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Nomogram of Thyroid in Northeastern Thai Fetuses at Gestational Age $20^{0/7}$- $36^{6/7}$ Weeks

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ABSTRACT

Objectives: To establish reference values of fetal thyroid glands from $20^{0/7}$ weeks to $36^{6/7}$ weeks of gestation.

Materials and Methods: This was cross-sectional study to measure fetal thyroid gland parameters in 184 pregnant women at gestational age (GA) $20^{0/7}$- $36^{6/7}$ weeks that had no systemic diseases or history of thyroid disorder. The fetal thyroid circumference (FTC), fetal thyroid area (FTA) and fetal thyroid transverse diameter (FTTD) were ascertained by 2-Dimension (2D) ultrasound. The exclusion criteria were abnormal maternal thyrotropin stimulating hormone (TSH) levels, fetal abnormalities, inability to identify the fetal thyroid gland, and abnormal neonatal TSH levels/ neonatal goiter. The parameters were calculated for the mean ± standard deviation (SD) and plotted against gestational age. The nomograms were presented according to gestational age as percentiles. The expected value of each measurement was established using a linear regression formula. The intraclass correlation coefficients (ICCs) had been used to evaluate the intraobserver and interobserver variations.

Results: Mean ± SD of FTC, FTA, and FTTD were 3.78 ± 0.68 cm, 1.12 ± 0.38 cm^2, and 1.36 ± 0.29 cm, respectively. All parameters tended to increase with gestational age. According to the regression model, the expected FTC, FTA, and FTTD could be calculated using the following formulas: FTC (cm.) = 0.289642 + [0.1239246 x GA (weeks)] ($p < 0.01$), FTA (cm^2) = [0. 068565 x GA (weeks)] - 0.8160961 ($p < 0.01$), and FTTD (cm.) = [0.0490783 x GA (weeks)] - 0.0185486 ($p < 0.01$). Intraobserver coefficients were 0.982, 0.977, and 0.935 for FTC, FTA, and FTTD, respectively. Interobserver coefficients were 0.989, 0.986, and 0.976 for FTC, FTA, and FTTD, respectively. Nomograms for each gestational age were also created.

Conclusion: We established normal reference values for the thyroid glands of fetuses in Northeastern Thai women. These reference values may be helpful in monitoring for fetal thyroid disorder in fetuses determined to be at high risk for the condition and providing appropriate antenatal management.

Keywords: fetal thyroid, fetal goiter, ultrasonography, prenatal diagnosis, reference range.

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ค่าอ้างอิงของขนาดต่อมไทรอยด์ทารกในครรภ์ที่มีอายุครรภ์ตั้งแต่ $20^{0/7}$ ถึง $36^{6/7}$ สัปดาห์ ในภาคตะวันออกเฉียงเหนือ

สุกัญญา ไชยราช, รัตนา คำวิลัยศักดิ์, เกียรติศักดิ์ คงวัฒนกุล, ศุภศิริ หะยะกังฉัตร, ปิยะมาศ ศักดิ์ศิริวุฒโฒ

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาค่าอ้างอิงของขนาดต่อมไทรอยด์ทารกในครรภ์ที่มีอายุครรภ์ตั้งแต่ $20^{0/7}$ ถึง $36^{6/7}$ สัปดาห์*

วัสดุและวิธีการ: *เป็นการวิจัยแบบ cross-sectional study โดยทำการอัลตร้าซาวด์เพื่อวัดขนาดต่อมไทรอยด์ของทารกในครรภ์ ทั้งขนาดเส้นรอบวง พื้นที่ และความกว้างของต่อมไทรอยด์ในแนวขวาง ในสตรีตั้งครรภ์เดี่ยว อายุครรภ์ $20^{0/7}$ สัปดาห์ ถึง $36^{6/7}$ สัปดาห์ ที่ไม่มีโรคเรื้อรังหรือประวัติเป็นโรคไทรอยด์ จำนวน 184 ราย โดยเกณฑ์การคัดออกจากการวิจัย ได้แก่ ตรวจพบระดับ thyroid stimulating hormone ในเลือดสตรีตั้งครรภ์ผิดปกติ ตรวจพบทารกในครรภ์มีความผิดปกติ ไม่สามารถตรวจหาตำแหน่งของต่อมไทรอยด์ที่เหมาะสมได้ หรือตรวจพบทารกแรกเกิด มีต่อมไทรอยด์โตหรือมีระดับ thyroid stimulating hormone ผิดปกติโดยนำข้อมูลที่ได้มาหาค่าเฉลี่ย (mean ± standard deviation) และมีการวิเคราะห์หาสูตรเพื่อคาดคะเนขนาดต่อมไทรอยด์ตามตามอายุครรภ์โดยใช้ linear regression formula รวมทั้งสร้างเป็น nomograms*

ผลการศึกษา: *ค่าเฉลี่ยบวกลบค่าเบี่ยงเบนมาตรฐานของขนาดเส้นรอบวง ขนาดพื้นที่ และความกว้างของต่อมไทรอยด์ในแนวขวางของทารกในครรภ์มีค่า 3.78 ± 0.68 ซม. 1.12 ± 0.38 ซม.2 และ 1.36 ± 0.29 ซม. ตามลำดับ โดยพบว่าค่าเฉลี่ยของขนาดต่อมไทรอยด์ทั้ง 3 พารามิเตอร์ มีแนวโน้มเพิ่มขึ้นตามอายุครรภ์ โดยสามารถหาค่าคาดคะเนของขนาดต่อมไทรอยด์ตามอายุครรภ์จากสูตรต่อไปนี้ ขนาดเส้นรอบวงต่อมไทรอยด์ (ซม.) = 0.289642 + [0.1239246 x อายุครรภ์ (สัปดาห์)] ขนาดพื้นที่ (ซม^2) = [0.068565 x อายุครรภ์ (สัปดาห์)] - 0.8160961 และความกว้างของต่อมไทรอยด์ในแนวขวาง (ซม.) = [0.0490783 x อายุครรภ์ (สัปดาห์)] - 0.0185486 ค่าสัมประสิทธิ์สหสัมพันธ์ในผู้วัดคนเดียวกันเท่ากับ 0.982, 0.977, 0.935 และระหว่างผู้วัดต่างคนเท่ากับ 0.989, 0.986 และ 0.976 สำหรับการวัดขนาดเส้นรอบวง ขนาดพื้นที่ต่อมไทรอยด์ และความกว้างของต่อมไทรอยด์ในแนวขวาง ตามลำดับ*

สรุป: *เนื่องจากค่าอ้างอิงปกติของขนาดต่อมไทรอยด์ทารกในครรภ์มีขนาดต่างกันไปในแต่ละพื้นที่และกลุ่มประชากรที่ทำการวิจัย การวิจัยนี้แสดงให้เห็นค่าอ้างอิงปกติของต่อมไทรอยด์ทารกในครรภ์ในสตรีตั้งครรภ์หญิงไทยในภาคตะวันออกเฉียงเหนือ ซึ่งอาจนำมาใช้เป็นประโยชน์เพื่อติดตามความผิดปกติของทารกในครรภ์กลุ่มเสี่ยง เพื่อให้การรักษาที่เหมาะสมต่อไป*

คำสำคัญ: *ขนาดต่อมไทรอยด์ทารกในครรภ์, อัลตร้าซาวด์, การวินิจฉัยก่อนคลอด, โรคไทรอยด์ของทารกในครรภ์*

Introduction

Disorders of the thyroid gland are common medical problem in pregnant women[1]. The incidence of hyperthyroidism in pregnant women has been shown to vary between 0.4% - 1.7 % and that of hypothyroidism has been shown to range from 0.002% - 0.012%[2]. Most thyroid disorders are linked to autoantibodies[2]. Thyrotropin-receptor antibodies (TRAb), which are specific to Graves' disease, can cross the placenta and may stimulate or block fetal thyrotropin stimulating hormone (TSH) receptors at around the 20th week of gestation, result in fetal thyroid abnormalities[3,4]. Because thyroid hormones are critical for fetal growth and development (especially neurodevelopment)[5, 6], thyroid abnormalities during fetal life may cause serious complications such as hydrops fetalis, upper airway obstruction due to the presence of a large goiter, fetal growth restriction, fetal tachycardia, or fetal death in utero. In addition, intellectual development may be affected if hypothyroidism is present[3, 7]. Thus, the early diagnosis of abnormal fetal thyroid status is essential in selecting an appropriate antenatal management strategy.

Prenatal ultrasonography is a useful tool for evaluating the fetal thyroid gland. A study of Bromley, et al demonstrated that the presence of a fetal goiter was the earliest sign of fetal thyroid disorder[8]. This finding was confirmed in a study conducted by Luton, et al, which found that this method yielded 92% sensitivity and 100% specificity for detecting clinically relevant fetal thyroid dysfunction[4]. Several guidelines recommend serial ultrasound monitoring to assess for evidence of fetal thyroid dysfunction[1,9-10]. The 2017 guidelines created by the American Thyroid Association recommend serial fetal ultrasound examinations to assess for signs of potential fetal thyroid disorders in cases which TRAb, uncontrolled hyperthyroidism, and preeclampsia are present[1]. Thus, the nomograms of fetal thyroid size are required as a screening test for the fetal thyroid dysfunction.

Several previous studies have produced nomograms of the fetal thyroid gland[7, 11-15], but the resulting data have varied among these studies. This variation might be caused by differences in ethnicity and iodine status[7, 13, 15]. The aim of the present study was to establish reference values for the thyroid glands of fetuses in Thai women, especially in northeastern Thailand.

Materials and methods

This was a cross-sectional study on fetal thyroid gland parameters conducted in 184 singleton pregnant women at GA $20^{0/7}$ - $36^{6/7}$ weeks (based on a reliable last menstrual period (LMP) or ultrasound dating in the first trimester) who visited Khon Kaen University Hospital for routine antenatal care. Pregnant women 18 years or older who had no systemic diseases or history of thyroid disorder were eligible for the study. Exclusion criteria were abnormal maternal TSH levels, fetal abnormalities, inability to identify the whole fetal thyroid gland, and neonatal thyroid disorder after birth (abnormal TSH levels or neonatal goiter). Fetal thyroid circumference (FTC), fetal thyroid area (FTA), and fetal thyroid transverse diameter (FTTD) were ascertained by 2D ultrasound measurement using a Voluson E8 Expert series (GE Healthcare, Milwaukee, WI, USA) with transabdominal (TA) probe Radio Access Bearer (RAB) 2-5Hz. The ultrasonography was performed by two operators. Measurements of the fetal thyroid were obtained by a transverse scan at the level of the fetal neck. The thyroid gland was visualized between the carotid arteries on both sides when the fetal spine was seen at the back and the trachea was in the middle of the thyroid gland. The thyroid width was adjusted to vertical plane and magnified the cross-sectional image of fetal neck until occupied 50% of the screen. The largest thyroid circumference was chosen to measure FTC and FTA using the ellipse function, and FTTD was measured with standard calipers, which were placed on the outside of the fetal thyroid just inside the carotid vessels. These measurements included the area of the fetal trachea (Fig. 1). Each parameter was measured three times and the average was used. The sample size was calculated based on 1.4 standard deviation (SD) of thyroid circumference reported by Achiron, et al[11] with a power of 0.80 and acceptable error of 15% of SD, the resulting sample size was 171.

Statistical analysis was performed using SPSS

version 17. The qualitative variable data were described using frequency and percentage, and quantitative variable data were calculated for the mean ± SD and plotted against gestational age. The nomograms of all parameters by gestational age were presented as percentiles. The expected value of each parameter was established via a linear regression mathematical formula. Intraclass correlation coefficients were used to evaluate the intraobserver and interobserver variations in 20 subgroup participants. This study was approved by the Khon Kaen University Ethics Committee for Human Research. Written informed consent was obtained from all participants.

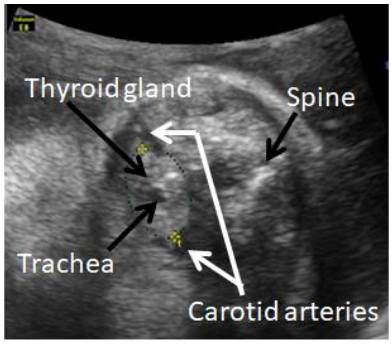

Fig. 1. Fetal thyroid gland measurement at 31 weeks of gestation.

Results

A total of 184 patients were included in the study. Ten patients were excluded due to abnormal maternal TSH levels (n = 5; 3 had hypothyroidism, 1 had subclinical hypothyroidism, and 1 had subclinical hyperthyroidism), the thyroid not being visible due to the fetus being in a prone position (n = 3; adequately visible thyroid in 98.4% of participants), fetal structural abnormalities (n = 1), and one neonate had abnormal TSH levels (congenital hypothyroidism). A total of 174 fetuses were included for data analysis.

The baseline characteristics of participants are described in Table 1. Mean ± SD of FTC, FTA, and FTTD of fetuses at GA 200/7 to 366/7 weeks were 3.78 ± 0.68 cm., 1.12 ± 0.38 cm^2, and 1.36 ± 0.29 cm., respectively. All parameters tended to increase with gestational age.

Table 1. Ultrasound measurements.

Baseline characteristics (N=174)	Mean ± Standard deviation	n (%)
Age (years)	29.85 ± 5.37	
Height (cm)	159.39 ± 5.20	
Pre-pregnancy weight (kilograms)	56.90 ± 9.20	
Pre-pregnancy BMI (kg/m^2)	22.46 ± 3.73	
No. of gravida		
G1		81 (46.55%)
G2		67 (38.51%)
G3		15 (8.62%)
G4		8 (4.60%)
G5		3 (1.72%)

BMI: body mass index

Nomograms of FTC, FTA, and FTTD by gestational age are shown in Fig. 2, 3, and 4. Percentiles of FTC, FTA and FTTD by gestational age are shown in Table 2, 3, and 4.

According to the linear regression model, the expected FTC, FTA, and FTTD can be calculated using the following formulas: FTC (cm.) = 0.289642 + [0.1239246 x GA (weeks)] ($p < 0.01$), FTA (cm.2) = [0. 068565 x GA (weeks)] - 0.8160961 ($p < 0.01$), and FTTD (cm.) = [0.0490783 x GA (weeks)] - 0.0185486 ($p < 0.01$). The ICCs for the evaluation of the intraobserver variations in measuring FTC, FTA, and FTTD in 20 subgroup participants were 0.982 (95% confidence interval (CI): 0.976 - 0.987), 0.977 (95% CI: 0.970 - 0.984) and 0.935 (95% CI 0.910 - 0.950). The ICCs for the evaluation of the interobserver variations in measuring each of these three parameters were 0.989 (95% CI 0.977 - 0.999), 0.986 (95% CI 0.972 - 0.999) and 0.976 (95% CI 0.949 - 0.996), respectively.

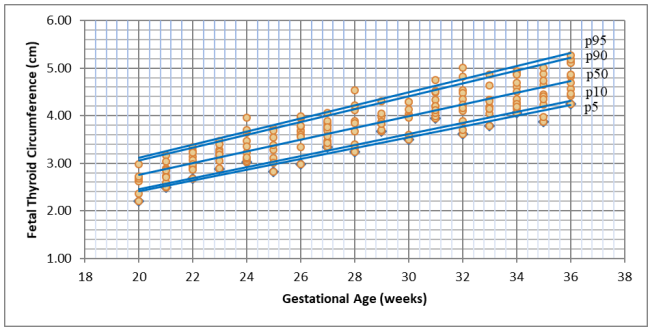

Fig. 2. Nomograms of fetal thyroid circumference according to gestational age.

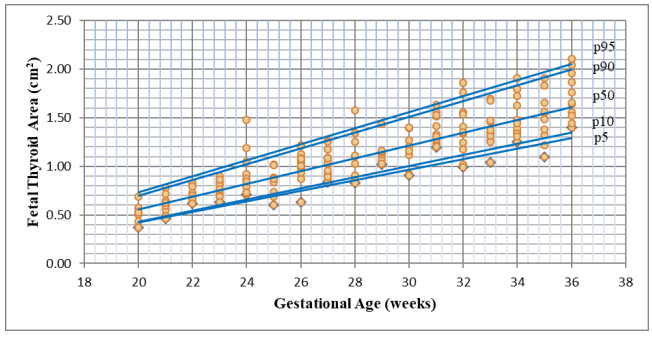

Fig. 3. Nomograms of fetal thyroid area according to gestational age.

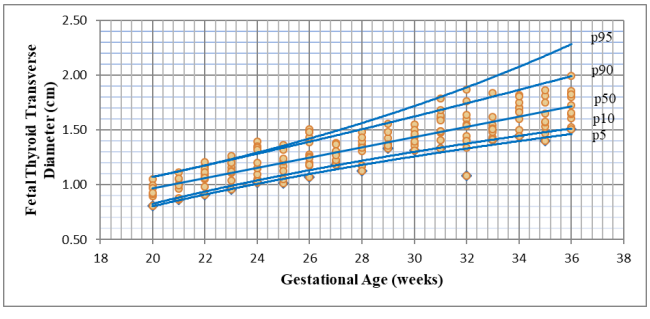

Fig. 4. Nomograms of fetal thyroid transverse diameter according to gestational age.

Table 2. Percentile of fetal thyroid circumference according to gestational age.

		Percentiles of fetal thyroid circumference (cm)				
Gestational age	**n**	**5th**	**10th**	**50th**	**90th**	**95th**
20 weeks	8	2.20	2.20	2.66	2.98	2.98
21 weeks	10	2.49	2.50	2.80	3.10	3.16
22 weeks	11	2.67	2.86	2.98	3.25	3.33
23 weeks	10	2.88	2.89	3.19	3.43	3.46
24 weeks	11	3.02	3.05	3.23	3.70	3.95
25 weeks	8	2.82	2.82	3.34	3.72	3.72
26 weeks	12	2.98	3.34	3.68	3.97	3.98
27 weeks	12	3.34	3.35	3.71	3.89	4.06
28 weeks	9	3.24	3.24	3.84	4.53	4.53
29 weeks	9	3.68	3.68	3.86	4.31	4.31
30 weeks	8	3.50	3.50	4.00	4.28	4.28
31 weeks	12	3.94	3.99	4.20	4.52	4.74
32 weeks	11	3.61	3.70	4.23	4.82	5.01
33 weeks	10	3.79	3.91	4.25	4.75	4.87
34 weeks	12	4.06	4.15	4.42	4.89	4.94
35 weeks	10	3.88	3.93	4.43	4.95	5.01
36 weeks	11	4.25	4.41	4.82	5.18	5.27

Table 3. Percentile of fetal thyroid area according to gestational age.

		Percentiles of fetal thyroid area (cm^2)				
Gestational age	**n**	**5th**	**10th**	**50th**	**90th**	**95th**
20 weeks	8	0.37	0.37	0.53	0.69	0.69
21 weeks	10	0.46	0.46	0.61	0.75	0.78
22 weeks	11	0.61	0.61	0.67	0.82	0.83
23 weeks	10	0.63	0.64	0.76	0.88	0.90
24 weeks	11	0.71	0.72	0.84	1.19	1.48
25 weeks	8	0.60	0.60	0.85	1.02	1.02
26 weeks	12	0.63	0.87	1.04	1.21	1.21
27 weeks	12	0.83	0.86	1.05	1.25	1.26
28 weeks	9	0.83	0.83	1.10	1.57	1.57
29 weeks	9	1.02	1.02	1.13	1.43	1.43
30 weeks	8	0.90	0.90	1.18	1.40	1.40
31 weeks	12	1.19	1.20	1.32	1.56	1.63
32 weeks	11	0.99	1.02	1.35	1.76	1.86
33 weeks	10	1.04	1.15	1.36	1.69	1.70
34 weeks	12	1.25	1.31	1.46	1.80	1.91
35 weeks	10	1.10	1.16	1.52	1.87	1.91
36 weeks	11	1.40	1.44	1.65	2.04	2.10

Table 4. Percentile of fetal thyroid transverse diameter according to gestational age.

Gestational age	n	Percentiles of fetal thyroid transverse diameter (cm)				
		5th	10th	50th	90th	95th
20 weeks	8	0.81	0.81	0.92	1.05	1.05
21 weeks	10	0.86	0.87	1.00	1.09	1.12
22 weeks	11	0.91	0.98	1.09	1.17	1.21
23 weeks	10	0.96	1.00	1.14	1.25	1.26
24 weeks	11	1.02	1.03	1.15	1.35	1.40
25 weeks	8	1.02	1.02	1.19	1.37	1.37
26 weeks	12	1.07	1.18	1.27	1.48	1.51
27 weeks	12	1.18	1.20	1.29	1.38	1.38
28 weeks	9	1.13	1.13	1.34	1.48	1.48
29 weeks	9	1.33	1.33	1.36	1.56	1.56
30 weeks	8	1.31	1.31	1.42	1.55	1.55
31 weeks	12	1.33	1.41	1.54	1.68	1.79
32 weeks	11	1.08	1.34	1.54	1.76	1.87
33 weeks	10	1.41	1.41	1.51	1.73	1.84
34 weeks	12	1.44	1.45	1.69	1.82	2.51
35 weeks	10	1.40	1.44	1.62	2.21	2.55
36 weeks	11	1.51	1.52	1.72	1.86	1.99

Discussion

Because thyroid disorders are common medical problem in pregnancy and can lead to severe adverse fetal complications, early prenatal diagnosis is essential to implement appropriate antenatal management. Several previous studies have produced nomograms of the fetal thyroid gland, but the resulting data have varied among these studies[7-8,11-15]. These variations might be caused by differences in ethnicity and iodine status. At Khon Kean University hospital, 35.5% of pregnant women had iodine deficiency[16].

The results of the present study showed that fetal thyroid gland parameters, including FTC, FTA, and FTTD tended to increase with gestational age, a finding that was consistent with those of previous studies[7-8,11,13,15]. The values for these thyroid circumference parameters were similar to those reported by Ranzini, et al[13] but smaller than in other studies[7,11,15] (Fig. 5). As mentioned above, these variations among studies may be caused by variations in ethnicity and iodine status. This was supported by a study by Achiron, et al, in Israel which found that up to 85% of pregnant women had iodine deficiency, reported larger thyroid glands compared to those in other studies[11, 17]. Likewise, a study from Europe found larger thyroid glands than one conducted in Americas and rate of iodine deficiency among pregnant women of 52% and 11%, respectively[18]. In addition, a study by Bernades et al, demonstrated that fetal thyroid gland parameters tended to increase with fetal weight[15]. The 2017 World Health Organization (WHO) Fetal Growth Charts reported that Asian women tended to have smaller fetuses compared to women of other ethnicities[19], which may explain why the average fetal thyroid size found in this study was smaller than those of other studies. This suggested that fetal thyroid reference values used in clinical practice should be population-based.

The parameters of the fetal thyroid gland are easily obtained using a cross-sectional plane at the level of fetal neck. The success rate in this study was

98.4%. However, the fetal being in a prone position and advanced gestational age (especially more than 34 weeks) affects the difficulty of measurement and make a process more time consuming. Because all three parameters correlate with gestational age and have low intraobserver and interobserver variations, they all may be useful in fetal thyroid assessment. However, the best reproducibility was found using FTC measurement which was consistent with the finding of earlier research conducted by Bernades, et al[15].

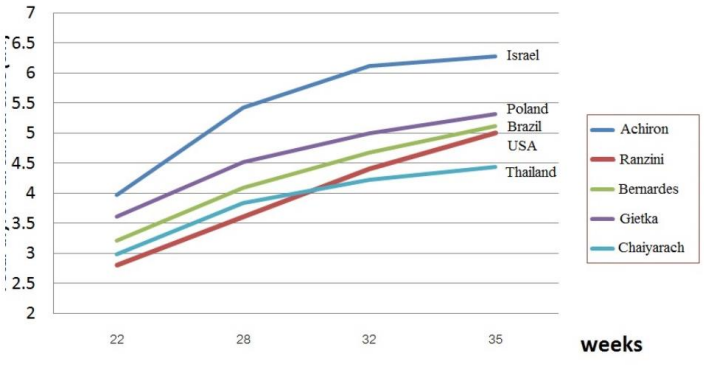

Fig. 5. Published fetal thyroid circumference nomograms according to gestational age.

We evaluated the maternal thyrotropin levels of all participants before enrolling them in the study in order to confirm that they had normal thyroid statuses, but it was not the routine laboratory testing in our practice. The thyroid statuses of all fetuses were later confirmed after birth. There were no anyone lost to follow-up or with incomplete neonatal data. Five of the women had abnormal TSH levels, three of whom (1.6%) had hypothyroidism, one of whom (0.5%) had subclinical hypothyroidism and one of whom (0.5%) had subclinical hyperthyroidism. The incidence of hypothyroidism has been shown to vary widely from 0.002%- 0.012% in the Americas and Europe[2] to up to 13% in India[20] based on maternal screening during the first trimester or within 20 weeks of gestation. Although the incidence of maternal hypothyroidism in this study was higher than those found in studies conducted in the Americas and Europe, the usefulness of universal maternal thyroid screening status in our population should be evaluated further.

We determined new normal reference values for thyroid glands in the fetuses of Northeastern Thai women. These nomograms may be useful in other areas in which anthropometric features and iodine status tend to be similar to those in our setting. However, the limitation of the study was small sample in each gestational age group. Moreover, the efficacy of this reference value prenatal sonographic screening has not yet been tested. Hence, further studies are necessary to validate these nomograms in clinical practice, and the sample size per gestational week should be calculated.

Conclusion

We established normal reference values of the fetal thyroid glands in Northeastern Thai women. These reference values may be helpful in monitoring for fetal thyroid disorder in fetuses determined to be high risk for the condition and providing an appropriate antenatal management.

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Potential conflicts of interest

The authors declare no conflict of interest.

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