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Epidemiology

Effect of maternal and neonatal factors on neonatal thyroid stimulating hormone: Results from a population-based prospective cohort study in China

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ABSTRACT

Objective: Neonatal TSH screening is effective in detecting congenital hypothyroidism and estimating iodine status in a given population, but various factors influence TSH levels. The aim of this study was to evaluate the effect of maternal and neonatal factors on neonatal TSH levels.

Design and setting: Data were obtained from an ongoing prospective cohort study. A total of 988 pregnant women and their newborn infants participated in the study from April 2015 to May 2017 at Tianjin Maternal and Child Health Center and Tanggu Maternity Hospital in Tianjin, China. Maternal demographic information, including age, height, and parity, was recorded by questionnaire. Fasting blood and urinary samples were collected from all pregnant women. After parturition, information on gestation duration, mode of delivery, neonatal sex, neonatal TSH, neonatal birth weight, and neonatal birth height were recorded.

Results: Maternal age, maternal BMI, gestation duration, parity, and neonatal birth weight and height were significantly correlated with neonatal TSH ($p < 0.05$). Quantile regression revealed that maternal age, TSH, FT_4, and gestation duration were positively correlated with neonatal TSH level. A logistic regression model identified maternal BMI, TSH, and birth height as risk factors for having neonatal TSH > 5 mIU/L ($p < 0.05$).

Conclusion: Neonatal TSH levels are dynamic and may be affected by several maternal and neonatal factors including maternal age, TSH, FT_4, and birth weight and height. Identification of these confounders is useful for assessing the status of neonatal thyroid development.

Strengths and limitations of this study: (1) Iodine deficiency disorder has generally been eliminated, so the median urinary iodine concentration of pregnancy is higher than 150 μg/L even in mildly or moderately iodine deficient areas. (2) Unlike many other studies, which did not consider the complexity of factors or examined only one or two variables, this study used a multivariate model to analyze the data. (3) This study examined numerous high-risk factors in pregnant women and considered the biological interrelation between them. Future studies should consider these confounding factors for neonatal TSH levels and establish a proper neonatal TSH range for monitoring the iodine status of a population or diagnosing congenital hypothyroidism.

1. Introduction

Iodine is an essential component of the hormones produced by the thyroid gland. Inadequate iodine intake may lead to iodine deficiency disorders, including endemic goiter and endemic cretinism [1]. During pregnancy, maternal iodide and iodothyronines are transferred to the fetus through the placenta [2]. Iodine deficiency during pregnancy results in neurological dysfunction and reduced IQ in the infant [3]. Serum thyroid stimulating hormone (TSH) is a sensitive indicator of iodine status in the period following birth [4]. Delange discovered that neonatal TSH was a sensitive predictive biomarker of impaired mental development and iodine status at the population level and could be used to evaluate the effect of iodine supplementation programs [5]. Burns et al. showed that a neonatal bloodspot TSH screening program could be used to diagnose a population's iodine deficiency and indicating its iodine status [6]. Since the 1970s, many countries have implemented TSH screening to detect congenital hypothyroidism [7–9]. According to World Health Organization (WHO) recommendations,

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a < 3% prevalence of > 5 mIU/L TSH concentration in newborn dried bloodspot samples indicates that a population has adequate iodine intake [10]. However, the sensitivity of 5 mIU/L as a cutoff point has been debated. In some studies, the prevalence of > 5 mIU/L TSH in a population was not high, yet other iodine status indicators showed that the population was slightly iodine deficient [11,12]. In addition, lowering the TSH threshold would allow greater sensitivity in identifying infants with thyroid dysfunctions [13], which may be explained by covariates influencing neonatal TSH concentrations. Studies have demonstrated that several factors may affect neonatal TSH concentration [14–16], such as mode of delivery, pregnancy duration, and maternal thyroid status. Without investigating the confounding factors, establishing the full effect of iodine deficiency on neonatal TSH concentration can be difficult.

The aim of this study was to evaluate the effect of maternal and neonatal factors on neonatal TSH concentrations measured through heel-prick bloodspot.

2. Subjects and methods

2.1. Subjects and design

The participants in this study were recruited from an ongoing prospective cohort study in Tianjin, China. A total of 2002 healthy pregnant women (527 at Tianjin Maternal and Child Health Center and 1475 at Tanggu Maternity Hospital) with no history of thyroid disease or any other chronic diseases were enrolled in the program from April 2015 to May 2017. Pregnant women who were taking iodine supplements during pregnancy or who had been living in Tianjin for less than 5 years were excluded. The participants were classified according to gestational week at their time of enrollment: first trimester, with gestational weeks (GW) < 13 weeks; second trimester (GW 13–27 weeks); and third trimester (GW ≥ 28 weeks). From May 2015 until May 2017, a total of 988 women successfully delivered their babies, and these 988 mother–newborn pairs were included in this study.

2.2. Data collection

Demographic and health information for the pregnant women were recorded on a questionnaire, including age, height, weight, gestational week, and parity. Height and weight were measured using standardized procedures. Body mass index (BMI) was calculated as weight (kg) divided by height squared (cm^2). After the participants had given birth, postnatal details were recorded, including mode of delivery, gestation duration, neonatal TSH concentration, and neonatal weight and height at birth.

2.3. Laboratory analysis

2.3.1. Blood sample measurements

2.3.1.1. Maternal thyroid function indicators. Morning fasting blood samples were obtained from each pregnant woman upon joining the cohort. All blood samples were frozen at −80 °C until analysis in the clinical laboratory of Tianjin Medical University General Hospital. Concentrations of TSH, free thyroxine (FT_4), and free triiodothyronine (FT_3) were analyzed through direct chemiluminescent reaction using an automated chemiluminescence immunoassay (ADVIA Centaur, Siemens Healthcare Diagnostics).

2.3.1.2. Neonatal TSH concentrations. Newborn TSH screening was a normal test offered to all babies born in Tianjin. Heel-prick bloodspot samples were collected on filter papers by skilled nurses at 48–72 h after birth. All the samples were sent to the Tianjin Maternal and Child Health Center for analysis. Dried bloodspot TSH was measured using dissociation-enhanced fluoroimmunoassay (DELFIA) on an auto DELFIA analyzer. The sensitivity of the TSH assay was 0.005 mIU/L.

According to WHO recommendations, < 3% prevalence of > 5 mIU/L TSH concentration in newborn blood-screening programs indicates adequate iodine intake in the population [10]. Thus, neonatal TSH concentrations in this study were categorized by the cutoff values TSH ≤ 5 mIU/L and TSH > 5 mIU/L in logistic regression analysis.

2.3.1.3. Urinary iodine content. Morning fasting spot urinary samples were obtained from each participant upon joining the cohort. All samples were frozen at −80 °C until analysis at the Tianjin Institute of Endocrinology of Tianjin Medical University. Urinary iodine concentration (UIC) was detected using ammonium persulfate digestion with spectrophotometric detection of the Sandell–Kolthoff reaction, and the coefficient of variation was 0.2%–3.2%. Based on WHO criteria [17], maternal urinary iodine concentration was classified as follows: < 150 μg/L, insufficient iodine intake; 150–249 μg/L, adequate iodine intake; 250–499 μg/L, more than adequate iodine intake; and ≥500 μg/L, excessive iodine intake.

2.4. Statistical analysis

Normally distributed data are expressed as means ($\bar{x}$ ± standard deviation) and nonnormally distributed data as medians (25th percentile, 75th percentile). A Kolmogorov–Smirnov test was performed to assess sample normality, and a Mann–Whitney rank test was performed for pairwise comparisons. Differences between groups were examined using contingency analysis (χ^2). Because not all factors were normally distributed, quantile regression was used to describe the correlation coefficient between neonatal TSH concentration and other factors with different neonatal TSH percentiles; the factors were gestation duration, mode of delivery, birth length, birth weight, neonatal sex, maternal UIC, age, BMI, TSH, FT_3, FT_4, thyroglobulin (Tg), TPOAb positive, and TgAb positive. Because the hormone levels of pregnant women fluctuate during the gestation period, the trimester when the mother joined the study cohort was considered a confounding factor. An associated odds ratio and 95% confidence interval were calculated using logistic regression, employing maternal age, maternal BMI, gestation duration, mode of delivery, parity, maternal TSH, maternal UIC, neonatal sex, and neonatal weight and height as dependent variables (with neonatal TSH > 5 mIU/L as the dichotomous outcome). All statistical analyses were performed using SAS for Windows (version 9.4, SAS Inc., Cary, NC) and Graph Prism (version 6.0c, Graph Pad Software, Inc.). Significance was set at two-tailed $\alpha < 0.05$.

3. Results

3.1. Characteristics of the study population

The characteristics of the 988 mothers are summarized in Table 1, along with thyroid function and UIC by pregnancy trimester at the time of enrollment. The mean age of the mothers in this study was 28 ± 3.8 years, and there were no significant age differences among the three trimester groups ($p = 0.158$). No differences in other maternal characteristics were found among the three trimester groups. Fasting blood samples were taken from 964 (98%) participants and spot urinary samples from 937 (95%) participants at their initial visit. The median maternal TSH was 1.57 mIU/L and was higher in the pregnant women in their third trimester. The median UIC was 158 μg/L among all the participants, which indicates adequate iodine intake but is only slightly above the lower limit for that level. Maternal UIC was much higher in the pregnant women recruited in their second than in their third trimester ($p < 0.05$). However, 130 (13%) infants had a TSH level of higher than 5 mIU/L. Of all the participants, 812 (82%) had parity of less than three, whereas for 176 (18%) parity was three or more; 563 (57%) gave birth by normal vaginal delivery, and 452 (43%) by caesarean section.

Boys represented 513 (52%) of the newborns, and 475 (48%) were