845
MODCS	1.911463	0.8429605	0.024
MODOFE	-2.038994	1.824368	0.264
BWCS	-.0005611	0.0002788	0.044
BWOFE	0.0007929	0.0006139	0.197
Cons	1.21411	0.6726668	0.071

specimen in all patients. The Northwest Regional Screening Program (NWRSP) in the US, which uses T_4 testing as the primary screen followed by supplemental TSH testing on a portion of the samples with low T_4, obtains an initial specimen in the newborn period and a routine second specimen at 4-6 weeks of life (La Franchi *et al*, 1985). Routine second testing has shown a detection rate for congenital primary hypothyroidism of 1:25,205. Infants detected by the second screen have shown higher T_4 and lower TSH values on filter paper as well as on serum specimens. Skeletal maturation has been found to be more likely normal in those detected by the second screen. These infants were predicted to have milder hypothyroidism probably due to a later age of onset or slower evolution of thyroid failure. They also found that it is cost effective to obtain a routine second specimen at a later time. Second screening was also found to be successful in detecting cases of CH in Texas (Levine and Therrell, 1985) and a review of data found that 7-10% of total hypothyroid cases in the states of Oregon, Texas, Maryland and Washington were detected on second screen, although approximately 50% of cases diagnosed on second testing had elevated TSH levels on the original specimen when retrospective testing was done on cases in Texas.

Another possible solution to the problem of early discharge is the use of age-adjusted cutoff criteria for TSH (Allen *et al*, 1990). The American Academy of Pediatrics has also suggested collecting the initial newborn screening specimen as close as possible to the time of discharge from the nursery and the collection of a second specimen before two weeks of age if the initial specimen was taken before 24 hours (American Academy of Pediatrics, 1996).

Additional solutions may include 1) performing screening consistently only after 24th hour of life, 2) repeating the procedure only when the first TSH value is abnormally elevated, and 3) organizing teams to collect appropriately timed specimens.

CONCLUSIONS

Based on our findings, we conclude that there is a statistically significant quantitative association between TSH_{12-24} and TSH_{48-72}. However, the magnitude of this association cannot fully account for the variance in TSH_{48-72} and by itself, TSH_{12-24} cannot be used to clinically predict TSH levels at 48-72 hours. Among the other factors that may affect TSH_{48-72}, sex and mode of delivery by cesarean section were found to be statistically significant.

RECOMMENDATIONS

To solve problems/obstacles to newborn screening that may stem from early discharge of infants delivered in hospitals, one or more of the following may be considered depending on the needs of the particular NBS program:

1. Collect a second sample for TSH testing within 2 weeks of initial testing – while this is a good solution, it would be too expensive and impractical for our purposes because it relies too heavily on meticulous follow-up.
2. Use age-adjusted cutoff criteria for TSH.
3. Perform screening consistently only after the 24th hour of life.
4. Do repeat screening only when TSH value is elevated in the first specimen.
5. Organize home visits by nurses to gather the appropriately timed specimens.

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