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MATERNAL-FETAL MEDICINE

Maternal hypothyroidism and future pediatric neurological morbidity of the offspring

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Abstract

Background Maternal hypothyroidism in pregnancy has been associated with neurocognitive impairment in exposed children, ranging from psychomotor-developmental delay to lower IQ scores.

Objective To investigate the long-term neurological morbidity of children to hypothyroid mothers during pregnancy.

Study design A population-based cohort study was performed including all deliveries occurring in a period of 20 years at a tertiary medical center. We excluded multiple pregnancies, fetuses with congenital malformations, perinatal mortality cases and women lacking prenatal care from the study. Neurological-related hospitalizations of children (up to 18 years) were evaluated using neurological morbidities that were predefined by ICD-9 codes. Kaplan–Meier survival curve was used to compare cumulative hospitalization rate in exposed and unexposed children. A Cox regression model was used to control for confounders.

Results During the study period, 217,910 deliveries met the inclusion criteria. Of them, 1.1% ($n=2403$) were in mothers with known hypothyroidism during pregnancy. The Kaplan–Meier survival curve demonstrated a significantly higher cumulative incidence of neurological-related hospitalizations in the hypothyroidism group (log rank $p=0.007$). Total hospitalization rate per person years was significantly higher in the maternal hypothyroidism group (5.5 vs. 3.1, HR = 1.37, 95% CI 1.10–1.73, $p=0.007$). The Cox regression model controlled for various possible confounders including maternal age, maternal obesity, birth weight, preterm birth, maternal diabetes, hypertensive disorders, induction of labor and mode of delivery, found maternal hypothyroidism to be independently associated with pediatric neurological morbidity in these children (adjusted HR = 1.33, 95% CI 1.05–1.68, $p=0.01$).

Conclusion Maternal hypothyroidism in pregnancy is independently associated with long-term pediatric neurological morbidity of the offspring.

Keywords Follow-up · Hypothyroidism · Long term · Neurological disease · Pediatric hospitalization · Pregnancy

Introduction

Hypothyroidism is a relatively common condition during pregnancy, with potential adverse effects on mother and child [1, 2]. Maternal hypothyroidism is defined as the presence of an elevated thyroid-stimulating hormone (TSH) during pregnancy and is divided into overt hypothyroidism (OH) and subclinical hypothyroidism (SCH), depending upon the severity of the biochemical abnormality. Prevalence of OH and SCH in pregnancy are reported to be 0.3–0.5% and 2–2.5%, respectively [3].

Risks of hypothyroidism in pregnancy are generally divided into two categories: pregnancy outcome and the offspring neurocognitive development.

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Women with hypothyroidism are at increased risk for an array of pregnancy complications, including preeclampsia, placental abruption, premature rupture of membranes (PROM), preterm delivery and even perinatal mortality [4–6].

Regarding offspring neurocognitive development, studies with hypothyroid mothers during pregnancy reported impaired offspring neurocognitive development ranging from lower scores on psychomotor developmental tests [7, 8] to lower IQ levels [9] and behavioral problems [10] compared to offspring to euthyroid mothers.

Thyroid hormones (TH) are crucial for the healthy development of fetal and neonatal central nervous system and continue to play an important role in the regulation of neuropsychological function in children and adults [11]. Brain development begins early in gestation before the onset of fetal TH synthesis and rely entirely on maternally synthesized hormones [11]. Hence, deficit of maternal TH early in pregnancy may adversely affect fetal brain development [12].

In this study, we sought to evaluate the long-term neurological impact of maternal hypothyroidism in pregnancy, while focusing on neuropsychological morbidities involving hospitalization of the offspring.

Material and methods

This was a population-based retrospective cohort study. We included all singleton deliveries occurring between 1991 and 2014 at a single tertiary medical center. Soroka University Medical Center (SUMC) is the sole tertiary medical center in the Negev (southern Israel) and the largest birth center in the country. Thus, the study is based on non-selective population data. The institutional review board (SUMC IRB Committee) approved of the study that has been performed in accordance with ethical standards.

The primary exposure was maternal hypothyroidism in pregnancy. This diagnosis was made by the primary care physician during the patients' prenatal visits, and consequently coded in hospital records upon admission to the delivery room. Admission to SUMC delivery room involves full assessment performed by an experienced obstetrician, which in addition to full medical history intake also examines each patient's medical records and codes maternal diagnoses accordingly. Thus, the hypothyroid diagnoses were based on maternal report as well as medical records from the hospital and/or ambulatory settings. We excluded multiple pregnancies, perinatal mortality cases (intrauterine fetal death, intra-partum death, and post-partum death), and fetuses with congenital malformations or chromosomal abnormalities. Women with no prenatal care were also excluded from the cohort.

The primary outcome evaluated was defined as neurological morbidity of the offspring involving hospitalization in SUMC. Hospitalizations of the offspring up to the age of 18 years involving any neurological morbidity were evaluated using a pre-defined set of ICD-9 codes detailed in Supplementary Table 5. The morbidities were collected during any encounter with the hospital, meaning that even if the child was hospitalized due to gastroenteritis, and had a comorbid neurological disorder, it would have been calculated as an event. Additional outcomes assessed included adverse perinatal outcomes, such as preterm delivery (< 37 weeks' gestation), low birth weight (LBW < 2500 g), cesarean delivery (CD) rates and low (< 7) Apgar scores.

Follow-up was terminated if any of the following occurred: first hospitalization with any of the pre-defined neurological morbidities, hospitalization resulting in death unrelated to neurological morbidity, end of the study period, or when the child reached 18 years of age. Since the cumulative follow-up time differed between the study groups, the rate of neurological-related hospitalization per 1000 person years was compared between the groups, and a hazard ratio was calculated.

Data were collected from two databases that were cross-linked and merged: the computerized pediatric hospitalization database of SUMC ("Demog-ICD9″), and the computerized perinatal database of the Obstetrics and Gynecology department. The Demog-ICD9 database includes demographic information and ICD-9 codes for all medical diagnoses made during hospitalizations in the SUMC pediatric departments. The perinatal database consists of information recorded immediately following delivery by an obstetrician. Experienced medical secretaries routinely review the information prior to entering it into the database to insure its maximal completeness and accuracy. Coding is performed after assessing medical prenatal care records as well as routine hospital documents.

Statistical analysis

Statistical analysis was performed using the SPSS package 23rd ed. (IBM/SPSS, Chicago, IL). Categorical data are shown in counts and rates and the differences were assessed by chi square for general associations. Student *t* test was used for comparison of continuous variables with normal distribution. Kaplan–Meier survival curves were used to compare cumulative hospitalization incidences over time among the study groups. The differences between the curves were assessed using the log-rank test. Only the first admission involving any neurological-related condition for a given individual was included in all analyses.

A Cox regression model was constructed to establish an independent association between maternal diagnosis of hypothyroidism in pregnancy and the future incidence of

neurological-related hospitalizations of the offspring while adjusting for confounders as well as clinically significant variables. These included maternal age, maternal obesity, maternal hypertensive disorders of pregnancy (chronic hypertension, gestational or preeclampsia with or without severe features), maternal diabetes (pre-gestational and gestational), preterm delivery (< 37 weeks' gestation), induction of labor, mode of delivery, and birth weight. Deliveries of euthyroid mothers were considered as reference. All analyses were two sided, and a p value of ≤0.05 was considered statistically significant.

Results

During the study period, 217,910 deliveries that met the inclusion criteria occurred at SUMC. Of them 2,403 (1.1%) deliveries were in mothers with hypothyroidism.

Selective maternal characteristics are summarized in Table 1. Mothers with hypothyroidism were older and more likely to have undergone fertility treatments. Obesity, diabetes (pre-gestational or gestational) and hypertension (pre-gestational, gestational or preeclampsia) were more prevalent in women with hypothyroidism. Likewise, rates of labor induction were significantly higher in the exposed group.

Table 2 summarizes perinatal outcomes for both groups. Mean birth weight was comparable between groups. Although gestational age at birth was lower in the hypothyroidism group, rates of preterm delivery (< 37 weeks' gestation) did not significantly differ. Higher rates of LBW and CD were noted in the hypothyroidism group, while low Apgar score (< 7) rates (at 1 and 5 min) were comparable between groups.

Table 3 presents the long-term neurological hospitalization rates of the offspring in both groups. Rates of most neurological morbidities evaluated were comparable between the groups, with the exclusion of movement disorders (including epilepsy) which were significantly more common in the maternal hypothyroidism group.

Table 1 Maternal characteristics of mothers with and without hypothyroidism in pregnancy

Maternal characteristics	Maternal hypothyroidism (n = 2403)	No maternal hypothyroidism (n = 215,507)	p value
Maternal age (years)	30.8 ± 5.2	28.2 ± 5.7	< 0.01
Parity			
Primipara	658 (27.4%)	53,370 (24.8%)	< 0.01
Multipara	1743 (72.6%)	162,106 (75.2%)	
Maternal obesity[a] (n)	43 (1.8%)	2303 (1.1%)	< 0.01
Fertility treatments[b] (n)	139 (5.8%)	3847 (1.8%)	< 0.01
Diabetes mellitus[c] (n)	233 (9.7%)	11,664 (5.4%)	< 0.01
Hypertensive disease[d] (n)	173 (7.2%)	11,299 (5.2%)	< 0.01
Induction of labor (n)	703 (29.3%)	59,277 (27.5%)	0.05

[a]Defined as body mass index (BMI) ≥ 30 kg/m^2

[b]Including any assisted reproductive techniques

[c]Including pre-gestational and gestational diabetes

[d]Including pre-gestational, gestational hypertension, and pre-eclampsia

Table 2 Pregnancy outcomes for mothers with and without hypothyroidism in pregnancy

Pregnancy outcome	Maternal hypothyroidism (n = 2403)	No maternal hypothyroidism (n = 215,507)	p value
Mean birth weight (g)	3212.0 ± 494	3221.4 ± 492	0.35
Gestational age at birth (weeks)	38.8 ± 1.7	39.1 ± 1.7	< 0.01
Cesarean delivery (n)	609 (25.3%)	30,166 (14.0%)	< 0.01
Preterm delivery[a] (n)	172 (7.2%)	13,773 (6.4%)	0.12
Low Apgar[b] at 1 min (n)	97 (4.0%)	7330 (3.4%)	0.08
Low Apgar[b] at 5 min (n)	10 (0.4%)	662 (0.3%)	0.33
Low birth weight[c] (n)	173 (7.2%)	13,324 (6.2%)	0.04

[a]Preterm < 37 weeks of gestational age

[b]Low APGAR < 7

[c]Low birth weight (LBW) < 2500 g

Table 3 Long-term neurological morbidity in children of mothers with and without hypothyroidism

Neurological morbidity	Maternal hypothyroidism ($n=2403$) n (rate per 1000 person years)	No maternal hypothyroidism ($n=215{,}507$) n (rate per 1000 person years)	HR (95% CI)	p value[a]
Autism disorders	1 (0.07)	27 (0.01)	5.22 (0.70–38.56)	0.10
Eating disorders	4 (0.30)	414 (0.19)	1.20 (0.45–3.22)	0.71
Sleep disorders	0 (0)	45 (0.02)		0.69
Movement disorders	54 (4.07)	4062 (1.85)	1.53 (1.17–2.01)	0.002
Cerebral palsy	1 (0.07)	179 (0.08)	0.88 (0.13–6.31)	0.90
Psychiatric emotional disorders	4 (0.30)	1091 (0.50)	0.45 (0.17–1.22)	0.12
Attention-deficit and hyperactivity disorder	1 (0.07)	136 (0.06)	2.25 (0.31–16.16)	0.42
Developmental disorders	2 (0.15)	207 (0.09)	1.14 (0.28–4.58)	0.86
Degenerative or demyelization disorders	1 (0.07)	170 (0.07)	0.75 (0.10–5.38)	0.78
Headache disorders	0 (0)	53 (0.02)		0.83
Myopathies	1 (0.07)	120 (0.05)	1.30 (0.18–9.35)	0.79
Other	6 (0.45)	833 (0.38)	2.20 (0.98–4.93)	0.06
Total hospitalization	73 (5.50)	6871 (3.13)	1.37 (1.10–1.73)	0.007

[a]Calculated using the Cox model adjusted for follow-up time

Total neurological hospitalization rate (per person years) was significantly higher in the exposed group of children.

In the Kaplan–Meier survival curve (presented in Fig. 1), children born to mothers with hypothyroidism exhibited a significantly higher cumulative incidence of neurological-related hospitalizations as compared with unexposed children (log rank $p<0.001$).

The Cox regression model presented in Table 4 confirmed the independent association between maternal hypothyroidism and the long-term risk for neurological-related hospitalizations in their offspring (up to the age of 18 years) with an adjusted hazard ratio of 1.33 (95% CI 1.05–1.68, $p=0.01$). The model adjusted for maternal age, maternal obesity, maternal hypertensive disorders, maternal diabetes, preterm delivery, induction of labor, mode of delivery, and birth weight.

Discussion

Our findings suggest that children of mothers with known hypothyroidism during pregnancy are at an increased and independent risk for neurological-related hospitalizations during their infancy, childhood and early adult life (until the age of 18 years). These results are in line with previous reports emphasizing the potentially harmful impact of maternal thyroid dysfunction on offspring neurodevelopment.

Since the 1990s, observational studies reported an association between maternal endocrine disorders [13], and specifically hypothyroidism in pregnancy and impaired cognitive development in offspring, ranging from psychomotor-developmental delay [7] to lower IQ scores [9]. Our study adds to existing data by highlighting the increased risk for neurological morbidities associated with hospitalizations during childhood. Specifically, we found movement disorders to be more prevalent among the exposed group. Movement disorders include not only epilepsy and seizure-related disorders, but also involuntary movements, spasm or dystonia, ataxia and gait abnormalities (Supplementary Table 5). This finding is consistent with earlier observations suggesting an increased risk for seizures in children of mothers with thyroid dysfunction [14]. Importantly, these disorders (and mainly epilepsy) have also been reported to be associated with cognitive impairment in children [15–17].

Other than movement disorders, rates of other morbidities involving hospitalizations were comparable between the study groups. In contrast, earlier studies on neurological outcomes of maternal hypothyroidism in pregnancy demonstrated higher rates of autism and attention deficit hyperactivity disorders (ADHD) [18–20]. Roman et al. found that severe maternal hypothyroxinemia (low T4) in early gestation was associated with a significant increase in the risk of parent-reported autistic symptoms in the offspring by 6 years of age [18].

Since autism and ADHD are usually diagnosed and treated in an ambulatory setting, while seizure disorders are usually hospitalized for preliminary investigation, we can speculate that the nature of the neurological disorder and that of our study explains the findings.

Maternal characteristics differed between the study groups. Women diagnosed with hypothyroidism were older, more obese, suffered from higher rates of diabetes (pre- or

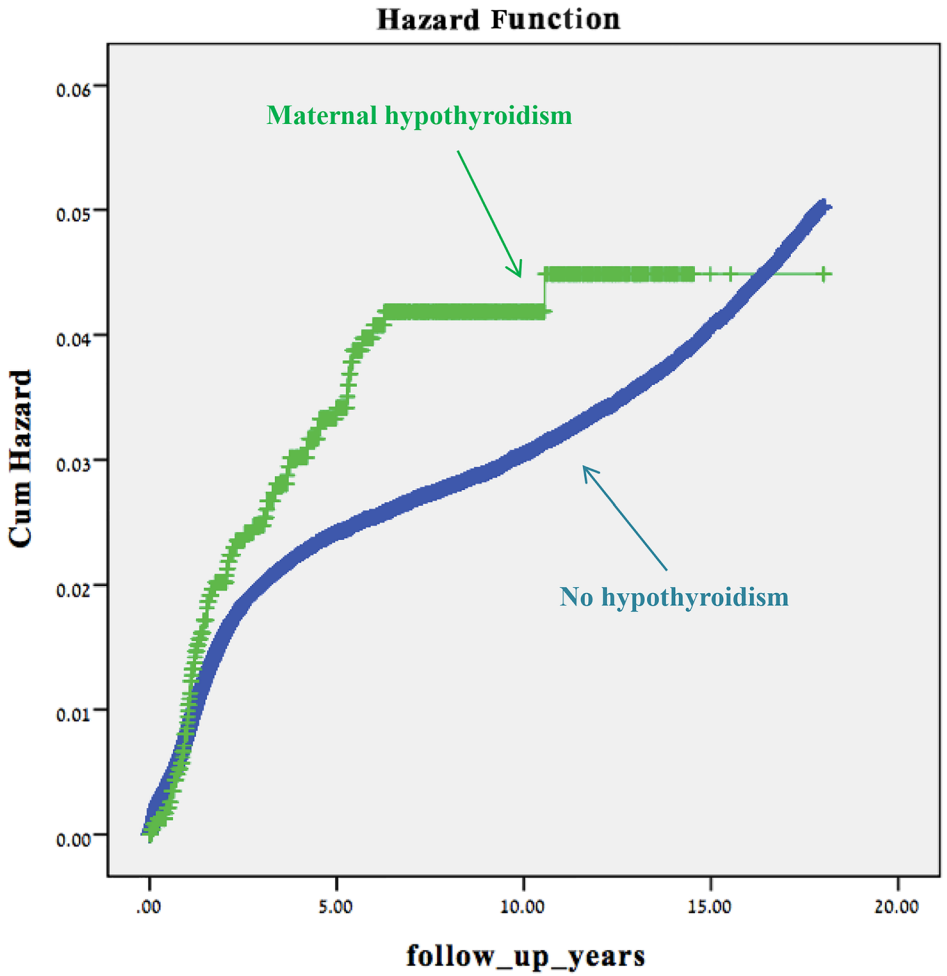

Fig. 1 Kaplan–Meier survival curve demonstrating the cumulative incidence of neurological hospitalizations in children of mothers with and without hypothyroidism (log rank *p* value = 0.007)

Table 4 Cox regression analysis of the association between maternal hypothyroidism and neurological-related hospitalization of the offspring

	Hazard ratio	95% CI	*p* value
Maternal hypothyroidism	1.33	1.05–1.68	0.01
Maternal obesity	0.97	0.78–1.20	0.78
Preterm delivery (< 37 weeks)	1.27	1.16–1.39	< 0.01
Induction of labor	1.18	1.12–1.25	< 0.01
Cesarean delivery	1.23	1.15–1.32	< 0.01

Also controlled for maternal age, birth weight, pre-gestational and gestational diabetes and hypertensive disorders of pregnancy (pre-gestational, gestational hypertension and pre-eclampsia)

gestational) and hypertension (pre-, gestational, or preeclampsia), and were more likely to have undergone labor induction. As these parameters may potentially have an impact on offspring neurocognitive outcome, we were careful in adjusting for them in our regression model. Similarly, cesarean delivery and low birth weight were more prevalent in the maternal hypothyroid group, and thus accounted for in the regression model, as was follow-up time. Since prematurity has a definite impact on neurocognitive outcome, and although rates of prematurity were comparable between the groups, we adjusted for this as well. Yet, an independent link between maternal hypothyroidism and neurological morbidity of the offspring remained significant.

Treatment for maternal hypothyroidism is also a matter of debate. Levothyroxine has been studied in both OH and SCH. To date, it is uncertain whether thyroid hormone replacement reduces the risk for adverse pregnancy outcomes or neurocognitive impairment in children. Some studies showed reduced risk for pregnancy complications [21, 22], while others found no significant difference in rates of adverse outcomes between groups of treated and untreated women [23, 24]. The later study by Casey et al. [24] also evaluated neurodevelopmental (IQ scores) and behavioral outcomes in 5-year-old children and found no significant differences between groups whether treated or not. This was in accordance with an earlier trial by Lazarus et al. [25] demonstrating no difference in neurocognitive outcomes (IQ scores).

Current guidelines from the American thyroid association (ATA), the endocrine society, and the European

thyroid association (ETA) differ in their recommendations regarding treatment for OH and SCH [26–28]. In Israel, most endocrinologists and obstetricians recommend treatment for hypothyroidism in pregnancy; however, we can only speculate that the majority of our study population was treated, as our database contains no information regarding maternal treatment or thyroid hormone levels. Thus, the main limitation of our study is the inability to extract data on maternal treatment or its adequacy, possible side effects of the treatment, and TSH or thyroid peroxidase (TPO) antibody levels during pregnancy.

Another limitation involves the retrospective design of the study which can thus offer only an association between the exposure and outcome rather than causation. Also, we have no data regarding environmental factors that might have influence on the child's neurological morbidity.

Importantly, we focused only on hospitalized children. The neurological morbidities evaluated in this study do not necessarily require hospitalization and most neurological morbidities assessed are dealt with in an ambulatory setting and, therefore, not accounted for. We assume the true prevalence of all neurological morbidities assessed to be higher in both groups.

The main strength of the study lies within its large population-based cohort that is assumed to be non-biased since SUMC is the only hospital serving the entire population of southern Israel (the Negev). Unless patients immigrate to different areas in Israel, they would probably be hospitalized, if required, in our hospital.

Another strength of the study is our ability to combine databases from the obstetrical department and the entire hospitals records. As the majority of our patients are born and later, if necessary, hospitalized in the same institution, we have a unique opportunity to match obstetrical and pediatric data.

Taking into account the nature and limitations of our study, we identified an independent association between maternal hypothyroidism and neurological morbidity of the offspring and believe that screening early in pregnancy for maternal thyroid dysfunction may prove important in identifying patients at risk.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

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