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Assessment of trimester-specific reference ranges for thyroid hormones in normal pregnant women

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Abstract
Pregnancy leads to significant physiological changes that require trimester-specific reference intervals for thyroid function tests. Accurate assessment of thyroid function is critical to both maternal and fetal health. However, normative data on thyroid hormones for healthy pregnant women in Bangladesh are currently lacking. This study aimed to assess the trimester-specific reference ranges for thyroid hormones in normal pregnant women.

Methods: This cross-sectional study was conducted at the Department of Fetomaternal Medicine and Obstetrics and Gynecology outpatient of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from September 2022 to October 2023. A total of 360 single-tone pregnant women between 18 and 35 years of age were enrolled purposively. Data were analyzed using SPSS version 27.0.

Results: The study revealed significant fluctuations in TSH levels across pregnancy trimesters ($p<0.05$). In the first trimester, the mean TSH level was 1.55±0.79 µIU/L, which increased to 1.85±0.93 µIU/L in the second trimester and further to 2.29±0.94 µIU/L in the third trimester. Reference intervals in the first, second, and third trimesters were as follows: TSH (0.1-3.09, 0.2-3.6, and 0.35-4.04 µIU/l), FT4 (10.29-20.05, 9.63-17.99, and 9.6-16.65 pmol/L), and FT3 (1.97-6.32, 2.36-5.87, and 2.52-5.74 pmol/L), respectively.

Conclusion: The reference ranges for thyroid function tests show significant differences between trimesters of pregnancy. The use of trimester-specific thyroid hormone reference intervals is imperative to reduce the risk of misclassification of thyroid dysfunction during pregnancy.

Keywords: Gestational age, maternal age, pregnant women, serum TSH level, trimester, thyroid hormone

1. Introduction

The thyroid gland undergoes significant physiological changes during pregnancy, including moderate enlargement and increased vascularization [1]. Physiological changes in pregnancy are associated with changes in thyroid function, which require a different biochemical interpretation than in non-pregnant women and require established trimester-specific reference ranges [2]. Thyroid hormone secretion is tightly regulated by the hypothalamic-pituitary-thyroid axis. Once the thyroid releases T_4, certain organs in the body convert it into T_3, allowing it to affect the body's cells and metabolism [3]. This stimulation results in a reduction in serum TSH levels during the first trimester, resulting in lower TSH concentrations in pregnant women compared to non-pregnant women [4]. These complicated hormonal and physiological changes during pregnancy are crucial for maintaining thyroid function and maternal and fetal well-being [1]. The fetus relies on maternal thyroxine (T_4) passed through the placenta. The fetus converts maternal T_4 to triiodothyronine (T_3) locally, crucial for neurological growth. Maternal T_3 doesn't cross the placenta, seemingly playing a minor role in development. Pregnancy brings changes like heightened thyroid-binding globulin (TBG), expanding thyroid hormone distribution, increased iodine excretion, and placental deiodinase activity, boosting thyroid hormone metabolism [5]. The prevalence of thyroid disorder ranged from 4.8% to 11% amongst Indian pregnant population [6]. In Bangladesh, the reported prevalence of thyroid disorders was high, reflecting 34.98% with the incidence rate of 22.45% [7]. Consequently, evaluating thyroid disease during pregnancy holds importance for maternal well-being, obstetric outcomes, and child development [8]. Many pathophysiological processes during pregnancy, including significant maternal hormonal and metabolic changes, can have potentially serious consequences for pregnancy outcomes [9].

The major obstetric complications are abortion, preeclampsia, placental abruption, preterm labor, and fetal complications are prematurity, low birth weight, stillbirth, and perinatal death. Children born to untreated mothers have profound implications for future intellectual development [10]. Prenatal and postnatal adverse events, including attention deficit disorder and hyperactivity disorder, have been reported in children born to mothers with hypothyroidism [11]. Different TSH breakpoints have been reported in population-based studies conducted in different countries. Subsequent results confirmed that ethnicity, iodine intake, gender, age and body mass index can influence the reference range of serum TSH [12]. The American Endocrine Society also reported 0.1-2.5 mIU/L as the normal range for TSH in the first trimester and recommended thyroxine treatment for women with TSH >2.5 mIU/L in the first trimester or >3.0 mIU/L in the second and third trimester (De Groot *et al*., 2012). The European Thyroid Association had similar recommendations [13]. Therefore, establishing reference ranges for thyroid function in pregnant women ensures accurate assessment of hormonal changes, early detection of irregularities, and prevention of undesirable consequences. These can play a crucial role in monitoring maternal and fetal health, adjusting treatments, and informing clinical decisions [14].

2. Methodology

This cross-sectional study was conducted at the Department of Fetomaternal Medicine and Obstetrics and Gynecology outpatient of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from September 2022 to October 2023. A total of 360 single-tone pregnant women, aged 18 to 35 years, who attended the hospital were included. Purposive sampling was used for sample selection. Inclusion criteria included maternal age between 18 and 35 years, confirmed gestational age by last menstrual period (LMP) and ultrasound, singleton pregnancy, and consent to participate. According to the exclusion criteria, patients with known thyroid disorders, complicated pregnancies (e.g., pregnancy-induced hypertension, hyperemesis, diabetes mellitus, heart diseases, endocrine disorders, polycystic ovarian disease, multiple pregnancies, and history of recurrent abortions), psychiatric illness or treatment for it, hepatitis, liver dysfunction, history of drug intake affecting thyroid function (e.g., amiodarone, lithium, biotin, dopamine agonists, somatostatin analogs) within the last 3 months, and those suffering from chronic illnesses or unwilling to participate were excluded. Gestational age was categorized into three groups: first trimester (≤13 weeks), second trimester (14-27 weeks), and third trimester (28 weeks to 40 weeks). The study was approved by the hospital's ethical committee, and data were analyzed using SPSS version 27.0.

3. Result

In this study, the majority of respondents (39.7%) belonged to the 24-29 year's age group, followed by 35.8% in the 30-35 years age group. The majority of the respondents (73.3%) were multigravida. The mean maternal age was 28.25±4.70 years in the first trimester, 27.04±4.73 years in the second trimester, and 26.61±5.12 years in the third trimester. The mean gestational ages were 9.78±1.88 weeks, 21.54±3.85 weeks, and 34.14±3.18 weeks, respectively. The average BMIs were 24.19±2.52 kg/m² in the first trimester, 24.57±2.94 kg/m² in the second trimester, and 25.32±3.41 kg/m² in the third trimester. The mean maternal serum TSH levels were 1.55±0.79 µIU/L in the first trimester, 1.85±0.93 µIU/L in the second trimester, and 2.29±0.94 µIU/L in the third trimester. The differences in TSH levels across trimesters were statistically significant (p<0.05). Serum TSH values showed significant differences between trimesters. The mean difference between the first and second trimesters was-0.29967 (p=0.010). The first and third trimesters had a significant mean difference of-0.74933 (p<0.001). The comparison between the second and third trimesters showed a mean difference of-0.44967 (p<0.001). The mean maternal serum FT3 levels in the first trimester were 4.06±0.92 pmol/L, in the second trimester 4.15±0.89 pmol/L, and in the third trimester 3.94±0.86 pmol/L. However, the differences in maternal serum FT3 levels between the trimesters were not statistically significant (p>0.05). The study found no statistically significant differences in serum FT3 levels between the first and second trimesters (p=0.406) or between the first and third trimesters (p=0.282). However, when comparing the second and third trimesters, a mean difference of 0.21225 was observed (p = 0.057), suggesting a possible trend toward increased thyroid hormone levels in the third trimester, though this was not statistically significant. The mean maternal serum FT4 levels were 14.04±2.92 pmol/L in the first trimester, 13.74±2.57 pmol/L in the second trimester, and 13.46±2.05 pmol/L in the third trimester. The differences in FT4 levels between the trimesters were not statistically significant (p>0.05). No statistically significant differences were observed in thyroid hormone levels when comparing the first and second trimesters, with a mean difference of 0.28950 (p=0.378). Similarly, the first and third trimesters showed no significant variation, with a mean difference of 0.57050 (p=0.083). The comparison between the second and third trimesters also revealed no significant differences, with a mean difference of 0.28100 (p=0.392). The study established trimester-specific thyroid normal reference ranges for each thyroid function index, based on the 2.5% to 97.5% percentiles. For TSH, the reference range was 0.10-3.09 µIU/L in the first trimester, 0.20-3.60 µIU/L in the second trimester, and 0.35-4.04 µIU/L in the third trimester. For FT3, the reference range was 1.97-6.32 pmol/L in the first trimester, 2.36-5.87 pmol/L in the second trimester, and 2.52-5.74 pmol/L in the third trimester. Lastly, for FT4, the reference range was 10.29-20.05 pmol/L in the first trimester, 9.63-17.99 pmol/L in the second trimester, and 9.60-16.65 pmol/L in the third trimester.

Table 1: Baseline characteristics of participants by trimester-specific groups.

Parameters	Trimester		
	First (n=120)	Second (n=120)	Third (n=120)
	Mean ± SD		
Maternal age (Years)	28.25±4.70	27.04±4.73	26.61±5.12
Gestational age (Weeks)	9.78±1.88	21.54±3.85	34.14±3.18
BMI (Kg/m2)	24.19±2.52	24.57±2.94	25.32±3.41

Table 2: The mean (±SD) serum TSH levels in different pregnancy trimesters.

Parameters	Trimester			P-value
	First	Second	Third	
	Mean ± SD	Mean ± SD	Mean ± SD	
S. TSH (µIU/L)	1.55±0.79	1.85±0.93	2.29±0.94	<0.001[a]

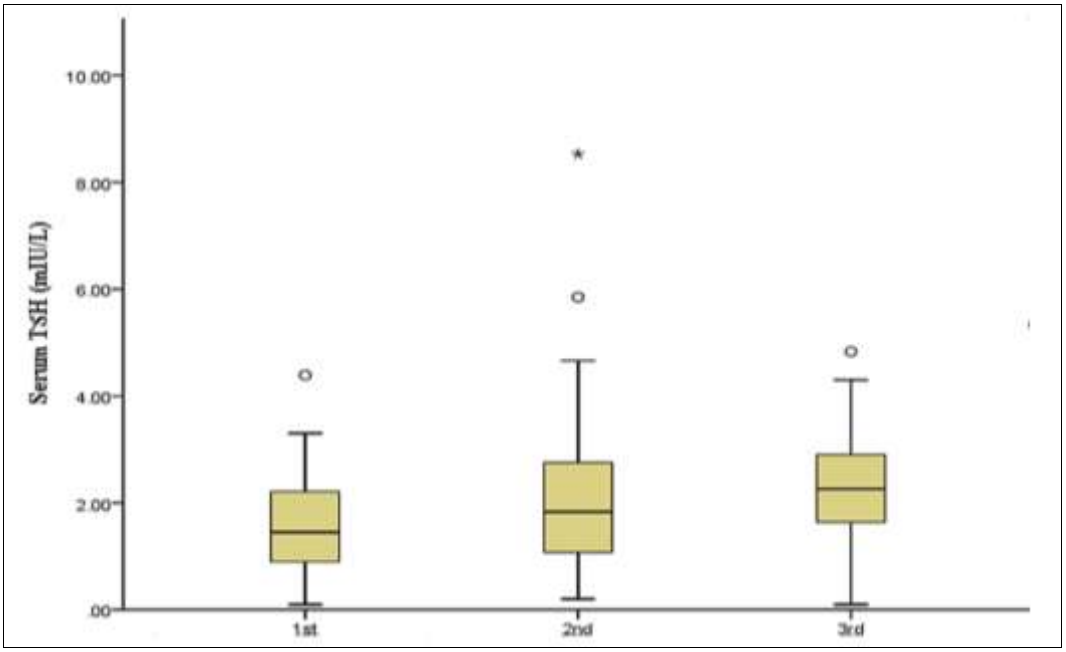

Fig I: Boxplot diagram showing average trimester-specific values of serum TSH in normal pregnant women

Table 3: Pair-wise comparison of mean (±SD) TSH values by trimester.

Trimester (I)	Trimester (J)	Mean Difference (I-J)	Std. Error	p-value	95% Confidence Interval Bound	
					Lower	Upper
1st	2nd	-0.29967	0.11552	0.01	-0.5268	-0.0725
	3rd	-0.74933	0.11552	<0.001	-0.9765	-0.5222
2nd	1st	0.29967	0.11552	0.01	0.0725	0.5268
	3rd	-0.44967	0.11552	<0.001	-0.6768	-0.2225
3rd	1st	0.74933	0.11552	<0.001	0.5222	0.9765
	2nd	0.44967	0.11552	<0.001	0.2225	0.6768

Table 4: The mean (±SD) serum FT3 levels in different pregnancy trimesters.

Parameters	Trimester			P-value
	First	Second	Third	
	Mean ± SD	Mean ± SD	Mean ± SD	
S. FT3 (pmol/L)	4.06±0.92	4.15±0.89	3.94±0.86	0.162[a]

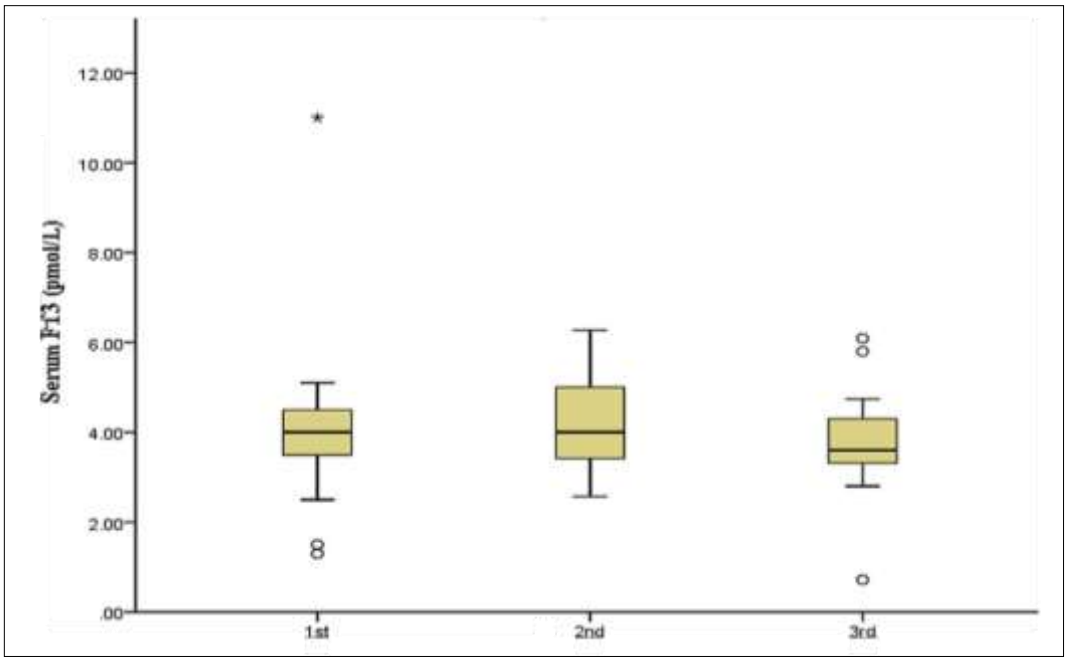

Fig 2: Boxplot diagram showing average trimester-specific values of serum FT3 in normal pregnant women

Table 5: Pair-wise comparison of mean (±SD) FT3 values by trimester.

Trimester (I)	Trimester (J)	Mean Difference (I-J)	Std. Error	*p*-value	95% Confidence Interval Bound	
					Lower	Upper
1st	2nd	-0.0925	0.11119	0.406	-0.3112	0.1262
	3rd	0.11975	0.11119	0.282	-0.0989	0.3384
2nd	1st	0.0925	0.11119	0.406	-0.1262	0.3112
	3rd	0.21225	0.11119	0.057	-0.0064	0.4309
3rd	1st	-0.11975	0.11119	0.282	-0.3384	0.0989
	2nd	-0.21225	0.11119	0.057	-0.4309	0.0064

Table 6: The mean (±SD) serum FT4 levels in different pregnancy trimesters.

Parameters	Trimester			p-value
	First (n=120)	Second (n=120)	Third (n=120)	
	Mean ± SD			
S. FT4 (pmol/L)	14.04±2.92	13.74±2.57	13.46±2.05	0.222[a]

a = one-way ANOVA

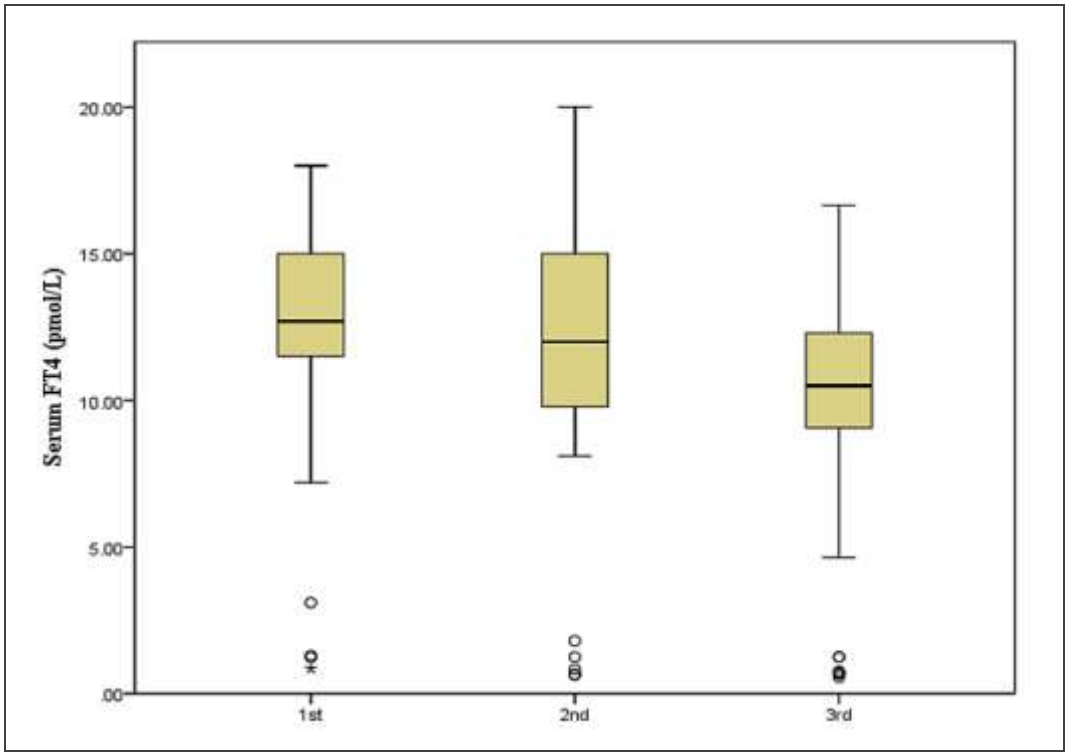

Fig 3: Boxplot diagram showing average trimester-specific values of serum FT4 in normal pregnant women

Table 7: Pair-wise comparison of mean (±SD) FT4 values by trimester.

Trimester (I)	Trimester (J)	Mean Difference (I-J)	Std. Error	p-value	95% Confidence Interval Bound	
					Lower	Upper
1st	2nd	0.2895	0.32813	0.378	-0.3558	0.9348
	3rd	0.5705	0.32813	0.083	-0.0748	1.2158
2nd	1st	-0.2895	0.32813	0.378	-0.9348	0.3558
	3rd	0.281	0.32813	0.392	-0.3643	0.9263
3rd	1st	-0.5705	0.32813	0.083	-1.2158	0.0748
	2nd	-0.281	0.32813	0.392	-0.9263	0.3643

Table 8: Trimester-wise values for 2.5th, 50th, and 97.5th centiles from the reference population for thyroid-stimulating hormone, free triiodothyronine, and free thyroxine.

Hormones	Percentile		Reference range
	2.5th	97.5th	
	TSH (µIU/mL)		
1st trimester	0.1	3.09	0.1-3.09
2nd trimester	0.2	3.6	0.2-3.6
3rd trimester	0.35	4.04	0.35-4.04
FT3 (pmol/L)			
1st trimester	1.97	6.32	1.97-6.32
2nd trimester	2.36	5.87	2.36-5.87
3rd trimester	2.52	5.74	2.52-5.74
FT4 (pmol/L)			
1st trimester	10.29	20.05	10.29-20.05
2nd trimester	9.63	17.99	9.63-17.99
3rd trimester	9.6	16.65	9.6-16.65

4. Discussion

In this study, 73.3% of respondents were multigravida and 26.7% were primigravida. The mean (±SD) gestational age for the first, second, and third trimesters was 9.78±1.88, 21.54±3.85, and 34.14±3.18 weeks, respectively. The average BMIs in these trimesters were 24.19±2.52, 24.57±2.94, and 25.32±3.41 kg/m², respectively. Similar results were found in Mumtaz *et al*.'s study, which reported average gestational ages of 8.79±2.15, 18.94±3.06, and 33.06±3.13 weeks for the first, second, and third trimesters. This study observed a significant increase in mean TSH values from the first to the third trimester ($p<0.05$), with values of 1.55±0.79 IU/L, 1.85±0.93 IU/L, and 2.29±0.94 IU/L, respectively. This increase likely reflects the thyroid gland's adjustment to meet the growing hormonal needs for fetal development. The mean FT3 values for the first, second, and third trimesters were 4.06±0.92 pmol/L, 4.15±0.89 pmol/L, and 3.94±0.86 pmol/L, respectively. While slight variations were observed, these changes were not clinically significant ($p>0.05$). The mean FT4 values for the first, second, and third trimesters were 14.04±2.92 pmol/L, 13.74±2.57 pmol/L, and 13.46±2.05 pmol/L, respectively. The study showed a slight decline in FT4 levels across trimesters ($p>0.05$), with the lowest mean in the third trimester. Mumtaz *et al*. [15] found a significant increase in TSH from the first to the third trimester (p=0.018), an increase in FT3 values ($p<0.001$), and a decrease in FT4 values (p=0.086), though the decrease in FT4 was statistically insignificant. This study establishes trimester-specific thyroid function reference ranges using the 2.5th to 97.5th percentile. For TSH, the ranges were 0.10-3.09 µIU/L in the first trimester, 0.20-3.60 µIU/L in the second trimester, and 0.35-4.04 µIU/L in the third trimester. For FT3, the reference ranges were 1.97-6.32 pmol/L in the first trimester, 2.36-5.87 pmol/L in the second trimester, and 2.52-5.74 pmol/L in the third trimester. The reference ranges for FT4 in this study were 10.29-20.05 pmol/L in the first trimester, 9.63-17.99 pmol/L in the second trimester, and 9.60-16.65 pmol/L in the third trimester. Xing *et al*. [16] also utilized the 2.5th to 97.5th percentiles to establish reference intervals for thyroid function. Their findings were: TSH ranges of 0.07-3.96, 0.27-4.53, 0.48-5.40, and 0.69-5.78 mIU/L for the first, second, and third trimesters of pregnancy, as well as nonpregnant controls. For FT4, the reference intervals were 9.16-18.12, 8.67-16.21, 7.80-13.90, and 8.24-16.61 pmol/L for the same groups, respectively. Mehran *et al*. [17] defined the 5th and 95th percentiles as reference intervals for each trimester, resulting in TSH ranges of 0.2-3.9, 0.5-4.1, and 0.6-4.1 mIU/L; TT4 ranges of 8.2-18.5, 10.1-20.6, and 9.0-19.4 µg/dL; and TT3 ranges of 137.8-278.3, 154.8-327.6, and 137.0-323.6 ng/dL for the first, second, and third trimesters, respectively. These trimester-specific thyroid hormone reference ranges enhance clinical interpretation and highlight the importance of tailored reference ranges for optimal maternal and fetal health management. They account for physiological fluctuations across trimesters, improving the accuracy of thyroid function assessment in pregnant women. When comparing these results to the American Thyroid Association (ATA) guidelines, which provide reference ranges for thyroid hormones during pregnancy, it's important to note that the lack of statistically significant differences in trimester-specific FT3 and FT4 values does not contradict the ATA guidelines. The ATA guidelines offer general reference ranges while accounting for individual variations influenced by factors like geography, population characteristics, and test methods. Therefore, the absence of significant differences in this study does not invalidate the ATA guidelines but emphasizes the need to consider local and population-specific data when interpreting thyroid function in pregnancy. Further studies with larger sample sizes could offer a more comprehensive comparison to the ATA guidelines.

5. Limitation of the study

The study population was selected from a single tertiary care hospital in Dhaka, which may limit the generalizability of the findings to the broader population. The relatively small sample size also restricts the ability to extrapolate the results. Additionally, the study did not consider pregnant women with underlying medical conditions or account for external factors such as dietary habits and iodine intake, which are known to influence thyroid function. Despite these limitations, the study provides valuable insights into trimester-specific reference ranges for thyroid hormones during pregnancy.

6. Conclusion and Recommendation

The study establishes trimester-specific reference ranges for thyroid hormones in the local population. The results show a significant increase in thyroid-stimulating hormone (TSH) levels from the first to third trimester, while FT3 and FT4 exhibit minor fluctuations with no clinical significance. These findings emphasize the need for country-specific reference intervals and highlight the relevance and applicability of well-established reference ranges in various geographical contexts. Conducting larger, multicenter studies with a more diverse sample could enhance the generalizability of trimester-specific reference ranges for thyroid hormones in pregnant women. Longitudinal studies tracking changes in thyroid function across trimesters would provide a better understanding of the dynamics over time

and help establish causal relationships. Furthermore, incorporating these trimester-specific reference ranges into clinical guidelines for the care of pregnant women would improve the accuracy of thyroid function assessments and ensure appropriate treatment.

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8. Conflict of interest: None declared.

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