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Maternal Thyroid Hormone Imbalance and Risk of Autism Spectrum Disorder

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Abstract

Context: Maternal thyroid hormones are essential for fetal neurodevelopment. Gestational thyroid imbalance has been associated with atypical neurodevelopment, including increased risk of autism spectrum disorder (ASD).

Objective: To examine the association between maternal thyroid dysfunction and ASD risk in offspring.

Design: Retrospective cohort study with follow-up through January 2021.

Setting: Single tertiary hospital in southern Israel (Soroka University Medical Center); linked to Clalit Health Services electronic records.

Patients or Other Participants: A total of 51 296 singleton births between January 2011 and December 2017.

Intervention(s): None.

Main Outcome Measure(s): Offspring ASD diagnosis (*Diagnostic and Statistical Manual of Mental Disorders*, fifth edition).

Results: A total of 4409 (8.6%) of the mothers showed abnormal thyroid function. ASD cumulative incidence was similar in the offspring of women with normal and abnormal thyroid function (log-rank $P = .27$). While chronic hypothyroidism only (reflecting likely adequate treatment) was not significantly associated with ASD [adjusted hazard ratio (aHR), 0.47; 95% confidence interval (CI), 0.15-1.48], combined chronic and gestational hypothyroidism was associated with higher ASD risk (aHR, 2.61; 95% CI, 1.44-4.74). Trimester-specific analysis indicated a dose-response effect, in which the longer the period of hypothyroidism, the higher the ASD risk, namely, for 1, 2, or 3 trimesters of exposure: aHR, 1.69 (95% CI, 1.19-2.83); aHR, 2.39 (95% CI, 1.24-5.78); aHR, 3.25 (95% CI, 1.07-7.21), respectively.

Conclusion: The findings suggest adequately treated chronic hypothyroidism is not associated with ASD in offspring, whereas persistent hormonal imbalance across trimesters conveys elevated risk. These findings underscore the importance of routine thyroid function screening and timely treatment throughout pregnancy.

Key Words: thyroid dysfunction, gestation, hypothyroidism, autism spectrum disorder

Abbreviations: aHR, adjusted hazard ratio; ASD, autism spectrum disorder; CHS, Clalit Health Services; CI, confidence interval; FT4, free T4; HR, hazard ratio; ICD-9, International Classification of Diseases, Ninth Revision; SUMC, Soroka University Medical Center.

Autism spectrum disorder (ASD) encompasses a range of neurodevelopmental conditions marked by the pervasive manifestation of deficits in social communication, along with restricted and repetitive patterns of behavior (1). ASD is characterized by a heterogeneity of phenotypic presentations, with its etiology lying in a range of genetic predispositions (2-8) in combination with environmental influences operating during sensitive developmental windows (9-15).

The prenatal period is a critical window for fetal brain development, and perturbations in neurodevelopmental pathways during this time have been linked to increased ASD risk. Multiple maternal exposures have been associated with elevated offspring risk (9, 15-20). Among these, maternal thyroid dysfunction during pregnancy has received particular attention. Thyroid hormones are essential for fetal neurogenesis and maturation, with the fetus relying largely on maternal derived hormone via placental transfer, particularly in the first trimester (21). Consequently, disruptions in maternal thyroid hormone levels during pregnancy have been associated with adverse developmental outcomes in offspring (22-24), including lower IQ scores and delays in expressive language and nonverbal cognition (25, 26). Additional studies report associations between gestational overt and subclinical hypothyroidism and poorer child cognitive function (27, 28), and a

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meta-analysis linked lower concentrations of early-pregnancy free T4 (FT4) with various neurodevelopmental outcomes (29). Furthermore, it has been suggested that autoimmune processes, which often play a role in both overt and subclinical hypothyroid etiology, may affect fetal neurodevelopment independent of maternal thyroid dysfunction (30). However, findings remain inconsistent, with a recent study on maternal thyroid autoimmunity and child IQ reporting conflicting results across 2 different birth cohorts, suggesting modification by iodine status or other contextual factors (31).

Growing evidence suggests that maternal thyroid dysfunction during pregnancy may alter fetal neurodevelopment, potentially increasing the likelihood of ASD. Some studies report higher ASD risk among offspring of mothers with untreated hypothyroidism (32, 33), and smaller studies investigating various maternal thyroid conditions have supplied supporting evidence for this association (34). Although gestational screening and therapy for the relevant thyroid anomalies were recommended in these previous studies, medication use was not directly investigated. One study of a large Israeli health fund reported that children of mothers who had been diagnosed with hypo- or hyperthyroidism at some stage in their lives had higher odds of developing ASD compared to children of mothers with no such diagnosis (35). Interestingly, the authors suggested that the mechanism underlying such an association did not reflect disruptions in gestational hormone concentrations but rather could be attributed to a confounder that was independently associated with increased risk of both maternal hypothyroidism and ASD (35).

Given the prevalence of thyroid dysfunction in women of reproductive age and the availability of accessible treatment (36), clarifying the relationship between these conditions and ASD is of clinical significance. Thus, this study specifically aims to explore the association between maternal thyroid dysfunction during pregnancy and the risk of ASD diagnosis in offspring.

Methods

Study Population

A retrospective cohort study of live singleton births at Soroka University Medical Center (SUMC) was conducted between January 2011 and December 2017, with follow-up until January 2021. Only births where both mothers and offspring were members of Clalit Health Services (CHS), the largest health maintenance organization in Israel, were included. SUMC serves as the sole tertiary medical center in the southern Israeli Negev region and is a referral center for patients with mild to complex conditions. The Negev population consists of approximately 1 million individuals, of which over 75% are members of the CHS. Notably, the Negev population has a unique ethnic composition in that more than 25% of its inhabitants are Bedouins, who are responsible for >50% of the births at SUMC. This minority ethnic group is characterized by unique cultural, socioeconomic, and medical traits (37, 38), as well as by high birth rates, a rapidly increasing population rate, and distinct healthcare utilization patterns (37, 38). Thus, the distinctive demographics of this region allow for exploration of the study hypothesis in diverse populations, hence enhancing the generalizability of its findings.

Data Collection

Mothers' ID numbers were used to cross-link and merge data from 3 medical resources: (1) the CHS electronic database, which includes sociodemographic information and data on chronic diagnoses for all women in the study; (2) the database of the Obstetrics and Gynecology Department at SUMC, which contains comprehensive prenatal and perinatal data on all women giving birth at SUMC since 1990; and (3) the database of the Azrieli National Center for Autism and Neurodevelopment Research, which contains data on all children who have been diagnosed with ASD according to *Diagnostic and Statistical Manual of Mental Disorders* (fifth edition) criteria (1) at SUMC since 2013 (39, 40). Prenatal and perinatal covariates for the study were selected a priori based on literature and causal considerations. Covariates with a high rate (>30%) of missing data were not included in the data analysis.

Maternal Thyroid Dysfunction

To accurately assess the association between maternal thyroid dysfunction and ASD risk, we distinguished between chronic thyroid dysfunction and gestational thyroid dysfunction, irrespective of a chronic thyroid dysfunction diagnosis. A flowchart depicting the study sample ascertainment is provided in Fig. 1. The classification of women into chronic thyroid dysfunction, gestational thyroid dysfunction, or both was determined as follows. Identification of women with chronic hypothyroidism or hyperthyroidism was based on International Classification of Diseases, Ninth Revision (ICD-9) (41) codes defining these conditions as recorded in the CHS database. Chronic hyperthyroidism was identified using the following ICD-9 codes: ICD_2420, ICD_24200, ICD_24201, ICD_24220, ICD_24241, ICD_2429, ICD_24290. Chronic hypothyroidism was defined using the following codes: ICD_2440, ICD_2441, ICD_2448, ICD_2449. Diagnoses of gestational hypothyroidism and hyperthyroidism were based on trimester-specific thyroid hormone level tests measured by electrochemiluminescence immunoassay routinely performed for pregnant women at SUMC. For each trimester, a woman's TSH and FT4 values were used to identify 1 of 3 types of thyroid dysfunction according to the SUMC Obstetrics and Gynecology clinical guidelines, which broadly parallel the thresholds recommended by the American Thyroid Association. For those with thyroid dysfunction, at least 1 thyroid function test was performed each trimester. Per trimester, *gestational hypothyroidism* was defined as a median free T4 < 0.8 ng/dL and a median TSH > 4 IU/mL (overt hypothyroidism) or a median FT4 = 0.8 to 1.5 ng/dL and a median TSH > 4 IU/mL (subclinical hypothyroidism). *Gestational hyperthyroidism* was defined as a median FT4 > 1.5 ng/dL and a median TSH < 0.4 IU/mL. If a woman had more than 1 thyroid hormone test per trimester, the median value of her test results was used for that trimester. The use of median values helped to reduce transient fluctuations and outliers that may not have accurately depicted a woman's thyroid status during the trimester and thus provided a more stable measure of gestational thyroid function. Consequently, a woman was defined as having gestational hypothyroidism (overt or subclinical) or hyperthyroidism if she met these criteria in 1 or more of her pregnancy trimesters. Any overt hypothyroidism in any trimester classified the pregnancy as overt for the severity-specific analysis; otherwise, if ≥1 trimester met subclinical criteria and

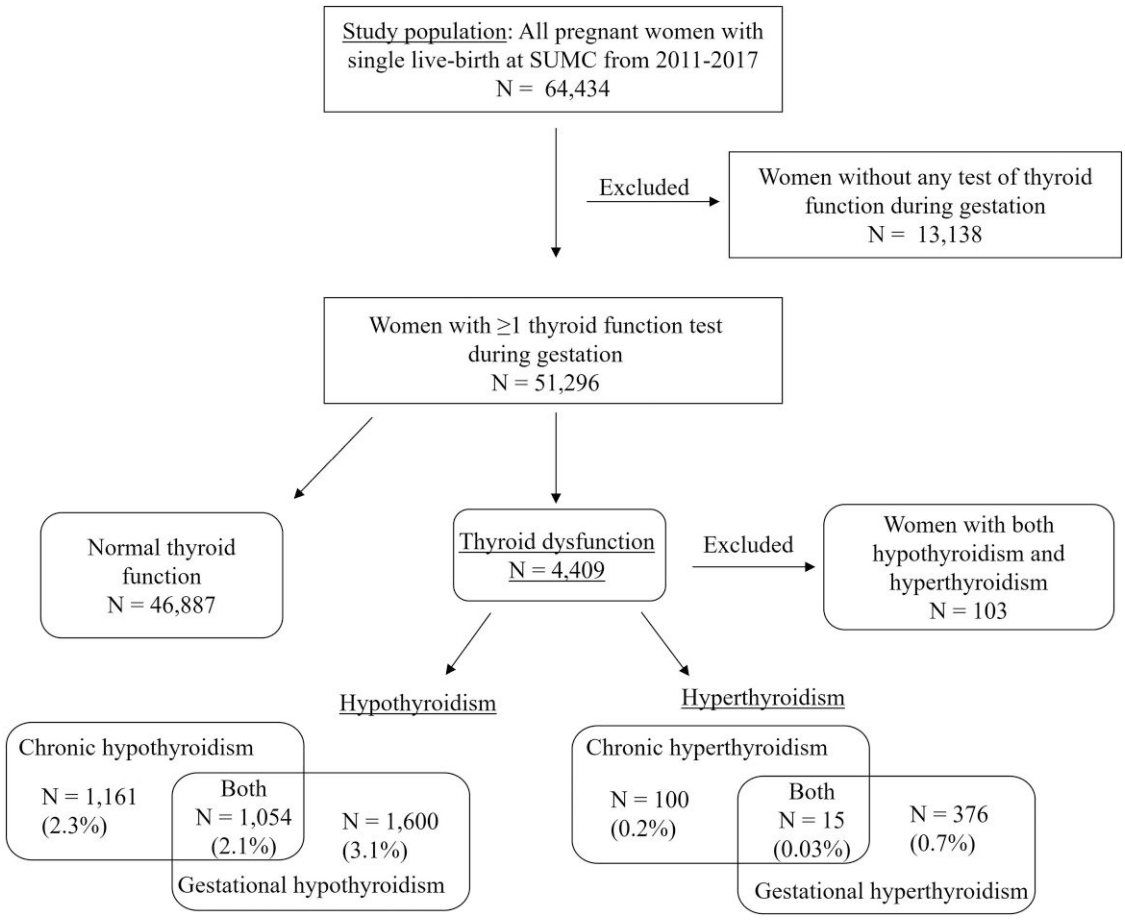

Figure 1. Flowchart depicting ascertainment of the study groups.

none met overt criteria, the pregnancy was classified as subclinical. Trimester-pattern exposure was analyzed separately from the severity analysis. No trimester laboratory data were missing among women included in the trimester-pattern analyses.

Data Analysis

The mean and SD values were calculated for continuous variables, while percentages were calculated for nominal variables. Univariate analyses were performed using either 2-tailed *t*-tests or Mann-Whitney U tests for continuous variables and 2-sided χ^2 tests for nominal variables. Kaplan-Meier curves were used to compare the cumulative incidence of ASD across exposure groups. Children without an ASD diagnosis who either died or moved out of the SUMC area prior to the study's conclusion were censored at the date of death or the date of their last SUMC visit. Cox regression models were performed to assess both the hazard associated with exposure to maternal hypothyroidism as well as the exposure across different trimesters, while adjusting for confounding. All statistical analyses were performed with SPSS version 28.0. Statistically significant results were determined at $P < .05$.

Results

Among the 51 296 women included in the study, 4409 (8.6%) were diagnosed with abnormal thyroid function. Of these, 1161 had chronic hypothyroidism, 1600 had gestational hypothyroidism, and 1054 had both chronic and gestational hypothyroidism; in addition, 100 women had chronic hyperthyroidism, 376 had gestational hyperthyroidism, and 15 women had both conditions (Fig. 1). Notably, 103 women had indications of both hypothyroidism and hyperthyroidism across different time points (Fig. S1) (42).

The sociodemographic and clinical characteristics of the study sample, divided into women with normal thyroid function and those with any thyroid dysfunction, are detailed in Table 1. Significant differences were observed between the 2 groups, particularly in ethnic composition (Jewish vs Bedouin). Among women with normal thyroid function, 43.3% were Jewish, compared to 49.6% in the thyroid dysfunction group ($P < .001$). Additional differences between women with normal thyroid function vs those with any thyroid dysfunction were seen in maternal age (29.0 ± 5.8 vs 29.9 ± 6.0 years, $P < .001$), rates of assisted reproductive therapy (4.4% vs 6.5%, $P < .001$), and rates of in vitro fertilization (0.3% vs 0.5%; $P = .023$), as well as in various prenatal and perinatal conditions, such as gestational diabetes (6.8% vs 9.5%, $P < .001$), hypertension (9.1% vs 10.9%, $P < .001$), Cesarean section (25.8% vs 29.2%, $P < .001$), and assisted delivery (36.2% vs 39.4%, $P < .001$). Regarding offspring characteristics, there was a slight overrepresentation of male children in the total sample, with no significant differences between the 2 groups (52.4% and 52.2%, respectively). The offspring of both groups also showed no significant differences in birth weight or gestational age.

Table 1. Sociodemographic and clinical characteristics of the study sample

Variable	Normal thyroid function (n = 46 887)	Any thyroid dysfunction (n = 4409)	*P*-value
Mothers			
Maternal age, mean (SD), years	29.0 (5.8)	30.0 (6.0)	<.001
Ethnicity (Jewish), n (%)	20 302 (43.3)	2136 (49.6)	<.001
Assisted reproductive therapy, n (%)	2063 (4.4)	279 (6.5)	<.001
In vitro fertilization, n (%)	140 (0.3)	21 (0.5)	.023
Gestational diabetes, n (%)	3188 (6.8)	409 (9.5)	<.001
Preeclampsia, n (%)	12 (0.0)	4 (0.1)	.115
Gestational hypertension, n (%)	4266 (9.1)	469 (10.9)	<.001
Cesarean section, n (%)	12 096 (25.8)	1257 (29.2)	<.001
Assisted delivery, n (%)	16 973 (36.2)	1696 (39.4)	<.001
Offspring			
Sex (male), n (%)	24 568 (52.4)	2248 (52.2)	.751
Birth weight, mean (SD), g	3194.0 (519.2)	3187.1 (516.2)	.398
Gestational age, mean (SD), days	272.9 (13.3)	272.6 (13.1)	.116

The median age at ASD diagnosis was 4.6 years (interquartile range, 3.8 to 5.7 years). The cumulative incidence of ASD in the offspring of women from the 2 study groups (normal vs any thyroid dysfunction) are depicted in Fig. 2. No significant difference in the ASD cumulative incidence was observed between offspring of women with normal thyroid function and those with any thyroid dysfunction (Fig. 2A; log-rank $P = .27$). In contrast, a significantly higher cumulative ASD incidence was observed in children born to mothers diagnosed with both chronic and gestational thyroid dysfunction when compared to those with normal thyroid function (Fig. 2B; log-rank test, $P = .0002$). Conversely, the cumulative ASD incidence in offspring of women with chronic thyroid dysfunction alone or gestational thyroid dysfunction alone did not differ from that of the normal thyroid function group (Fig. 2B). Among ASD cases, Autism Diagnostic Observation Schedule comparison scores were modestly elevated (more severe ASD symptoms) for children exposed to both chronic and gestational thyroid dysfunction compared to controls (8.4 ± 2.3 vs, 7.0 ± 2.4, $P = .009$) (Table S1) (42). No other significant differences in ASD symptoms were observed between the study groups.

Cox regression models were used to assess the hazard ratios (HRs) for various types of maternal thyroid dysfunction associated with offspring ASD risk. The results of these analyses are presented in Table 2. No significant association was found between "any thyroid dysfunction" (hypo- or hyperthyroidism, gestational or chronic) and ASD risk in either the crude or adjusted models [HR, 1.52; 95% confidence interval (CI), 0.92-2.46, and adjusted hazard ratio (aHR), 1.33; 95% CI, 0.81-1.90]. Examining hypothyroidism and hyperthyroidism separately indicated opposite but nonsignificant directions (aHR, 1.31; 95% CI, 0.83-2.07; aHR, 0.49; 95% CI, 0.07-3.53). Importantly, having both chronic and gestational thyroid dysfunction was associated with more than a 2-fold increase in ASD risk (aHR, 2.68; 95% CI, 1.52-4.72), whereas chronic-only and gestational-only thyroid dysfunction were not associated with ASD. This increased risk of ASD remained statistically significant for women with both chronic and gestational hypothyroidism (aHR, 2.61; 95% CI,1.44-4.74; aHR). No associations between chronic-only and gestational-only hypothyroidism and ASD risk were determined (aHR, 0.47; 95% CI, 0.15-1.48; aHR, 1.19; 95% CI, 0.52-2.70, respectively). Similar analysis of the different hyperthyroidism groups was not done due to the small number of ASD cases in these groups, which led to unstable HR estimates. Further classification of gestational hypothyroidism into subclinical and overt hypothyroidism indicated a possible dose-response effect of thyroid hormone levels, in that offspring of women with the overt condition were at a higher risk of ASD compared to those with the subclinical condition (aHR, 2.11; 95% CI, 0.86-5.18; aHR, 1.65, 95% CI, 1.10-2.48, respectively). It should be noted, however, that increased aHR associated with gestational overt hypothyroidism was not statistically significant.

These analyses were repeated separately for the Jewish and Bedouin subpopulations (Table S2) (42). The findings revealed that despite the variation in the HRs between these 2 subpopulations, their 95% CIs overlapped substantially, suggesting that ethnicity did not significantly modify the association between thyroid dysfunction and ASD in the study cohort.

The association between maternal gestational hypothyroidism across different pregnancy trimesters and offspring ASD risk was also examined (Table 3). Once again, an interesting dose-response relationship was observed in that a longer duration of hypothyroidism was associated with a higher risk of ASD, with each additional trimester of thyroid dysfunction associated with a 28% to 39% increase in risk (aHR, 1.39; 95% CI, 1.16-1.68 and aHR, 1.28; 95% CI, 1.02-1.93 for gestational hypothyroidism only and both chronic + gestational hypothyroidism respectively). Specifically, the aHR for ASD in offspring of women with gestational hypothyroidism only in any single pregnancy trimester was 1.69 (95% CI, 1.19-2.83), while gestational hypothyroidism only occurring in any 2 trimesters increased the risk to aHR, 2.39 (95% CI, 1.24-5.78), and gestational hypothyroidism only throughout the entire pregnancy further increased the risk to aHR, 3.25 (95% CI, 1.07-7.21). A parallel, within-group analysis among women with both chronic and gestational hypothyroidism showed similar duration-response trends, with the aHR 1.35 (95% CI, 1.02-2.44) for exposure for any single trimester, 2.04 (95% CI, 1.20-6.19) for a duration of any 2 trimesters, and 2.87 (95% CI, 1.10-9.94) for a duration of all 3 trimesters. Of note, some of the HRs associated with exposures in specific trimesters were not statistically significant, but these could be due to

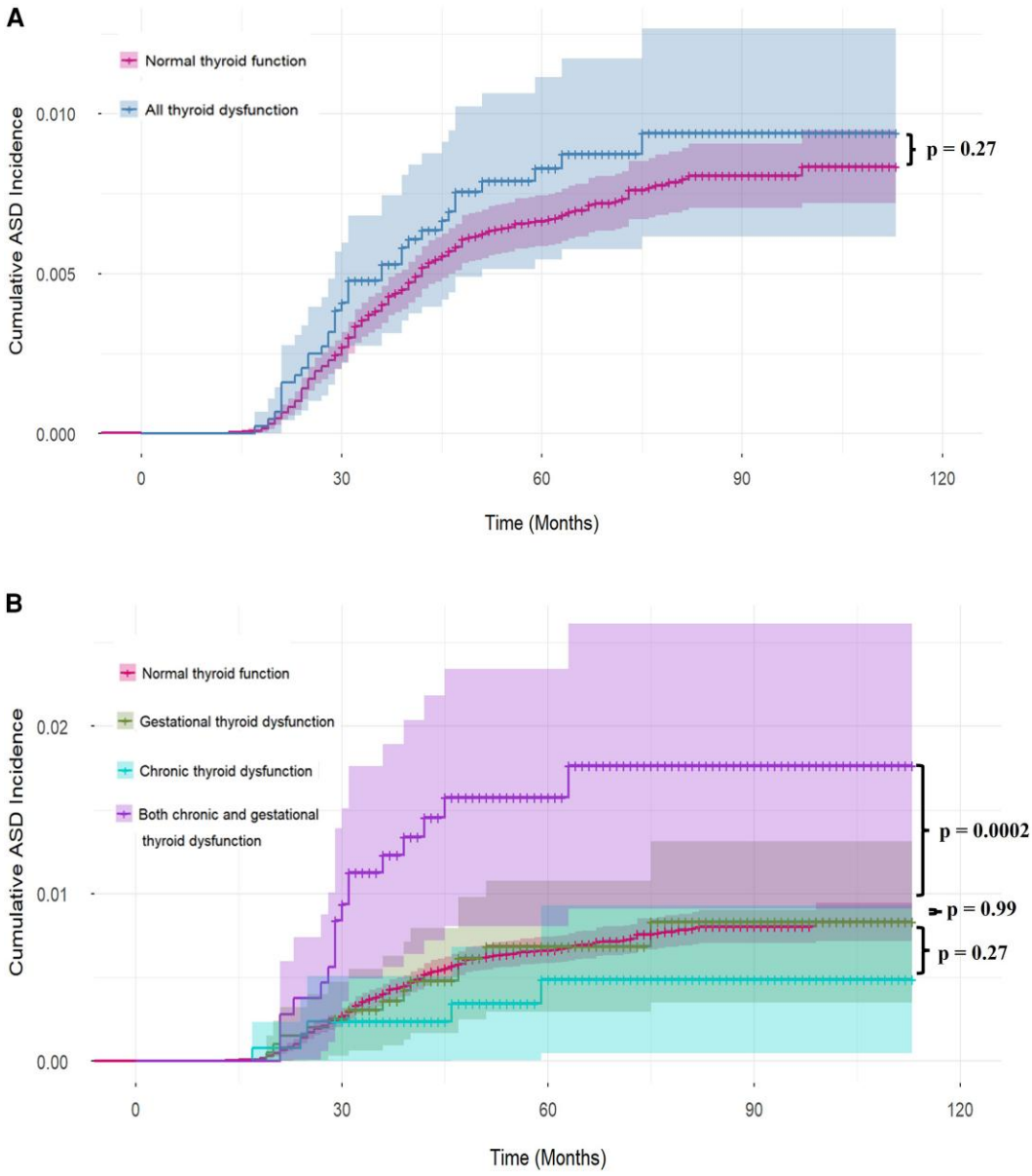

Figure 2. Kaplan-Meier plots for cumulative incidence of ASD onset in various thyroid function states. (A) ASD incidence in women with normal thyroid function vs in those with overall thyroid dysfunction (hypothyroidism/hyperthyroidism; chronic/gestational). (B) ASD incidence in women with chronic, gestational, and both chronic and gestational thyroid dysfunction vs in those with normal thyroid function. Note: Y-axis scales differ between panel A and panel B to allow for better visualization of trends across subgroups.

Abbreviation: ASD, autism spectrum disorder.

the small sample sizes associated with these analyses. Further comparison of the ASD symptoms between children with ASD who were exposed to maternal thyroid dysfunction in different pregnancy trimesters revealed no significant differences between the groups (Table S3) (42). However, these null findings may also be due to the insufficient statistical power associated with the small number of cases in each of the study groups. Unfortunately, a similar analysis for gestational hyperthyroidism was not possible due to the small number of women with this condition.

Discussion

The results of this study suggest that maternal thyroid dysfunction is associated with elevated ASD risk when both prepregnancy and gestational thyroid conditions are present. Furthermore, the findings highlight a trimester-specific dose-response, in which longer durations of hypothyroid imbalance were associated with higher ASD risk. Importantly, these findings primarily address maternal hypothyroidism, rather than hyperthyroidism, due to the low prevalence of gestational hyperthyroidism and, subsequently, the low number of ASD cases in this group, precluding the examination of its independent association—and its subclasses—with ASD risk in offspring.

The study findings align with a growing body of evidence indicating that irregular maternal thyroid hormone levels during gestation are associated with various fetal neurodevelopmental outcomes, including ASD (43-46). Supporting studies include a large epidemiological analysis that showed abnormal

Table 2. HR of thyroid conditions associated with ASD risk

Status	HR	95% CI	Adjusted HR[a]	95% CI
Thyroid dysfunction (n = 4409)	1.52	0.92-2.46	1.33	0.81-1.90
All hypothyroidism (n = 3815)	1.47	0.93-2.31	1.31	0.83-2.07
All hyperthyroidism (n = 491)	0.52	0.07-3.69	0.49	0.07-3.53
Chronic condition only (n = 1261)	0.56	0.18-1.75	0.43	0.14-1.35
Gestational condition only (n = 1976)	0.82	0.37-1.86	0.87	0.39-1.96
Chronic and gestational conditions (n = 1069)	**3.03**	**1.73-5.31**	**2.68**	**1.52-4.72**
Chronic hypothyroidism only (n = 1161)	0.64	0.20-1.99	0.47	0.15-1.48
Gestational hypothyroidism only (n = 1600)	1.11	0.49-2.50	1.19	0.52-2.70
Chronic and gestational hypothyroidism (n = 1054)	**2.87**	**1.59-5.17**	**2.61**	**1.44-4.74**
Subclinical hypothyroidism (n = 2414)	**1.72**	**1.15-2.57**	**1.65**	**1.10-2.48**
Gestational overt hypothyroidism (n = 388)	2.01	0.83-4.88	2.11	0.86-5.18

The sample sizes for women with "chronic hyperthyroidism only" (n = 100) and "gestational hyperthyroidism only" (n = 376) were too small to provide reliable analyses and were therefore omitted from this table. Statistically significant HRs are highlighted in bolded text.
Abbreviations: ASD, autism spectrum disorder; CI, confidence interval; HR, hazard ratio.
[a]Adjusted for sex, ethnicity, gestational age, maternal age, birth weight, assisted reproductive therapy, in vitro fertilization, gestational diabetes, gestational hypertension, preeclampsia, Cesarean section, and assisted delivery.

Table 3. HR of gestational hypothyroidism associated with ASD across trimesters

Trimester	HR	95% CI	Adjusted HR[a]	95% CI
Any single trimester				
n = 1249[b]	1.73	1.17-2.87	1.69	1.19-2.83
n = 784[c]	1.41	1.01-2.56	1.35	1.02-2.44
Any double trimesters				
n = 263[b]	2.66	1.39-5.57	2.39	1.24-5.78
n = 211[c]	2.09	1.21-6.25	2.04	1.20-6.19
All trimesters				
n = 88[b]	3.23	1.01-7.76	3.25	1.07-7.21
n = 59[c]	2.99	1.12-10.54	2.87	1.10-9.94
Per trimester exposed				
n = 1600[b]	1.37	1.15-1.63	1.39	1.16-1.68
n = 1054[c]	1.25	1.04-2.26	1.28	1.02-1.93
First trimester only				
n = 571[b]	1.71	1.14-3.09	1.82	1.22-3.21
n = 329[c]	1.36	0.87-2.23	1.30	0.92-2.17
Second trimester only				
n = 432[b]	1.43	0.95-3.43	1.39	0.91-3.22
n = 264[c]	1.15	0.71-2.88	1.27	0.79-2.67
Third trimester only				
n = 246[b]	1.88	1.30-4.17	1.84	1.21-4.09
n = 191[c]	1.78	1.19-3.45	1.63	1.13-3.23
First and second trimesters				
n = 189[b]	2.61	1.73-5.22	2.59	1.79-5.34
n = 103[c]	2.22	1.33-6.87	2.34	1.55-6.01
Second and third trimesters				
n = 54[b]	2.32	0.98-5.15	2.22	0.87-5.87
n = 67[c]	2.01	1.16-7.12	1.98	1.09-6.98
First and third trimesters				
n = 20[b]	2.78	0.75-10.57	2.81	0.76-11.35
n = 41[c]	2.10	0.94-5.97	1.97	0.87-5.46

Abbreviations: ASD, autism spectrum disorder; CI, confidence interval; HR, hazard ratio.
[a]Adjusted for sex, ethnicity, gestational age, maternal age, birth weight, assisted reproductive therapy, in vitro fertilization, gestational diabetes, gestational hypertension, preeclampsia, Cesarean section, and assisted delivery.
[b]Gestational hypothyroidism only.
[c]Both chronic + gestational hypothyroidism.

first-trimester thyroid hormone levels to be associated with child ASD risk in mothers with no prior thyroid diagnoses (45). Another study found that while chronic hypothyroidism did not increase ASD risk in offspring when TSH and T4 levels during pregnancy were normal due to medication use, thyroid dysfunction was still a key factor (46).

The results of the present study further demonstrate that ASD risk increases in direct relation to the severity and duration of thyroid hormone imbalance during pregnancy. While several studies with smaller sample sizes have failed to establish clear patterns linking thyroid dysfunction severity to ASD risk (45, 47), our findings are supported by research indicating that both subclinical and overt hypothyroidism are associated with ASD, with overt hypothyroidism being associated with a higher ASD risk (48). This estimate, however, was nonsignificant and should be interpreted cautiously given the wide CI, likely reflecting a limited number of cases. Additionally, certain studies have reported an inverse association between ASD-related traits and TSH levels in the second trimester (49, 50), which was the trimester most weakly associated with ASD risk in our trimester-specific analysis.

Notably, the conclusions of the present study are somewhat in disagreement with those of another study conducted in Israel (35). The authors of that study suggested that the association between maternal thyroid dysfunction and ASD in the offspring is not directly driven by gestational thyroid imbalance but rather by another factor underlying both gestational thyroid dysfunction and ASD (35). Discrepancies between the 2 studies may be attributed to differences in exposure ascertainment: while we exclusively used blood levels of thyroid hormones (TSH and T4) during gestation to determine thyroid dysfunction status, Rotem et al primarily relied on ICD-9 classification and medication dispensing records (35). Thus, they assumed that the levels of thyroid hormones of women with thyroid disease were balanced by medication—an assumption that was shown to be invalid for a considerable portion of women in the present study.

A key strength of the present study lies in the availability of both data for laboratory-determined thyroid hormone levels throughout pregnancy and data for chronic thyroid conditions for the women in the study sample. Consequently, this allowed for the distinction, with a high degree of certainty, between women with a thyroid hormone imbalance during pregnancy and those diagnosed with a chronic thyroid condition likely treated with thyroid medications, thereby conferring normal thyroid hormone levels during pregnancy. In addition, this study is among the first to consider the association between maternal hypothyroidism and risk of ASD across all the trimesters of pregnancy. Most previous studies investigating the association between maternal thyroid hormone levels and ASD have determined thyroid hormone levels only at a single time point during gestation, thereby limiting a comprehensive understanding of the exposure-outcome relationship. Furthermore, the relatively large cohort, extracted from Israel's largest healthcare provider and encompassing a uniquely diverse ethnic population—including both Jewish and Bedouin births—enhances the generalizability of the findings. The lack of effect modification by ethnicity further strengthens the external validity of the study. Indeed, the cumulative incidence of ASD in the study cohort was approximately 1.2%, consistent with national prevalence estimates reported in Israel during the same time period (51). Furthermore, the observed differences in ASD incidence between the Jewish and Bedouin subgroups (1.4% vs 0.9%) are also consistent with previous studies in these populations (52, 53). These trends further support the generalizability of the study findings.

Nevertheless, the results of this study should be considered in light of the following limitations. First, the trimester-specific analyses were limited by reduced statistical power, primarily due to the small number of women with gestational hypothyroidism in each trimester. This likely reflects the typical clinical course, in which once thyroid dysfunction is identified and promptly treated, most women exhibit a positive response to the treatment within 6 weeks (54). Second, data regarding levothyroxine treatment were not available for analysis, preventing a more nuanced understanding of maternal thyroid hormone replacement on ASD risk. Additionally, data regarding maternal iodine status and maternal thyroid antibody status were lacking, with future studies needed to incorporate these measures to better account for these critical factors in thyroid function. Third, although our regression analyses included a range of important maternal and gestational covariates, the possibility of residual confounding due to unmeasured variables should be taken into consideration when interpreting results. A notable example of such important missing data is socioeconomic status, which was insufficiently represented in the database. Yet, prior research has demonstrated that ethnicity designation, which was included in the study models, may serve as a reasonable proxy for socioeconomic status in this region (55, 56). Lastly, women with thyroid dysfunction were significantly older and more likely to have conceived using assisted reproductive technologies. Although these variables were adjusted for in the multivariable analyses, they may still represent underlying reproductive risk profiles that may confound the observed associations between thyroid dysfunction and offspring neurodevelopment.

Conclusions

The findings of the present study suggest that an imbalance of maternal thyroid hormone concentrations during gestation—particularly when chronic disease co-occurs with gestational hypothyroidism—is associated with an increased risk of ASD in offspring and followed a dose-response pattern. In contrast, chronic hypothyroidism alone (likely reflecting adequate treatment during pregnancy) was not found to be associated with ASD. While causal conclusions are premature, these results are consistent with recommendations for routine monitoring of thyroid hormone levels and treatment of imbalanced thyroid function with thyroid hormone medications to maintain euthyroidism in pregnancy.

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Disclosures

The authors have no conflicts of interest to declare.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Ethics Approval

The research was prospectively reviewed and approved by the SUMC Ethics Committee (#21-237). Informed consent was waived.

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