

RESEARCH

The role of triiodothyronine (T3) and T3/free thyroxine (fT4) in glucose metabolism during pregnancy: the Ma'anshan birth cohort study

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Abstract

Objectives: Compared with other thyroid markers, fewer studies have explored the associations between triiodothyronine (T3), T3/free thyroxine (fT4) and glucose abnormality during pregnancy. Thus, we aimed to: (i) examine the associations of T3 and T3/fT4 with glucose metabolism indicators and (ii) evaluate, in the first trimester, the performance of the two markers as predictors of gestational diabetes mellitus (GDM) risk.

Methods: Longitudinal data from 2723 individuals, consisting of three repeated measurements of T3 and fT4, from the Ma'anshan birth cohort study (MABC), China, were analyzed using a time-specific generalized estimating equation (GEE). The receiver operating characteristic curve (ROC) – area under the curve (AUC) and Hosmer–Lemeshow goodness of fit test was used to assess the discrimination and calibration of prediction models.

Results: T3 and T3/fT4 presented stable associations with the level of fasting glucose, glucose at 1h/2 h during pregnancy. T3 and T3/fT4 in both the first and second trimesters were positively associated with the risk of GDM, with the larger magnitude of association observed in the second trimester (odds ratio (OR) = 2.50, 95% CI = 1.95, 3.21 for T3; OR = 1.09, 95% CI = 1.07, 1.12 for T3/fT4). T3 (AUC) = 0.726, 95% CI = 0.698, 0.754 and T3/fT4 (AUC = 0.724, 95% CI = 0.696, 0.753) in the first trimester could improve the performance of the prediction model; however, the overall performance is not good.

Conclusion: Significant and stable associations of T3, T3/fT4 and glucose metabolism indicators were documented. Both T3 and T3/fT4 improve the performance of the GDM predictive model.

Key Words

- ▶ longitudinal studies
- ▶ triiodothyronine
- ▶ triiodothyronine/free thyroxine
- ▶ glucose
- ▶ pregnancy

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Introduction

The thyroid gland experiences great stress during pregnancy, increasing about 10–40% in size, with the production of thyroxine (T4) and triiodothyronine (T3) surging by 50% (1). As a result, thyroid dysfunction such

as hypothyroidism, hyperthyroidism and autoantibody positivity complicates up to 17% of all pregnancies (1). It is well accepted that thyroid function abnormalities have a deleterious impact on pregnancy (2, 3).

Hyperglycemia during pregnancy typically diagnosed as gestational diabetes mellitus (GDM) is a highly prevalent complication during pregnancy and affects around 15–20% of pregnancies (4) and the world has been witnessing a rapid increase in GDM incidence (5). Its negative health consequences for women and their offspring occur both during pregnancy (5) and beyond (6).

Thyroid hormones are involved in glucose metabolism and homeostasis through multiple ways (7, 8, 9, 10), and the associations between thyroid dysfunction and glucose abnormality have been well established. However, previous studies mainly focused on thyroid-stimulating hormone (TSH), fT4 and T4. T3 has long been overlooked, even though T3 plays a significant role in glucose regulation (11). In recent years, T3 has gained popularity in the scientific literature due to it being the active metabolic form of thyroid hormone that can induce endogenous glycemic activity (12). Most peripheral T3 is produced in part by the conversion of T4 by two deiodinase enzymes, type 1 and type 2 iodothyronine deiodinases (D1 and D2, respectively) (13), with the rest produced directly by the thyroid gland. Therefore, the ratio of T3 (or fT3) to T4 (or fT4) is attracting attention as well but requires extensive further exploration.

As such, based on repeated measurements from a prospective cohort study, we aimed to: (i) examine the associations of T3 and T3/fT4 with glucose metabolism indicators during pregnancy; (ii) evaluate the performance of the two markers, in the first trimester, as predictors of the risk for GDM.

Material and methods

Study population

The Ma'anshan birth cohort study (MABC) is a population-based prospective study conducted in Ma'anshan city of Anhui Province in China. Between May 2013 and September 2014, the MABC recruited 3474 pregnant women who were attending their first prenatal health visit. The participants were then followed until labor for a maximum of four visits (i.e. the first, second, and third trimesters and delivery). Of these participants, we first excluded those who lacked information on GDM status and were diagnosed with diabetes before conception, yielding a sample of 3308 women. In addition, we excluded participants without thyroid function data in any trimesters, yielding a final sample of 2723 women. The present study was approved by the ethics committee of Anhui Medical University. Written informed consent was obtained from all pregnant women.

GDM diagnosis

At 24–28 weeks of gestation, women underwent a GDM screening that consisted of a 'one-step' standardized 75 g oral glucose tolerance test (OGTT). Venous blood samples were collected at 0, 1, and 2 h after a glucose load. A positive GDM diagnosis was made when any of the following criteria were met: fasting plasma glucose ≥ 5.1 mmol/L, plasma glucose at 1 h ≥ 10 mmol/L, or plasma glucose at 2 h ≥ 8.5 mmol/L (14). These data, along with fasting glucose in each trimester, were extracted from medical records, and plasma glucose was measured using the glucose oxidase method.

Thyroid hormone measurement

Blood samples were collected at the first, second, and third health visits. Fasting blood was drawn in the morning before 10:00 h, and serum specimens were isolated and stored at -80°C for further examination. Serum samples were assayed for levels of fT4, T3, thyrotropin (TSH), antithyroperoxidase autoantibody (TPOAb) and antithyroglobulin autoantibody (TgAb) with electrochemiluminescence using the Cobas e411 automated immunoassay platform (Roche Diagnostics GmbH). All samples were tested blindly and each batch included two quality control samples. The coefficients of variation for these thyroid profile assays were all below 10%. The detection limits of fT4, T3, TSH, TPOAb and TgAb were 0.300 pmol/L, 0.300 nmol/L, 0.005 $\mu\text{IU/mL}$, 5.0 IU/mL and 10.0 IU/mL, respectively. TPOAb and TgAb were considered positive if concentrations were greater than 34.0 and 115.0 IU/mL, respectively.

Covariates

Extensive data were collected using a structured self-report questionnaire that was administered by trained interviewers at each health visit. Smoking in early pregnancy was defined as either ongoing smoking or former smoking that ceased after the woman became aware of her pregnancy status. Alcohol consumption was categorized as never, occasional, or regular. Education level was categorized into five groups: (i) primary school or below; (ii) middle school; (iii) high school; (iv) junior college and (v) undergraduate or above. Monthly income levels (Chinese Yuan) were divided into four groups: (i) < 1000 ; (ii) 1000–2500; (iii) 2500–4000 and (iv) ≥ 4000 . Seasons for the Northern Hemisphere were defined as spring (i.e. February to April),

summer (i.e. May to July), fall (i.e. August to October) and winter (i.e. November to January).

Statistical analysis

After log transformation, values outside ± 4 s.d. of the mean were regarded as either laboratory error or undiagnosed disease and were treated as outliers. The outliers were omitted as following, in each trimester: 8 outliers for T3, 17 for fT4 and 12 for TSH in the first trimester; 1 for T3, 7 for fT4 and 13 for TSH in the second trimester; 5 for T3, 5 for fT4 and 10 for TSH in the third trimester.

The Mann-Whitney *U*-test was used to compare median concentrations of the different thyroid markers between the GDM and non-GDM groups. Fasting glucose differences between different trimesters were compared using paired samples *t*-test. A generalized estimating equation (GEE) was used to examine the associations of demographic or lifestyle factors with thyroid markers. The multiple informant model with a nonstandard version of GEE was used to examine trimester-specific associations of thyroid markers with fasting plasma glucose, plasma glucose at 1 h/2 h, and the risk of GDM. For fasting plasma glucose, data from three trimesters were analyzed, while for glucose at 1 h/2 h and the risk of GDM, only data from the first and second trimesters were included in the model.

Stratified analyses of the associations between thyroid markers and the risk of GDM were conducted according to pre-pregnancy BMI, parity, smoking status, TPOAb and TgAb status using logistic regression. The multiplicative interaction term was evaluated by a likelihood ratio test. Sensitivity analyses of the association between T3, fT4 and T3/fT4 and the risk of GDM were conducted according to the item with which the diagnosis of GDM was made (i.e. high fasting glucose vs high postprandial glucose vs both).

To further specify the clinical significance of T3 and T3/fT4, we built multivariate predictive models along with routine variables (i.e. maternal age, pre-pregnancy BMI, history of family diabetes, gestational seasons, fasting plasma glucose) and compared each of their performances in predicting GDM. Sensitivity, negative predictive value (NPV) and positive predictive value (PPV) were calculated under a fixed specificity of 90.0% and a fixed false-positive rate of 10% for different models. The receiver operating characteristic curve (ROC)-area under curve (AUC) was drawn, and the Z statistic was used to compare the discrimination of different models. Hosmer-Lemeshow goodness of fit test was conducted to assess the calibration of predictive models.

Analyses were conducted using Stata 13.0, R 3.5.1. and MedCalc 18.11.3. Statistical significance was set at $P < 0.05$. All tests were two-sided.

Results

Table 1 presents the characteristics of the 2723 participants in our study. A total of 336 (12.3%) patients with GDM were documented. There was detectable difference of GDM incidence between individuals with ($n=336$; 12.3%) and without thyroid function data ($n=585$; 15.9%) ($P_{\text{for } \chi^2}=0.02$). The average age was 26.7 years. Fasting glucose level decreases with increasing gestational age ($P_{\text{for the difference between 1st and 2nd trimester}} < 0.001$; $P_{\text{for the difference between 2nd and 3rd trimester}} < 0.001$).

Table 2 presents the concentrations of different thyroid hormones in different gestational age groups as a whole and according to GDM status. T3 concentration increases gradually with increasing gestational age, from 2.35 nmol/L in the first trimester to 2.69 nmol/L in the third trimester. fT4 drops sharply from the first to the second trimester from 16.7 to 11.9 pmol/L and increases slightly afterward to 13.3 pmol/L. T3/fT4 increases substantially from 139 in the first trimester to 214 in the second trimester, while decreases a little bit to 202 in the third trimester. TSH increases significantly from 1.58 $\mu\text{IU/mL}$ in the first trimester to 2.42 $\mu\text{IU/mL}$ in the second trimester, while decreases slightly to 2.21 $\mu\text{IU/mL}$ in the third trimester. There are differences in T3 concentrations between the GDM and non-GDM groups across all three periods, as was similar for T3/fT4 concentrations. For fT4 and TSH, the difference was only detected in the second trimester.

Figure 1 shows the consistent percentage of individuals whose concentrations of T3, fT4 and T3/fT4 were above 75% or below 25% across the three trimesters. For T3, the top of 25% individuals in the first trimester became 11.9% in the second trimester and 6.3% in the third trimester. Likewise, the change for fT4 progressed from 25% in the first trimester to 12.2% in the second trimester, and 7% in the third trimester. T3/fT4 changed from 25% in the first trimester to 12.3% in the second trimester and 10.5% in the third trimester.

Supplementary Table 1 (see section on [supplementary materials](#) given at the end of this article) shows the associations between different thyroid markers and related factors. Independent of the adjusted factors, all three thyroid markers were significantly associated with

Table 1 Characteristics of subjects included in the current study.

Variables	All subject	GDM	Non-GDM
<i>n</i>	2723	336 (12.3)	2387 (87.7)
Age	26.7 (3.6)	28.0 (4.3)	26.5 (3.4)
BMI	20.8 (2.8)	22.2 (3.1)	20.6 (2.7)
Gestational age			
First trimester	10.0 (2.1)	9.9 (2.0)	10.0 (2.1)
Second trimester	25.6 (1.0)	25.6 (0.9)	25.6 (1.0)
Third trimester	34.0 (1.0)	34.0 (1.1)	34.0 (1.0)
Multiparous	290 (10.7)	47 (14.0)	243 (10.2)
Ethnic			
Han	2682 (98.5)	329 (97.9)	2353 (98.6)
Hui	23 (0.8)	4 (1.2)	19 (0.8)
Other	18 (0.7)	3 (0.9)	15 (0.6)
Residence			
Urban	2134 (78.4)	272 (81.0)	1862 (78.0)
Suburb	316 (11.6)	42 (12.5)	274 (11.5)
Town	48 (1.7)	7 (2.1)	41 (1.7)
Rural	226 (8.3)	15 (4.5)	210 (8.8)
Education			
Primary school or below	33 (1.2)	4 (1.2)	29 (1.2)
Middle school	500 (18.4)	76 (22.6)	425 (17.8)
High school	606 (22.3)	69 (20.5)	537 (22.5)
Junior college	851 (31.3)	101 (30.1)	749 (31.4)
Undergraduate or above	733 (26.9)	86 (25.6)	647 (27.1)
Family income per capital (Chinese Yuan)			
<1000	50 (1.8)	8 (2.4)	42 (1.8)
1000–2500	669 (24.6)	104 (31.0)	566 (23.7)
2500–4000	1167 (42.9)	142 (42.3)	1042 (43.7)
>4000	837 (30.7)	82 (24.4)	755 (31.6)
Smoking			
No	2614 (96.0)	323 (96.1)	2291 (96.0)
Yes	109 (4.0)	13 (3.9)	96 (4.0)
Drinking			
Never	2505 (92.0)	309 (92.0)	2196 (92.0)
Occasionally	214 (7.9)	26 (7.7)	188 (7.9)
Regularly	4 (0.1)	1 (0.3)	3 (0.1)
Fast glucose			
First trimester	4.7 (0.4)	4.8 (0.6)	4.7 (0.5)
Second trimester	4.3 (0.5)	5.0 (0.7)	4.2 (0.5)
Third trimester	4.2 (0.6)	4.7 (0.9)	4.2 (0.6)

Data are presented as mean (s.d.), or *n* (%), as applicable.

pre-pregnancy BMI, gestational weeks, smoking, and sampling seasonality. As for other factors, age was significantly related to T3 and fT4 concentrations; drinking was significantly associated with T3 and T3/fT4 ratio; parity was significantly associated with fT4 concentrations; gestational age and smoking were significantly associated with TSH concentrations.

Table 3 presents trimester-specific associations between thyroid markers and glucose metabolism indicators by GEE. The effect sizes for T3, fT4, T3/fT4 and TSH are indicated in per nmol/L, per pmol/L, per 10 unit and per μ IU/mL, respectively. Regarding fasting glucose and glucose at 1 h/2 h, T3 in all periods were significantly associated with all three indicators, except fasting glucose

in the first trimester, with the largest magnitude of association observed in the second trimester ($\beta=0.16$, 95% CI=0.11, 0.20 for fasting glucose; $\beta=0.41$, 95% CI=0.28, 0.55 for glucose at 1 h; $\beta=0.21$, 95% CI=0.11, 0.31 for glucose at 2 h). fT4 in all periods were significantly associated with all the three indicators, except fasting glucose in the third trimester, with the largest magnitude of association observed in the second trimester ($\beta=-0.02$, 95% CI=-0.03, -0.01 for fasting glucose; $\beta=-0.14$, 95% CI=-0.18, -0.10 for glucose at 1 h; $\beta=-0.08$, 95% CI=-0.11, -0.05 for glucose at 2 h). T3/fT4 in all periods were significantly associated with all the three indicators, with the largest magnitude of association observed in the second trimester ($\beta=-0.02$,

Table 2 Concentrations of thyroid markers according to GDM status in three trimesters.

Variables	Combined	Non-GDM	GDM	P
First trimester				
T3	2.35 (1.54, 3.53)	2.33 (2.01, 2.68)	2.50 (2.14, 2.84)	<0.001
fT4	16.7 (12.6, 23.5)	16.7 (15.4, 18.4)	16.7 (15.1, 18.0)	0.09
T3/fT4	139 (86, 221)	137 (117, 162)	148 (125, 175)	<0.001
TSH	1.58 (0.02, 5.59)	1.58 (0.87, 2.54)	1.58 (0.95, 2.39)	0.87
Second trimester				
T3	2.56 (1.76, 3.56)	2.53 (2.26, 2.84)	2.78 (2.46, 3.15)	<0.001
fT4	11.9 (9.1, 15.3)	12.0 (11.0, 13.0)	11.5 (10.5, 12.5)	<0.001
T3/fT4	214 (142, 328)	211 (184, 243)	240 (209, 276)	<0.001
TSH	2.42 (0.70, 5.89)	2.46 (1.74, 3.35)	2.13 (1.56, 3.02)	<0.001
Third trimester				
T3	2.69 (1.68, 3.75)	2.68 (2.30, 3.05)	2.82 (2.46, 3.20)	<0.001
fT4	13.3 (9.5, 17.2)	13.3 (11.9, 14.8)	13.2 (11.8, 14.4)	<0.24
T3/fT4	202 (128, 303)	199 (172, 233)	214 (185, 248)	<0.001
TSH	2.21 (0.51, 5.57)	2.21 (1.55, 3.08)	2.19 (1.51, 2.98)	0.21

Combined samples are presented as median (2.5th and 97.5th percentile). GDM and non-GDM groups are presented as median (25th and 75th percentile). Unit of T3, fT4 and TSH was nmol/L, pmol/L and μ IU/mL. Boldface indicates statistically significant.

95% CI = -0.03, -0.01 for fasting glucose; β = -0.14, 95% CI = -0.18, -0.10 for glucose at 1 h; β = -0.08, 95% CI = -0.11, -0.05 for glucose at 2 h); TSH in both first and second trimester was significantly associated with glucose at 1/2 h. In the first trimester, only T3 (OR = 1.67, 95% CI = 1.33, 2.10) and T3/fT4 (OR = 1.08, 95% CI = 1.04, 1.12) were significantly associated with the risk of GDM, while in the second trimester, T3 (OR = 2.50, 95% CI = 1.95, 3.21), fT4 (OR = 0.89, 95% CI = 0.82, 0.96), T3/fT4 (OR = 1.09, 95% CI = 1.07, 1.12) and TSH (OR = 0.91, 95% CI = 0.83, 0.99) in the second trimester were all significantly associated with the risk of GDM.

Stratified analyses of associations between three thyroid markers and the risk of GDM are presented in Supplementary Table 2. Sensitivity analyses of the associations of three thyroid markers and the risk of GDM according to the item with which the GDM is diagnosed are shown in Supplementary Table 3.

Because T3 and T3/fT4 in the first trimester were both significantly associated with the risk of GDM, we further assessed their performances in predicting GDM. As shown in Table 4 and Fig. 2, adding T3 and T3/fT4 in the models respectively, the performance of model 3 (AUC = 0.726, 95% CI = 0.698, 0.754) and model 4 (AUC = 0.724, 95% CI = 0.696, 0.753) improved and showed comparable medium degree of discriminative ability, and the AUC of the models ranked as model 3 (0.726) > model 4 (0.724) > model 2 (0.710) > model 1 (0.703). As shown in Supplementary Table 4, the comparison between model 3 and model 1 (P = 0.004); model 3 and model 2 (P = 0.02); model 4 and model 1 (P = 0.01); model 4 and model 2 (P = 0.04) reached statistical significance.

The Hosmer–Lemeshow goodness of fit test indicated that the calibration capability of the four models was good (P value > 0.05). However, the calibration diagram indicated that the calibration capability of model 4 (Fig. 3B) was better than model 3 (Fig. 3A). The best multivariate predictive model of GDM including T3 (or T3/fT4), maternal age, pre-pregnancy BMI, fasting plasma glucose in the first trimester, sampling gestational week, the season of conception and family history of diabetes.

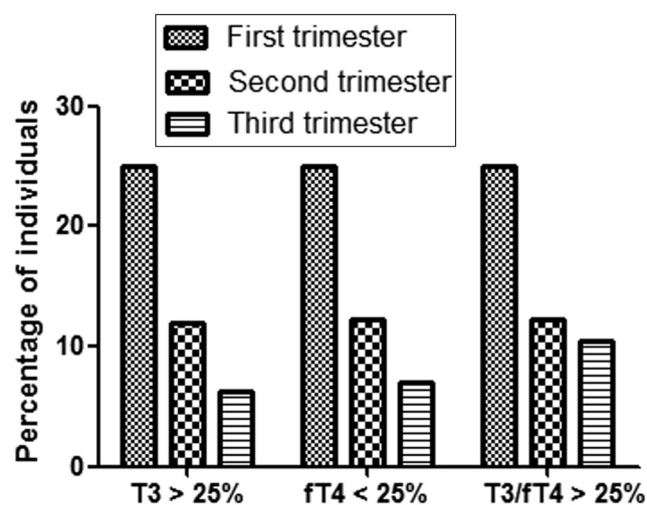


Figure 1 Consistency of the three thyroid markers across three trimesters of pregnancy. The first bar indicates the highest or lowest 25%. The following two bars indicate the percentage of individuals who are above 75% or below 25% in the first trimester, persisting through the second and third trimesters.

Table 3 Trimester-specific associations between three thyroid markers and glucose metabolism indicators by GEE.

Variables	Fasting glucose			Glucose at 1 h			Glucose at 2 h			GDM		
	β (95% CI)	<i>P</i>		β (95% CI)	<i>P</i>		β (95% CI)	<i>P</i>		OR (95% CI)	<i>P</i>	
T3												
First trimester	-0.03 (-0.07, 0.06)	0.10		0.22 (0.10, 0.35)	<0.001		0.07 (-0.02, 0.17)	0.15		1.67 (1.33, 2.10)	<0.001	
Second trimester	0.16 (0.11, 0.20)	<0.001		0.41 (0.28, 0.55)	<0.001		0.21 (0.11, 0.31)	<0.001		2.50 (1.95, 3.21)	<0.001	
Third trimester	0.13 (0.10, 0.16)	<0.001										
ft4												
First trimester	0.01 (0.006, 0.02)	<0.001		-0.03 (-0.05, -0.01)	0.001		-0.03 (-0.05, -0.01)	0.001		1.00 (0.95, 1.04)	0.84	
Second trimester	-0.02 (-0.03, -0.01)	0.003		-0.14 (-0.18, -0.10)	<0.001		-0.08 (-0.11, -0.05)	<0.001		0.89 (0.82, 0.96)	<0.001	
Third trimester	-0.005 (-0.01, 0.004)	0.29										
T3/ft4												
First trimester	-0.01 (-0.02, -0.01)	0.01		0.04 (0.02, 0.06)	<0.001		0.02 (0.01, 0.04)	<0.001		1.08 (1.04, 1.12)	<0.001	
Second trimester	0.02 (0.01, 0.02)	<0.001		0.05 (0.04, 0.06)	<0.001		0.03 (0.02, 0.04)	<0.001		1.09 (1.07, 1.12)	<0.001	
Third trimester	0.01 (0.01, 0.02)	<0.001										
TSH												
First trimester	-0.01 (-0.01, 0.00)	0.21		0.04 (0.01, 0.07)	0.01		0.05 (0.03, 0.08)	<0.001		1.03 (0.99, 1.08)	0.13	
Second trimester	-0.01 (-0.02, 0.01)	0.33		-0.09 (-0.13, -0.05)	<0.01		-0.04 (-0.07, -0.01)	<0.001		0.91 (0.83, 0.99)	0.03	
Third trimester	-0.01 (-0.002, 0.01)	0.16										

β and OR were adjusted for age, pre-pregnancy BMI, sampling seasonality, family diabetes history, parity, smoking in early pregnancy, drinking status, gestational weeks, education, income, and residence. β and OR indicated the effect size of per nmol/L, per pmol/L, per 10 unit and per μ U/mL for T3, ft4, T3/ft4 and TSH, respectively. Boldface indicates statistically significant OR, odds ratio.

Discussion

Our current study demonstrated trimester-specific associations between T3, ft4 and T3/ft4 with glucose metabolism indicators, with the largest magnitude of association observed in the second trimester for all three thyroid markers, and the most stable associations for T3/ft4 during pregnancy. Along with routine factors, T3 and T3/ft4 in the first trimester could improve the performance of the GDM prediction model and exhibited a comparable degree of discrimination ability and good calibration.

Our study echoed, and built upon, a recent nested case-control study from the US which indicated that both ft3 and ft3/ft4 were significantly positively associated with the risk of GDM (15). T3 is the primary active hormone involved in glucose metabolism (16) (12), yet it has long been neglected regarding its association with GDM. Given low ft4 hormonal activity, it is unlikely to influence plasma glucose directly. As a result, two studies (17, 18) reporting the associations between ft4 concentrations and the risk of GDM proposed that deiodinase activity might be the underlying factor. Only a handful of longitudinal studies (15, 19, 20) explored the associations of T3, ft3, or deiodinase activity (often indicated as ft3/ft4 or T3/ft4) with the risk of GDM. Neither a study from the United Arab Emirates with 301 participants (19) nor a study from Greece with 1170 participants (20) indicated that early pregnancy ft3 concentrations were associated with the risk of GDM. To our knowledge, the remaining studies were all cross-sectional in nature. Other than dichotomous GDM status (21, 22), some also focused on the glucose metabolic profile (23, 24, 25), and all reported significant associations between ft3/ft4 or T3/ft4 and glucose metabolism-related indicators.

In addition to stimulating endogenous glucose production (12), T3 could be involved in glucose metabolism in various ways. For example, T3 can positively regulate mitochondrial function and induce mitochondria biogenesis (26, 27), dysfunction of the latter emerged as a new insight into the etiology of diabetes and glucose abnormality (11). In addition, T3 can exert an important effect on the control of energy expenditure. For instance, under the effect of T3, skeletal muscle energy metabolism is switched into oxidative mitochondrial metabolism mediated by PGC-1 α (28), which plays an indispensable role in glucose and fatty acid metabolism (29). Furthermore, T3 can increase glucose uptake independent of insulin in skeletal muscle cells, such as through rapidly increasing GLUT4 expression (30), and the latter plays an important role in whole-body glucose homeostasis.

Table 4 Performance of multivariate predictive model of GDM including thyroid hormones and routine variables at a fixed false-positive rate of 10%.

Models	AUC (95% CI)	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Cut-off	P
Model 1	0.703 (0.686,0.720)	26.5	90.0	89.7	27.1	0.208	0.060
Model 2	0.710 (0.693,0.729)	29.2	90.0	90.0	29.1	0.211	0.477
Model 3	0.726 (0.709,0.743)	30.8	90.0	90.2	30.1	0.215	0.072
Model 4	0.724 (0.707,0.741)	32.4	90.0	90.4	31.3	0.215	0.685

P value of Hosmer-Lemeshow good of fit test. Model 1 including maternal age, pre-pregnancy BMI, history of family diabetes, and season of conception; Model 2 based on model 1, plus fasting plasma glucose and sampling gestational week; Model 3 based on model 2, plus T3; Model 4 based on model 2, plus T3/ft4.

AUC, area under curve; NPV, negative predictive value; PPV, positive predictive value.

Collectively, our data strongly support the authentic roles of T3 in the etiology of GDM.

T3 and T3/ft4 in the first trimester could improve the performance of the GDM prediction model; however, even along with routine factors, judging from the NPV and PPV of the predictive model, the performance of the model is not good. A recent review (31) indicated that universal vs risk-based screening for thyroid problems did not affect the risk of GDM, and the evidence was originally derived from a trial (32) that included 4516 women. All women from the trial in the universal screening group and high-risk women in the case finding group had their sera immediately tested for TSH, ft4, and TPOAb

to identify thyroid dysfunction; however, subsequent medication interventions did not benefit those women in preventing GDM. Our study does not conflict with this trial, because we emphasized the importance of T3 and T3/ft4, although the extent to which the screening of

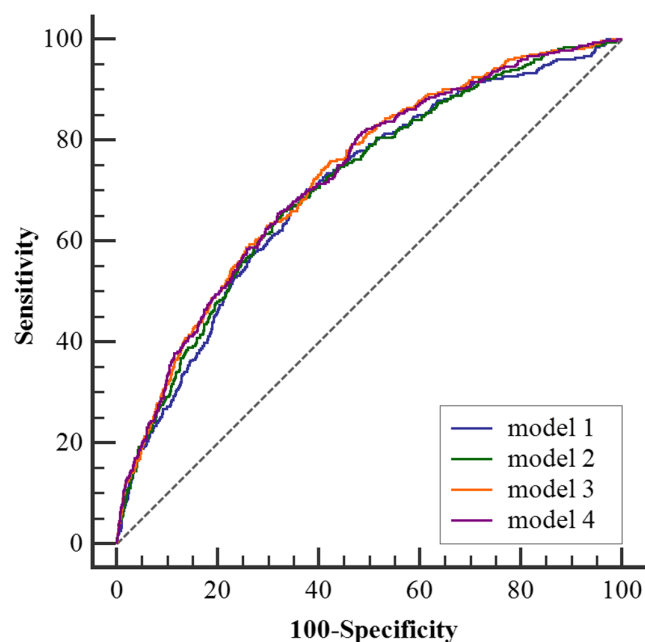


Figure 2 Comparison of multivariate predictive models. Model 1 including maternal age, pre-pregnancy BMI, history of family diabetes, and season of conception; Model 2 based on model 1, plus fasting plasma glucose and sampling gestational week; Model 3 based on model 2, plus T3; Model 4 based on model 2, plus T3/ft4.

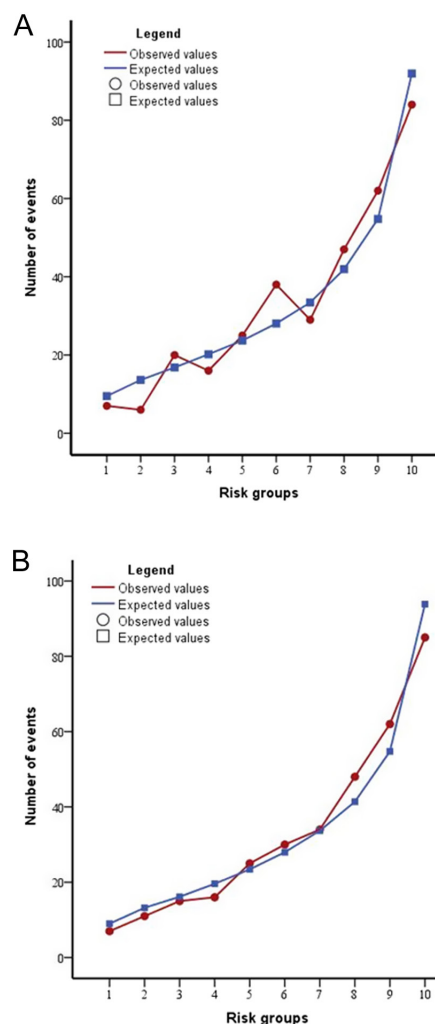


Figure 3 Calibration chart of multivariate predictive models including thyroid hormones. (A) Model including T3; (B) Model including T3/ft4.

T3 and T3/ft4 in the first trimester could benefit women, regarding GDM prevention, is still uncertain and requires the collection of more data. Although OGTT becomes a routine test, given its inconvenience, not every woman may opt to undergo this test. While thyroid function TSH and T4 testing is being routinely adopted in early pregnancy around China, our study justifies adding T3 into this routine, which would help identify high-risk individuals for GDM. Recently, a large sample-sized study (33) from China attempted to build a GDM prediction model. The study team selected 17 variables from 73 extracted variables, of which thyroid function (i.e. TT3 and TT4) was included. Interestingly, the results indicated the TT3 and TT4 levels had better predictive power than FT3 and FT4.

Another interesting finding was that the consistency of fasting glucose throughout pregnancy is better than thyroid markers. Previous studies on thyroid function mainly focused on early pregnancy and lacked longitudinal data to illustrate the natural course of gestational thyroid function. Our study showed that individuals with T3, ft4, and T3/ft4 levels among the highest or lowest 25% of the populations, in the first trimester, persisted in 6.3, 7.0, and 10.5% of the population in the third trimester is in line with a recent study (34) which indicated that early pregnancy thyroid disease only persists until the third trimester in 8.4–24.8% of cases when left untreated. So, the necessity of further thyroid function tests during pregnancy should not only be decided by previous measures.

Our study has several strengths. GDM diagnoses are often made during the second trimester (24–28 gestational weeks), which presents a limited time for an intervention. Our study innovatively proposed including thyroid function in the GDM prediction model, which could help identify high-risk individuals at an early stage. In addition, taking advantage of the MABC longitudinal data with repeated measurements, we were able to assess the persistence of the thyroid markers across three trimesters, which could aid clinicians in making decisions regarding thyroid function testing during pregnancy. Some limitations also need to be noted. First, iodine status at the individual level was not determined in our study, which could have influenced our results to some extent. However, according to 2019 statistics from the Centers for Disease Control and Prevention (CDC), people in Ma'anshan city are generally exposed to appropriate iodine conditions, and the median urinary iodine concentration of women is 174.05 µg/L. Secondly, the level of ft3 was not evaluated in our study, which limits comparisons of its importance with that of T3. Thirdly, since we do not have data on thyroxine-

binding globulin (TGB), this could affect the interpretation of our results.

Our current study documented significant and stable associations between T3, T3/ft4 and glucose metabolism indicators and both T3 and T3/ft4 could improve the performance of the GDM prediction model.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-21-0088>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

Beibei Zhu: formal analysis and writing original draft; Yan Han: resources; Fen Deng: methodology; Shuangqin Yan and Kun Huang: project administration; Jiahu Hao and Peng Zhu: writing review and editing; Fangbiao Tao and Beibei Zhu: funding acquisition. Fangbiao Tao: conceptualization and supervision.

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