Relationship of Trimester-Specific Maternal Thyroid Function With Gestational Weight Gain And Birth Weight In Pregnant Women With Normal Thyroid Autoimmunity

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Abstract

Background: Gestational weight gain (GWG) and birth weight are important indicators of maternal and infant health outcomes. Thyroid function may affect body composition and fetal growth during pregnancy. So far, on the premise of excluding thyroid autoimmunity interference, the correlation of thyroid function in different pregnancy with neonatal birth weight and maternal weight gain is still controversial.

Methods: This study used data from a prospective birth cohort in Shanghai, China. Serum concentration of TSH, total thyroxine (TT4), free thyroxine (FT4), total triiodothyronine (TT3), free triiodothyronine (FT3), thyroglobulin antibody (TGAb), thyroid peroxidase antibody (TPOAb) were determined using chemiluminescence assay. Maternal GWG and neonatal sex-specific birth weight-for-gestational age Z-score was calculated.

Results: Subjects with a higher BMI before pregnancy turned to have a lower GWG and an infant with a higher birth weight. GWG was negatively associated with maternal FT4 at the first and third trimester ($p < 0.05$), and TT4 at the third trimester ($p < 0.05$). GWG was positively associated with maternal FT3 at the second trimester ($p < 0.05$). Lower birth weight Z-score were associated with higher FT4 at the second and third trimester ($p < 0.05$), and higher TT4 at the second trimester ($p < 0.05$).

Conclusions: In the general pregnant population with normal thyroid autoimmunity, higher maternal FT4 and TT4 and lower FT3 are associated with less GWG. Higher maternal FT4 and TT4 have an infant with lower birth weight.

Background

Gestational weight gain (GWG) is an important indicator of maternal and fetal health outcomes [1, 2]. Excessive or insufficient GWG have been associated with higher risk of various unfavorable maternal and infant outcomes, such as gestational diabetes mellitus, exacerbation of asthma, large for gestational age (LGA), small for gestational age (SGA) and preterm birth [2–4]. The Institute of Medicine (IOM) recommends maintaining proper GWG during pregnancy, taking into account pre-pregnancy BMI, to reduce the risk of adverse birth outcomes [5]. Birth weight could comprehensively reflect fetal development, nutrition and adaptation to intrauterine environments. It is considered to be an important indicator of fetal and postnatal health growth and development, and some studies have even shown that it may be associated with risks of chronic non-communicable diseases, such as obesity, diabetes mellitus in adulthood [6–8].

Thyroid hormones regulate body weight, body temperature, total and rest energy expenditure related to basal metabolic rate and body composition [9]. It was found that TSH correlates positively with body mass index (BMI), whereas total thyroxine (TT4) and free thyroxine (FT4) are negatively correlated with BMI in adults [10, 11]. During pregnancy, the thyroid gland increases in size by 10%–40% with T3 and T4 synthesis increasing by nearly 50% [12]. Maternal weight gain and fetal birth weight could also be affected by maternal thyroid hormone-related changes. Previous studies showed maternal FT4 level was related to pregnancy BMI and GWG [13]. A prospective study of 430 mother-infant pairs found that maternal and neonatal free triiodothyronine (FT3) were also significantly associated with infant birth weight [14]. In a recent large prospective study of Chinese population, Zhou observed that maternal TSH and FT4 concentration were negatively associated with birth weight, while GWG may play a synergistic role [15]. Thus far, there is still controversy about which trimester and to what extent thyroid hormone plays effect on GWG and birth weight. Meanwhile, these studies almost ignored thyroid antibodies, although the incidence of TPOAb-positive or TGAb-positive during pregnancy reached 2–17% and increased the risk of adverse birth outcomes [12, 16].

Therefore, the objective of the present study was to investigate the association between trimester-specific maternal thyroid function with GWG and birth weight in pregnant women with normal thyroid autoimmunity.

Methods

2.1 Study design

The present data was from a prospective birth cohort focusing on iodine nutritional status of pregnant women, thyroid function and the growth and development of their offspring in Shanghai, China, from April to October, 2017. A detailed description of the cohort is given in a previous paper [17]. This study was approved by the Ethical Committee of the Shanghai Center for Disease Control and Prevention (No. 2017-13). All participants provided written informed consents. The study enrolled 5485 pregnant women living in 16 districts of Shanghai over 6 months. The number of pregnant women fairly equally recruited from three trimesters (0–12 weeks, first trimester; 13–27 weeks, second trimester; and 28–40 weeks, third trimester). At enrollment, demographic data were collected using a face-to-face questionnaire interview. We excluded pregnant women with a prior history of diabetes, thyroid medication usage, thyroid disease, those treated using assisted reproductive, and twin pregnancies ($n = 303$); we also excluded those women lacking thyroid function test parameters or anthropometry data ($n = 502$), or outside the extreme value of thyroid function parameters ($n = 56$), as well as those with TPO-Ab positive or TgAb positive ($n = 579$). The final analytic sample thus comprised 4045 women.

2.2 Maternal anthropometrics and GWG and birth weight Z-score

Maternal anthropometrics were assessed at the recruitment visit. Maternal weight (kg) and height (cm) were determined without heavy clothing and shoes. Pre-pregnancy body mass index (BMI) was calculated by dividing the self-reported pre-pregnancy weight (kg) by the square of height (m) ($\text{BMI} = \text{weight [kg]} / \text{height squared [m}^2\text{]}$).

Subjects were categorized as underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$), normal weight ($\text{BMI} = 18.5–24.9 \text{ kg/m}^2$), and overweight/obese ($\text{BMI} \geq 25.0 \text{ kg/m}^2$) based on their pre-pregnancy BMI ($\text{weight (kg)} / \text{height squared (m}^2\text{)}$). Maternal postpartum weight, infant birth weight and gestational age at birth were obtained from medical records. Postpartum weight was measured just after delivery, and $\text{GWG} = \text{postpartum weight} - \text{pre-pregnancy weight}$ [18]. Sex-specific birth weight-for-

gestational age Z-score were established using the GAMLSS package in R [19]. Covariates information about maternal age, pre-pregnancy BMI, parity, maternal educational level and household income was assessed by questionnaires.

2.3 Assessment of maternal thyroid function and urinary iodine

Venous blood was acquired from consenting participants at enrollment. Coagulant vacuum tubes were centrifuged 10 min at $1800 \times g$ and serum was separated and stored at -80°C until testing. Serum levels of thyroid function parameters (TSH, FT3, FT4, TT4, TT3, TGAb, TPOAb) were detected by automatic luminescent immune analyzer (Cobas e 602; Roche., Switzerland or ADVIA Centaur XP; Siemens., German or DSI 800; Beckmen., the USA) at community medical service centers. The intra- and inter-assay coefficients of variation in all detection systems accorded to the clinical requirement. TPOAb positivity and TGAb positivity was defined as $\text{TPOAb} \geq 34 \text{ IU/mL}$ or $\text{TgAb} \geq 115 \text{ IU/mL}$ for Cobas e 602, $\text{TPOAb} \geq 9 \text{ IU/mL}$ or $\text{TgAb} \geq 4 \text{ IU/mL}$ for DXI800, $\text{TPOAb} \geq 60 \text{ U/mL}$ or $\text{TgAb} \geq 60 \text{ U/mL}$ for ADVIA Centaur XP. Spot urine sample were collected from pregnant women. The urinary iodine concentrations were determined using the acid digestion method (As^{3+} - Ce^{4+} catalytic spectrophotometry) in the Shanghai Municipal Center for Disease Prevention and Control.

2.4 Statistical analyses

Descriptive statistics were presented by pre-pregnancy BMI group. The demographic characteristics were presented as frequency [proportion (%)]. GWG and birth weight were expressed as the mean [standard deviance (SD)], respectively.

Because of the deviation of reference ranges caused by the instruments, the data of the thyroid function in each research center cannot be analyzed directly. Therefore, the data of the thyroid function in each research center were divided into quartiles for subsequent statistical analysis and comparison. Multiple linear regression models were constructed using neonatal birth weight-Z score and GWG as dependent variables and single thyroid hormone quartiles as predictors. The lowest quartile of the thyroid hormone was used as the reference group. The initial crude regression models were subsequently adjusted for maternal age, gestational age at sampling, parity, maternal education, pre-pregnancy BMI, urinary iodine, and household income.

Data were analyzed using the R software (R Institute, Inc., Cary, NC, USA). A two-sided P value ≤ 0.05 was considered statistically significant.

Results

3.1 Participants' characteristics

Among the 4045 participants, 2845 pregnant women had a normal pre-pregnancy BMI (70.33%). The study participants were primarily 26–30 years old (43.85%), pregnant with their firstborn (60.74%). In addition, approximately half of the participants had a Bachelor's degree or higher (43.97%), and many had a medium annual household income (59.26%). Only three women reported cigarette smoking and about 1% of the women consumed alcohol during pregnancy. Subjects with a higher BMI before pregnancy turned to have a lower GWG and an infant with a higher birth weight. The GWG values were $8.36 \pm 5.80 \text{ kg}$, $7.06 \pm 1.96 \text{ kg}$, and $4.22 \pm 3.74 \text{ kg}$, and the neonatal birth weights were $3222.89 \pm 397.04 \text{ g}$, $3325.11 \pm 442.04 \text{ g}$, and $3438.24 \pm 449.77 \text{ g}$ for women categorized as pre-pregnancy underweight, normal weight, and overweight/obesity, respectively (Table 1).

Table 1
Demographic, pregnancy and delivery characteristics of study participants, stratified by pre-pregnant body mass index (BMI)

Demographic features	Pre-pregnant BMI								P
	All		Underweight		Normal weight		Overweight		
	N	%/Mean(sd)	n	%/Mean(sd)	n	%/Mean(sd)	n	%/Mean(sd)	
Age	4045		523	28.25(4.13)	2845	29.38(4.39)	677	30.30(4.43)	
20 ~ 25,yrs	506	12.51%	91	17.40%	352	12.37%	63	9.31%	
26 ~ 30	1774	43.85%	262	50.10%	1256	44.15%	256	37.81%	
31 ~ 35	1225	30.28%	127	24.28%	850	29.88%	248	36.63%	
36 ~ 40	540	13.35%	43	8.22%	387	13.60%	110	16.25%	
Parity			523		2845		677		
firstborn	2457	60.74%	358	68.45%	1727	60.70%	372	54.95%	
secondborn	1588	39.26%	165	31.55%	1118	39.30%	305	45.05%	
Educational level			521		2841		677		
High school or less	997	24.68%	119	22.84%	695	24.46%	183	27.03%	
College	1266	31.34%	150	28.79%	875	30.80%	241	35.60%	
University or higher	1776	43.97%	252	48.37%	1271	44.74%	253	37.37%	
Income			520		2837		676		
Low	692	17.15%	78	15%	482	16.99%	132	19.53%	
Middle	2391	59.26%	303	58.27%	1689	59.53%	399	59.02%	
High	950	23.54%	139	26.73%	666	23.48%	145	21.45%	
Smoking habits			521		2838		676		
Never smoker	3934	97.50%	507	97.31%	2779	97.92%	648	95.86%	
Stopped before pregnancy	98	2.43%	13	2.50%	57	2.01%	28	4.14%	
Current smoker	3	0.07%	1	0.19%	2	0.07%	0	0%	
Alcohol intake			520		2831		675		
Never drinker	3611	89.70%	473	90.96%	2534	89.51%	604	89.48%	
Stopped before pregnancy	373	9.26%	37	7.12%	270	9.54%	66	9.78%	
Current drinker	42	1.04%	10	1.92%	27	0.95%	5	0.74%	
pregnant features									
Gestational weight gain(kg)	4041	6.75(4.86)		8.36(5.80)		7.06(4.96)		4.22(3.74)	
Birth weight(g)	4040	3328.04(463.07)		3222.89(397.04)		3325.11(442.04)		3438.24(449.77)	
a Demographic characteristics were presented as frequency [proportion (%)]. Gestational weight gain and birth weight were expressed as the mean [standard deviance (SD)].									
b Subjects were categorized as underweight (BMI < 18.5kg/m ²), normal weight (BMI = 18.5–24.9kg/m ²), and overweight/obese (BMI≥25.0kg/m ²) based on their pre-pregnancy BMI.									

3.2 Association between trimester-specific quartiles of thyroid hormone and GWG

Table 2 shows the association between trimester-specific quartiles of thyroid hormones and GWG. For the first and third trimester, there was a substantially inverse association between maternal FT4 and GWG. After adjustment for covariates, GWG was lower for participants with an FT4 level in the 4th quartile ($\beta = -1.45\text{kg}$, 95% CI: $-2.48, -0.42$) compared with that in the 1st quartile at the first trimester ($p = 0.01$). At the third trimester, GWG was lower for participants with an FT4 level in the 2nd quartile ($\beta = -1.27\text{kg}$, 95% CI: $-2.03, -0.51$) and 3rd quartile ($\beta = -1.10\text{kg}$, 95% CI: $-1.95, -0.24$) compared with that in the 1st quartile ($p < 0.001$, $p = 0.01$). A significant inverse association for TT4 and GWG was observed at the third trimester (Q2 vs. Q1: $\beta = -0.92\text{kg}$, 95% CI: $-1.77, -0.07$, $p = 0.03$; Q3 vs. Q1: $\beta = -1.18\text{kg}$, 95% CI: $-2.06, -0.30$, $p = 0.01$; Q4 vs. Q1: $\beta = -1.67\text{kg}$, 95% CI: $-2.54, -0.81$, $p < 0.001$). We detected a significant positive association for FT3 with GWG at the second trimester. Increased GWG was observed in the 2nd quartile ($\beta = 0.81\text{kg}$, 95% CI: $0.02, 1.61$, $p = 0.04$) and the 4th quartile ($\beta = 1.44\text{kg}$, 95% CI: $0.59, 2.28$, $p < 0.001$) for FT3 compared with that in the 1st quartile. No other thyroid function parameters were associated with GWG.

Table 2
Multivariate associations between maternal thyroid hormone quartiles and gestational weight gain, stratified by trimesters

		First trimester			Second trimester			Third trimester	
		Crude β (95%CI)	Adjusted β (95%CI)	p	Crude β (95%CI)	Adjusted β (95%CI)	p	Crude β (95%CI)	Adjusted β (95%CI)
TSH	Quartile 1	0.00	0.00		0.00	0.00		0.00	0.00
	Quartile 2	0.48(-0.30,1.26)	0.43(-0.35,1.21)	0.28	0.30(-0.53,1.13)	0.08(-0.73,0.90)	0.84	-0.15(-1.10,0.80)	-0.10(-1.05,0.85)
	Quartile 3	0.54(-0.23,1.32)	0.51(-0.28,1.30)	0.21	-0.01(-0.84,0.82)	-0.25(-1.07,0.58)	0.55	2.44(-0.69,1.19)	0.26(-0.68,1.20)
	Quartile 4	0.44(-0.39,1.26)	0.46(-0.36,1.29)	0.27	0.06(-0.78,0.90)	-0.09(-0.92,0.74)	0.83	2.30(-0.61,1.20)	0.18(-0.73,1.09)
FT3	Quartile 1	1.00	1.00		1.00	1.00		1.00	1.00
	Quartile 2	0.19(-0.89,1.27)	0.35(-0.71,1.42)	0.52	0.52(-0.28,1.33)	0.81(0.02,1.61)	0.04	0.13(-0.62,0.89)	0.41(-0.35,1.16)
	Quartile 3	0.38(-0.63,1.39)	0.65(-0.36,1.66)	0.21	0.17(-0.65,0.99)	0.65(-0.16,1.47)	0.12	0.66(-0.17,1.51)	0.69(-0.15,1.54)
	Quartile 4	-0.44(-1.41,0.51)	-0.06(-1.04,0.91)	0.90	0.53(-0.31,1.38)	1.44(0.59,2.28)	< 0.001	0.73(-0.33,1.79)	0.92(-0.16,1.99)
FT4	Quartile 1	1.00	1.00		1.00	1.00		1.00	1.00
	Quartile 2	-0.18(-1.36,1.00)	-0.18(-1.34,0.98)	0.76	-0.02(-0.79,0.75)	-0.34(-1.10,0.42)	0.38	-1.14(-1.89,-0.38)	-1.27(-2.03,-0.51)
	Quartile 3	-0.91(-1.99,0.16)	-0.93(-2.00,0.14)	0.09	-0.20(-1.00,0.59)	-0.55(-1.34,0.23)	0.17	-1.04(-1.90,-0.19)	-1.10(-1.95,-0.24)
	Quartile 4	-1.00(-2.01,0.03)	-1.45(-2.48,-0.42)	0.01	0.28(-0.60,1.17)	-0.14(-1.02,0.73)	0.74	-0.44(-1.49,0.60)	-0.58(-1.63,0.45)
TT3	Quartile 1	1.00	1.00		1.00	1.00		1.00	1.00
	Quartile 2	-0.30(-1.05,0.43)	-0.10(-0.85,0.64)	0.78	-0.45(-1.37,0.45)	-0.16(-1.05,0.74)	0.73	-0.47(-1.39,0.43)	-0.46(-1.37,0.44)
	Quartile 3	0.47(-0.30,1.26)	0.71(-0.08,1.51)	0.08	0.50(-0.37,1.37)	0.81(-0.04,1.67)	0.06	-0.71(-1.63,0.20)	-0.64(-1.56,0.27)
	Quartile 4	-0.39(-1.26,0.48)	0.48(-0.40,1.37)	0.29	-0.21(-1.05,0.64)	0.82(-0.03,1.67)	0.06	-0.35(-1.25,0.54)	0.11(-0.80,1.02)
TT4	Quartile 1	1.00	1.00		1.00	1.00		1.00	1.00
	Quartile 2	0.15(-0.67,0.96)	0.07(-0.74,0.88)	0.87	-0.30(-1.16,0.55)	-0.64(-1.48,0.20)	0.13	-0.64(-1.49,0.20)	-0.92(-1.77,-0.07)
	Quartile 3	-0.44(-1.23,0.36)	-0.48(-1.28,0.32)	0.24	0.12(-0.72,0.96)	-0.09(-0.92,0.74)	0.83	-1.00(-1.87,-0.13)	-1.18(-2.06,-0.30)
	Quartile 4	-0.20(-1.02,0.61)	-0.15(-0.97,0.66)	0.71	-0.07(-0.91,0.76)	-0.41(-1.24,0.41)	0.32	-1.69(-2.55,-0.83)	-1.67(-2.54,-0.81)

a Abbreviations: TSH, thyroid stimulating hormone; TT4, total thyroxine; FT4: free thyroxine; TT3, total triiodothyronine; FT3, free triiodothyronine; TRAb, thyrotrophin receptor antibody; TPOAb, thyroid peroxidase antibody; TGAb, anti-thyroglobulin.

b Model was adjusted for age, parity, maternal education, pre-pregnancy BMI, urinary iodine, household income and gestational age.

c Bold red text indicates $P < 0.05$.

3.3 Association between birth weight Z-score and trimester-specific quartiles of thyroid hormones

As shown in Table 3, multivariate analysis revealed a clear negative association between FT4 and birth weight Z-score in the second and third trimesters. At the second trimester, mothers with the 2nd, 3rd, and 4th quartile of FT4 levels were associated with lower birth weight Z-score of -0.14 (95% CI: -0.01, -0.28, $p = 0.04$), -0.19 (95%CI: -0.33, -0.05, $p = 0.01$), and -0.19 (95% CI: -0.35, -0.03, $p = 0.05$), respectively, compared with mothers with the 1st quartile of FT4 levels.

The mothers with the 2nd quartile of FT4 levels were associated with lower birth weight Z-score of -0.12 (95% CI: -0.25, -0.01, $p = 0.05$) at the third trimester. Additionally, the birth weight Z-score of the newborns of mothers with the 4th quartile of total T4 levels was associated with a decrease in birth weight Z-score of -0.15 (95% CI: -0.30, -0.01, $p = 0.04$) compared with that of the 1st quartile of total T4 levels at the second trimester. Other maternal thyroid function parameters showed no statistically significant associations with neonatal birth weight.

Table 3
Multivariate associations between maternal thyroid hormone quartiles and birth weight, stratified by trimesters

		First trimester			Second trimester			Third trimester		
		Crude	Adjusted	p	Crude	Adjusted	p	Crude	Adjusted	p
TSH	Quartile 1	1.00	1.00		1.00	1.00		1.00	1.00	
	Quartile 2	-0.01(-0.15,0.14)	0.03(-0.10,0.15)	0.68	-0.05(-0.22,0.10)	-0.08(-0.23,0.06)	0.25	0.08(-0.08,0.25)	0.07(-0.08,0.23)	0.40
	Quartile 3	0.09(-0.05,0.24)	0.07(-0.05,0.20)	0.26	0.06(-0.09,0.22)	-0.01(-0.15,0.14)	0.99	0.02(-0.14,0.18)	0.00(-0.15,0.15)	0.98
	Quartile 4	0.06(-0.10,0.21)	0.07(-0.06,0.20)	0.32	0.01(-0.14,0.18)	-0.04(-0.19,0.10)	0.54	0.04(-0.11,0.20)	0.03(-0.12,0.17)	0.79
FT3	Quartile 1	1.00	1.00		1.00	1.00		1.00	1.00	
	Quartile 2	-0.07(-0.28,0.13)	-0.03(-0.21,0.14)	0.67	0.01(-0.14,0.17)	0.01(-0.13,0.16)	0.87	0.09(-0.03,0.22)	0.07(-0.04,0.19)	0.20
	Quartile 3	0.01(-0.17,0.21)	0.08(-0.08,0.24)	0.35	0.11(-0.04,0.27)	0.09(-0.05,0.24)	0.22	0.09(-0.05,0.23)	0.05(-0.08,0.19)	0.20
	Quartile 4	0.12(-0.06,0.30)	0.14(-0.02,0.30)	0.09	0.12(-0.04,0.29)	0.06(-0.09,0.21)	0.45	0.14(-0.04,0.32)	0.02(-0.15,0.19)	0.79
FT4	Quartile 1	1.00	1.00		1.00	1.00		1.00	1.00	
	Quartile 2	0.12(-0.10,0.34)	0.17(-0.01,0.36)	0.08	-0.16(-0.31,-0.01)	-0.14(-0.28,-0.01)	0.04	-0.12(-0.25,0.01)	-0.12(-0.25,-0.01)	0.03
	Quartile 3	0.03(-0.17,0.24)	0.12(-0.05,0.29)	0.19	-0.22(-0.37,-0.06)	-0.19(-0.33,-0.05)	0.01	-0.13(-0.27,0.02)	-0.12(-0.26,0.01)	0.10
	Quartile 4	0.07(-0.13,0.26)	0.16(-0.01,0.33)	0.06	-0.28(-0.45,-0.10)	-0.19(-0.35,-0.03)	0.02	-0.13(-0.31,0.04)	-0.09(-0.26,0.07)	0.10
TT3	Quartile 1	1.00	1.00		1.00	1.00		1.00	1.00	
	Quartile 2	0.03(-0.11,0.17)	0.06(-0.06,0.18)	0.35	0.01(-0.17,0.18)	-0.05(-0.21,0.11)	0.51	-0.11(-0.26,0.04)	-0.07(-0.21,0.08)	0.34
	Quartile 3	-0.01(-0.16,0.13)	-0.01(-0.13,0.12)	0.94	0.07(-0.10,0.24)	0.05(-0.10,0.21)	0.52	0.09(-0.06,0.25)	0.07(-0.07,0.22)	0.34
	Quartile 4	0.00(-0.16,0.16)	0.05(-0.09,0.20)	0.48	0.11(-0.05,0.28)	0.04(-0.11,0.20)	0.58	0.14(-0.01,0.30)	0.05(-0.09,0.20)	0.34
TT4	Quartile 1	1.00	1.00		1.00	1.00		1.00	1.00	
	Quartile 2	-0.03(-0.18,0.12)	0.05(-0.08,0.19)	0.44	-0.08(-0.25,0.08)	-0.04(-0.19,0.11)	0.59	-0.14(-0.29,-0.01)	-0.05(-0.19,0.09)	0.20
	Quartile 3	-0.07(-0.22,0.08)	-0.00(-0.13,0.13)	0.10	-0.14(-0.31,0.02)	-0.12(-0.27,0.02)	0.10	-0.20(-0.35,-0.05)	-0.12(-0.26,0.02)	0.03
	Quartile 4	-0.00(-0.15,0.15)	0.04(-0.09,0.17)	0.57	-0.20(-0.36,-0.04)	-0.15(-0.30,-0.01)	0.04	-0.09(-0.24,0.05)	-0.07(-0.21,0.07)	0.20

a Abbreviations: TSH, thyroid stimulating hormone; TT4, total thyroxine; FT4: free thyroxine; TT3, total triiodothyronine; FT3, free triiodothyronine; TRAb, thyrotrophin receptor antibody; TPOAb, thyroid peroxidase antibody; TGAAb, anti-thyroglobulin.

b Model was adjusted for age, parity, maternal education, pre-pregnancy BMI, household income and gestational age.

c Bold red text indicates $P < 0.05$.

Discussion

In this large prospective study, on the premise of thyroid antibody-negative pregnant women, we found that maternal GWG was negatively correlated with FT4 level at the first and third trimester, TT4 level at the third trimester ($p < 0.05$), and positively correlated with FT3 level at the second trimester ($p < 0.05$). Pregnant women with higher FT4 at the second and third trimester and higher TT4 at the second trimester would have an infant with lower birth weight Z-score ($p < 0.05$).

Compared with several previous studies that showed FT4 in early pregnancy is inversely related to GWG, our study found that the third trimester is also the key period for FT4 and TT4 is to affect GWG [13, 20, 21]. FT3 in the second trimester of pregnancy was also positively correlated with GWG. We did not observe an association between TSH and maternal weight in all trimesters, which is in line with the results of the FaSTER Trial among 9209 euthyroid pregnant women [21]. However, a previous study involving 1035 Dutch Caucasian pregnant women and the Generation R study of 5206 mothers mainly Dutch origin showed that in early pregnancy, higher maternal TSH level was associated with an increased risk of excessive GWG [13, 20]. These inconsistencies may be caused by ethnic differences in the study population and TSH has a significant effect on gestational weight gain in the Dutch population cohort. Another possibility is that due to the stimulation of TSH receptor by hCG, the TSH level decreased significantly in early pregnancy, so the variations in gestational weeks at sampling time and detection methods can also cause differences in the analysis results.

Maternal subclinical hypothyroidism is associated with a higher risk of SGA and lower birth weight, whereas isolated hypothyroxinaemia is associated with lower risk of SGA and higher birth weight [22]. Previous studies also found an inverse correlation between TSH and birth weight in euthyroid pregnant women [23, 24]. Significant inverse associations between birth weight and maternal FT4 in early pregnancy were reported [25]. The present study further showed that the second and third trimesters are the critical period during which maternal FT4 and TT4 affect birth weight. This is consistent with the rule that fetuses gain weight mainly after 24 weeks of gestation [26]. However, our study did not find the association between TSH and birth weight, which may be because TSH was detected by different instruments and was not analyzed as a continuous variable. Maternal FT4 and TT4's influence on intrauterine growth and development might act via maternal and/or placental mechanisms. The direct impact might be due shifts in the placental FT4 concentration playing a causal role in affecting the fetal bioavailability of growth factors (e.g., insulin like growth factors) and growth-related hormones (e.g., prostaglandins and growth hormones), and the stimulation of fetal metabolism (i.e., the consumption of glucose and oxygen), resulting in the induction of a direct catabolic state in the fetus [27]. Alternatively, an indirect mechanism might be that higher maternal FT4 levels increase lipid and protein degradation, and enhance insulin sensitivity [28, 29], which results in a state of chronic caloric deficiency in the mother, producing a negative feedback on birth weight [30, 31].

Our study has several strengths, firstly, this was a large sample size of mother and baby pairs and participants were almost equally distributed from the first, second, and third trimesters of pregnancy. Secondly, our study comprehensively tested thyroid function and excluded interference of TPOAb-positive and TGAb-positive pregnant women. In women who were positive for TPOAb, TGAb, or both, TSH levels increased as gestation progressed, even hypothyroidism may occur because of the stress of pregnancy [32, 33]. In 2017, new guidelines of American Thyroid Association (ATA) recommended that euthyroid pregnant women with positive TPOAb or TGAb should measure serum TSH level every 4 weeks from the confirmation of pregnancy to the mid-pregnancy [12]. Thirdly, our analysis carefully included several key confounding factors, such as pre-pregnancy BMI [34, 35], that have been largely ignored by previous studies. For example, we include urinary iodine level which may reflect iodine intake and iodine nutrition status. The present study had several limitations. First, thyroid function parameters were measured by different community medical centers and instruments, so we only modeled quartiles of thyroid parameters replacing direct measurement data for statistical analysis. In the future, we may analyze the data generated by the same instrument as continuous variables. Second, pre-pregnancy weight was self-reported thus might lead to underestimation and misclassification. Third, the crosssectional design of this study meant that we could not draw conclusions about causes and directions of the observed associations.

Conclusion

Higher maternal FT4 and TT4 levels are associated with less GWG lower birth weight when maternal thyroid parameters were modeled as quartiles.

Abbreviations

GWG gestational weight gain

LGA large for gestational age

SGA small for gestational age

TT4 total thyroxine

FT4 free thyroxine

TT3 total triiodothyronine

FT3 free triiodothyronine

TGAb hyroglobulin antibody

TPOAb thyroid peroxidase antibody

SD tandard deviance

BMI body mass index

Declarations

Ethics approval and consent to participate: All methods were performed in accordance with the relevant guidelines and regulations (**Declaration of Helsinki**). This study was approved by the Ethical Committee of the Shanghai Center for Disease Control and Prevention (No. 2017-13). All participants provided written informed consents.

Consent for publication: The authors provide consents for publication.

Availability of data and materials: The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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