Hypothyroxinemia and Risk for Transient Tachypnea of Newborn

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Transient tachypnea of newborn is associated with hypothyroxinemia in animals via decreased stimulation of beta-adrenergic receptors and Na-K-ATPase activity. In 26 549 term neonates, serum total thyroxine <14 ug/dL, male sex, and elective cesarean delivery were significantly associated with greater risk for transient tachypnea of newborn. *(J Pediatr 2016;179:266-8).*

Transient tachypnea of newborn (TTN) is caused by retained fetal lung fluid and sometimes requires respiratory support. TTN occurs significantly more often after cesarean delivery. Reduced fetal triidothyronine (T3) level in umbilical cord blood and congenital hypothyroidism[1,2] reportedly decrease lung fluid clearance by reduction of both Na-K-ATPase activity[3,4] and decreased beta-adrenergic receptor stimulation in the lungs and lymphatics.[5,6] This decreases lymph flow out of the lung into the thoracic duct and, thus, slows fetal lung fluid clearance, leading to TTN. We assessed whether serum total thyroxine (TT4) levels after birth are associated with TTN in an Israeli sample of term births.

Methods

This study was performed by retrospective analysis of data from the nursery between 2010 and 2015 at Rambam Health Care Campus in Haifa. The institutional Helsinki Committee approved this study and waived obtaining written informed consents. We included 26 549 term (>37 weeks' gestation) neonates, but excluded 2637 preterm (<37 weeks' gestation) neonates, 2 cases of neonatal hyperthyroidism (TT4 > 40 ug/dL), and 5 neonates with congenital hypothyroidism. Blood for neonatal metabolic screening was collected at 40-48 hours of age, and TT4 was measured. Measuring free T4 concentration on the dry Guthrie paper is not feasible. In cases of TT4 <10 ug/dL, thyroid-stimulating hormone (TSH) was measured. TTN was defined as tachypnea after birth of 80 or more breaths per minute with mild-moderate respiratory distress with no risk factors for early-onset sepsis, often requiring oxygen supplementation, and resolving within 48 hours.

Logistic regression was used for bivariate and step-wise multivariable analysis of variables potentially associated with TTN. The area under curve of the receiver operating characteristic (AUCROC) was used as a measure of model discrimination.

Youden statistics[7] was used to determine the optimal cutoff for TT4 plasma levels of our infants. The workflow of cutoff finder includes the following steps: (1) upload data for analysis (such as T4 levels in our study); (2) select variables; (3) select method for cutoff determination; (4) select plots; and (5) determine cutoff and generate plots.

AUCROC	Area under curve of the receiver operating characteristic
TSH	Thyroid-stimulating hormone
TTN	Transient tachypnea of newborn
TT4	Total thyroxine
T3	Triiodothyronine

Results

A total of 355 of 26 549 (1.34%) neonates had TTN, of whom 26 (7.3%) were transferred to the neonatal intensive care unit because of worsening respiratory distress. These 26 neonates were mostly males (n = 21), born at 37-39 weeks' gestation (n = 22), born by cesarean delivery (n = 16), and with TT4 <14.4 ug/dL (n = 21). The severity of TTN was significantly associated with TT4 <14.4 ug/dL ($P = .004$, OR = 4.99; 95% CI 1.7-14.8).

In our results, the TT4 cut-off value was 14.4 ug/dL. Univariate analysis showed 9 variables significantly associated with increased risk for TTN: TT4 <14.4 ug/dL, male sex, 37-39 weeks gestational age, birth weight >4000 g, vacuum extraction delivery, nonemergent cesarean delivery, and both gestational- and insulin-dependent maternal diabetes mellitus. Conversely, emergency cesarean delivery and epidural anesthesia were significantly associated with a lower risk for TTN.

Multivariable logistic regression analysis showed a significant and independent association between the risk for TTN and male sex ($P < .001$, OR = 1.59, 95% CI 1.2-2.1), elective cesarean delivery ($P < .001$, OR = 2.27, 95% CI 1.7-3.04), and serum TT4 < 14.4 ug/dL ($P < .001$, OR = 1.98, 95% CI 1.49-2.64). In order to more precisely determine the relative importance of TT4 ≤ 14.4 ug/dL, we reanalyzed a model without TT4 and AUCROC emerged as 0.637, 95% CI 0.60-0.67, $P < .001$ (**Figure 1**). To more precisely determine the relative importance of TT4 < 14.4 ug/dL, we reanalyzed the model without TT4, and the AUCROC was 0.637, 95% CI 0.60-0.67,

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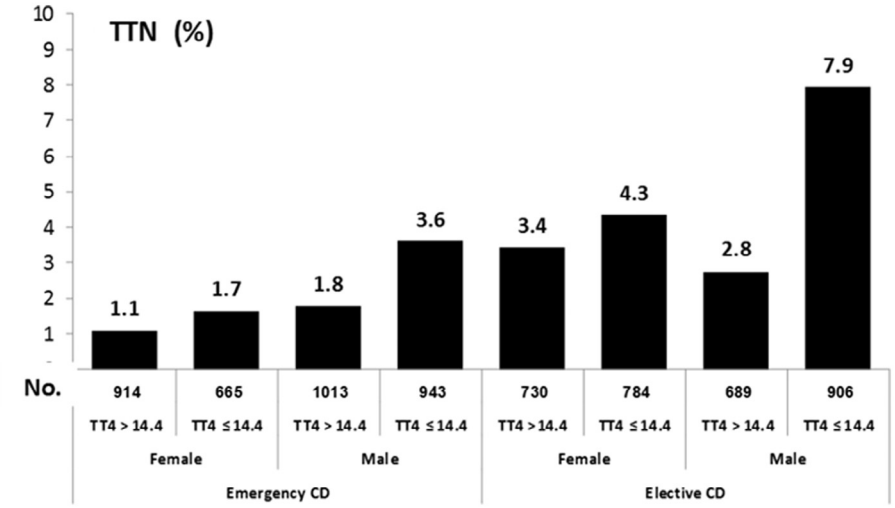

Figure 1. Male sex, elective cesarean delivery, and serum TT4 <14.4 ug/dL significantly and independently increased the risk for TTN by 1.59-, 2.27-, and 1.98-folds; respectively. Being a male infant, born by elective cesarean delivery, and with a TT4 <14.4 ug/dL inferred the highest risk for TTN.

$P < .001$. Inclusion of TT4 in the model led to a slight increase in the model prediction ability.

Discussion

We show that male sex, elective cesarean delivery, and TT4 <14.4 ug/dL significantly increase the risk for TTN. The first 2 conditions are well-established risk factors for TTN.[8-10] Thyroid hormone has been reported to accelerate lung fluid clearance in animal trials[5,6] and in one case report,[2] in part by increasing Na-K-ATPase activity[3] and augmenting stimulation of beta-adrenergic receptors in lung epithelial cells.[5] (**Figure 2**; available at www.jpeds.com).

Acquisition of T3-sensitive Na-K-ATPase stimulatory capability is thyroid hormone-dependent and is gained toward day 19 in rodents, corresponding to 36 weeks human gestation.[4] Hypothyroidism inhibits perinatal fetal lung fluid resorption[2]; conversely, T3 supplementation stimulates adult rodent alveolar epithelial cell Na-K-ATPase.[4] Newborn rodents infused with T3 after thyroidectomy had an 83% increase in lung beta-adrenergic receptors vs untreated thyroidectomized pups, suggesting that beta-adrenergic receptors are highly responsive to thyroid hormones. Lung fluid clearance is augmented by T3. In rats with hyperoxia induced lung injury, intraperitoneal injections of T3 increased Na-K-ATPase hydrolytic activity and increased lung fluid clearance by 52.7% compared with saline controls.[11] Moreover, in adult rats, 48 hours of pretreatment with dexamethasone or T3 increased epithelial fluid transport: dexamethasone, T3, or both increased alveolar fluid clearance by 80%, 65%, and 132%, respectively.[5]

Atasay et al[1] compared umbilical cord blood concentrations of epinephrine, cortisol, adrenocorticotropic hormone, free T4, free T3, and TSH between infants born by cesarean (>34 weeks gestation) with TTN or without respiratory distress. Umbilical cord blood adrenocorticotropic hormone, cortisol, and free T3 were significantly lower and epinephrine was higher in infants that developed TTN, indicating a possible functional effect of these hormones in regulating fetal lung fluid.

TSH surges during the first 5 days,[12] resulting in higher T4 and 3- to 4-fold higher T3 concentrations than in the fetus. Thus, the newborn infant is transformed from a state of chemical T3 deficiency to a state of chemical T3 thyrotoxicosis. The mean umbilical cord blood TT4 and free T4 concentrations increase from umbilical cord blood values of 11.9 ug/dL and 2.9 ng/100 mL to peak values of 16.2 ug/dL and 7 ng/100 mL by 24-48 hours of age, respectively.[13] The mean TT4 was lower in our study (14.7 ug/dL) compared with Erenberg et al[13] of 16.2 ug/dL, but this could be due to our sampling age of 40-48 hours compared with 24-48 hours.

The limitation of this study is the therapeutic utility of the information, as the blood spot T4 is taken after TTN has resolved. We plan to measure TT4 and TSH levels during the first 48 hours to identify the typical thyroid-hormonal profile for neonates with and without TTN. This could lead to possible treatment of moderate-severe TTN with a dose of thyroid hormone.

We conclude that male sex, birth by elective cesarean delivery, and TT4 <14.4 ug/dL significantly increased the risk for TTN. Future study should evaluate whether correction of relative hypothyroidism benefits severe cases of TTN with low thyroid hormone levels. ■

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