Gestational Thyrotoxicosis, Antithyroid Drug Use and Neonatal Outcomes Within an Integrated Healthcare Delivery System

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Background: Increasing attention has focused on the prevalence and outcomes of hyperthyroidism in pregnancy, given concerns for hepatotoxicity and embryopathy associated with antithyroid drugs (ATDs).

Methods: In an integrated health care delivery system, we examined the prevalence of thyrotoxicosis and gestational ATD use (propylthiouracil [PTU] or methimazole [MMI]) in women with delivered pregnancies from 1996 to 2010. Birth outcomes were compared among all infants and those born to mothers with diagnosed thyrotoxicosis or ATD therapy during gestation, with examination of ATD-associated hepatotoxicity and congenital malformations in the latter subgroups.

Results: Among 453,586 mother–infant pairs (maternal age 29.7 ± 6.0 years, 57.1% nonwhite), 3.77 per 1000 women had diagnosed thyrotoxicosis and 1.29 per 1000 had gestational ATD exposure (86.5% PTU, 5.1% MMI, 8.4% both). Maternal PTU-associated hepatotoxicity occurred with a frequency of 1.80 per 1000 pregnancies. Infants of mothers with diagnosed thyrotoxicosis (odds ratio [OR] 1.28, 95% confidence interval [CI] 1.05–1.55) or gestational ATD use (OR 1.31 [1.00–1.72]) had an increased risk of preterm birth compared to those born to mothers without thyrotoxicosis or ATD. The risk of neonatal intensive care unit (NICU) admission was also higher with maternal thyrotoxicosis (OR 1.30 [1.07–1.59]) and ATD exposure (OR 1.64 [CI 1.26–2.13]), adjusting for prematurity. Congenital malformation rates were low and similar among infants born to mothers with thyrotoxicosis or ATD exposure (30–44 per 1000 infants).

Conclusions: Gestational ATD exposure occurred in 1.29 per 1000 mother–infant pairs while a much larger number had maternal diagnosed thyrotoxicosis but no drug exposure during pregnancy. Infants of mothers with gestational ATD use or diagnosed thyrotoxicosis were more likely to be preterm and admitted to the NICU. The rates of congenital malformation were low for mothers diagnosed with thyrotoxicosis and did not differ by ATD use. Among women with gestational PTU therapy, the frequency of PTU-associated hepatotoxicity was 1.8 per 1000 delivered pregnancies. These findings from a large, population-based cohort provide generalizable estimates of maternal and infant risks associated with maternal thyrotoxicosis and related pharmacotherapy.

Introduction

THE LEADING CAUSE OF CLINICAL THYROTOXICOSIS during pregnancy is Graves' disease (1,2), with an estimated prevalence of 0.1%–0.4% of all pregnancies (2–6). Other infrequent causes of thyrotoxicosis during pregnancy include toxic nodular goiter, toxic adenoma, and thyroiditis (4). Expectant mothers may also experience gestational transient

hyperthyroidism due to the rise in human chorionic gonadotropin during early pregnancy associated with thyrotropin (TSH) suppression (7) and hyperemesis gravidarum (8–10). Treatment is usually not required except in rare instances of severe or persistent symptoms (6,11).

The primary treatment for hyperthyroid Graves' disease during pregnancy is antithyroid drug (ATD) therapy, including propylthiouracil (PTU) and methimazole (MMI).

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Historically, PTU was recommended as the first-line therapy during pregnancy, with MMI as the alternative (12). These recommendations were due to concerns for congenital malformations because rare cases of aplasia cutis (a cutaneous scalp defect), choanal atresia, or esophageal atresia were reported with MMI exposure during early pregnancy (13–16). However, recent reports of hepatotoxicity associated with PTU therapy in children (17,18), as well as cases of maternal (19) and neonatal PTU hepatotoxicity (20), have led to a re-examination of the optimal management of hyperthyroidism during pregnancy. Since 2010, new warnings have been included in the labeling for PTU (21), along with revised clinical management guidelines emphasizing MMI as first-line therapy (22) (already the preferred thionamide due to its once daily dosing and greater relative efficacy) (23), with the exception of early pregnancy and thyroid storm. For women with active Graves' disease during pregnancy, recommendations from the American Thyroid Association (2011) and the Endocrine Society (2012) advise PTU therapy in the first trimester followed by MMI therapy for the second and third trimester, with the goal of minimizing both early teratogenic exposure and overall risk of hepatic injury (4,24).

There is currently little data describing the burden of clinical hyperthyroidism during pregnancy, and population-based estimates of ATD use and pregnancy outcomes. A recent nationwide study of more than 800,000 women provided the first contemporary estimates of the prevalence of diagnosed thyrotoxicosis in pregnant women, estimated in the range of 2.46–5.88 per 1000 per year (5), where 39% of diagnosed women received an ATD during pregnancy. These data suggest that not all women with diagnosed thyrotoxicosis manifest active disease requiring pharmacologic treatment during pregnancy.

In the current study, we further examined the prevalence of diagnosed thyrotoxicosis and gestational ATD treatment in a community-based population of pregnant women receiving care from an integrated health care delivery system in Northern California. Within this large pregnancy birth cohort of more than 450,000 mother–infant pairs, we conducted a systematic examination of ATD-induced hepatotoxicity, adverse neonatal outcomes, and congenital malformations in the subgroup of women with ATD exposure during pregnancy and the broader population of women with diagnosed thyrotoxicosis.

Materials and Methods

Study population

Kaiser Permanente Northern California (KPNC) is a large integrated health care delivery system with over 3.4 million members, 14 delivery hospitals, and more than 30,000 total births per year (25). Central electronic databases provide systematic capture of all hospitalizations (including deliveries), pharmacy prescriptions, laboratory data, and ambulatory visits. The Perinatal Research Unit at the Division of Research tracks all infant deliveries, with linkage to maternal identifiers, mode of delivery, and gestational age and weight at birth. In addition, the KPNC Neonatal Minimum Data Set (26) tracks all level III neonatal intensive care unit (NICU) admissions with chart abstraction of neonatal diagnoses, procedures, and outcomes as previously described (26). For

this study, we identified all pregnancies resulting in a live birth between January 1, 1996, and December 31, 2010, among women age 15–49 years at the time of delivery. Estimated date of conception was calculated from the gestational age as determined from the maternal record and defined according to the obstetrically assigned estimated date of confinement. Infant and maternal data were linked to establish the maternal–infant cohort, enabling efficient tracking of maternal, gestational and neonatal outcomes. The KPNC Institutional Review Board approved the study and a waiver of informed consent was obtained due to the nature of the study.

Treatment with antithyroid drugs and characterization of maternal hyperthyroid status

Additional maternal demographic data, relevant clinical diagnoses, laboratory findings, and pharmacologic exposures were obtained from health plan electronic databases among women with diagnosed thyrotoxicosis and women who received ATD during pregnancy. To identify pregnant women with thyrotoxicosis during gestation and the subset most likely to have Graves' disease, we identified women with a hospitalization or ambulatory diagnosis of thyrotoxicosis with or without goiter (242.x), toxic diffuse goiter (242.0x, Graves' disease), or thyrotoxicosis without specified cause (242.9x) between the estimated date of conception and date of delivery, defined as the pregnancy window. Within each thyrotoxicosis diagnostic subgroup (242.x, 242.0x, and 242.9x), we examined the proportion receiving ATD or thyroid hormone (thyroxine or triiodothyronine) during pregnancy. In women with diagnosed thyrotoxicosis but no ATD or thyroid hormone treatment during pregnancy, we reviewed available levels of TSH and thyroid stimulating immunoglobulins (TSI).

For all women receiving an ATD during pregnancy, the underlying mechanism of hyperthyroid disease was determined based upon review of ambulatory diagnoses, thyroid imaging studies, and laboratory data by an endocrinologist and classified as 1) Graves' disease (presence of ophthalmopathy, elevated TSI, diagnostic radioactive iodine uptake/scan or physician diagnosis (93.8% by an endocrinologist), 2) hyperthyroidism due to nodular thyroid disease or thyroiditis, and 3) hyperthyroidism with cause not specified.

Ascertainment of ATD-associated hepatotoxicity

For women who received an ATD during pregnancy, we identified mothers who received an ambulatory or hospital discharge diagnosis of acute or chronic liver disease or other liver disorders (ICD-9 570.x, 571.x, 572.x, 573.x, and 646.7x) or had an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level more than twice the upper normal range during gestation. For infants exposed to gestational ATD, we identified those with a diagnosis of liver disease or evidence of elevated transaminases during the neonatal period. These maternal and infant cases were reviewed to identify cases of ATD-induced hepatotoxicity.

Neonatal outcomes

Preterm birth was defined as delivery at less than 37 completed gestational weeks. Admission to a level III NICU

was examined by chart review (26,27). Small- and large-for-gestational-age (SGA and LGA) infants were determined by applying the infant's birth weight and gestational age to the Fenton growth curves; SGA was defined as <5th percentile and LGA >95th percentile (28,29). We used International Classification of Diseases, 9th Revision (ICD-9) codes for congenital anomalies (740.X–756.X) from hospitalization and ambulatory visit records to identify infants with a possible congenital anomaly and chart review was conducted by a neonatologist (MK) to adjudicate/confirm congenital anomalies in all infants exposed to ATDs *in utero* or born to mothers with a diagnosis of thyrotoxicosis.

Statistical methods

Differences between subgroups were compared using the chi-square or Fisher exact test for categorical variables and Student's *t*-test for continuous variables. Prevalence estimates and frequencies were reported as a point estimate with 95% confidence intervals (CI). Multivariable logistic regression was used to examine the relationship of thyrotoxicosis or ATD treatment status with adverse neonatal outcome. All analyses were conducted using SAS Version 9.3 or STATA Version 12.1. A two-sided *p* value <0.05 was considered statistically significant.

Results

Between 1996 and 2010, we identified 453,586 infants born to women aged 15–49 years at delivery, ascertaining the first birth for each woman per calendar year. The average maternal age at delivery was 29.7 ± 6.0 years; 20.0% delivered at age 35 years or older. The maternal cohort demonstrated considerable racial/ethnic diversity with 42.9% white, 7.4% black, 25.3% Hispanic, 19.7% Asian, and 4.8% other or unknown race.

There were 1712 mother–infant pairs with a maternal diagnosis of thyrotoxicosis (ICD-9 242.x for 1559 unique

women) during gestation, yielding a prevalence of 3.77 [CI 3.60–3.96] per 1000 delivered pregnancies. As shown in Figure 1, 541 (31.6%) received ATD and 385 (22.5%) received thyroid hormone during pregnancy. Of the remaining 786 women with no ATD and no thyroid hormone during pregnancy, 431 (54.8%) had a normal TSH and 263 (33.5%) had a low TSH during pregnancy (in this latter group, 93.2% achieved normal TSH during pregnancy); only 55 (7.0%) of those with no ATD and no thyroid hormone treatment had an elevated TSI level consistent with Graves' disease, although TSI levels were not tested in the majority of women.

Among the 744 mother–infant pairs with a specific maternal diagnosis of toxic diffuse goiter (ICD-9 242.0x), accounting for 1.64 per 1000 pregnancies, 286 (38.4%) received ATD and 238 (32.0%) received thyroid hormone during pregnancy. Of the remaining 220 (29.6%) with no ATD or thyroid hormone during pregnancy, 146 (66.4%) had normal TSH and 51 (23.2%) had low TSH during pregnancy (in this latter group 98.0% achieved normal TSH during pregnancy); 38 (17.3%) of those with a diagnosis of toxic diffuse goiter but no ATD or thyroid hormone treatment during pregnancy had an elevated TSI. Collectively, these data suggest that the majority of pregnant women with diagnosed thyrotoxicosis, but no ATD or thyroid hormone treatment during pregnancy, do not have sustained hyperthyroidism during pregnancy.

There were 586 mother–infant pairs with maternal ATD treatment during pregnancy (543 unique women), yielding a prevalence of 1.29 [CI 1.19–1.40] per 1000 pregnancies. Most received only PTU (507, 86.5%) during pregnancy (Fig. 2), followed by a combination of PTU and MMI (49, 8.4%) and MMI alone (30, 5.1%). The annual prevalence of gestational ATD therapy ranged from 0.92 to 1.59 per 1000 pregnancies across the 15-year observation period.

Gestational ATD use also varied by race/ethnicity (Fig. 2), with higher frequency (per 1000 pregnancies) among Asians

FIG. 1. Prevalence and treatment of pregnant women with diagnosed thyrotoxicosis categorized by diagnostic subtype. International Classification of Diseases, Ninth Revision (ICD-9) codes and sub-codes for thyrotoxicosis with or without goiter (ICD-9 242.x), including type not otherwise specified (NOS).

FIG. 2. Prevalence of antithyroid drug therapy during pregnancy overall and by race/ethnicity during 1996–2010. **p* < 0.01 compared to white and Hispanic women. The percentage of women receiving propylthiouracil (PTU), methimazole (MMI), or both during gestation is indicated for each racial/ethnic subgroup.

(2.25) and blacks (1.83) and lower frequency among whites (1.04) and Hispanics (0.88). Nearly all ATD-treated women (95.7%) had a diagnosis of thyrotoxicosis (242.x) prior to or during pregnancy. Classification of hyperthyroidism for ATD-treated women included 393 (72.4%) with confirmed Graves' disease, 33 (6.1%) with hyperthyroidism due to thyroid nodule(s) or thyroiditis and 117 (21.5%) with hyperthyroidism cause unspecified. This last group also included women with transient hyperthyroidism during pregnancy requiring ATD therapy followed by normalization of thyroid status post delivery, likely reflecting transient gestational thyrotoxicosis.

Table 1 examines maternal characteristics and neonatal birth outcomes among mother–infant pairs classified by 1) gestational ATD exposure, 2) maternal thyrotoxicosis diagnosis but no gestational ATD, and 3) no thyrotoxicosis and no gestational ATD. Infants were more likely to be born preterm if their mother had a thyrotoxicosis diagnosis or ATD use and also more likely to be admitted to a level III NICU compared to infants born to mothers with no thyrotoxicosis or ATD use. Multivariable analyses were conducted to adjust for maternal age and race/ethnicity, classifying maternal thyroid status as having 1) no diagnosed thyrotoxicosis or gestational ATD, 2) diagnosed thyrotoxicosis but no gestational ATD, and 3) receipt of gestational ATD (Table 2). Infants born to mothers with gestational ATD exposure and those born to mothers with a thyrotoxicosis diagnosis but no ATD had increased odds of preterm birth compared to infants born to mothers with no thyrotoxicosis or ATD use (Table 2). Differences in admission to a level III NICU

were also seen (adjusting for maternal age, race/ethnicity and prematurity), with greater risk of NICU admission among infants born to mothers who received an ATD and mothers who had a thyrotoxicosis diagnosis and no ATD during pregnancy compared to those with no ATD or thyrotoxicosis diagnosis during pregnancy.

Table 3 reports the congenital anomalies by maternal ATD and recent thyrotoxicosis diagnosis status. Overall, there were no significant differences in the rate of congenital anomalies in fetuses exposed to ATDs compared to those born to mothers with diagnosed thyrotoxicosis and no ATD, although the number of infants within each group was small. There were 15 anomalies among 507 children identified in the PTU-only exposure group, including atrial and/or ventricular septal defect, pulmonary stenosis, club foot (talipes equinovarus), syndactyly of the toes, hypospadias, jejunal atresia, patent urachus, pyloric stenosis, and laryngomalacia. Only one anomaly was found among the 30 infants in the MMI-only exposure group (talipes equinovarus), and two anomalies among the 49 infants with both PTU and MMI exposure during pregnancy (ventricular septal defect and hypospadias). While no significant differences were seen in the proportion of congenital anomalies based on additional ATD exposure in the 2 months prior to conception, the numbers within each subgroup were too small for comparison of differences in congenital anomaly rates. Additional chart review for adjudication of congenital anomalies was not

TABLE 1. CHARACTERISTICS OF MOTHER–INFANT PAIRS BY MATERNAL THYROID STATUS CATEGORY AND ANTITHYROID DRUG EXPOSURE DURING GESTATION

	Maternal thyroid status category ^a		
	No thyrotoxicosis diagnosis, no gestational ATD	Thyrotoxicosis diagnosis, no gestational ATD	Received gestational ATD
<i>N</i>	451,829	1171	586
Maternal age, years	29.7 ± 6.0	31.9 ± 5.3*	31.3 ± 5.7*†
Race/ethnicity, %		*	*
White	42.9	35.3	34.6
Black	7.4	8.1	10.4
Hispanic	25.3	21.2	17.2
Asian	19.7	31.7	34.3
Other	4.8	3.8	3.4
Birth weight, g	3405 ± 571	3322 ± 603*	3268 ± 610*
Small-for-gestation age, %	1.9	2.9*	2.9 [§]
Large-for-gestation age, %	4.5	4.6	4.4
Preterm birth, %	7.3	9.5*	9.7*
Level III neonatal intensive care, %	8.5	11.7*	14.0*

^aColumn percentages provided.

* $p < 0.05$ (or $^{\dagger}p = 0.06$) compared to no thyrotoxicosis diagnosis and no gestational ATD group.

[†] $p < 0.05$ compared to thyrotoxicosis diagnosis but no gestational ATD group.

ATD, antithyroid drug.

TABLE 2. THE ASSOCIATION OF MATERNAL THYROTOXICOSIS AND GESTATIONAL ANTITHYROID DRUG EXPOSURE WITH DELIVERY OUTCOME

	Birth outcome, adjusted OR [CI] ^a	
	Preterm birth (<37 weeks gestation)	Neonatal intensive care admission (level III)
Maternal age, years	1.02 [1.01–1.02]	1.01 [1.01–1.01]
Race/ethnicity		
White	Referent	Referent
Black	1.49 [1.43–1.55]	1.47 [1.41–1.54]
Hispanic	1.02 [0.99–1.05]	0.95 [0.92–0.97]
Asian	1.09 [1.06–1.13]	1.20 [1.16–1.24]
Other	1.36 [1.29–1.43]	1.36 [1.29–1.43]
Maternal thyroid status ^b		
No thyrotoxicosis or gestational ATD	Referent	Referent
Thyrotoxicosis but no gestational ATD	1.28 [1.05–1.55]	1.30 [1.07–1.59]
Received gestational ATD	1.31 [1.00–1.72]	1.64 [1.26–2.13]

^aMultivariable logistic regression models examining the association of maternal thyroid status and birth outcome. Models are adjusted for age and race/ethnicity, with additional adjustment for infant prematurity (birth at <37 weeks gestation) in the model examining neonatal intensive care unit admission as the outcome.

^bWomen receiving gestational ATD and women with thyrotoxicosis (but no ATD) were at greater risk for each birth outcome than those without thyrotoxicosis or ATD. Women receiving gestational ATD were not at a significantly higher risk for either birth outcome compared to those with thyrotoxicosis (but no ATD).

CI, 95% confidence interval; OR, odds ratio.

TABLE 3. CONGENITAL ANOMALIES BY ANTITHYROID DRUG EXPOSURE AND THYROTOXICOSIS DIAGNOSIS STATUS

<i>Gestational ATD exposure</i>	<i>N</i>	<i>Congenital anomalies</i>	<i>Rate per 1000 infants [CI]</i>	<i>ATD within 2 months prior to conception</i>		<i>No congenital anomalies, n (%)</i>	<i>Congenital anomalies, n (%)</i>
Gestational ATD ^a	586	18	31 [18–48]	No	497	484 (97.4)	13 (2.6)
				Yes	89	84 (94.4)	5 (5.6)
PTU only ^b	507	15 ^c	30 [17–48]	No	433	422 (97.5)	11 (2.5)
				Yes	74	70 (94.6)	4 (5.4)
MMI only ^d	30	1 ^e	33 [1–172]	No	25	24 (96.0)	1 (4.0)
				Yes	5	5 (100)	0
PTU and MMI ^f	49	2 ^g	41 [5–140]	No	39	38 (97.4)	1 (2.6)
				Yes	10	9 (90.0)	1 (10.0)
Thyrotoxicosis diagnosis, no gestational ATD	1171	52 ^h	44 [33–58]	No	1144	1094 (95.6)	50 (4.4)
				Yes	27	25 (92.6)	2 (7.4)

^aThe racial/ethnic distribution of mothers with gestational ATD who had an infant with congenital anomaly were 27.8% white, 11.1% black, 27.8% Hispanic, and 33.3% Asian.

^bAnomalies in PTU group: atrial and/or ventricular septal defect, pulmonary stenosis, talipes equinovarus, hypospadias, jejunal atresia, laryngomalacia, patent urachus, pyloric stenosis, syndactyly of the toes.

^cFour of 15 infants were born to mothers who also received ATD within 2 months prior to conception (two received MMI and two received PTU).

^dAnomalies in MMI group: talipes equinovarus.

^eOne infant of a mother who received PTU during gestation but did not receive ATD within the 2 months prior to conception.

^fAnomalies in PTU and MMI group: ventricular septal defect, hypospadias.

^gGestational ATD sequence was MMI and then PTU; one of two infants was born to a mother who also received MMI within 2 months prior to conception.

^hTwo of 52 infants were born to mothers who received ATD within 2 months prior to conception (one PTU, one MMI); none received ATD during gestation.

conducted for the larger background population without diagnosed thyrotoxicosis or ATD use during gestation due to the large cohort size ($N=451,829$).

Hepatotoxicity associated with ATD use was rare in this cohort. Among the subset of 586 mother infant pairs with gestational ATD exposure, we identified 15 women with diagnosed liver disease and/or elevated liver transaminases more than twice the upper normal limit whose cases were reviewed for possible ATD-associated liver toxicity (records were unavailable for two with modest liver transaminase elevation). Within this subgroup, only one maternal case of overt PTU-associated hepatotoxicity was identified, presenting with jaundice, gastrointestinal symptoms, and bilirubin and liver transaminase elevations exceeding five times the upper normal limit. Resolution of hepatotoxicity occurred with PTU cessation (originally at 450 mg/d in divided doses) and transient glucocorticoid therapy, with favorable neonatal outcome. The remaining maternal cases of liver disease or elevated transaminases were related to other etiologies, including hyperemesis, pancreatitis, hepatitis, cholestasis of pregnancy, pre-eclampsia, or other unspecified cause. No cases of ATD-associated hepatotoxicity were identified among the eight infants with elevation in liver transaminases or diagnosed liver disease. All were found to have other etiologies of hepatic dysfunction, including cholestasis, choledochal cyst, or prolonged parenteral nutrition. One infant with normal ALT but elevation of AST to nearly 240 U/L after birth had normal levels by discharge; maternal records indicated that ATD therapy ceased during the second trimester. Hence, among the 586 mother–infant pairs with gestational ATD exposure of whom 556 had PTU exposure, the prevalence of PTU-associated maternal hepatotoxicity was calculated at 1.80 per 1000 delivered pregnancies [CI 0.05–9.98]. No cases of MMI-associated maternal hepato-

toxicity were identified, although only 79 women received MMI during pregnancy.

Discussion

Within a large diverse Northern California population, the prevalence of gestational ATD use was 1.29 per 1000 births during 1996–2010. These rates are within the range of nationwide data from MarketScan Commercial Claims and Encounters (5) but in the lower range of historical estimates for hyperthyroidism complicating pregnancy (2–6), likely due to the focus on active treatment. Gestational ATD use varied by race/ethnicity (highest in Asians and blacks), supporting observed racial/ethnic variation in autoimmune thyroid disease incidence (30). Similar to MarketScan data (5), a larger number of pregnant women with diagnosed thyrotoxicosis and no gestational ATD were identified, likely including transient gestational hyperthyroidism and postablative Graves' disease. While a diagnosis of toxic diffuse goiter was more specific for Graves' disease, pharmacy data were necessary to define hyperthyroid populations undergoing active treatment. The majority of ATD-treated pregnant women had Graves' disease, with most receiving PTU.

Infants of mothers with diagnosed thyrotoxicosis and/or gestational ATD use were more likely to be preterm, consistent with prior studies showing increased rates of preterm delivery associated with maternal Graves' disease and elevated thyroid hormone (31–33). These infants had a greater tendency to be SGA, although whether this relates to more active or poorly controlled disease or thyroid autoimmunity requires further investigation. We noted that infants of mothers with diagnosed thyrotoxicosis or receiving gestational ATD also had a higher risk of NICU admission compared to those born to mothers without

thyrotoxicosis or ATD. The greater proportion admitted to the NICU was not due to prematurity alone and may reflect both symptomatic infants as well as increased surveillance of exposed infants.

Similar rates of congenital anomalies were observed for infants with PTU or MMI exposure and those born to mothers with diagnosed thyrotoxicosis but no gestational ATD. However, the relatively small number of prenatally exposed infants restricted our power to detect subgroup differences. None of the 79 MMI-exposed infants had choanal atresia or esophageal atresia, whereas other studies have identified an increased prevalence of these anomalies associated with MMI (13–15,34–36). Given the low estimated background prevalence of choanal atresia (0.33/10,000) and esophageal atresia (1.17/10,000 live births) (37), identifying MMI-associated risk within our small exposure subset would be challenging. In a large study of 6744 women with Graves' disease in Japan where 1231 infants were exposed to MMI, only seven had an omphalo-mesenteric duct anomaly, six had an omphalocele, and one had esophageal atresia (38). MarketScan data (5) showed similar rates of congenital anomalies for infants exposed to MMI or PTU-only, but higher risk with both MMI and PTU compared to infants of mothers without thyrotoxicosis.

Major ATD-associated hepatotoxicity occurred rarely, with a frequency of 1.8 per 1000 pregnant women receiving PTU. This rate is lower compared to other reports in which liver transaminases were systematically monitored following PTU initiation (39–42) and asymptomatic cases with mild transaminase elevation were included (39,40). While no cases of MMI hepatotoxicity were identified in the small number of exposed women, historic data support a higher frequency of PTU hepatotoxicity compared to MMI (42). We did not examine the incidence of non-ATD-associated liver dysfunction during pregnancy in this study.

The strengths of our study include a large racially and ethnically diverse community-based population of pregnant women with linkage to both maternal data and infant records in which gestational exposures, congenital malformations, and other adverse neonatal outcomes were systematically examined. Since this study was not limited to claims data, we were able to examine pharmacy records, relevant diagnoses, and laboratory findings to determine ATD use, maternal thyrotoxicosis indication, hepatotoxicity, and cases of congenital malformations in an extremely large cohort of mother–infant pairs. These population data complement findings from other birth registries and claims databases by providing exposure and outcome data from a single large integrated healthcare delivery system.

Our study also has several limitations. First, although we included over 450,000 women with a delivered pregnancy, the proportion receiving gestational ATD treatment was relatively low and of these, only 13.5% received MMI, restricting our ability to examine differences by ATD exposure and subtype. We also do not have background rates of congenital anomalies relevant to the source population, although congenital anomalies were examined in women with diagnosed thyrotoxicosis but no gestational ATD. Second, this study focused on identification of mother–infant pairs based on live births; therefore, spontaneous abortions and preterm delivery of pre-viable infants or still births would have been missed. Third, we did not have specific infor-

mation pertaining to maternal thyroxine levels, indication for thyrotoxicosis diagnosis, and the dose and duration of ATD exposure, including ATD taper and pregnancy exposure intervals relevant to safety and risk (43), factors that may have influenced neonatal outcome. Because women with ATD represent an actively treated hyperthyroid subgroup (and the subgroup of greatest interest in this study), we classified maternal thyroid status based on ATD treatment, diagnosed thyrotoxicosis but no ATD, and no thyrotoxicosis or ATD, given the challenges in classifying women solely based on thyroid function labs obtained during gestation. Women with a diagnosis of thyrotoxicosis but no gestational ATD were separately characterized to determine whether they represent a subgroup at increased risk, although we were not able to differentiate indications for thyrotoxicosis diagnosis. Finally, while our goal was to identify women with Graves' disease receiving gestational ATD, the diagnosis of thyrotoxicosis was not specific for Graves' disease and identified women with other hyperthyroid etiologies, including transient gestational thyrotoxicosis managed briefly with ATD. Larger studies examining adverse consequences of ATD exposure should separately consider women based on underlying hyperthyroid etiology where treatment exposure may differ.

In summary, within a large integrated health care delivery system, the prevalence of ATD use was 1.29 per 1000 births overall and varied by race/ethnicity. The majority received PTU during pregnancy, consistent with the time period of the study, and the risk of major PTU hepatotoxicity was low (estimated 2 per 1000 women). No significant differences were seen in rates of congenital anomaly by ATD exposure subtype, although few received MMI. While further studies are needed in larger populations with MMI exposure to determine the optimal management of hyperthyroidism in pregnancy, these data provide important real world estimates of gestational ATD exposure and preliminary estimates of adverse outcomes within a large, racially, and ethnically diverse community-based population of women with delivered pregnancy.

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Author Disclosure Statement

All of the authors have no conflicts of interest to declare.

References

1. Burrow GN 1993 Thyroid function and hyperfunction during gestation. *Endocr Rev* **14**:194–202.
2. Galofre JC, Davies TF 2009 Autoimmune thyroid disease in pregnancy: a review. *J Womens Health (Larchmt)* **18**:1847–1856.
3. Negro R, Mestman JH 2011 Thyroid disease in pregnancy. *Best Pract Res Clin Endocrinol Metab* **25**:927–943.

4. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W 2011 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* **21**:1081–1125.
5. Korelitz JJ, McNally DL, Masters MN, Li SX, Xu Y, Rivkees SA 2013 Prevalence of thyrotoxicosis, antithyroid medication use, and complications among pregnant women in the United States. *Thyroid* **23**:758–765.
6. Glinoe D 1998 Thyroid hyperfunction during pregnancy. *Thyroid* **8**:859–864.
7. Lockwood CM, Grenache DG, Gronowski AM 2009 Serum human chorionic gonadotropin concentrations greater than 400,000 IU/L are invariably associated with suppressed serum thyrotropin concentrations. *Thyroid* **19**:863–868.
8. Rodien P, Jordan N, Lefevre A, Royer J, Vasseur C, Savagner F, Bourdelot A, Rohmer V 2004 Abnormal stimulation of the thyrotrophin receptor during gestation. *Hum Reprod Update* **10**:95–105.
9. Kimura M, Amino N, Tamaki H, Ito E, Mitsuda N, Miyai K, Tanizawa O 1993 Gestational thyrotoxicosis and hyperemesis gravidarum: possible role of hCG with higher stimulating activity. *Clin Endocrinol* **38**:345–350.
10. Hershman JM 1999 Human chorionic gonadotropin and the thyroid: hyperemesis gravidarum and trophoblastic tumors. *Thyroid* **9**:653–657.
11. Chan L 2003 Gestational transient thyrotoxicosis. *Am J Emerg Med* **21**:506.
12. Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoe D, Mandel SJ, Stagnaro-Green A 2007 Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* **92**:S1–S47.
13. Barbero P, Valdez R, Rodriguez H, Tiscornia C, Mansilla E, Allons A, Coll S, Liascovich R 2008 Choanal atresia associated with maternal hyperthyroidism treated with methimazole: a case-control study. *Am J Med Genet A* **146A**:2390–2395.
14. Clementi M, Di Gianantonio E, Pelo E, Mammi I, Basile RT, Tenconi R 1999 Methimazole embryopathy: delineation of the phenotype. *Am J Med Genet* **83**:43–46.
15. Di Gianantonio E, Schaefer C, Mastroiacovo PP, Cournot MP, Benedicenti F, Reuvers M, Occupati B, Robert E, Bellemin B, Addis A, Arnon J, Clementi M 2001 Adverse effects of prenatal methimazole exposure. *Teratology* **64**:262–266.
16. Rivkees SA, Mandel SJ 2011 Thyroid disease in pregnancy. *Horm Res Paediatr* **76**(Suppl 1):91–96.
17. Rivkees SA, Mattison DR 2009 Ending propylthiouracil-induced liver failure in children. *N Engl J Med* **360**:1574–1575.
18. Rivkees SA, Mattison DR 2009 Propylthiouracil (PTU) hepatotoxicity in children and recommendations for discontinuation of use. *Int J Pediatr Endocrinol* **2009**:132041.
19. Sequeira E, Wanyonyi S, Dodia R 2011 Severe propylthiouracil-induced hepatotoxicity in pregnancy managed successfully by liver transplantation: a case report. *J Med Case Rep* **5**:461.
20. Hayashida CY, Duarte AJ, Sato AE, Yamashiro-Kanashiro EH 1990 Neonatal hepatitis and lymphocyte sensitization by placental transfer of propylthiouracil. *J Endocrinol Invest* **13**:937–941.
21. Rivkees SA 2010 63 years and 715 days to the “boxed warning”: unmasking of the propylthiouracil problem. *Int J Pediatr Endocrinol* **2010**:658267.
22. Bahn RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, Laurberg P, McDougall IR, Montori VM, Rivkees SA, Ross DS, Sosa JA, Stan MN 2011 Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocr Pract* **17**:456–520.
23. Cooper DS 2005 Antithyroid drugs. *N Engl J Med* **352**:905–917.
24. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, Eastman CJ, Lazarus JH, Luton D, Mandel SJ, Mestman J, Rovet J, Sullivan S 2012 Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* **97**:2543–2565.
25. Lo JC, Feigenbaum SL, Escobar GJ, Yang J, Crites YM, Ferrara A 2006 Increased prevalence of gestational diabetes mellitus among women with diagnosed polycystic ovary syndrome: a population-based study. *Diabetes Care* **29**:1915–1917.
26. Escobar GJ, Fischer A, Kremers R, Usatin MS, Macedo AM, Gardner MN 1997 Rapid retrieval of neonatal outcomes data: the Kaiser Permanente Neonatal Minimum Data Set. *Qual Manag Health Care* **5**:19–33.
27. Wilson A, Gardner MN, Armstrong MA, Folck BF, Escobar GJ 2000 Neonatal assisted ventilation: predictors, frequency, and duration in a mature managed care organization. *Pediatrics* **105**:822–830.
28. Fenton TR 2003 A new growth chart for preterm babies: Babson and Benda's chart updated with recent data and a new format. *BMC Pediatr* **3**:13.
29. Fenton TR, Sauve RS 2007 Using the LMS method to calculate z-scores for the Fenton preterm infant growth chart. *Eur J Clin Nutr* **61**:1380–1385.
30. McLeod DS, Caturegli P, Cooper DS, Matos PG, Hutfless S 2014 Variation in rates of autoimmune thyroid disease by race/ethnicity in US military personnel. *JAMA* **311**:1563–1565.
31. Davis LE, Lucas MJ, Hankins GD, Roark ML, Cunningham FG 1989 Thyrotoxicosis complicating pregnancy. *Am J Obstet Gynecol* **160**:63–70.
32. Millar LK, Wing DA, Leung AS, Koonings PP, Montoro MN, Mestman JH 1994 Low birth weight and preeclampsia in pregnancies complicated by hyperthyroidism. *Obstet Gynecol* **84**:946–949.
33. Momotani N, Ito K 1991 Treatment of pregnant patients with Basedow's disease. *Exp Clin Endocrinol* **97**:268–274.
34. Barbero P, Ricagni C, Mercado G, Bronberg R, Torrado M 2004 Choanal atresia associated with prenatal methimazole exposure: three new patients. *Am J Med Genet A* **129A**:83–86.
35. BOURNAUD C, Orgiazzi J 2003 Antithyroid agents and embryopathies [in French]. *Ann Endocrinol (Paris)* **64**:366–369.
36. Wolf D, Foulds N, Daya H 2006 Antenatal carbimazole and choanal atresia: a new embryopathy. *Arch Otolaryngol Head Neck Surg* **132**:1009–1011.
37. Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, Anderson P, Mason CA, Collins JS, Kirby RS, Correa A 2010 Updated National Birth Prevalence

- estimates for selected birth defects in the United States, 2004–2006. *Birth Defects Res A Clin Mol Teratol* **88**: 1008–1016.
38. Yoshihara A, Noh J, Yamaguchi T, Ohye H, Sato S, Sekiya K, Kosuga Y, Suzuki M, Matsumoto M, Kunii Y, Watanabe N, Mukasa K, Ito K 2012 Treatment of Graves' disease with antithyroid drugs in the first trimester of pregnancy and the prevalence of congenital malformation. *J Clin Endocrinol Metab* **97**:2396–2403.
 39. Gurlek A, Cobankara V, Bayraktar M 1997 Liver tests in hyperthyroidism: effect of antithyroid therapy. *J Clin Gastroenterol* **24**:180–183.
 40. Liaw YF, Huang MJ, Fan KD, Li KL, Wu SS, Chen TJ 1993 Hepatic injury during propylthiouracil therapy in patients with hyperthyroidism. A cohort study. *Ann Intern Med* **118**:424–428.
 41. Yoshihara A, Noh JY, Watanabe N, Iwaku K, Kobayashi S, Suzuki M, Ohye H, Matsumoto M, Kunii Y, Mukasa K, Sugino K, Ito K 2014 Frequency of adverse events of antithyroid drugs administered during pregnancy. *J Thyroid Res* **2014**:952352.
 42. Otsuka F, Noh JY, Chino T, Shimizu T, Mukasa K, Ito K, Taniyama M 2012 Hepatotoxicity and cutaneous reactions after antithyroid drug administration. *Clin Endocrinol* **77**:310–315.
 43. Laurberg P, Andersen SL 2014 Therapy of endocrine disease: antithyroid drug use in early pregnancy and birth defects: time windows of relative safety and high risk? *Eur J Endocrinol* **171**:R13–R20.

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