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Association of maternal thyroid dysfunction and autoimmunity with adverse birth outcomes

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Abstract

This study aimed to explore the relationship between thyroid function and autoimmunity and adverse birth outcomes. Serum levels of thyroid function were detected by electrochemiluminescence assay. Urine iodine concentration was detected using the acid digestion method. We used multiple linear regression to assess the correlation between thyroid function indicators and birth weight according to trimester stratification and binary logistic regression to evaluate the correlation between thyroid dysfunction and adverse birth outcomes. Reference ranges for trimester-specific thyroid hormones were established in our 2564 pregnant women cohort with mild iodine deficiency. The higher the maternal thyroid-stimulating hormone in the first trimester (B = 0.09, $P = 0.048$) and total triiodothyronine (TT3) in the third trimester (B = 0.16, $P < 0.001$) of TPOAbnegative women, the higher the birth weight Z-score, whereas in the second trimester, free-thyroxine of mothers with TPOAb negative was lower (B = −0.10, $P = 0.026$) and the birth weight Z-score was higher. Pregnant women with overt and subclinical hyperthyroidism had a higher risk of preterm births than euthyroid women (11.9% vs 4.5%; odds ratio (OR): 2.84; $P = 0.009$). Women with higher TT3 had a higher risk of preterm (17.0% vs 4.5%; OR: 4.19; $P < 0.001$) and LGA (34.0% vs 11.1%; OR: 3.70; $P < 0.001$) births than euthyroid women. In conclusion, thyroid function during pregnancy could affect birth weight and birth outcome.

Introduction

Birth weight is an important index of intrauterine growth and fetus development and its adaptation to the intrauterine environment. Birth weight is associated with the growth and development of the fetus after delivery. Some studies have shown that birth weight may even be related to the risk of chronic non-communicable diseases during adulthood (1). Small for gestational age (SGA), which reflects fetal intrauterine growth restriction, is a major risk factor for perinatal morbidity and adult cardiovascular metabolic syndrome (2, 3, 4). In contrast, large for gestational age (LGA) is associated with increased risk for obstructed labor, postpartum hemorrhage,

newborn hypoglycemia, obesity, and diabetes mellitus in adulthood (2, 5, 6).

Thyroid hormones can regulate metabolism associated with basal metabolic rate and body composition (7, 8). In general, the thyroid-stimulating hormone (TSH) is positively correlated with BMI, whereas total thyroxine (TT4) and free thyroxine (FT4) are negatively correlated with BMI in adults (9). Maternal TSH and FT4 can pass through the placental barrier and affect fetal growth and development, especially before the maturation of the thyroid gland at 18–20 weeks of gestational age (10, 11). Overt hypothyroidism and hyperthyroidism have a

high risk of light birth weight or SGA births (11). Mild thyroid dysfunction, which is more prevalent than overt hypothyroidism, is associated with SGA and LGA according to some studies (12, 13, 14, 15) but not in other studies (16, 17). In euthyroid pregnant women, the effect of thyroid hormones on birth weight remains controversial (18, 19). In addition, the effects of total triiodothyronine (TT3) on birth outcomes remain to be confirmed (20).

Due to the physiological characteristics of pregnancy, thyroid volume increases by 10–40% and is accompanied by a ~50% increase in T3 and T4 levels (21). TSH levels significantly decrease during early pregnancy in response to elevated placental human chorionic gonadotropin (hCG)-stimulating TSH receptors and vary based on geography, ethnicity, BMI, iodine nutritional status, and detection method (22, 23, 24). In 2017, the American Thyroid Association (ATA) recommended the establishment of population-, trimester-, and method-specific reference ranges for thyroid hormones during pregnancy, which is helpful to more scientifically determinate thyroid dysfunction in pregnant women (21).

The objective of our study was to investigate the relationship between trimester-specific maternal thyroid function and birth weight and birth outcomes, on the premise of considering iodine status, reference range of thyroid hormones, and thyroid autoimmunity of pregnant women.

Methods

Study design

We obtained the data from a pregnant study conducted in Shanghai, China, from April to October 2017 (25). The Ethical Committee of the Shanghai Center for Disease Control and Prevention approved the study (no. 2017-13), and all participants provided written informed consent. The study recruited pregnant women at different trimesters living in Shanghai for the past 6 months. On enrollment, we obtained demographic information (e.g. maternal age, pre-pregnancy height and weight, parity, maternal educational level, and household income) using a face-to-face questionnaire interview. Information on infant birth weight, gestational age, and infant sex was obtained from medical records. Exclusion criteria included participants who had a previous history of diabetes, thyroid disease, and goiter or thyroid drug use; participants using assisted reproductive treatment; participants with twin pregnancies; participants without

thyroid function test or anthropometric data. We finally analyzed 2564 analytic samples using a Cobas e 602 (Roche) instrument.

Birth weight Z-score and definition of birth outcomes

The primary outcomes of our study were preterm birth, SGA, LGA, and birth weight Z-score as a continuous variable. We established the sex-specific birth weight-for-gestational age Z-scores using the GAMLSS package in R (26). We defined SGA as neonatal sex and gestational age at delivery-adjusted birth weight less than 10th percentile of this study cohort, LGA as neonatal sex and gestational age at delivery-adjusted birth weight more than 90th percentile of this study cohort (2), and preterm birth as gestational age at birth less than 37 weeks (27).

Assessment of maternal thyroid function test

We obtained 5 mL of venous blood from the mothers and centrifuged the samples at 1800 $\boldsymbol{g}$ for 10 min. The serum was separated and stored at –80°C. We detected serum levels of TSH, FT3, FT4, TT4, TT3, TGAb, and TPOAb using an automatic luminescent immune analyzer (Cobas e 602; Roche). The intra- and interassay coefficients of variation were 1.0–1.8% for TSH, 1.3–2.1% for FT4, 1.5–2.5% for FT3, 1.1–2.4% for TT3, 0.9–2.1% for TT4, and 3.9–5.0% for both TGAb and TPOAb. TPOAb positivity was defined as TPOAb ≥ 34 IU/mL, and TGAb positivity was defined as TgAb ≥ 115 IU/mL (28). The reference range of thyroid hormones was defined according to cohort-specific 2.5thand 97.5th percentiles for TSH, FT3, FT4, TT3, and TT4 after excluding TPOAb-positive or TgAb-positive women without thyroid disease history and goiters.

We defined overt hypothyroidism as TSH concentration over the 97.5th percentile with an FT4 concentration below the 2.5th percentile. Subclinical hypothyroidism was defined as TSH concentration above the 97.5th percentile with an FT4 concentration within the normal range (2.5th to 97.5th percentile). We defined isolated hypothyroxinemia as FT4 concentration below the 2.5th percentile with a TSH concentration within the normal range. Overt hyperthyroidism was defined as TSH concentration below the 2.5th percentile with an FT4 concentration above the 97.5thpercentile, while subclinical hyperthyroidism was defined as TSH concentration below the 2.5th percentile with an FT4 concentration within the normal range. We defined high TT3 as TT3 concentration above the 97.5th percentile (29).

Analysis of urine iodine concentration

We collected spot urine samples from the pregnant women and determined urinary iodine concentration (UIC) using the acid digestion method (As^{3+}-Ce^{4+}catalytic spectrophotometry) in the Shanghai Municipal Center for Disease Prevention and Control (30). The iodine status of pregnant women was determined according to WHO criteria (2007) (31). The median UIC in pregnant women <150, 150–249, 250–499, and ≥ 500 μg/L were indicative of insufficient iodine intake, adequate iodine intake, intake above requirements, and excessive iodine intake, respectively. The pregnant women with median UIC 100–149 μg/L were considered to have mild iodine deficiency (31).

Statistical analyses

Descriptive statistics of demographic characteristics were presented by different trimesters. The first, second, and third trimesters are at gestational weeks 0–12, 13–27, and 28–40, respectively. Maternal age and gestational week at the time of sampling were continuous variables of normal distribution expressed as the mean (s.d.). Other categorical variables were described as frequencies and percentages (proportion (%)).

We expressed trimester-specific thyroid function test results and UIC as median and reference intervals. The reference range of thyroid function tests and UIC were estimated by the 2.5th and 97.5th percentile of the distribution of the study population. We reported the prevalence of positive thyroid autoimmunity as proportions and 95% CIs. We used Mann–Whitney test to compare thyroid function tests and UIC in different trimesters.

We established multiple linear regression models with neonatal birth weight Z score as the dependent variable and single thyroid function parameter as the independent variable. After analyzing the crude regression model, maternal age, parity, maternal education, pre-pregnancy BMI, educational level, and gestational age at sampling were subsequently added to the model. We used logistic mixed regression models to study the association between thyroid function test abnormalities (compared with euthyroidism) and SGA, LAG, and preterm births. We used multilevel multiple imputation for missing data on covariates (28).

For data analysis, we used the Statistical Package of Social Sciences version 22.0 for Windows (IBM Corp) and R statistical software version 3.4.1 (R Institute, Inc., Cary, NC, USA). Two-sided $P < 0.05$ was considered statistically significant.

Results

Characteristics of participants

Among 2564 pregnant women, 801 were in the first trimester, 1001 were in the second trimester, and 762 were in the third trimester. Each participant was surveyed only once during pregnancy. The average maternal age was 29.43 (s.d. 4.40) years, and the average neonatal birth weight was 3328.04 (s.d. 463.07) g. The median gestational age was 20.00 (95% CI: 7.00–37.00) weeks, and gestational age at birth was 39.00 (95% CI: 36.00–41.00) weeks. Maternal demographic information for women at different trimesters was presented in Table 1. The prevalence of preterm birth, SGA, and LGA was 4.6, 11.0, and 11.1%, respectively. Except for maternal age ($P = 0.02$), education level ($P = 0.02$), and prevalence of preterm birth ($P = 0.04$), there were no significant differences in the distribution of other demographic characteristics among the three trimesters (Table 1).

Trimester-specific reference range of thyroid function

In the first, second, and third trimesters, the positive rates of TPOAb were 5.48, 3.47, and 1.82%, respectively, and the positive rates of TgAb were 13.97, 11.91, and 8.24%, respectively. The positive rates of both TPOAb and TGAb were 3.99, 2.85, and 0.96% in the first, second, and third trimesters, respectively. Median UIC was 156.05, 133.00, and 135.25 μg/L, respectively. After excluding the existing thyroid diseases and thyroid autoimmunity positive, the median and reference interval (2.5–97.5th percentile) in the first, second, and third trimesters was presented in Table 2. There were significantly different thyroid hormone levels among the three trimesters (All $P < 0.001$). According to the median and 95% CIs, serum TSH levels had an upward trend during pregnancy with the lowest level in the first trimester. FT4 and FT3 levels had the opposite pattern; the highest levels in the first trimester gradually declined during pregnancy (Table 2).

Association between birth weight Z-score and trimester-specific thyroid hormones in women with TPOAb-negative

After excluding 46 TPOAb-positive pregnant women, adjusting for covariates, including maternal age, parity, gestational week at blood sampling, pre-pregnancy BMI, the Z-score of newborn birth weight was significantly positively correlated with TSH in the first trimester and TT3 in the third trimester but negatively correlated with FT4 in

Table 1 Comparison of demographic and pregnancy characteristics between study groups at different trimesters.

	All		First trimester		Second trimester		Third trimester		P value
	n	%/mean (S.D.)/median (95% range)	n	%/mean (S.D.)/median (95% range)	n	%/mean (S.D.)/median (95% range)	n	%/mean (S.D.)/median (95% range)	
Age, years	2564	29.43 (4.40)	801	29.78 (4.29)	1001	29.29 (4.33)	762	29.24 (4.60)	0.02[a]
Gestational week at sampling, weeks	2564	20.00 (7.00–37.00)	801	10.00 (6.00–12.00)	1001	20.00 (13.00–27.00)	762	32.00 (28.00–38.00)	<0.001[b]
Gestational week at birth, weeks	2477	39.00 (36.00–41.00)	747	39.00 (35.00–41.00)	975	39.00 (36.00–41.00)	755	39.00 (36.00–41.00)	0.17
Birth weight, g	2472	3328.04 (463.07)	746	3305.92 (470.12)	974	3336.86 (475.89)	752	3338.57 (438.38)	0.30
Parity	2563		800		1001		762		0.05
Firstborn	2524	98.5%	781	97.6%	988	98.7%	755	99.1%	
Secondborn	39	1.5%	19	2.4%	13	1.3%	7	0.9%	
Educational level	2291		753		906		632		**0.02**
High school or less	500	21.8%	135	17.9%	205	22.6%	160	25.3%	
College	734	32.0%	252	33.5%	290	32.0%	192	30.4%	
University or higher	1057	46.1%	366	48.6%	411	45.4%	280	44.3%	
Total annual household income	2283		751		902		630		0.19
Low, ≤99,000 yuan per year	400	17.5%	120	16.0%	154	17.1%	126	20.0%	
Middle, 10,000–249,000 yuan per year	1352	59.2%	440	58.6%	545	60.4%	367	58.3%	
High, ≥250,000 yuan per year	531	23.3%	191	25.4%	203	22.5%	137	21.7%	
Smoking habits	2295		754		908		633		0.65
Never smokes	2219	96.7%	727	96.4%	875	96.4%	617	97.5%	
Stopped before pregnancy	61	2.7%	21	2.80%	28	3.1%	12	1.9%	
Current smoker	15	0.6%	6	0.8%	5	0.6%	4	0.6%	
Alcohol intake	2295		754		908		633		0.08
Never drinker	2051	89.4%	687	91.1%	792	87.2%	572	90.4%	
Stopped before pregnancy	212	9.2%	56	7.4%	102	11.2%	54	8.5%	
Current drinker	32	1.4%	11	1.5%	14	1.5%	7	1.1%	
Pre-pregnant BMI, kg/m²	2292		753		906		633		0.56
Underweight, BMI <18.5 kg/m²	304	13.3%	108	14.3%	119	13.1%	77	12.2%	
Normal weight, BMI = 18.5–24.9 kg/m²	1749	76.3%	562	74.6%	690	76.2%	497	78.5%	
Overweight/Obesity, BMI ≥25.0 kg/m²	239	10.4%	83	11.0%	97	10.7%	59	9.3%	
Adverse birth outcomes									
Prevalence of preterm birth	113/2468	4.6%	45/744	6.0%	43/972	4.4%	25/752	3.3%	**0.04**
Prevalence of SGA	245/2225	11.0%	63/679	9.3%	112/866	12.9%	70/680	10.3%	0.06
Prevalence of LGA	247/2227	11.1%	67/683	9.8%	108/862	12.5%	72/682	10.6%	0.21

[a]ANOVA, $P < 0.05$; [b]Kruskal–Wallis test, $P < 0.05$. Demographic characteristics were presented as frequency (proportion (%)). Gestational weight gain and birth weight were expressed as the mean (S.D.). LGA, large for gestational age; SGA, small for gestational age.
Bold indicates statistical significance among different pregnancy periods.

the second trimester. An increase of 1 mU/L maternal TSH in the first trimester was associated with an increase in the newborn's birth weight Z score by 0.09 units (95% CI: 0.00 to 0.13; $P = 0.048$) in women. For each 1 nmol/L increase of TT3 in the third trimester for TPOAb negative women, the newborn's birth weight Z-score increased by 0.16 units (95% CI: 0.14 to 0.50; $P < 0.001$). In contrast, an increase of 1 pmol/L FT4 in the second trimester was associated with a –0.10 units (95% CI: –0.08 to –0.01) reduction in the newborn's birth weight Z-score ($P = 0.026$) (Table 3). Other thyroid hormones were not significantly associated with newborn's birth weight Z-score after adjustment.

Effect of thyroid function abnormalities on preterm birth, SGA, and LGA

There were 113/2468 (4.6%) preterm, 245/2225 (11.0%) SGA, and 247/2227 (11.1%) LGA births (Fig. 1A, B and C). Thyroid dysfunction was defined according to the cohort-specific 2.5th to 97.5th percentile cutoffs. Among the pregnant women, a total of 50 (2.0%) had overt or subclinical hypothyroidism (increased TSH concentration), 53 (2.2%) had isolated hypothyroxinemia (decreased FT4 concentration with normal TSH concentration), 59 (2.4%) had overt or subclinical hyperthyroidism (decreased TSH concentration), 53 (2.2%) had high TT3 (increased TT3 concentration), and 301 (12.3%) were TPOAb or TgAb positive.

The risk of preterm births was higher in women with overt or subclinical hyperthyroidism than in euthyroid women (11.9% vs 4.5%; odds ratio (OR), 2.84; 95% CI: 1.25–6.43; $P = 0.009$) (Fig. 1A). Women with high TT3 had a higher risk of preterm (17.0% vs 4.5%; OR: 4.19; 95% CI: 2.00–8.78; $P < 0.001$) (Fig. 1A) and LGA births (34.0% vs 11.1%; OR: 3.70; 95% CI: 2.06–6.67; $P < 0.001$) compared to euthyroid women (Fig. 1C). Compared with euthyroid pregnant women, women with thyroid autoimmunity and hypothyroidism (overt or subclinical hypothyroidism and isolated hypothyroxinemia) had no significant risks of adverse birth outcomes (e.g. preterm, SGA, and LGA births).

Discussion

In this large pregnant women study, we established a cohort-specific reference range of thyroid hormones for three trimesters. Our findings revealed that neonatal birth weight Z-score was positively associated with maternal TSH levels in the first trimester ($P = 0.048$) and TT3 levels in the third trimester ($P < 0.001$) and

inversely associated with the FT4 levels in the second trimester ($P = 0.026$) of TPOAb-negative pregnant women. According to the cohort-specific cut-off values of TSH, FT4, and TT3 for thyroid dysfunction, overt and subclinical hyperthyroidism was risk factors for preterm births compared to euthyroidism. Women with higher TT3 levels had a significantly greater incidence of preterm and LGA births.

In our pregnant women cohort with mild iodine deficiency (31), median TSH was 1.21 (0.02–4.43), 1.76 (0.09–4.49), and 1.92 (0.50–4.99) mU/L for the first, second, and third trimesters, respectively ($P < 0.001$), showing a significantly increasing trend. The clear trend was consistent with previous investigations (32, 33, 34). Most previous studies have paid more attention to the cut-off values of TSH in early pregnancy, which is considered to have a considerable impact on fetal development due to immature thyroid glands. The upper limit of TSH in early pregnancy in our study was 4.43 mU/L, which was close to the value (4.0 mU/L) established by the American Thyroid Association (ATA) in 2017 (21), lower than the upper limit (5.0 mU/L) in India (35), and higher than 3.39 mU/L from the Netherlands, and 3.75 mU/L from Northern Finland (36, 37). The differences among the studies may be attributed to ethnicity, assay method, and iodine status. In view of the cohort differences in the reference range of TSH, when using the TSH upper limit of 2.5 mU/L recommended by ATA in 2011 or 4.0 mU/L recommended by ATA in 2017, a certain proportion of pregnant women in the present study would be misdiagnosed with subclinical hypothyroidism (21, 38).

Pregnant women with hyperthyroidism are prone to fetal growth restriction (39, 40). The present study supported this finding and further suggested that the critical period affecting neonatal birth weight is the first trimester for maternal TSH and the second trimester for maternal FT4. One potential explanation is the effect of hyperthyroidism on increasing the degradation of proteins and lipids, leading to chronic caloric deficiency and birth weight loss (41). Another hypothesis is that higher FT4 levels may promote insulin release and lower glucose levels, thereby limiting fetal weight gain (42). The finding that FT4 plays a major metabolic effect at mid-pregnancy is consistent with the fact that fetal weight gain weight mainly occurs after 24 weeks of gestation (43). Even though some studies support positive correlations between birth weight and maternal TSH in early pregnancy (14, 18), there are studies that have found no or an inverse correlation (10, 12, 13, 20), which may be explained by the role of human chorionic gonadotropin and the differences in timing of blood sampling and fetal sex. The

Table 2 Reference interval of thyroid function parameters by different trimesters.

	First trimester		Second trimester		Third trimester		**P**[b]
	Median	2.5th–97.5th[a]	Median	2.5th–97.5th	Median	2.5th–97.5th	
Thyroid function							
TSH, mU/L	1.21	0.02–4.43	1.76	0.09–4.49	1.92	0.50–4.99	<0.001
FT4, pmol/L	16.02	12.48–24.89	13.33	9.91–18.12	12.11	9.01–17.01	<0.001
TT4, pmol/L	128.00	82.25–203.00	128.00	84.47–187.69	123.00	79.07–176.75	<0.001
FT3,pg/mL	4.67	3.63–6.84	4.15	3.22–5.64	3.86	3.06–5.08	<0.001
TT3, nmol/L	2.06	1.35–3.24	2.31	1.46–3.49	2.27	1.43–3.34	<0.001
Thyroid antibodies							
TPOAb, IU/mL	10.98	2.50–27.51	10.20	2.50–44.23	11.55	4.99–37.30	<0.001
TPOAb positive[c], %	5.48		3.47		1.82		<0.001
Tg-Ab,IU/mL	10.00	5.00–22.71	10.00	2.68–23.96	10.00	5.00–24.66	0.78
Tg-Ab positive[c], %,	13.97		11.91		8.24		0.002
TPOAb and Tg-Ab positive, %	3.99		2.85		0.96		0.001
Urine iodine							
UIC, µg/L	156.05	21.52–923.30	133.00	15.55–583.21	135.25	21.03–461.87	<0.001

[a]Trimester-specific reference ranges calculated for this study population with mild iodine deficiency (100–149 µg/L) who are free of thyroid autoantibodies; [c]TPOAb titers greater than 34 IU/mL and Tg-Ab titers greater than 115 IU/mL were considered positive.

impact of subclinical hypothyroidism on birth outcomes remains controversial. Recent studies have shown that subclinical hypothyroidism may be related to some adverse pregnancy outcomes, such as premature delivery and low birth weight (12, 14, 44). Unfortunately, the association was not found in this study and some other studies (16, 17). This may be due to the difference in the proportion of women in early pregnancy in different studies. For example, 46.7% of early pregnancy participants in Sun Y. Lee' study found a correlation between the two (44), while only one-third of early pregnant women in this study did not find such a correlation. After all, subclinical hypothyroidism in early pregnancy may have a greater impact on birth outcomes (14, 44).

Another important finding of our study is that maternal TT3 levels in the third trimester were positively correlated with neonatal birth weight Z score and that higher maternal TT3 levels were associated with increased risks of preterm and LGA births. Researchers have paid more attention to the effect of TSH and FT4 on birth outcomes, while TT3 level has received less attention and

detection in previous studies. Fortunately, some recent studies conducted in China and United States reported similar findings. Zhang and his colleagues found that lower levels of TT3 in early and late pregnancy were associated with lower birth weight in 46,186 pregnant women (20). Another study involving 5016 mother and infant pairs suggested that higher TT3 levels were positively associated with a greater incidence of LGA and macrosomic infants (19). Study results from LIFECODES cohort presented a positive relationship between TT3 and birth weight Z scores at about 26 weeks of gestation (13). Our research further supported this conclusion. However, the mechanism by which TT3 promotes fetal weight remains unclear. It is possible that TT3 may increase fetal weight by promoting fetal anabolism and stimulating fetal mitochondrial oxidative capacity, especially in fetal fat and skeletal muscle (45). TT3 may also play an indirect role in controlling the bioavailability of growth regulatory factors and regulation of endocrine systems that affect fetal development and growth, such as catecholamines and insulin-like growth factor (10). Interestingly, we also found

Table 3 Multivariate line associations between maternal thyroid hormones and birth weight Z-score in women with TPOAb-negative.

Indicators	First trimester (*n* = 746)		Second trimester (*n* = 958)		Third trimester (*n* =745)	
	B (95% CI)	*p*	B (95% CI)	*p*	B (95% CI)	*p*
TSH	**0.09 (0.00, 0.13)**	**0.048**	−0.02 (−0.09, 0.06)	0.62	−0.04 (−0.10, 0.04)	0.34
FT3	0.02 (−0.07, 0.11)	0.74	0.06 (−0.04, 0.22)	0.19	0.03 (−0.08, 0.18)	0.51
FT4	−0.01 (−0.03, 0.02)	0.89	**−0.10 (−0.08, −0.01)**	**0.026**	−0.06 (−0.06, 0.01)	0.15
TT3	0.03 (−0.12, 0.23)	0.52	0.06 (−0.04, 0.28)	0.15	**0.16 (0.14, 0.50)**	**<0.001**
TT4	−0.00 (−0.01, 0.01)	0.93	−0.06 (−0.01, 0.01)	0.13	0.05 (−0.00, 0.01)	0.27

[b]Model was adjusted for maternal age, parity, gestational age at blood sample, pre-pregnancy BMI, maternal education level, and family income level. Bold text indicates *P* < 0.05.
TT3, total triiodothyronine; TT4, total thyroxine; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine.
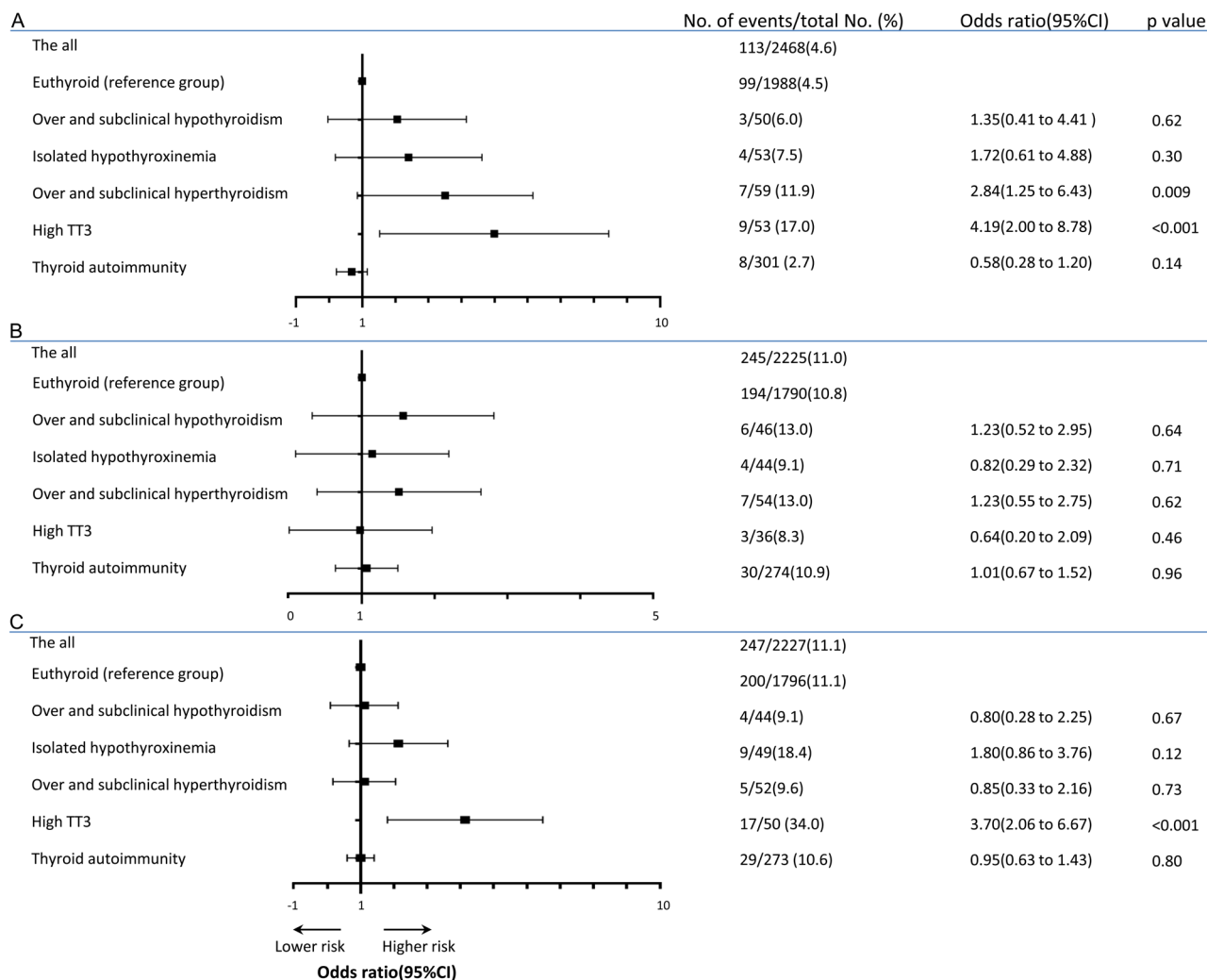
Figure 1
Odds ratio (95%CI) of thyroid dysfunction to (A) preterm birth, (B) SGA, and (C) LGA births.

that high levels of TT3 increased the risk of preterm birth, which reflected the role of TT3 in promoting *prepartum* maturation. The synergistic effect of T3 and cortisol can change the cell cycle from proliferation to differentiation in a series of fetal tissues necessary for neonatal survival (10). The increase of prenatal T3 bioavailability may at least partially mediate the maturation effect of endogenous cortisol and exogenous synthetic glucocorticoids. These changes may make various fetal tissues mature, such as lung gas exchange, cardiac function adaptation, hepatic glycogen production, and thermogenesis (46). These changes are essential for fetal survival and adaptation to the extrauterine environment immediately after birth while more studies are needed to confirm our results.

Our study had several advantages. First, this study is a large sample of mother and infant pairs. We determined the trimester-specific reference range of thyroid hormones

for pregnant women with normal thyroid autoimmunity and used trimester-specific reference ranges in this cohort to define thyroid function abnormalities. Secondly, our participants were evenly recruited from three pregnancy periods. Therefore, we were able to assess the impact of thyroid function during different stages of pregnancy on offspring birth weight. Thirdly, because TPOAb positive may aggravate the effect of TSH on fetal development, we analyzed the correlation between thyroid hormone and birth weight under different TPO AB States, and there were few studies in this regard. Fourthly, we comprehensively analyzed confounding factors, including pre-pregnancy BMI, which affects thyroid function during pregnancy and neonatal birth weight; UIC, which reflects the iodine nutritional status of the study population and affects T4 biosynthesis during pregnancy. However, our study had some limitations. First, due to different laboratory assays

used to assess thyroid function, we excluded data from 1654 pregnant women, which may affect the integrity of the results. Secondly, pre-pregnancy weight was self-reported, thereby possibly contributing to underestimation.

Conclusion

In conclusion, thyroid function during pregnancy could affect birth weight and birth outcomes.

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