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Assessing maternal thyroid function and its relationship to duration of the first stage of labor

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Abstract

Introduction: Maternal thyroid function plays a critical role in the normal labor process. Whether maternal thyroid function affects the duration of the first stage of labor is still unknown. Methods: Maternal serum levels of free thyroxine (FT4), thyroid-stimulating hormone (TSH) and thyroid peroxidase antibody (TPOAb) were detected in 31,382 pregnant women. A multiple linear regression model was applied to investigate the effect of maternal thyroid function on the duration of the first stage of labor. Results: FT4 level in the second trimester and in the third trimester was found to be negatively associated with duration of the first stage of labor ($\beta = -1.30$ h, 95% CI: -2.28, -0.32, P < 0.01; $\beta = -0.35$ h, 95% Cl: -0.61, -0.10, P < 0.01). TSH level in the third trimester was found to be positively associated with the duration of the first stage of labor ($\beta = 0.12$ h, 95% CI: 0.06, 0.18, P < 0.001). Per unit increase in TPOAb (IU/mL) in the second trimester and in the third trimester was significantly associated with prolonged first stage of labor $(\beta = 0.08 \text{ h}, 95\% \text{ Cl}: 0.01, 0.14, P = 0.02; \beta = 0.09 \text{ h}, 95\% \text{ Cl}: 0.02, 0.15, P = 0.01)$. For pregnant women suffering from subclinical hypothyroidism combined without TPOAb, TSH level in the third trimester exhibited a significant positive association with the length of the first stage of labor (β = 2.44 h, 95% CI: 0.03, 4.84, P = 0.04).

Conclusions: These findings suggest that maternal FT4, TSH and TPOAb might be important predictors of the first stage of labor.

Key Words

- vaginal deliveries
- free thyroxine
- thyroid-stimulating hormone
- thyroid peroxidase antibody
- ▶ the first stage of labor

Introduction

Inappropriate cesarean delivery rates have posed a tremendous toll on maternal and neonatal health (1). China has made plenty of local, regional and national efforts to encourage vaginal delivery (2, 3). Although cesarean delivery rate reached 34.9% in 2018, the majority

of pregnant women still achieved vaginal delivery, even for those who experienced labor dystocia (4).

The natural labor process is divided into three stages. The first stage of labor occurs when women begin to feel regular contractions, which cause the cervix to open



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(dilate) and soften, shorten and thin (effacement). This allows the baby to move into the birth canal. The first stage is the longest of the three stages. The second stage of labor describes the period of time from when the cervix is fully dilated to when the baby is born, and the third stage of labor begins after the baby is born and finishes when the placenta and membranes have been delivered. Prior studies have shed light on the extended first stage of labor being associated with increased risk of cesarean section, chorioamnionitis, hysterorrhexis, postpartum hemorrhage and other adverse maternal outcomes (5, 6, 7). Increasing and compelling evidence has emerged that prolonged first stage of labor could take a heavy toll on the well-being of mothers and infants, which deserves more concern (8, 9). It remains to be fully elucidated whether perinatal biological changes affect the first stage of labor. Current evidence suggests that maternal thyroid function, acting as an essential biological indicator during pregnancy, plays a critical role in normal reproduction in several pathways, and thyroid dysfunction is among the most prevalent endocrine disorders during pregnancy (10, 11). It is commonly acknowledged that free thyroxine (FT4), thyroid-stimulating hormone (TSH) and thyroid peroxidase antibody (TPOAb) serve as the primary indicators of thyroid function. Moreover, maternal thyroid dysfunction has been demonstrated to be associated with adverse pregnancy outcomes, namely spontaneous abortion, preterm birth and even infant mortality (12, 13, 14, 15, 16). However, epidemiological evidence for the association between maternal thyroid function and the first stage of labor is still lacking.

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Given such a lack of information on the relationship between maternal thyroid function and duration of the first stage of labor, we therefore sought to quantitate FT4, TSH and TPOAb throughout pregnancy, and to evaluate their potential impact on the first stage of labor. If an association between maternal thyroid function and a prolonged first stage of labor could be found, it would be of great significance to further reach a better understanding of the association between thyroid dysfunction and adverse birth outcomes.

Materials and methods

Study design and participants

The data collected from a hospital affiliated with Nanjing Medical University between May 2016 and March 2019 were analyzed retrospectively. This study was approved by the Medical Ethics Committee of Nanjing Medical University. Data used in this work were anonymous; no individually identifiable information was available. Informed consent was obtained from the study participants.

In total, 71,348 pregnant women were registered. Out of which, 2865 pregnant women without accurate registration information and 6924 pregnant women without at least one thyroid function measurement were excluded, and 187 pregnant women who had no accurate information about their gestational age were also excluded. Participants with diagnosed hypothyroidism, subclinical hypothyroidism, hyperthyroidism, subclinical hyperthyroidism and other thyroid diseases (n = 767), type 1/2 diabetes (n = 378) and hypertension (n = 217) before pregnancy were excluded. Subsequently, the following participants were also excluded: 3001 resulted from assisted conception, 741 resulted from twin, 63 resulted from abortion, 91 resulted from stillbirth and 303 resulted from birth defects. Considering that we focused on the length of labor of healthy newborns, we excluded the women who delivered by cesarean sections (n = 22,592), assisted vaginal delivery (n = 453), as well as preterm birth (n = 1373) and malposition (n = 11). Finally, 31,382 pregnant women, all of whom were not treated with thyroid hormone replacement or anti-thyroid drugs, were included (Fig. 1).

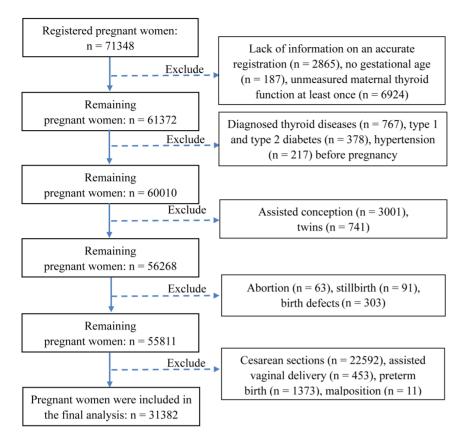
Maternal and neonatal characteristics

Maternal age, maternal ethnicity, marriage status, medical insurance, parity, mode of delivery, type of labor, fetal positions, length of the first and the second stage of labor, birth weight and length, baby gender, Apgar score (1 min/5 min) and gestational age at delivery were abstracted from medical records reported by obstetricians. Gestational complications (e.g. thyroid dysfunction) were diagnosed by obstetricians based on the guidelines.

Maternal thyroid function

Maternal serum samples were collected in the first (\leq 13 gestational weeks), second (14–27 gestational weeks) and third trimester (\geq 28 gestational weeks), respectively. Maternal serum FT4, TSH and TPOAb levels were detected during each trimester by electrochemiluminescent microparticle immunoassays using the Architect system (Roche). The intra-assay coefficients of variation (CV) of serum FT4, TSH and TPOAb were 4.74, 4.17, and 6.34%, respectively. The detection limit for the TPOAb assay is 10 IU/mL, and the cut-off value is 1.75 IU/mL. Since most







pregnant women in the first trimester were assessed for thyroid function at the different community medical service centers using different reagents and platforms, rather than at the Nanjing Maternity and Child Care Center, the number of participants varied from the first trimester to the third trimester. The diagnostic criteria for gestational hypothyroidism are: TSH >5.17 mIU/L and FT4 <12.91 pmol/L in the first trimester; TSH >5.22 mIU/L and FT4 <9.81 pmol/L in the second trimester; and TSH >6.84 mIU/L and FT4 <9.12 pmol/L in the third trimester. The diagnostic criteria for gestational subclinical hypothyroidism are: TSH >5.17 mIU/L with normal FT4 level in the first trimester; TSH >5.22 mIU/L with normal FT4 level in the second trimester; and TSH >6.84 mIU/L with normal FT4 level in the third trimester. The diagnostic criteria for gestational hyperthyroidism are: TSH <0.05 mIU/L and FT4 >22.35 pmol/L in the first trimester; TSH <0.39 mIU/L and FT4 >17.26 pmol/L in the second trimester; and TSH <0.60 mIU/L and FT4 >15.71 pmol/L in the third trimester.

Statistical analysis

Continuous variables were presented as mean \pm S.D., median and interquartile range, and categorical variables were described as counts and percentage. In addition,

concentrations of FT4, TSH and TPOAb were ln-transformed to improve a normal distribution. Model 1 was unadjusted; model 2 was adjusted for potential confounders, which included maternal age, parity, gestational age at delivery, baby gender, birth weight, gestational weeks when maternal thyroid function indicators were measured, gestational hypertension and diabetes; model 3 was further adjusted for type of labor. Additionally, spontaneous or induced labor-stratified sensitivity analysis was conducted.

Analysis was performed in the following three steps: first, a multiple linear regression model was used to examine the associations between concentrations of maternal FT4, TSH and TPOAb in each trimester and the length of the first stage of labor. Using tertiles to stratify thyroid dysfunction was considered as a sensitivity analysis. Secondly, we averaged concentrations of maternal FT4, TSH and TPOAb across the three trimesters to better estimate maternal thyroid function indicators-outcome associations throughout pregnancy (17). Repeated measurements analyses (i.e. mixed linear models) were applied additionally. Thirdly, the participants were divided into two groups according to whether they had gestational thyroid diseases: (1) the associations between maternal FT4, TSH and TPOAb and the length of the first stage of labor in pregnant women with normal thyroid function



were investigated; and (2) the relationships between different gestational thyroid diseases and the length of the first stage of labor were explored. Fourthly, according to the result of the third step, the associations between maternal subclinical hypothyroidism with different TPOAb status in the third trimester and the length of the first stage of labor were analyzed separately.

Results

A total of 31,382 pregnant women were analyzed and their characteristics were shown in Table 1. In our study, the mean age of pregnant women was 29.13 years (S.D.: 3.64). Almost all participants (99.91%) were Han Chinese. 99.68% of the participants were married and 76.45% of them had medical insurance. The rate of multiparae and spontaneous labor was 72.80 and 64.01%, respectively. Among all newborns, 50.61% were boys and 49.39% were girls. The mean neonatal birth weight was 3.37 kg (S.D.: 0.37). Table 2 showed the distribution of maternal FT4, TSH and TPOAb concentrations in different trimesters as well as the length of labor. The median length of the first and second stages of labor was 7.17 and 0.53 h, respectively.

Figure 2 showed the associations between maternal thyroid function indicators in different trimesters and the length of the first stage of labor. Adjusted for potential confounders, FT4 level in the second trimester and in the third trimester were found to be negatively associated with duration of the first stage of labor ($\beta = -1.30$ h, 95% CI: $-2.28, -0.32, P < 0.01; \beta = -0.35 h, 95\% CI: -0.61, -0.10,$ P < 0.01). A marginally significant association ($\beta = 0.06$ h, 95% CI: -0.004, 0.12, P=0.07) between TSH level in the second trimester and duration of the first stage of labor was observed, while TSH level in the third trimester was found to be significantly positively associated with duration of the first stage of labor (β =0.12 h, 95% CI: 0.06, 0.18, P < 0.001). Per unit increase in TPOAb (IU/mL) in the second trimester and in the third trimester were significantly associated with prolonged duration of the first stage of labor $(\beta = 0.08 \text{ h}, 95\% \text{ CI}: 0.01, 0.14, P = 0.02; \beta = 0.09 \text{ h}, 95\% \text{ CI}:$ 0.02, 0.15, P=0.01). However, no statistically significant associations were observed between maternal FT4, TSH and TPOAb levels in the first trimester and the duration of the first stage of labor. Detailed information was shown in Supplementary Table 1. A sensitivity analysis that removed induced labor cases showed that the associations were robust (Supplementary Table 2). Consistent associations between duration of the first stage of labor and maternal FT4, TSH and TPOAb levels were obtained from the

https://etj.bioscientifica.com https://doi.org/10.1530/ETJ-21-0071 **Table 1** Characteristics of 31,382 pregnant women withnormal pre-pregnancy thyroid function.

Characteristics	\boldsymbol{n} (%) or mean \pm s.p.
Maternal age (years)	29.13 ± 3.64
<35	28,473 (90.73)
>35	2909 (9.27)
Maternal marriage status	2909 (9.27)
Married	31,281 (99.68)
Unmarried	91 (0.29)
Divorced	10 (0.03)
	10 (0.03)
Maternal ethnicity	21 252 (00 01)
Han nationality	31,353 (99.91)
Other nationalities	29 (0.09)
Medical insurance	
Yes	23,992 (76.45)
No	7390 (23.55)
Gestational hypertension	
Normal	30,803 (98.15)
Hypertension	327 (1.04)
Preeclampsia	214 (0.68)
Eclampsia	38 (0.12)
Gestational diabetes	
Yes	6359 (20.26)
No	25,023 (79.74)
Parity	
Nulliparae	22,847 (72.80)
Multiparae	8535 (27.20)
Infant gender	
Воу	15,882 (50.61)
Girl	15,500 (49.39)
Type of labor	
Spontaneous	20,088 (64.01)
Induced	11,294 (35.99)
Gestational week (weeks)	39.83 ± 1.19
Birth weight (kg)	3.37 ± 0.37
Birth length (cm)	50.14 ± 1.13
Apgar 1 min	9.96 ± 0.31
≥7	31,366 (99.95)
<7	16 (0.05)
Apgar 5 min	9.99 ± 0.16
≥7	31,378 (100.00)
- <7	4 (0.00)

comparison of high tertiles, medium tertiles and low tertiles, respectively (Supplementary Tables 3, 4 and 5).

We averaged concentrations of maternal FT4, TSH and TPOAb across the three trimesters to estimate whether maternal thyroid function indicators–outcome associations still held throughout the whole pregnancy. After adjustment for potential confounders, maternal FT4, TSH and TPOAb level exhibited significant associations with the length of the first stage of labor (β =–0.64 h, 95% CI: –1.10, –0.18, *P*=0.01; β =0.08 h, 95% CI: 0.02, 0.14, *P*=0.04 and β =0.09 h, 95% CI: 0.04, 0.15, *P* < 0.001) (Supplementary Table 6). Mixed linear models showed that maternal FT4, TSH and TPOAb level exhibited significant associations with the length of the first stage of labor (β =–0.01) (Supplementary Table 6). Mixed linear models showed that maternal FT4, TSH and TPOAb level exhibited significant associations with the length of the first stage of labor



	n	25th	50th	75th	95th	Range
Maternal thyroid function indicators						
In the first trimester ^a						
FT4 (pmol/L)	2260	15.58	16.98	18.57	22.29	6.15-100.00
TSH (mIU/L)	2260	1.08	1.82	2.72	4.54	0.01-82.31
TPOAb (IU/mL)	894	8.45	12.16	17.97	127.60	0.00-570.10
In the second trimester ^b						
FT4 (pmol/L)	26,341	12.13	13.21	14.39	16.26	7.55-41.49
TSH (mIU/L)	26,341	1.54	2.17	2.98	4.57	0.01-12.49
TPOAb (IU/mL)	18,945	9.75	13.21	18.55	47.07	0.00-592.50
In the third trimester ^c						
FT4 (pmol/L)	27,436	11.79	12.91	14.11	16.04	6.76-44.43
TSH (mIU/L)	27,436	2.01	2.80	3.79	5.79	0.01-14.37
TPOAb (IU/mL)	23,741	9.53	13.13	19.05	39.60	0.00-554.40
The length of the stage of labor						
The first stage (h)	31,382	4.50	7.17	9.50	13.50	0.03-26.92
The second stage (h)	31,382	0.35	0.53	0.65	1.17	0.02-9.00

Table 2 Measurement of maternal thyroid function indicators in different trimesters, and the length of the first and second stage of labor.

^aAmong 31,382 subjects, maternal serum FT4 and TSH were measured in 2260 subjects and TPOAb was measured in 894 subjects in the first trimester. ^bMaternal serum FT4 and TSH were measured in 26,341 subjects and TPOAb was measured in 18,945 subjects in the second trimester. ^cMaternal serum FT4 and TSH were measured in 27,436 subjects and TPOAb was measured in 23,741 subjects in the third trimester.

FT4, free thyroxine; TPOAb, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone.

 $(\beta = -0.34 \text{ h}, 95\% \text{ CI:} -0.54, -0.15, P < 0.001; \beta = 0.07 \text{ h}, 95\% \text{ CI:} 0.02, 0.11, P < 0.01 and \beta = 0.08 \text{ h}, 95\% \text{ CI:} 0.02, 0.14, P < 0.001) (Supplementary Table 7).$

Subsequently, we grouped participants according to whether they had gestational thyroid diseases and a sensitivity analysis was conducted. There were 9.69% (219/2260), 5.88% (1548/26,341) and 11.58% (3176/27,436) pregnant women suffering from gestational thyroid diseases in the first, second and third trimester, respectively. In the analysis of pregnant women with normal thyroid function, after adjustment for the same potential confounders, the β coefficient of duration of the first stage of labor significantly associated with per unit increment in the concentration of FT4 (pmol/L) and TPOAb (IU/mL) in the second trimester was -0.68 h (95% CI: -1.04, -0.32, P < 0.001) and 0.09 h (95% CI: 0.02, 0.16, P=0.01), respectively. The β coefficient of the duration of the first stage of labor significantly associated with per unit increment in the concentration of FT4 (pmol/L), TSH (mIU/L) and TPOAb (IU/mL) in the third trimester was -0.66 h (95% CI: -1.02, -0.31, P < 0.001), 0.12 h (95% CI: 0.04, 0.21, P < 0.01) and 0.07 h (95% CI: 0.01, 0.14, P=0.03), respectively (Supplementary Table 8).

Further on, the associations between pregnant women with different gestational thyroid diseases and the length of the first stage of labor were examined. Compared with euthyroid, subclinical hypothyroidism in the third trimester exhibited a significantly prolonged length of the first stage

Per unit increase (In)	n	β (95% Cl)		Р
FT4				
1 st trimester	2260	0.55 (-0.22, 1.32)	H	0.16
2 ^{ed} trimester	26341	-1.30 (-2.28, -0.32)	*	<0.01
3 rd trimester	27436	-0.35 (-0.61, -0.10)	┝━━━┥ *	<0.01
TSH				
1 st trimester	2260	-0.10 (-0.22, 0.01)	()	0.09
2 ^{ed} trimester	26341	0.06 (-0.004, 0.12)	•	0.07
3 rd trimester	27436	0.12 (0.06, 0.18)	₩ *	<0.001
TPOAb				
1 st trimester	894	0.06 (-0.19, 0.30)	H	0.64
2 ^{ed} trimester	18945	0.08 (0.01, 0.14)	⊨ *	0.02
3 rd trimester	23741	0.09 (0.02, 0.15)	₩ *	0.01
			-2.5 -2 -1.5 -1 -0.5 0 0.5 1 1.5	

Figure 2

The associations between maternal thyroid function indicators and the length of the first stage of labor. FT4, free thyroxine; TSH, thyroid-stimulating hormone; TPOAb, thyroid peroxidase antibody. *Statistically significant (P < 0.05).

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of labor after adjustment for potential confounders (β = 0.30 h, 95% CI: 0.001, 0.56, *P*=0.04). However, no other type of thyroid dysfunction during pregnancy was found to be significantly associated with the length of the first stage of labor (Fig. 3 and Supplementary Table 9).

Then, we specifically focused on maternal subclinical hypothyroidism in the third trimester, stratifying them into subclinical hypothyroidism with positive TPOAb and negative TPOAb. As shown in Table 3, with regard to pregnant women with subclinical hypothyroidism combined without TPOAb, maternal TSH level in the third trimester exhibited a significant positive association with the length of the first stage of labor. With each unit increment of TSH (mIU/L), the length of the first stage of labor was 2.44 (95% CI: 0.03, 4.84, P=0.04) h longer after adjustment for potential confounders.

Discussion

Maternal thuroid diseases in

On the basis of a population-based retrospective cohort study, we constituted the first exploration of the associations between maternal thyroid hormone level as well as autoimmunity status and the duration of the first stage of labor.

Previous studies indicated that maternal thyroid hormone (e.g. FT4 and TSH) disturbance was associated with adverse outcomes including low birth weight, prematurity, respiratory distress syndrome, epilepsy, attention deficit hyperactivity disorder and autism spectrum disorder in offspring (11, 18). Additionally, thyroid autoimmunity (TAI) (e.g. TPOAb positivity) was reported to regulate the effect of thyroid status unfavorably on the labor process and the developing fetus (19, 20). We found that maternal TSH and TPOAb were positively associated with the duration of the first stage of labor, while FT4 was negatively associated with the duration of the first stage of labor. Underlying mechanisms remain speculative, but it has been shown that TSH, regulated by negative-feedback control of FT4, might have an impact on the release of oxytocin (OXT), which could prolong labor (21, 22). Although an association between maternal TPOAb and the duration of the first stage of labor was discovered, no causality could be inferred from the study and the mechanisms remained obscure. One hypothesis was that TPOAb could catalyze tyrosine iodization and its coupling

Maternal thyroid diseases n β (95% CI)				
1 st trimester				
Euthyroid	2041	Ref.		
Hypothyroidism	6	-1.18 (-3.53, 1.17)	H	0.33
Subclinical hypothyroidism	50	-0.17 (-0.98, 0.65)		0.69
Hypothyroxinemia	31	0.48 (-0.56, 1.52)	F	0.36
Hyperthyroidism	49	0.56 (-0.26, 1.39)	8B	0.18
Subclinical hyperthyroidism	20	-0.02 (-1.31, 1.27)		0.97
Hyperthyroxinemia	63	0.22 (-0.51, 0.94)	61	0.56
2 ^{ed} trimester				
Euthyroid	25217	Ref.		
Hypothyroidism	4	-0.30 (-3.19, 2.58)	·	0.84
Subclinical hypothyroidism	625	-0.10 (-0.33, 0.13)	•	0.40
Hypothyroxinemia	318	0.03 (-0.30, 0.35)	8+8	0.87
Hyperthyroidism	0	—		_
Subclinical hyperthyroidism	177	-0.20 (-0.63, 0.24)	F1	0.37
Hyperthyroxinemia	0	—		—
3 rd trimester				
Euthyroid	26595	Ref.		
Hypothyroidism	1	0.20 (-5.56, 5.60)		0.94
Subclinical hypothyroidism	378	0.30 (0.001, 0.56)	► *	0.04
Hypothyroxinemia	219	-0.02 (-0.41, 0.37)	++1	0.92
Hyperthyroidism	0	—		_
Subclinical hyperthyroidism	243	0.05 (-0.33, 0.42)	++	0.81
Hyperthyroxinemia	0	_		_
		-6-	-5-4-3-2-10 1 2 3 4 5 6	

B (05% CI)

Figure 3

The associations between maternal thyroid diseases in different trimesters and the length of the first stage of labor. *Statistically significant (P < 0.05).

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Table 3 The associations between maternal subclinical hypothyroidism with different TPOAb status in the third trimester andthe length of the first stage of labor.

	Maternal duration of labor in the first stage								
	Model 1ª β (95% CI)	р	Model 2 ^b β (95% CI)	р	Model 3 ^c β (95% Cl)	р			
Maternal subclinical hypothyroidism with negative TPOAb in the third trimester ($n = 345$)									
LnFT4 (pmol/L)	0.36 (-2.96, 3.69)	0.83	–1.44 (–4.53, 1.66)	0.36	–1.27 (–4.19, 1.66)	0.40			
LnTSH (mIU/L)	3.05 (0.32, 5.78)	0.03	2.89 (0.35, 5.44)	0.03	2.44 (0.03, 4.84)	0.04			
Maternal subclinical hypothyroidism with positive TPOAb in the third trimester ($n = 33$)									
LnFT4 (pmol/L)	5.54 (-5.42, 16.49)	0.31	2.59 (–7.15, 12.33)	0.58	1.40 (–7.39, 10.19)	0.74			
LnTSH (mIU/L)	7.32 (–4.97, 19.61)	0.23	7.95 (–1.94, 17.83)	0.11	2.82 (-7.92, 13.56)	0.59			

Statistically significant results (P < 0.05) are bolded.

^aModel 1: unadjusted model, ^bmodel 2: adjusted for maternal age, parity, gestational age at delivery, baby gender, birth weight, gestational weeks at which maternal thyroid function biomarkers were measured, gestational hypertension and gestational diabetes, ^cmodel 3: further adjusted for type of labor (spontaneous or induced).

FT4, free thyroxine; TPOAb, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone.

with iodotyrosyl residues to form free triiodothyronine and FT4, ultimately regulating the release of OXT.

Of note, in the third trimester, elevated TSH, TPOAb and reduced FT4 were associated with prolonged duration of the first stage of labor. Similar associations were observed in the second trimester, in spite of a marginally significant association between TSH and the first stage of labor. Furthermore, the same trend was obtained throughout the pregnancy. However, intriguingly, the above associations could not be validated in the first trimester. We conjectured that there could be two potential reasons behind this phenomenon. On the one hand, it was noteworthy that the sample size of pregnant women who had thyroid function measured in the first trimester was much smaller than those in the second and the third trimester, probably reducing the statistical power and misleading any conclusions made. On the other hand, the fact might be that maternal thyroid function was not associated with the duration of the first stage of labor, even though the sample size was big enough to reach a higher statistical power. In terms of chronology, the second and the third trimester were much closer to the labor process than the first trimester, probably contributing more with regard to the duration of labor, which led to the contradiction between conclusions in the first trimester and in the whole pregnancy.

One of our novel findings was that maternal TPOAb could be a potential predictor of the length of the first stage of labor. Thyroid hormone fluctuated during pregnancy under the influence of human chorionic gonadotropin (23); however, TPOAb, the most common type of thyroid autoantibody found in euthyroid individuals, was relatively stable. Previous studies focused on the increased risk of pregnancy complications (e.g. abortion and preterm birth) due to maternal elevated TPOAb with normal thyroid hormone; nevertheless, there were few randomized

controlled trials of intervention therapy. In clinical practice, there were no criteria (recommended or opposed) for intervention therapy against maternal elevated TPOAb with normal thyroid hormone (24). In addition, TPOAb was not fully screened throughout the whole pregnancy. Our research provided evidence to emphasize the necessity to screen pregnant women for TPOAb during the whole pregnancy.

The other novel finding was, for pregnant women suffering from subclinical hypothyroidism combined without TPOAb in the third trimester, that higher TSH level was associated with prolonged length of the first stage of labor. Maternal thyroid function was closely related to neurological development in newborns, among which the association between maternal subclinical hypothyroidism and adverse fetal neurological development was biologically plausible, but not clearly demonstrated (23). Levothyroxine has been recommended for pregnant women with subclinical hypothyroidism combined with TPOAb positivity. In contrast, for pregnant women with subclinical hypothyroidism combined with TPOAb negativity in the first trimester, the American Thyroid Association and Chinese Society of Endocrinology guidelines neither opposed nor recommended a treatment due to insufficient medical evidence (23, 24). Whether the effect of subclinical hypothyroidism without TPOAb on the labor process can provide a reference for clinical therapy requires an in-depth study.

Additionally, the reason that we concentrated on the first stage of labor rather than the second stage of labor was that the former lasts longer, was prone to be regulated by maternal endocrine and immune status, and to be related to adverse perinatal outcomes, compared with the second stage of labor (25, 26). Besides, the measurement of the length of the second stage of labor was affected greatly



by subjective factors and forceps were frequently used in the second stage of labor, which could have influenced the course of the second stage (27, 28). However, further research should pay more attention to the second stage of labor.

Our study had several strengths. First, a populationbased retrospectively design was used to evaluate the associations between maternal thyroid function indicators and the length of the first stage of labor, an understudied topic of the clinic. Secondly, an in-depth analysis after dividing continuous variables into low, medium and high tertiles was performed to explore the dose-response relationship. Finally, we found maternal TPOAb could be a potential predictor of the length of the first stage of labor, and for pregnant women suffering from subclinical hypothyroidism combined without TPOAb in the third trimester, a higher TSH level was associated with prolonged length of the first stage of labor.

Our study had several limitations. We did not systematically measure and explore the effects of all thyroid antibodies during pregnancy on the labor process, such as thyroglobulin antibodies and TSH receptor antibodies. In addition, since most pregnant women in the first trimester were assessed for thyroid function at different community medical service centers using different reagents and platforms rather than at the Nanjing Maternity and Child Care Center, the number of participants varied from the first trimester to the third trimester. Only 894 pregnant women had TPOAb measured in the first trimester, so the power of the TPOAb model in the first trimester and labor process could be lower than that in the other trimesters. In the analysis of the relationship between different thyroid diseases and labor processes, the sample size was also not sufficient. These findings need to be substantiated through further research.

Conclusion

We observed that maternal FT4, TSH and TPOAb levels were associated with the duration of the first stage of labor, and for pregnant women suffering from subclinical hypothyroidism combined without TPOAb in the third trimester, higher TSH level was associated with prolonged length of the first stage of labor. These findings suggest that maternal FT4, TSH and TPOAb might be important predictors of the first stage of labor.

Supplementary materials

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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Statement of ethics

This study was approved by the Medical Ethics Committee of Nanjing Medical University. Data used in this work were anonymous; no individually identifiable information was available here. Informed consent was obtained from the study participants.

Data availability statement

The corresponding authors hve full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contribution statement

Concept and design: Xu Wang and Yankai Xia. Acquisition, analysis, or interpretation of data: Hongcheng Wei and Quanquan Guan. Drafting of the manuscript: Hongcheng Wei and Quanquan Guan. Revision: Qiurun, Yu and Ting Chen. Supervision: Xu Wang and Yankai Xia.

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