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Original Contribution

Neonatal Outcomes and Birth Weight in Pregnancies Complicated by Maternal Thyroid Disease

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Maternal hypothyroidism has previously been shown to increase risk for neonatal intensive care treatment, but otherwise the association between thyroid diseases and neonatal morbidity is understudied. The Consortium on Safe Labor, a retrospective cohort (2002–2008), included 223,512 singleton deliveries of which 0.2% had hyperthyroidism, 1.4% primary and 0.1% iatrogenic hypothyroidism, and 1.3% other/unspecified thyroid disease. Logistic regression with generalized estimating equations estimated adjusted odds ratios of adverse outcomes. Intensive care treatment was more common for neonates of women with thyroid disease. Hyperthyroidism and primary hypothyroidism were associated with sepsis, respiratory distress syndrome, transient tachypnea, and apnea. Iatrogenic hypothyroidism was associated with sepsis and neonatal anemia. Hyperthyroidism was also associated with rare outcomes (prevalence, <1%) including cardiomyopathy, retinopathy of prematurity, and neonatal thyroid diseases. Hyperthyroid non-Hispanic black women had higher odds of term infants that weighed <2,500 g, and hypothyroid non-Hispanic white women had higher odds of large-for-gestational-age infants. These analyses were stratified by race/ethnicity due to interaction. Associations were similar in analyses restricted to term infants. In conclusion, thyroid diseases were associated with increased neonatal morbidity. Although we lacked data on treatment during pregnancy, these nationwide data suggest a need for better thyroid disease management to reduce neonatal morbidity.

anemia, neonatal; birth weight; intensive care, neonatal; pregnancy; respiratory distress syndrome, newborn; thyroid diseases

Abbreviation: NICU, neonatal intensive care unit.

Maternal thyroid disease in pregnancy is common, with hypothyroidism affecting 2.0%–2.5% and hyperthyroidism up to 0.5% of all pregnancies (1). If untreated, overt thyroid disease is associated with an increased risk of obstetrical and labor complications such as fetal losses (1), hypertensive disorders during pregnancy (2), and preterm birth (1), and adequate treatment has been shown to reduce these risks (3, 4). There is no consensus regarding diagnosis and treatment of subclinical hypothyroidism during pregnancy, as data on the effectiveness of treatment to reduce adverse outcomes are limited (1, 5).

Hyperthyroidism has been associated with intrauterine growth restriction and low birth weight (6–8), which is probably at least partly due to increased risk of preterm birth and hypertension in pregnancy (1, 2). Maternal thyroid hormone excess without symptoms of hyperthyroidism (i.e., thyroid hormone resistance) also has independent detrimental effects on fetal growth by causing a thyrotoxic and catabolic state in the fetus (9).

Thyroid hormones are essential for maintaining normal growth and development (10), but the reported associations between both overt and subclinical hypothyroidism and birth weight are inconsistent as some studies show no association (11–18), while others report an increased incidence of low birth weight (19–21) or higher birth weight (22). Since the fetus is completely dependent on maternal thyroid

hormones in the first trimester and partially so after formation of the fetal thyroid gland (23), suboptimal maternal thyroid function might adversely affect neonatal health and is associated with poorer neuropsychological development in children (24).

Previous studies have found an association between maternal hypothyroidism and neonate admission to intensive care units (11, 12), and subclinical hypothyroidism has been associated with increased rates of respiratory distress syndrome (11), but these reports did not evaluate other thyroid diseases. Other studies have been underpowered to evaluate the association between thyroid diseases and low birth weight at term or less common neonatal outcomes (7, 8, 11, 12).

Given the sometimes conflicting findings of smaller studies and lack of data on many neonatal outcomes, we studied the effect of maternal thyroid diseases on birth weight and neonatal morbidity and mortality in a large, diverse US cohort with 223,512 singleton deliveries.

MATERIALS AND METHODS

The Consortium on Safe Labor was a large, racially/ethnically diverse observational cohort from 2002 to 2008 including 12 clinical centers comprising 19 hospitals (8 university-affiliated teaching hospitals, 9 teaching community hospitals, and 2 nonteaching community hospitals; refer to the Acknowledgements section for a list of locations). Births at ≥23 weeks of gestation were included, resulting in a total of 228,562 deliveries with 233,736 newborns (including multiples), with 87% of births occurring between 2005 and 2007 (25). We restricted this analysis to singleton pregnancies ($n = 223,512$) among 204,180 women because risks and prevalence of neonatal complications are higher among multiples than in singletons. Most women ($n = 185,785$; 91.0%) contributed only 1 pregnancy.

Detailed information was extracted from electronic medical records including maternal demographic characteristics; medical, reproductive, and prenatal history; labor and delivery summary; and neonatal outcomes and classified into predefined categories. Maternal and neonatal discharge summaries (with *International Classification of Diseases, Ninth Revision,* codes) were linked to each delivery and infant. The Consortium on Safe Labor was approved by the institutional review boards of all participating institutions. Data linkage, cleaning, recording, and validation have been previously described (25).

Thyroid diseases

Maternal thyroid disease diagnoses were established by using discharge diagnoses and notation in the medical record of nonspecific "history of thyroid disease." No treatment or laboratory data were available in the Consortium on Safe Labor. Wherever available, the discharge diagnoses were used to categorize disease status (refer to Web Table 1 available at http://aje.oxfordjournals.org/ for definitions):

1. No thyroid disease, no indication of thyroid disease in discharge records or medical charts ($n = 216,901$).
2. Primary hypothyroidism ($n = 3,183$).
3. Iatrogenic hypothyroidism (hypothyroidism due to surgery or other treatment) ($n = 178$).
4. Hyperthyroidism ($n = 417$).
5. Other or unspecified thyroid diseases: simple or nontoxic goiter ($n = 88$), thyroiditis ($n = 66$), other thyroid disorders including benign and malignant thyroid nodules ($n = 109$), and medical record mention of history of thyroid disease or unspecified discharge diagnosis code ($n = 2,570$), for a total of 2,833.

Once a thyroid disease diagnosis was recorded, it was deemed to affect all subsequent pregnancies. Since 2002 (during the Consortium on Safe Labor data collection), the American College of Obstetricians and Gynecologists has recommended screening pregnant women for thyroid diseases only if they had a personal history of thyroid disease or symptoms of thyroid disease (26).

Covariate data

Medical record data included maternal race/ethnicity, age, parity, insurance type, prepregnancy body mass index (weight (kg)/height $(m)^2$), and smoking during pregnancy. History of chronic diseases (diabetes, hypertension, asthma, depression, and chronic heart, gastrointestinal, or renal disease) was as recorded in the medical record and supplemented with discharge diagnoses (Web Table 1). Once a mother was diagnosed with a chronic disease, all subsequent pregnancies were assumed to be affected.

Outcome data

Gestational age was determined by best obstetric estimate as recorded in the medical record. Gestational age–specific birth weight percentiles were separately calculated for male ($n = 112,714$; 51.0%) and female ($n = 107,833$; 48.8%) infants after excluding missing or improbable birth weights ($n = 2,649$; 1.2%) and infants with ambiguous or unknown sex ($n = 316$; 0.1%). "Appropriate for gestational age" was birth weight between the 10th and 90th percentiles per gestational week, "small for gestational age" was birth weight ≤10th percentile, and "large for gestational age" was birth weight ≥90th percentile per gestational week (Web Table 2).

Separate estimates of low (<2,500 g) and high (≥4,000 g) absolute birth weights were established for term infants (born at ≥37 but <42 weeks' gestation) after excluding missing and improbable values of birth weight and fetal sex.

Perinatal mortality was defined as intrauterine deaths, intrapartum deaths, or deaths during the first 7 days of neonatal intensive care unit (NICU) admission. Neonates requiring resuscitation or NICU treatment, the length of stay in the NICU if admitted, and the level of resuscitation needed were extracted from the medical charts.

Neonatal outcomes that were extracted from both medical records and discharge diagnoses included respiratory distress syndrome, intracerebral hemorrhage, seizures, oliguria, cardiomyopathy, peri- or intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, sepsis, transient tachypnea, anemia, apnea, asphyxia, infectious

pneumonia, and aspiration (Web Table 1). Neonatal thyroid diseases were extracted by using only discharge data.

Statistical analyses

Pregnancy was the unit of analysis for all statistical testing. For rare outcomes (prevalence in the Consortium on Safe Labor, <1%), we combined cases of primary and iatrogenic hypothyroidism (total $n = 3,361$) to increase the power of the analyses.

Linear (for continuous data) or logistic (for binary or count data) regression with generalized estimating equations was used for significance testing with results presented as 2-sided P values or odds ratios with 95% confidence intervals. Generalized estimating equations were used with a first-order autoregressive structure correlation matrix to account for correlations between pregnancies to the same mother. All analyses were adjusted for site, and full models were also adjusted for maternal age, race/ethnicity, parity, insurance status, smoking, and presence of other chronic diseases. Site-adjusted and fully adjusted results were similar, and the site-adjusted results are presented as Web Tables 3–5.

Maternal race/ethnicity was a significant effect modifier ($P < 0.001$) in analyses estimating the association between thyroid diseases and birth weight. Hence, we stratified the data by maternal race/ethnicity. These analyses were adjusted for the same covariates as the main analyses, with the exception of maternal race/ethnicity.

Sensitivity analyses were conducted to address missing data, which were often clustered by site. Missing demographic data were treated as an unknown category in the main analyses. With respect to outcomes, some sites did not report apnea (9.2% missing) or level of resuscitation (1% missing among infants needing resuscitation), so we restricted those analyses only to sites that reported those outcomes. Second, data were restricted to women without any missing data. Third, we evaluated the impact of patient prepregnancy weight. Although maternal overweight and obesity are important risk factors for several outcomes studied, thyroid diseases are known to cause weight gain or loss. As such, maternal weight was regarded as an intermediate in the thyroid disease-outcome pathway and adjustment for weight would have introduced bias in the analyses (27). To assess the robustness of our findings with respect to maternal weight, we repeated the analyses restricting to women with a normal prepregnancy body mass index (18.5–24.99 kg/m^2). As thyroid diseases can increase the risk of preterm birth (1) and the neonatal outcomes under study are more prevalent in preterm infants, we restricted the analysis to term births (born at ≥37 but <42 weeks' gestation) to estimate whether the observed associations persisted among babies born at term. All statistical analyses were performed by using SAS, version 9.3, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The prevalence of thyroid disease was 0.2% hyperthyroidism, 1.4% primary hypothyroidism, 0.1% iatrogenic hypothyroidism, and 1.3% other or unspecified thyroid disease. Women with thyroid diseases were older, more often multiparous, and more likely to have additional chronic diseases than women without thyroid diseases (Table 1). Women with hypothyroidism and other or unspecified thyroid disease were heavier, more likely to be non-Hispanic white, and to have private insurance than those without thyroid diseases. Women with primary hypothyroidism and other or unspecified thyroid disease were less often smokers.

Hyperthyroidism

Neonates of women with hyperthyroidism were more likely to need resuscitation in the delivery room and to be admitted to the NICU (Table 2). Once admitted to the NICU, the infants of hyperthyroid women had nonsignificantly longer median length of stay than did infants of women without thyroid diseases. Neonates of hyperthyroid women had from 1.6- to 2.0-fold odds of respiratory distress syndrome, transient tachypnea, apnea, and sepsis (Table 2), as well as increased odds of cardiomyopathy, retinopathy of prematurity, and neonatal thyroid disease (Table 3).

Primary hypothyroidism

Neonates of women with primary hypothyroidism more often needed NICU treatment and had from 1.3- to 1.4-fold increased odds for neonatal sepsis, respiratory distress syndrome, transient tachypnea of the newborn, and apnea (Table 2).

Iatrogenic hypothyroidism

Neonates of women with iatrogenic hypothyroidism had higher odds of being admitted to the NICU, sepsis, and anemia (Table 2). Many associations between iatrogenic hypothyroidism and neonatal morbidity had a stronger magnitude than primary hypothyroidism, although the confidence intervals did slightly overlap.

Hypothyroidism was not associated with any of the rare outcomes studied (Table 3).

Other or unspecified thyroid disease

Other or unspecified thyroid diseases were associated with higher odds of neonates being admitted to the NICU and with apnea (Table 2). No association was seen with the rare neonatal outcomes (Table 3).

Birth weight

Non-Hispanic black women with hyperthyroidism had increased odds of low-birth-weight infants at term, and infants of Hispanic women with hyperthyroidism had increased odds of being small for gestational age compared with non-Hispanic black women or Hispanic women without thyroid diseases (Table 4).

The odds of infants being large for gestational age were higher in non-Hispanic white women with hypothyroidism

Table 1. Singleton Pregnancy Demographic Data[a] by Thyroid Disease Status in the Consortium on Safe Labor, 2002–2008

	No Thyroid Disease (*n* = 216,901)		Primary Hypothyroidism (*n* = 3,183)		Iatrogenic Hypothyroidism (*n* = 178)		Hyperthyroidism (*n* = 417)		Other or Unspecified Thyroid Disease (*n* = 2,833)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Pregnancies contributed										
1	198,265	91.4	2,829	88.9	145	81.5	357	85.6	2,577	91.0
2	17,726	8.2	338	10.6	32	18.0	51	12.2	240	8.5
≥3	910	0.4	16	0.5	1	0.6	9	2.2	16	0.6
Prepregnancy weight[b]										
Underweight	7,804	3.6	87	2.7	5	2.8	14	3.4	89	3.1
Normal weight	76,917	35.5	1,003	31.5	53	29.8	111	26.6	1,027	36.3
Overweight	32,358	14.9	528	16.6	25	14.0	55	13.2	533	18.8
Obese	15,232	7.0	257	8.1	21	11.8	27	6.5	248	8.8
Morbidly obese	11,630	5.4	244	7.7	17	9.6	27	6.5	246	8.7
BMI unknown	72,960	33.6	1,064	33.4	57	32.0	185	44.4	690	24.4
Nulliparous	87,127	40.2	1,118	35.1	55	30.9	132	31.7	809	28.6
Race/ethnicity										
Non-Hispanic white	105,802	48.8	2,420	76.0	127	71.4	189	45.3	1,965	69.4
Non-Hispanic black	49,588	22.9	209	6.6	27	15.2	144	34.5	294	10.4
Hispanic	38,380	17.7	300	9.4	14	7.9	48	11.5	327	11.5
Asian/Pacific Islander	8,977	4.1	109	3.4	4	2.3	20	4.8	101	3.6
Other	5,202	2.4	32	1.0	2	1.2	3	0.7	57	2.0
Unknown	89,521	4.1	113	3.6	4	2.3	13	3.1	89	3.1
Health insurance										
Private	120,044	55.4	2,412	75.8	144	80.9	227	54.2	2,140	75.5
Public or self-pay	73,608	33.9	483	15.2	29	16.3	161	38.6	584	20.6
Other	310	0.1	6	0.2	1	0.6	2	0.5	0	0
Unknown	22,939	10.6	282	8.9	4	2.3	27	6.5	109	3.9
Any chronic disease[c]	35,233	16.2	829	26.0	47	26.4	125	30.0	590	20.8
Smoking	14,591	6.7	144	4.5	12	6.7	43	10.3	143	5.1

Abbreviations: BMI, body mass index; SD, standard deviation.

[a] Age is missing for 0.1% of observations. Maternal age is expressed in years as the mean (SD): for no thyroid disease, 27.5 (6.2); for primary hypothyroidism, 31.5 (5.3); for iatrogenic hypothyroidism, 31.0 (5.3); for hyperthyroidism, 28.9 (5.9); and for other or unspecified thyroid disease, 30.4 (5.6).

[b] Maternal prepregnancy weight is calculated as BMI (weight (kg)/height $(m)^2$) and is categorized as underweight if BMI < 18.5; normal weight if BMI = 18.5–24.9; overweight if BMI = 25.0–29.9; obese if BMI = 30.0–34.9; and morbidly obese if BMI ≥ 35.0.

[c] Chronic diseases include depression; asthma; diabetes; heart, renal, or gastrointestinal disease; and hypertension.

or other or unspecified thyroid disease compared with non-Hispanic white women without thyroid diseases (Table 4).

Conversely, higher odds of small for gestational age were seen in infants of hypothyroid non-Hispanic black women compared with those of non-Hispanic black women without thyroid diseases. Hispanic women with hypothyroidism had increased odds of having infants with low birth weight at term compared with Hispanic women without thyroid disease (Table 4).

Sensitivity analyses

In the sensitivity analyses restricted to sites with complete reporting of outcome and exposure data, with no missing data on outcomes or covariates (complete case analyses) or among normal weight women, the results generally remained similar, although some loss of precision was observed because of diminished statistical power.

Most associations were similar in the main analyses and among the term births, suggesting that the associations of thyroid diseases and adverse neonatal outcomes were not solely due to an increased risk of preterm birth. In fact, the association between neonatal anemia and iatrogenic hypothyroidism and those between respiratory distress syndrome, apnea, retinopathy of prematurity, and hyperthyroidism were higher in term infants (data not shown). When restricting the birth weight analyses to term births, we noted that the

Table 2. Singleton Neonatal Outcomes Associated With Maternal Thyroid Diseases in the Consortium on Safe Labor, 2002–2008

Neonatal Complications	No Thyroid Disease ($n = 216,901$)			Primary Hypothyroidism ($n = 3,183$)				Iatrogenic Hypothyroidism ($n = 178$)				Hyperthyroidism ($n = 417$)				Other or Unspecified Thyroid Disease ($n = 2,833$)			
	No.	%	aOR[a]	No.	%	aOR[a]	95% CI	No.	%	aOR[a]	95% CI	No.	%	aOR[a]	95% CI	No.	%	aOR[a]	95% CI
Perinatal mortality	1,421	0.7	1.00	16	0.5	0.93	0.57, 1.53	1	0.6	1.05	0.15, 7.35	5	1.2	1.82	0.74, 4.44	19	0.7	1.15	0.72, 1.82
Neonatal resuscitation	49,508	22.8	1.00	894	28.1	1.05	0.95, 1.15	65	36.5	1.43	0.98, 2.09	113	27.1	1.41	1.10, 1.80	885	31.2	0.98	0.89, 1.08
Level of resuscitation CPAP or higher[b]	3,647	1.7	1.00	74	2.3	1.07	0.84, 1.36	6	3.4	1.56	0.66, 3.68	12	2.9	1.72	0.95, 3.11	46	1.6	1.02	0.75, 1.37
Neonate admitted to NICU[c]	26,317	12.1	1.00	434	13.6	1.22	1.10, 1.35	34	19.1	1.71	1.16, 2.51	87	20.9	1.66	1.30, 2.12	373	13.2	1.13	1.01, 1.26
Respiratory distress syndrome	7,058	3.3	1.00	128	4.0	1.29	1.08, 1.55	11	6.2	1.82	0.97, 3.41	28	6.7	1.77	1.20, 2.61	110	3.9	1.18	0.98, 1.44
Apnea[d]	4,532	2.3	1.00	91	2.9	1.34	1.08, 1.66	7	3.9	1.70	0.77, 3.75	23	5.6	2.01	1.31, 3.07	66	2.7	1.41	1.10, 1.81
Transient tachypnea	7,743	3.6	1.00	146	4.6	1.29	1.09, 1.53	9	5.1	1.41	0.71, 2.77	27	6.5	1.58	1.07, 2.35	88	3.1	0.97	0.78, 1.20
Sepsis	6,017	2.8	1.00	99	3.1	1.42	1.16, 1.74	12	6.7	2.86	1.58, 5.17	22	5.3	1.61	1.03, 2.49	79	2.8	1.25	0.99, 1.57
Anemia	4,058	1.9	1.00	68	2.1	1.28	1.00, 1.64	9	5.1	2.66	1.32, 5.39	16	3.8	1.55	0.94, 2.57	56	2.0	1.18	0.90, 1.55

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; CPAP, continuous positive airway pressure; NICU, neonatal intensive care unit.

[a] aORs are obtained from multivariate logistic regression with generalized estimating equations to account for correlated data. All results are adjusted for site, maternal age, insurance status, parity, smoking, race/ethnicity, and other chronic diseases.

[b] Level of resuscitation is missing for 498 infants with documented need of resuscitation.

[c] Once the infant was admitted, the median length of NICU stay (minimum – maximum) was 7.0 days (0–483 days) if the mother did not have thyroid disease; 7.7 days (0–189 days) if the mother had primary hypothyroidism; 8.0 days (1–99 days) if the mother had iatrogenic hypothyroidism; 10.0 days (0–131 days) if the mother had hyperthyroidism; and 7.0 days (0–175 days) if the mother had other or unspecified thyroid disease. The differences were not statistically significant when comparing the length of NICU stay of infants of mothers with thyroid disease with those of mothers without thyroid disease.

[d] Apnea information is missing for all observations from 1 study site ($n = 20,596$).

Table 3. Rare Neonatal Outcomes of Pregnancies Associated With Maternal Thyroid Diseases in the Consortium on Safe Labor, 2002–2008

Rare Neonatal Complications	No Thyroid Disease ($n = 216,901$)			Hypothyroidism ($n = 3,361$)				Hyperthyroidism ($n = 417$)				Other or Unspecified Thyroid Disease ($n = 2,833$)			
	No.	%	aOR[a]	No.	%	aOR[a]	95% CI	No.	%	aOR[a]	95% CI	No.	%	aOR[a]	95% CI
Peri- or intraventricular hemorrhage	1,266	0.58	1.00	26	0.77	1.40	0.94, 2.08	5	1.2	1.57	0.64, 3.83	14	0.49	1.04	0.61, 1.76
Intracerebral hemorrhage	558	0.26	1.00	7	0.21	1.25	0.59, 2.66	0	0	N/A		6	0.21	0.91	0.41, 2.03
Seizure	461	0.21	1.00	4	0.12	0.68	0.25, 1.85	0	0	N/A		4	0.14	0.75	0.28, 2.00
Oliguria	85	0.04	1.00	1	0.03	0.72	0.10, 5.24	0	0	N/A		1	0.04	1.37	0.19, 10.1
Cardiomyopathy	200	0.09	1.00	2	0.06	3.34	0.80, 14.0	1	0.24	10.3	1.33, 79.1	8	0.28	2.00	0.97, 4.12
Necrotizing enterocolitis	439	0.20	1.00	6	0.18	1.19	0.53, 2.67	2	0.48	2.09	0.51, 8.61	8	0.28	1.61	0.80, 3.26
Retinopathy of prematurity	973	0.45	1.00	16	0.48	1.27	0.77, 2.11	6	1.44	2.35	1.04, 5.32	14	0.49	1.58	0.92, 2.70
Asphyxia	572	0.26	1.00	8	0.24	0.92	0.45, 1.86	3	0.72	2.23	0.71, 6.94	7	0.25	0.92	0.43, 1.96
Aspiration with or without pneumonia	1,113	0.51	1.00	10	0.30	0.59	0.31, 1.10	2	0.48	0.87	0.22, 3.52	19	0.67	1.31	0.83, 2.08
Infective pneumonia	1,377	0.63	1.00	18	0.54	0.74	0.47, 1.19	4	0.96	1.27	0.47, 3.42	24	0.85	1.38	0.92, 2.08
Neonatal thyroid disease[b]	51	0.02	1.00	3	0.09	2.87	0.88, 9.35	7	1.68	44.3	19.5, 100	1	0.04	1.96	0.26, 14.7

Abbreviation: aOR, adjusted odds ratio; CI, confidence interval; N/A, not applicable.

[a] aORs are obtained from multivariate logistic regression with generalized estimating equations to account for correlated data. All results are adjusted for site, maternal age, insurance status, parity, smoking, race/ethnicity, and other chronic diseases.

[b] The respective number of neonates with congenital hypothyroidism and neonatal thyrotoxicosis was 49 (0.02%) and 2 (0.00%) among neonates of women without thyroid disease; 2 (0.06%) and 1 (0.03%) among neonates of mothers with hypothyroidism; 4 (0.96%) and 3 (0.72%) among neonates of mothers with hyperthyroidism; and 0 (0.00%) and 1 (0.04%) among neonates of women with other or unspecified thyroid disease.

Table 4. Association of Maternal Thyroid Diseases and Indicators of Fetal Growth in the Consortium on Safe Labor (2002–2008), Stratified by Race/Ethnicity

	No Thyroid Disease (n = 216,901)			Hypothyroidism (n = 3,361)				Hyperthyroidism (n = 417)				Other or Unspecified Thyroid Disease (n = 2,833)			
	No.	%	aOR[a]	No.	%	aOR	95% CI	No.	%	aOR	95% CI	No.	%	aOR	95% CI
Non-Hispanic white															
Term birth weight, <2,500 g[b]	1,528	1.6	1.00	35	1.6	1.14	0.81, 1.60	5	3.1	1.78	0.74, 4.30	26	1.5	1.05	0.71, 1.56
Term birth weight, ≥4,000 g[b]	8,751	9.3	1.00	246	11.2	1.06	0.92, 1.21	14	8.8	0.87	0.50, 1.50	178	10.3	1.11	0.95, 1.31
Small for gestational age[b]	8,256	7.8	1.00	171	6.7	1.05	0.89, 1.23	18	9.5	1.29	0.79, 2.10	141	7.2	1.06	0.89, 1.26
Large for gestational age[b]	11,823	11.2	1.00	379	14.9	1.15	1.02, 1.29	23	12.2	0.98	0.63, 1.51	265	13.5	1.19	1.04, 1.36
Non-Hispanic black															
Term birth weight, <2,500 g	1,509	3.7	1.00	8	4.6	1.32	0.64, 2.70	9	9.1	2.72	1.37, 5.39	1	0.5	0.12	0.02, 0.84
Term birth weight, ≥4,000 g	2,270	5.6	1.00	6	3.4	0.48	0.21, 1.10	3	3.0	0.51	0.16, 1.59	12	5.5	0.82	0.46, 1.47
Small for gestational age	7,179	14.5	1.00	43	18.2	1.50	1.07, 2.10	18	12.5	0.99	0.61, 1.62	43	14.7	1.06	0.76, 1.48
Large for gestational age	3,589	7.3	1.00	17	7.2	0.82	0.50, 1.36	14	9.7	1.22	0.69, 2.15	19	6.5	0.77	0.48, 1.26
Hispanic															
Term birth weight, <2,500 g	690	2.1	1.00	10	3.9	1.94	1.00, 3.77	1	3.1	1.15	0.14, 9.17	5	1.8	0.95	0.39, 2.31
Term birth weight, ≥4,000 g	2,859	8.6	1.00	28	10.9	1.25	0.83, 1.90	0	0	N/A		28	10.2	0.96	0.65, 1.43
Small for gestational age	3,669	9.6	1.00	32	10.2	1.17	0.80, 1.73	9	19.6	2.29	1.10, 4.74	23	7.1	0.83	0.54, 1.28
Large for gestational age	3,972	10.4	1.00	47	15.0	1.37	0.99, 1.91	4	8.7	0.85	0.31, 2.32	54	16.6	1.33	0.98, 1.80

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; N/A, not applicable.

[a] aORs are obtained from multivariate logistic regression with generalized estimating equations to account for correlated data. All results are adjusted for site, maternal age, insurance status, parity, smoking, and other chronic diseases.

[b] Birth weight was missing or improbable for 2,649 (1.2%) observations and excluded from all analyses; 41,990 preterm births are excluded from the analysis of term birth weight. All babies with unknown or ambiguous sex (n = 316) are excluded.

association between hyperthyroidism and small for gestational age in Hispanic women became nonsignificant (data not shown), indicating that the association might have been a product of early birth.

DISCUSSION

In this large, contemporary, nationwide cohort study from the United States, we found that infants born to women with thyroid diseases were more likely to need NICU admission and to have higher rates of respiratory distress syndrome, transient tachypnea, apnea, sepsis, and anemia than neonates of women without thyroid diseases. Hypothyroidism was associated with a higher rate of large-for-gestational-age infants in non-Hispanic white women, whereas hyperthyroidism was associated with increased odds of infants being low birth weight at term in non-Hispanic black women.

Our findings that infants born to women with any thyroid disease were more likely to be admitted to the NICU are consistent with those from a study by Casey et al. (11), where NICU admission was associated with subclinical hypothyroidism, but to our knowledge our study is the first to show this association with the other thyroid diseases. In addition, our novel finding that infants of hyperthyroid women were more likely to need resuscitation in the delivery room was not surprising since delivery room resuscitation is associated with increased risk for NICU admission. Perhaps our study was able to find this association because of the large numbers and the detailed information provided by the medical records that other studies have not had.

We also found an increased odds for several specific neonatal morbidities, including respiratory distress syndrome, apnea, and transient tachypnea of the newborn among infants of women with hyperthyroidism and primary hypothyroidism, increased odds of sepsis among those of women with hyperthyroidism and any hypothyroidism, and a higher rate of neonatal anemia among infants of women with iatrogenic hypothyroidism, when women without thyroid diseases were compared. We also studied very rare neonatal outcomes and found that hyperthyroidism was associated with cardiomyopathy and retinopathy of prematurity.

Our results support those of Casey et al. (11) who found increased prevalence of respiratory distress syndrome in infants of women with subclinical hypothyroidism. Our results are novel for the other outcomes, as our study has both sufficient power and detailed data to study the association of a spectrum of maternal thyroid diseases and neonatal outcomes.

It may be that thyroid diseases are associated with these outcomes through the mediating effects of preterm birth (1) although, in our analyses restricted to term births, that did not seem to be the case. We acknowledge the fact that such restriction may cause bias due to unmeasured confounding, although we presume the bias to be smaller in term than in preterm pregnancies (28, 29). As thyroid hormones cross the placenta and the fetus is totally dependent on the maternal thyroid hormone supply in early pregnancy (23), a direct effect of thyroid hormone deficiency or excess on fetal development is plausible.

We also observed that neonates of women with hyperthyroidism had higher odds of neonatal thyroid diseases, both congenital hypothyroidism and neonatal thyrotoxicosis. Both are known complications of the passage of thyroid-stimulating or -inhibiting antibodies through the placenta to the fetus (30). Such antibodies can be detected with high titers even in controlled hyperthyroid pregnancies and may affect fetal growth and development (30).

We observed significant racial/ethnic variation in the association between thyroid diseases and birth weight. Increased odds of large-for-gestational-age infants were observed in non-Hispanic white women with hypothyroidism compared with non-Hispanic white women without thyroid disease. However, non-Hispanic black women with hypothyroidism had increased odds of small-for-gestational-age infants, and Hispanic women with hypothyroidism had higher odds of infants with low birth weight at term. These observed associations between hypothyroidism and small for gestational age and low birth weight at term in non-Hispanic black and Hispanic women might be attributable to other, unmeasured factors than hypothyroidism. Hyperthyroidism was associated with low term birth weight in non-Hispanic black women and small-for-gestational-age infants in Hispanic women.

Hypothyroidism is associated with increased risk of gestational diabetes (12, 31), which might explain the currently observed association with large-for-gestational-age infants. Männistö et al. (22) have previously shown that infants of hypothyroid women have a higher ponderal index, also supporting our current results. The association between hyperthyroidism and low birth weight is also previously established (6–8), and it has been speculated that it might be due to preterm births. Our study is the first to show that hyperthyroidism leads to low birth weight in term infants, although the risk was statistically significant only in non-Hispanic black women. Our results are supported by those of Anselmo et al. (9), who found that thyroid hormone excess without maternal symptoms (i.e., in women with thyroid hormone resistance) increased the risk of intrauterine growth restriction, possibly by causing a catabolic state in the fetus.

Maternal hypothyroidism has been associated with a lower intelligence quotient and poorer motor development in children (24, 32), but whether such association is due to hypothyroidism itself or due to prematurity and neonatal morbidity associated with prematurity is currently unstudied. Our study suggests that long-term morbidity could be influenced by poor neonatal health, as well as by maternal thyroid function.

The strength of our study was its large, contemporary, and nationwide data collection with sufficient power to study even rare outcomes with the ability to evaluate and adjust for confounding factors. We were able to separate primary and iatrogenic hypothyroidism for some, but not all, outcomes due to lack of power for rare outcomes or stratified analyses. The prevalence of hypothyroidism in our study is consistent with the 2%–3% generally reported in the pregnant population in the United States (1). We might have missed some cases of subclinical hypothyroidism given that thyroid disease ascertainment was likely based on symptoms

and we did not have any laboratory data, but such misclassification is unlikely to be substantive enough to impact our findings given the detailed clinical data available for study. Although the Consortium on Safe Labor data collection covered 7 years, during which the knowledge on thyroid diseases during pregnancy increased, the proportion of cases with thyroid disease did not change over time. We note the large number of statistical tests used, which could have led to some chance findings, but the strength of the associations observed is generally reassuring. We also acknowledge the potential adjustment bias introduced by controlling for mediating chronic diseases but note that the adjusted and unadjusted results were very similar.

In addition, we did not have data on treatment but, on the basis of a survey performed during the data collection for the Consortium on Safe Labor, only 52%–66% of obstetricians would have recommended antepartum thyroid function testing for their pregnant patients with hypothyroidism or hyperthyroidism (33). Hence, a large number of women with thyroid disease with or without medication could have had no treatment control during pregnancy. Also, one study found that 60% of women with previously diagnosed thyroid disease have laboratory values indicating inadequate treatment at least once during pregnancy, and only half of these women had any changes in their treatment (34). There is a possibility of underdetection of thyroid disease during pregnancy, as this is not routinely screened in all pregnant women (1). We expect that at least some portion of our population was undertreated. Previous studies have shown that adequate treatment of thyroid diseases reduces the risk of adverse outcomes (3, 4, 35), and potentially the observed neonatal outcomes could have been prevented by adequate management of maternal thyroid disease.

In conclusion, maternal hypothyroidism and hyperthyroidism were associated with higher risk of NICU admission and neonatal morbidities. These adverse outcomes could potentially be prevented with adequate treatment of thyroid disease during pregnancy. More attention to thyroid diseases is needed in pregnant patients.

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