CLINICAL STUDY

Neonatal hyperthyrotropinemia is associated with low birth weight: a twin study

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Abstract

Objective: Contradictory reports ascribe neonatal hyperthyrotropinemia (HT) to prematurity or small weight for gestational age. We aimed to evaluate the association between neonatal HT and birth weight (BW), recovery rate of the disorder, and possible association with perinatal stress.

Design: Based on a neonatal screening database, a retrospective twin study was designed where within-pair differences in thyroid function were evaluated while controlling for differences in gestational age and thyroid-affecting environmental confounders.

Methods: Two thousand five hundred and ninety-five twin pairs that were screened both for TSH and thyroxine (T₄) over 3 years were included. TSH and T₄ levels were evaluated along with BW, birth order, gender, and 17-hydroxyprogesterone (17OHP) that was considered as a surrogate marker for stress.

Results: Of all the twin pairs, 7.2% had neonatal HT. Among 156 pairs, HT was more prevalent in the smaller twins (64%; $P < 0.001$), especially in the discordant pairs (76%; $P = 0.001$). Seventy-five percent of the twins demonstrated a recovery within the first few weeks of life. 17OHP levels were similarly distributed between twins with and without HT. In a cohort of 1534 twin pairs with normal thyroid function, mean TSH levels were significantly higher in the smaller than in the larger twin in the whole group (4.1 ± 3.2 vs 3.8 ± 2.9 mIU/l; $P < 0.001$) and especially among discordant twins (4.7 ± 3.4 vs 3.8 ± 3.0 mIU/l; $P < 0.001$).

Conclusions: Elevated TSH levels are associated with low BW, both in infants with HT and in normal neonates. A rapid recovery rate is expected in most cases.

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Introduction

Neonatal hyperthyrotropinemia (HT), defined by elevated TSH and normal thyroxine (T₄), is a mild form of thyroid disorder with questionable long-term clinical implications. In a multicenter retrospective study, we observed a high prevalence of prematurity (21%), small size for gestational age (SGA) (7%), or both (14%) among neonates identified with HT (1). This observation corroborates a previous report by Kohler *et al.* (2) who also found a high prevalence of prematurity in a cohort of newborns with transient congenital hypothyroidism (CH) (38%) and transient congenital HT (18%). Radetti *et al.* (3) have reported a long-lasting effect of intrauterine growth retardation on thyroid function in a group of children that displayed significantly higher levels of TSH with normal levels of thyroid hormones. Yet, in a following study, the same group has reported that a history of prematurity rather than small birth weight (BW) is associated with HT (4). These studies reflect the complexity in recognizing the

main factor that contributes to the development of neonatal HT: BW, gestational age, or both.

As both SGA and premature newborns share in common low BW, we hypothesized that low BW is associated with HT, irrespective of the gestational age. Yet, identifying the most influential characteristic that affects HT is challenging as many neonates embody both prematurity and low BW for gestational age. Furthermore, several environmental factors unrelated to gestational age or BW can cause neonatal HT. These factors include iodine deficiency (5) or iatrogenic iodine overload (6) and transplacental passage of thyroid-blocking antibodies and antithyroid drugs from the mother to the fetus (7, 8).

In order to overcome these methodological obstacles, we designed a twin study, aiming to compare the prevalence of HT between weight-differed twins. This study design enabled us to control for confounding factors that may affect the results such as differences in gestational age and environmental and maternal factors, which are equally shared by both twins. In addition, we

also aimed to assess a possible association between HT and prenatal stress using screening levels of 17-hydroxyprogesterone (17OHP) that was considered as a surrogate marker for intrauterine stress (9).

Materials and methods

Subjects

This study is based on the Israeli national newborn screening program database. During the study period, newborn screening for CH was routinely practised by measuring total T_4 (TT_4), with a subsequent measurement of TSH at low levels of TT_4 (10). However, samples of neonates that were admitted to the neonatal intensive care unit (NICU) were initially tested for TSH, followed by TT_4 measurement at high levels of TSH (≥ 15 mIU/l). The blood samples for neonatal thyroid screening were taken at 48–72 h of age. A second, confirmatory measurement of TT_4 was routinely performed for the NICU infants at 2–4 weeks of age or on the day of discharge from the hospital. In our study, we included only newborns that were initially checked for TSH.

Data on twin pairs that were born between 1/1/2008 and 31/12/2010 and stayed at the NICU during the first screening were obtained from the national center for newborn screening. The clinical and endocrine data that were considered prerequisites for patient inclusion were BW, gestational age, gender, order of birth, sample collected within 48–72 h from birth, initial TSH, and TT_4 when TSH levels were ≥ 15 mIU/l. The exclusion criteria were confirmed primary CH and suspected CH. Suspected CH was determined as mildly elevated TSH associated with TT_4 below the normal range in both the initial and the confirmatory measurement. Subnormal TT_4 levels were defined as levels in the lowest 10th percentile for the same day's samples.

Out of 2609 twin pairs that were born during the 3-year period, 14 pairs were excluded for unequivocal or suspected primary CH. Two thousand five hundred and ninety-five twin pairs fulfilled the inclusion criteria (five of them were triplets). One hundred and eighty-seven pairs (7.2%) had at least one twin with HT (TSH ≥ 15 mIU/l) on the initial measurement and normal TT_4 on subsequent measurement. In 31 pairs, both twins had HT. In the five triplets, only the largest and the smallest twins were included. The population selection and groups' assignment are depicted in Fig. 1. At the 3-year period of the study, the prevalence rates of neonatal HT in the NICU population of preterm (birth before 37 weeks of gestation) and term singleton newborns were 3.94 and 6.3% respectively. Both TT_4 and TSH (in the screening and the subsequent, confirmatory samples) were assayed in the neonatal screening laboratories by AutoDelfia time-resolved fluoroimmunoassay (Perkin Elmer Life Sciences, Wallac OY, Turku, Finland). The study protocol was approved by the Ethics Committee of Kaplan Medical Center.

Figure 1 Population selection and groups' assignment based on TSH levels and within-pairs differences in birth weight. CH, congenital hypothyroidism; HT, hyperthyrotropinemia; BW, birth weight.

Study design

As the main objective of this research was the effect of BW on HT, 31 pairs with HT in both twins were excluded, leaving 156 twin pairs in the study. Among the excluded twin pairs, 80% were born at gestational age of 35 weeks or later compared with 67% of the study cohort. We compared the mean BW and the distribution of gender, birth order and BW order (i.e. smaller vs larger twin) between the HT twins and their normal birth sibs, who served as controls. All comparisons were performed for the whole group and separately for discordant pairs and for pairs with similar BW (Table 1).

Discordant twins were defined as twins with BW discordance of more than 20% calculated from the weight of the larger twin, whereas similar BW twins had BW difference of $< 20\%$ (11). Prematurity was defined as birth before 37 weeks of gestation and SGA as BW of 2 s.d. below the mean according to the standards for Israeli newborns (12). A distinction between transient and persistent HT was based on the last available measurement of TSH, where TSH levels ≤ 10 mIU/l marked a recovery.

In the second part of the study, we evaluated the effect of BW on thyroid hormones in a population of twin pairs with normal thyroid function. Therefore, we compared TSH levels between smaller vs larger twin in a cohort of twin pairs who were born between 1/1/2008 and 31/10/2009 ($n=1534$).

For evaluating the intensity of stress among the twins, we used 17OHP as a surrogate marker for stress. It has been reported that postnatal 17OHP levels may be considered as a measure for severity of intrauterine stress (9). Since January 2008, the national neonatal screening program includes 17OHP measurement, a marker for congenital adrenal hyperplasia.

Figure 2 Neonatal screening TSH levels in similar birth weight twin pairs ($n=1247$) and discordant twin pairs ($n=287$) with normal thyroid function. Data are displayed as box-plots with median, upper and lower quartiles, minimal and maximal non-extreme values (error bars) and extreme values (stars).

Statistical analysis

For comparison of continuous variables (TSH, 17OHP, and BW) between twins with HT and their normal counterparts, we used paired *t*-test with Wilcoxon signed ranks test applied for nonparametric data. A comparison of paired observations (gender, order of birth, and weight order) between HT and control twins was performed by one-sample χ^2 test (for birth and weight order) and two-tailed McNemar test (for gender). Similar statistical analysis was performed for comparing the same variables between the smaller and the larger twin in a cohort of 1534 twin pairs with normal thyroid function, except for comparison of birth order that was performed by Sign test. Comparison between many groups was performed by one-way ANOVA and Kruskal–Wallis test was applied for nonparametric data.

Data are presented as mean $\pm$ s.d. A *P* value of <0.05 was considered significant. Statistical analysis was performed by SigmaPlot/SigmaStat software and SPSS version 18.

Results

Twins with HT

This group had 156 pairs where one twin had HT comprising 45 male pairs, 45 female pairs, and 66 pairs with opposite genders. Altogether, the study population

included 156 males and 156 females. A distinction between monozygotic and dizygotic twin pairs was not available based on the national screening database.

One hundred and forty-five out of 156 twin pairs (93%) were born prematurely, among them 52 pairs at 36 weeks (36%), 41 at 35 weeks (28%), 25 at 34 weeks (17%), and 27 pairs at 33 weeks of gestation or earlier (19%). Only three neonates were born SGA. The mean BW was 2083 ± 467 g (median 2120 g; range 742 to 3376 g). Forty-one twin pairs (26%) were discordant.

Gender (male vs female) and birth order (first vs second) were equally distributed between twins with HT and control twins, in the whole group and in the subgroups of discordant pairs and similar BW pairs, except for birth order in discordant twin pairs (Table 1). HT was significantly more common in the smaller twin in the whole group, among discordant pairs and to a lesser extent among similar BW pairs. Similarly, mean BW was significantly lower in neonates with HT than in controls, in the whole group, in discordant pairs and to a lesser extent in the similar BW pairs (Table 1). Notably, mean TSH levels in the HT twins stratified by their gestational age were similar: 17.2 ± 1.9 , 19.6 ± 4.2 , 19.2 ± 4.9 , 20.0 ± 6.0 , and 21.0 ± 12.3 mIU/l for those who were born at term, at 36, 35, 34, and 33 weeks of gestation or earlier respectively (*P* value not significant by ANOVA).

Additional TSH measurements (following the initial screening) were available in 140 out of 156 twins with HT. One hundred and five of these twins (75%) have shown a recovery (i.e. TSH ≤ 10 mIU/l at the last test) at a mean age of 12.3 ± 8.3 days (range 6–61 days). However, 35 twins maintained elevated TSH levels (20.9 ± 13.4 ; range 10.2–66.9 mIU/l) in the last measurement taken at a mean age of 11.4 ± 4.8 days (range 7–29 days). Seven of the neonates who remained with HT (20%) were discordant twins, in line with their proportion in the whole cohort (26%).

In 25 twin pairs, TT₄ levels in correspondence with TSH were available both in the HT twin (according to the screening protocol) and in the normal twin. Mean TT₄ levels were mildly lower in the HT than in the normal twins: 10.3 ± 3.5 vs 11.5 ± 3.8 μ g/dl respectively ($P=0.098$). The mean 17OHP levels were similar for twins with HT and their normal counterparts both in the whole group and in the subgroups of discordant pairs and similar BW pairs (Table 1).

Twins with normal TSH levels

In 1534 twin pairs with normal thyroid function, mean TSH levels were significantly higher in the smaller than in the larger twin in the whole group, among discordant pairs and to a lesser extent among similar BW pairs (Table 2 and Fig. 2). Gender and mean 17OHP levels were similarly distributed between the smaller and the larger twins in the whole group and in both subgroups. Yet, in the discordant subgroup, the larger twins tended to be born first in the birth order ($P<0.001$, Table 2).

Table 1 The distribution of gender, birth order, weight order (smaller vs larger of the twins), birth weight (BW), and 17-hydroxyprogesterone (17OHP) between neonates with hyperthyrotropinemia (HT) and their normal counterparts (control). Data are presented as mean $\pm$ s.d. Data were analyzed for the whole group and separately for discordant twin pairs and pairs with similar BW twins (percentage and ranges are in brackets).

	All twins (n=156)			Discordant twins (n=41)			Similar BW twins (n=115)		
	HT	Control	P value	HT	Control	P value	HT	Control	P value
TSH (mIU/l)	19.3 $\pm$ 4.6 (15.1–36.3)	7.5 $\pm$ 3.8 (0.5–14.9)		20.3 $\pm$ 5.3 (15.4–35.7)	6.5 $\pm$ 3.9 (0.8–14.2)		19.0 $\pm$ 4.3 (15.1–36.3)	7.8 $\pm$ 3.7 (0.5–14.9)	
Gender									
Male	74 (47%)	82 (53%)	NS	15 (37%)	22 (54%)	NS	59 (51%)	60 (52%)	NS
Female	82 (53%)	74 (47%)		26 (63%)	19 (46%)		56 (49%)	55 (48%)	
Birth order									
1st	72 (46%)	84 (54%)	NS	13 (32%)	28 (68%)	0.019	59 (51%)	56 (49%)	NS
2nd ^a	84 (54%)	72 (46%)		28 (68%)	13 (32%)		56 (49%)	59 (51%)	
Weight order ^b									
Smaller	99 (64%)	55 (36%)	<0.001	31 (76%)	10 (24%)	0.001	68 (60%)	45 (40%)	0.030
Larger	55 (36%)	99 (64%)		10 (24%)	31 (76%)		45 (40%)	68 (60%)	
BW (g)	2007 $\pm$ 434 (742–3320)	2141 $\pm$ 455 (770–3376)	<0.001	1748 $\pm$ 439 (742–2655)	2109 $\pm$ 528 (770–2960)	<0.001	2101 $\pm$ 394 (930–3320)	2152 $\pm$ 428 (916–3376)	0.018
17OHP (nmol/l)	16.2 $\pm$ 11.4 (2.2–63.9)	15.5 $\pm$ 11.7 (2.2–56.0)	NS	18.3 $\pm$ 12.3 (4.0–44.7)	16.5 $\pm$ 13.0 (4.0–56.0)	NS	15.5 $\pm$ 11.1 (2.2–63.9)	15.1 $\pm$ 11.3 (2.2–52.3)	NS

NS, not significant.

^aIncluding two neonates (belonged to triplets) that were born third in birth order.

^bTwo twin pairs with identical BW were excluded from that analysis.

Discussion

In a large cohort of 156 twin pairs, we found that neonatal HT is more common in the smaller twin, particularly in a subgroup of discordant twin pairs where the within-pair difference in BW exceeds 20%. An association between BW and TSH was also observed in the large cohort of twin pairs with normal thyroid function, where mean TSH levels were significantly higher in the smaller than the larger twins. Similar to the HT group, these differences were more prominent in the discordant twin pairs. Apparently, HT is more prevalent in the smaller twin in pairs with high difference in BW rather than in pairs with similar BW, an observation that further supports the association between TSH and BW. Most neonates with HT (93%) were born prematurely, mainly between 34 and 36 weeks of gestation. Kohler *et al.* (2) have also found a high prevalence of prematurity in a cohort of children born with transient CH or HT. Based on our study, we suggest, however, that HT is mainly associated with low BW rather than premature birth, as all twin pairs shared a similar gestational age. A somewhat intriguing observation is that HT was more common in the NICU population of full-term singletons with apparently higher BW compared with the smaller BW population of preterm singletons. While some of the preterm newborns were admitted to the NICU due to low BW only, apparently all full-term newborns were sick on admission and so were probably affected by euthyroid sick syndrome or exposed to various treatments (i.e. dopamine or glucocorticoids) with well-known effects on the hypothalamic–pituitary–thyroid axis. This observation further emphasizes the importance of controlling for confounding factors that may affect the results and the benefit of twin study design.

The clinical significance of neonatal HT is in debate. Several small-size studies have shown normal growth and school achievements in children with neonatal HT (2, 13, 14, 15). In three of the studies, however, cognitive development was assessed qualitatively, based on caregivers, reports (2, 14, 15), whereas only one study reported normal psychomotor development based on validated tests (13). Using standard psychological tests in a large cohort of 178 children, Freire *et al.* (16) recently found that higher cord-blood TSH levels (mostly near the upper limits of the normal range) were related to lower intelligence and impairment of higher psychological processes at 4 years of age. In line with our study, TSH concentrations were not affected by gestational age but were slightly higher in infants with lower BW (16).

Do elevated TSH levels that we observed among the smaller twins similarly affect their cognitive development later in life? A recent study among 71 monozygotic twin pairs (29 of them were born prematurely) found a progressive verbal IQ score advantage for the larger twins, which was directly proportional to

Table 2 The distribution of TSH, gender, birth order, birth weight (BW), and 17-hydroxyprogesterone (17OHP) between the smaller and the larger twins in a cohort of 1534 twin pairs with normal thyroid function tests. Data are presented as mean $\pm$ s.d. Data were analyzed for the whole group and separately for discordant twin pairs and pairs with similar BW twins (percentage are in brackets).

	All twins (n=1534)			Discordant twins (n=287)			Similar BW twins (n=1247)		
	Smaller	Larger	P value	Smaller	Larger	P value	Smaller	Larger	P value
TSH (mIU/l)	4.1 $\pm$ 3.2	3.8 $\pm$ 2.9	<0.001	4.7 $\pm$ 3.4	3.8 $\pm$ 3.0	<0.001	4.0 $\pm$ 3.1	3.8 $\pm$ 2.9	0.016
Gender									
Male	775 (52%)	729 (48%)	NS	152 (53%)	134 (47%)	NS	623 (51%)	595 (49%)	NS
Female	759 (49%)	805 (51%)		135 (47%)	153 (53%)		624 (49%)	652 (51%)	
Birth order ^a									
1st	717 (48%)	768 (52%)	NS	102 (37%)	173 (63%)	<0.001	615 (51%)	595 (49%)	NS
2nd	768 (52%)	717 (48%)		173 (63%)	102 (37%)		595 (49%)	615 (51%)	
BW (g)	1836 $\pm$ 465	2094 $\pm$ 481	<0.001	1524 $\pm$ 412	2144 $\pm$ 518	<0.001	1908 $\pm$ 446	2083 $\pm$ 484	<0.001
17OHP (nmol/l)	18.1 $\pm$ 17.8	19.5 $\pm$ 33.3	NS	18.2 $\pm$ 16.0	20.7 $\pm$ 58.6	NS	18.1 $\pm$ 18.2	19.2 $\pm$ 24.2	NS

NS, not significant.

^aData on birth order was available only for 1485 twin pairs.

the difference in BW between the twins (17). Similarly, in two previous large twin studies, the twins with the lowest BW had a lower IQ than their larger cotwins (18, 19). A similar positive association between BW and cognition and educational attainment was reported in two large cohorts comprising the general population with normal BW from the UK and the USA (20, 21). Thyroid hormones were not evaluated in these studies, however, and the differences in IQ were attributed to the effect of suboptimal intrauterine nutrition on certain brain areas in the smaller twins (17). By combining our results with the current knowledge on the association between BW and IQ, it is possible that mild perinatal thyroid dysfunction in the smaller twins may contribute to their inferior intelligence score later in life. Previous studies have attributed lower mental development outcome in preterm infants to low serum triiodothyronine (T₃) levels (22), which were negatively correlated with gestational age and further reduced in various disease conditions (low-T₃ syndrome) (23). Low T₃ levels in preterm infants derive both from immaturity of the hypothalamic–pituitary–thyroid axis and immaturity of type 1 deiodinase enzyme, leading to reduced T₄ to T₃ conversion (23, 24). Other studies have shown that low T₄ levels in premature neonatal populations (transient hypothyroxinemia of prematurity) had a negative effect on neurological and mental development at 2 and 5 years of age (25, 26) and school performance at 9 years of age (26). Unlike our cohort with HT, however, all these thyroid dysfunction states were characterized by low-normal TSH levels. We hypothesized that elevated TSH levels in the smaller twins are mediated by *in utero* stress in the twins with growth retardation. While several animal studies support this hypothesis (27, 28), the data in humans are scanty and controversial, although a small stimulatory activity on TSH secretion was suggested for endogenous adrenergic pathways (29). Alternatively, higher TSH levels in the smaller twins may reflect a rebound increase in serum TSH during a recovery from

stress-associated non-thyroidal illness (30). In our study, however, 17OHP levels that were previously suggested as a measure for severity of intrauterine stress (9) were not elevated in the smaller twins compared with their larger counterparts. It should be emphasized that in the study by Ersch *et al.* (9), 17OHP levels were obtained within the first few hours of life, unlike our study where these levels were measured between 48 and 72 h of life. Therefore, we cannot conclusively exclude an association between prenatal stress and HT, although 17OHP levels do not support such an association.

Alternatively, elevated TSH levels may reflect a compensatory response to mild suppression of the thyroid gland in the smaller twins. In 25 twin pairs with HT and sufficient data on TT₄ levels, we found that TT₄ levels tended to be lower in the HT neonates compared with their normal counterparts. This observation supports a mild resistance to TSH in the thyroid gland rather than unresponsiveness to the negative feedback of thyroid hormones in the pituitary gland, which would have yielded elevated TT₄ levels. Neonatal HT was found to be associated with low basal metabolic rate, with a recovery of the metabolic rate following normalization of TSH levels (31). Other studies demonstrated low metabolic rate in association with caloric restriction in infants with malnutrition and severe protein deprivation (32, 33). Regarding our study, HT in the smaller twins may be similarly associated with lower basal energy expenditure, which is beneficial in a condition of (intrauterine) limited accessibility to nutrients. Unfortunately, without available levels of T₃, the most active thyroid metabolite, we cannot support this hypothesis.

Our observation that the smaller twin in the discordant pairs was usually the second-born is in line with the current knowledge (34). Similar association between HT and birth order probably reflects the high prevalence of HT among the smaller twins in the discordant pairs.

The main strength of our work is the twin study design, where various environmental variables and differences in gestational age are controlled. In addition, using a national screening database, we had the opportunity to include a large number of twin pairs with normal thyroid tests and, to our knowledge, the largest series of neonates with HT. The main limitation of the study is the population selection of exclusively NICU infants, purposely selected as TSH levels are routinely screened only in these infants. In this population, we should also be concerned about possible effects of prematurity-associated diseases on the thyroid hormone status. Yet, results of previous studies examining that issue are reassuring. In a large group of intensively treated premature infants (23–34 weeks gestational age), TSH levels over the first month of life were unchanged at various postnatal ages and in all levels of intensive care, with concomitant reduction only in T_4 and T_3 in infants requiring maximal intensive care (35). Other studies have similarly found neutral effect of illness on TSH levels during the postnatal period in premature infants with respiratory distress syndrome (36) and full-term infants with various adverse clinical conditions (37, 38). In summary, our study was performed in a population with special characteristics; therefore, the ability to extrapolate the results to a population of healthy singletons is limited.

In conclusion, elevated TSH levels are associated with low BW, both in infants with HT and in those with normal thyroid function. The distribution of TSH levels over the entire study population may indicate that HT is merely an extreme presentation of a BW-associated trend in TSH levels. The hypothesis that elevated TSH levels reflect an adaptation mechanism for energy conservation in calories-restricted newborns better fits our current knowledge. A prospective study is required to substantiate this hypothesis.

Declaration of interest

A Yehieli is an employee of Gamidor Diagnostics, which is the local distributor of Perkin Elmer. Perkin Elmer's kits were used in the neonatal screening process. The other authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

A Zung initiated the study, researched the data, and wrote the manuscript. A Yehieli researched the data, contributed to the statistical analysis, and critically reviewed the manuscript. S Almashanu arranged the database, contributed to the study design, and critically reviewed the manuscript. All authors have seen and approved the final version.

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