Research Article

Establishment of Trimester-Specific Reference Intervals for TSH and Thyroid Hormones in Pregnant Women living in Oran, Western Algeria

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Abstract

Background and Aim: The thyroid gland undergoes physiological changes during pregnancy, leading to variations in reference intervals (RIs) for TSH and free thyroid hormones across the different trimesters. To ensure accurate interpretation of these tests, the American Thyroid Association (ATA) recommends the use of trimester-specific and population-based reference intervals. The aim of our study was: to establish trimester-specific reference intervals of TSH, FT3, and FT4 in pregnant women living in Oran western Algeria.

Materials and Methods: The reference intervals were established accordingly to the CLSI guideline (EP28-A3c). The study included 401 apparently healthy pregnant women, classified as follows: 120 in the first trimester, 154 in the second trimester, and 127 in the third trimester. Reference subjects were selected based on NACB exclusion criteria. Hormone assays were performed using the Roche Cobas e411 analyzer.

Results: The established RIs corresponding to the 2.5th and 97.5th percentiles were in the First, Second and Third trimester for TSH: 0.25–3.57 mIU/L, 0.15–3.43 mIU/L,0.57–4.23 mIU/L, FT4 : 11.41–20 pmol/L, 10.56–18 pmol/L, 9.43–17.54 pmol/L, and FT3 : 3.16–7.02 pmol/L, 3.02–7.54 pmol/L, 3.2–7.37 pmol/L.

Conclusion: In the absence of population-specific reference intervals for TSH and thyroid hormones in our country, establishing such values represents a significant advancement, enabling more accurate diagnosis and improved management of thyroid disorders.

Introduction

Thyroid hormones play a crucial role in maintaining pregnancy and ensuring proper fetal development [1,2]. However, the fetal thyroid gland does not reach functional maturity until approximately the 18th–20th week of gestation, making maternal thyroid hormones the primary fetal source during the first half of pregnancy and even in the second half of pregnancy, the fetus remains partially dependent on maternal thyroid hormones [3]. Therefore, requirements for thyroid hormone and iodine increase by approximately 50% during pregnancy [4-6]. To ensure adequate fetal Thyroid hormones supply, maternal thyroid gland undergoes several physiological changes including: a transient reduction in thyroid-stimulating hormone (TSH) levels due to the TSH-like stimulatory effect of human chorionic gonadotropin (hCG) [7], increased production of thyroid-binding globulin (TBG) [8], enhanced degradation of thyroid hormones by placental deiodinases, increased urinary iodide clearance [9]. These changes lead to dynamic variations in maternal serum TSH and thyroid hormone levels, particularly free thyroxine (FT4), across different trimesters of pregnancy [10].

Maternal thyroid dysfunction during pregnancy increases the risk of adverse maternal and child outcomes, such as pregnancy loss, miscarriage, premature delivery, low birth weight, impaired neuropsychological development, pre-eclampsia and gestational hypertension [11-14].

Considering the adverse outcomes, accurate assessment of thyroid function during pregnancy is essential to prevent both maternal and fetal complications. Due to the physiological alterations occurring during pregnancy, reference intervals (RIs) established in non-pregnant individuals are not applicable to pregnant women. Given the impact of thyroid dysfunction on both the mother and the fetus, the American Thyroid Association (ATA) [15], and other guidelines [16,17], recommend the use of population-based and trimester-specific reference ranges for TSH and thyroid hormones to ensure proper diagnosis and management. Several studies have established trimester-specific reference intervals in diverse populations, showing variability influenced by ethnicity, iodine status, assay methodology, and environmental factors [15,18,19]. However, there is a lack of specific data for Algerian pregnant women, which underscores the need to establish population- and trimester-specific reference intervals in order to improve clinical decision-making and pregnancy outcomes. This study aims to establish the reference intervals of TSH and free thyroid hormones in pregnant women living in Oran (western Algeria), thereby providing essential data to improve the screening and management of thyroid disorders during pregnancy.

Materials and Methods

In this study, we established reference intervals for TSH and free thyroid hormones following the EP28A3c protocol published by the Clinical and Laboratory Standards Institute (CLSI). This guideline provides standardized recommendations for defining, establishing, and verifying reference intervals in clinical laboratories to ensure reliability and clinical relevance [20]. A total of 401 apparently healthy pregnant women living in Oran with singleton pregnancies were included in the study. Only women who provided informed consent were enrolled. Participants were recruited between September 2022 and April 2024 from outpatient clinics in Oran where prenatal follow-up is performed. Pregnancy was confirmed by the presence of fetal cardiac activity on obstetric ultrasound. Gestational age was determined using early obstetric ultrasound.

Reference subjects were selected using an a priori direct sampling method, which is the CLSI recommended approach [20]. Population selection was based on exclusion criteria defined by the National Academy of Clinical Biochemistry (NACB) [21]: personal or family history of thyroid dysfunctions, positive thyroid peroxidase antibodies (TPO-Ab), goiter or thyroid nodules and medications that affect thyroid function. Additionally, the study excluded smoker women, multiple gestation, acute pathology within the past three months, chronic diseases, use of any medication, pregnancies resulting from assisted reproductive technologies, complicated pregnancies (gestational diabetes, preeclampsia, gestational hypertension, retroplacental hematoma, threatened miscarriage or preterm labor, preterm premature rupture of membranes, genital bleeding, severe anemia, Hemolysis Elevated Liver enzymes Low Platelets “HELLP” syndrome), hyperemesis gravidarum, intrauterine growth retardation and women in active labor.

Venous bloods were collected between 8:00 and 10:00 AM in a non-fasting state and serum stored at -20°c for further analysis. TSH and thyroid hormone tests were performed on the Cobas e411 immunoassay analyzer (Roche Diagnostics), a widely used platform known for its precision and accuracy in hormonal assays which use the Electrochemiluminescence Immunoassay.

Results were validated through internal quality control. The precision of the assays was assessed through intra- and inter-assay imprecision of TSH, free triiodothyronine (FT3), and FT4.

As our population lacks specific reference intervals for TPO-Ab, we performed a study to verify the transference of the manufacturer cutoff according to CLSI (EP28-A3c) guideline. We carried out this verification on 20 men. Subject selection was based on NACB criteria [21]: we included healthy men younger than 30 years, with TSH levels between 0.5 and 2 mIU/L, and excluded smokers, men with a personal or family history of thyroid disease, or those with goiter and thyroid nodules. The measurement of TPO-Ab was also performed using the Cobas e411 analyzer.

In our study, since urinary iodine measurement was not feasible, we subjectively assessed the iodine status of the participants by considering their intake of iodine-rich nutrients. The main dietary sources considered were fish, milk, and salt.

Notably, the salt available on the Algerian market is iodized. As recommended by EP28A3c CLSI guideline [20], we eliminated outliers using Tukey method.

Reference intervals covering 95% of the population were determined using the non-parametric method. The lower and upper reference limits were defined as the 2.5th and 97.5th percentiles, respectively.

After outliers removing, a total of 401 pregnant women were included in the study: 120 in the first trimester (5 - 13 weeks (w)), 154 in the second trimester (13w+ 1day - 28 w), and 127 in the third trimester (28 w+1 day - 40 w).

Statistical analysis

Statistical analysis was performed using MedCalc software. The normality of data distribution was assessed using the Shapiro–Wilk test. Results are expressed as mean ± standard deviation (SD) for normally distributed variables, and as median for non-normally distributed variables. Outliers were identified and excluded using Tukey's method. Reference intervals were determined using the non-parametric approach, and 90% confidence intervals (CI) were computed for the upper and lower limits of the reference range.

Results

The median maternal age was 29 years in the first trimester (range: 18–43 years), and 30 years in both the second trimester (range: 19–43 years) and the third trimester (range: 18–47 years). The median gestational age was 8 weeks in the first trimester, 19.8 weeks in the second trimester, and 36.2 weeks in the third trimester. Median parity was 1 in all three trimesters. The consumption of salt and milk, the main sources of iodine, was satisfactory with a reported daily intake among the participants. However, fish consumption was infrequent. Verification of TPO-Ab cut-off showed that all values were below the manufacturer's threshold of 34 IU/mL. Summary statistics and reference intervals of TSH, FT4, FT3 are shown in Table 1.

Table 1: Trimester specific Reference intervals of TSH, FT3 and FT4.

	1st trimester	2nd trimester	3rd trimester
TSH			
Median	1.28	1.53	2.17
RI	0.25 – 3.57	0.15 – 3.43	0.57 – 4.08
LL 90% CI	0.019 – 0.39	0.013 – 0.41	0.011 – 0.75
UL 90% CI	3.29 – 4.03	3.22 – 3.84	3.87 – 4.57
FT4			
Median	15.20	13.24	13.63
RI	11.41 - 20	10.56 - 18	9.43 – 17.54
LL 90% CI	10.68 – 11.93	10.32 – 11.13	8.8 – 11
UL 90% CI	19.67- 20.33	17 - 18	16.86 – 18
FT3			
Median	4.93	5.49	5.47
RI	3.65 – 7.33	3.23 – 7.72	3.2 – 7.37
LL 90% CI	3.30 – 3.88	2.97 – 3.58	2.97 – 3.37
UL 90% CI	6.71 – 7.55	7.41 – 7.86	– 8.21

RI: reference interval, LL: lower limit, UL: upper limit, CI: confidence interval

Reference intervals estimated were in the First, Second and Third trimester respectively, for:

TSH: 0.25–3.57 mIU/L, 0.15–3.43 mIU/L, 0.57–4.23 mIU/L (Figure 1),

FT4 : 11.41–20 pmol/L, 10.56–18 pmol/L, 9.43–17.54 pmol/L (Figure 2),

FT3 : 3.16–7.02 pmol/L, 3.02–7.54 pmol/L, 3.2–7.37 pmol/L (Figure 3).

Figure 1: Trimester-specific reference intervals of TSH during pregnancy.

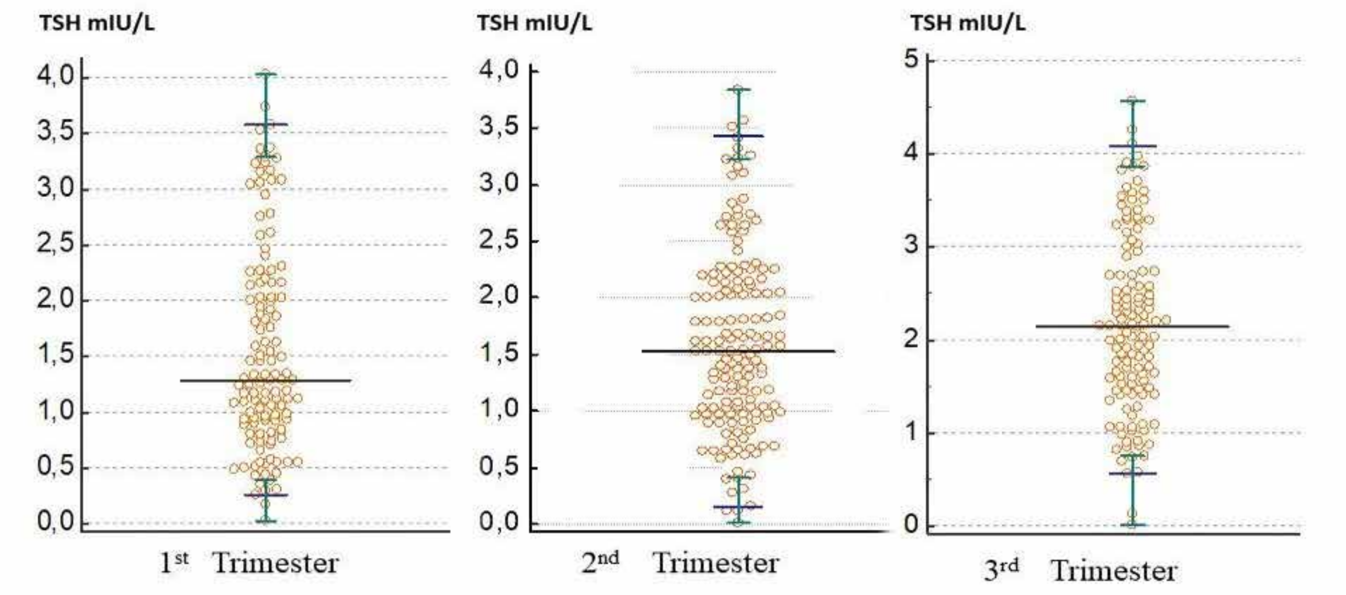


Figure 2: Trimester-specific reference intervals of FT4 during pregnancy.

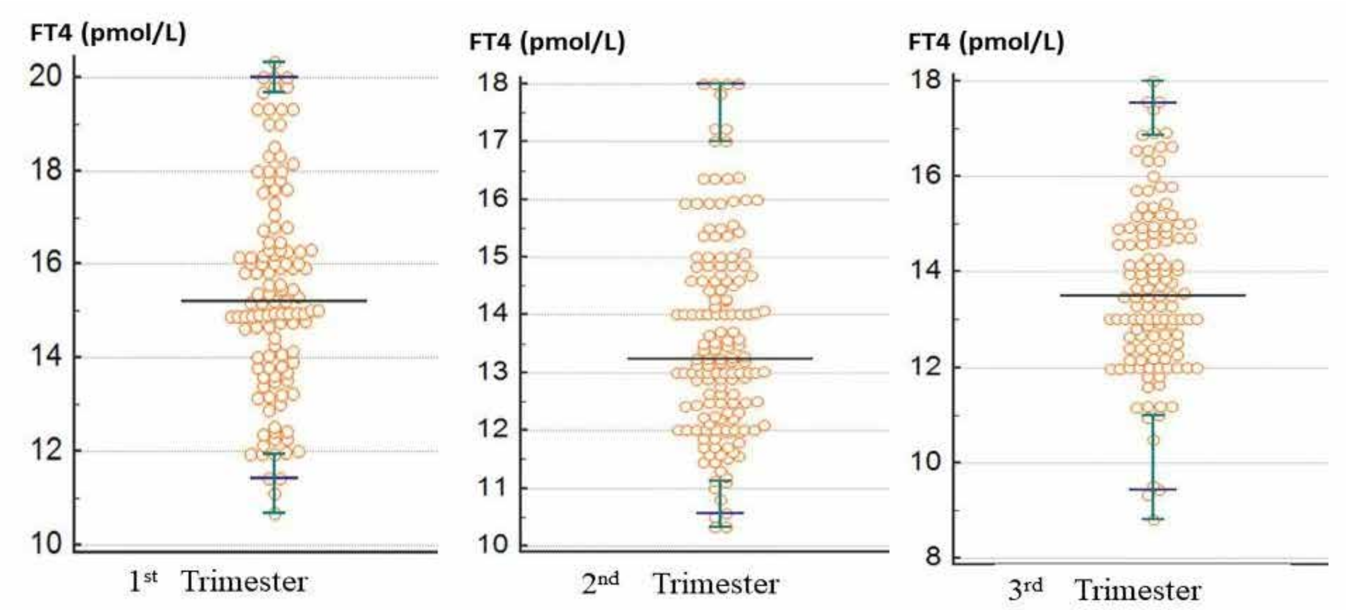
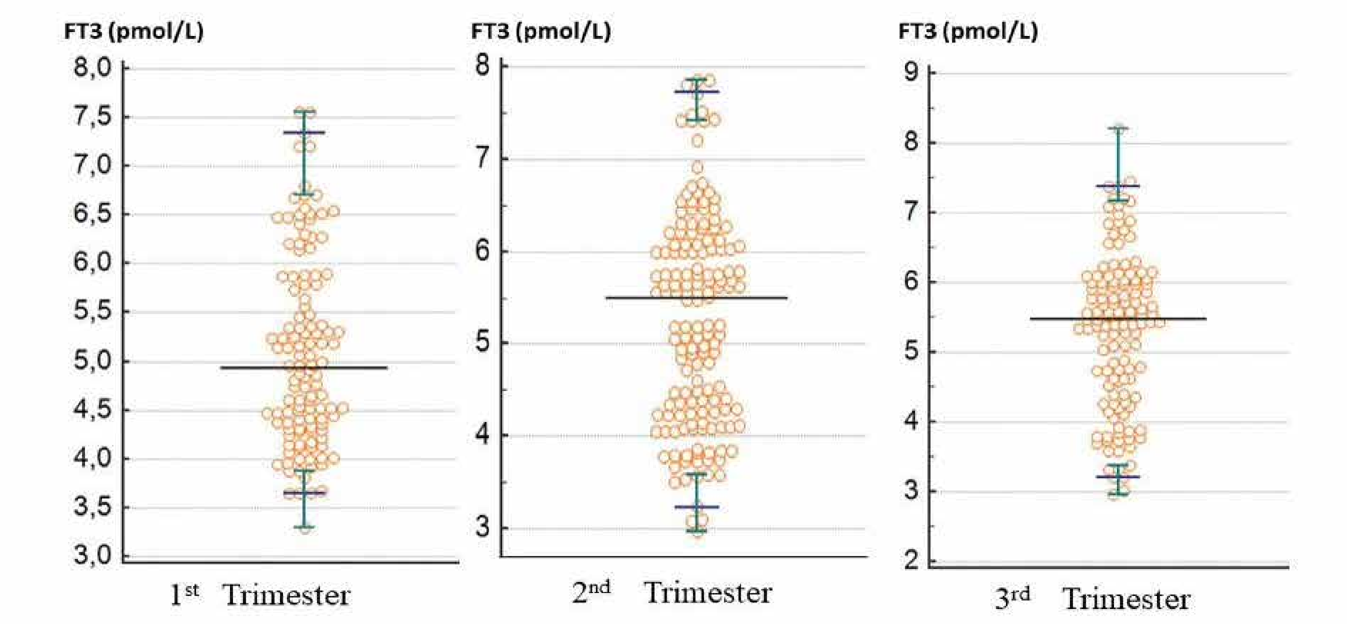


Figure 3: Trimester-specific reference intervals of FT3 during pregnancy.



Discussion

TSH is considered the primary and most sensitive biomarker for assessing thyroid function [15]. During pregnancy, early detection of thyroid dysfunction is crucial to prevent adverse outcomes affecting both fetal development and postnatal neurocognitive growth. Accordingly, the ATA guideline recommend applying trimester-specific and population-based reference intervals to ensure accurate interpretation [15].

In this work, we established population- and trimester-specific RIs of TSH, FT3, and FT4 in a cohort of pregnant women living in Oran, western Algeria. To the best of our knowledge, this is the first nationwide study in Algeria to establish pregnancy-specific reference intervals for TSH and thyroid hormones. For this purpose, healthy participants were carefully selected according to NACB exclusion criteria. Moreover, additional stringent exclusions were applied (see above).

The manufacturer-provided TPO-Ab cut-off was verified as appropriate for our population, with all measured concentrations falling below the specified threshold. This allowed us to use the manufacturer's cut-off to exclude women with positive TPO-Ab from the sample.

Repeatability and reproducibility tests confirmed excellent analytical precision, with coefficients of variation less than 5% for TSH, FT3, and FT4.

In our study, outliers accounted for less than 5% of the total population, underscoring both the rigorous selection of reference subject and the robustness of the analytical system.

Regarding the iodine status of the population, the ATA 2017 guidelines recommended establishing TSH reference intervals in subjects with adequate iodine intake [15]. Since direct urinary iodine assessment was not feasible, iodine status was evaluated based on dietary intake, particularly iodized salt and milk, both of which were consumed daily by participants. The overall pattern suggested no severe iodine deficiency, a finding further supported by a recent study in Oran reporting a mean urinary iodine concentration of 131.4 µg/L [22], consistent with adequate iodine status in the population.

The median TSH concentration showed a gradual increase throughout the three trimesters. Other studies [23–25], performed using Roche analyzers, have reported upper reference limit values for TSH across all trimesters, similar to those observed in our study, as shown in Table 2. Although these results show similarities with ours, variations persist across populations, emphasizing the need to establish population-specific RIs for reliable interpretation of TSH values. The lower-limit of RIs reported in other studies [23-29], summarized in Table 2, whether performed on Roche analyzers or other analytical platforms, reported lower values for TSH compared with our findings. This discrepancy may be explained by differences in gestational age at the time of sampling. In our study, at first trimester recruitment began as early as the 5th week, whereas in those studies, participants were enrolled later, typically from the 9th, 12th, or even 14th week of gestation. These findings may be explained by the progressive influence of hCG on TSH, which becomes more evident on the reference interval as gestational age increases and hCG concentrations rise. At second trimester, we note that the lower limit of our RI is similar to that observed in the study of Yuen LY [25], where recruitment began at 16th week. By contrast, the study of Joosen AM [27], which recruited later (27 weeks), reported a slightly higher lower limit. At the third trimester, we started recruitment at 28th week and we notice that the lower limit of our RI is comparable to that reported in other studies where recruitment began at 30, 32 or even 36 weeks. We observe that in the third trimester, the lower limit of the TSH reference interval is less influenced by gestational age at recruitment than in the earlier trimesters. This may be explained by the significant decline in hCG levels at this stage of pregnancy, stabilization of thyroid function, and reduction in TSH fluctuations.

Table 2: Trimester specific Reference intervals of TSH, FT3 and FT4 in other studies.

Study	Analysing platform	Gestation week	TSH (mIU/L)	FT4 (pmol/L)	FT3 (pmol/L)
Dorizzi et al. 2023 Italy (23)	Roche Elecsys	14–16 24–26 30–32	0.34-3.81 0.68 - 4.07 0.63 - 4	11-17 9.98-15.25 9.49 -15.1	3.81 - 6.05 3.61-5.38 3.99-5.37
Sekhri et al. 2016 India (29)	Roche Elecsys	10.8 2nd T 3rd T	0.09-6.65 0.51-6.66 0.91-4.86	9.81-18.53 8.52-19.52 7.39-18.28	3.1-6.35 2.39-5.12 2.57-5.68
Joosen et al. 2016 Spain (27)	Roche Elecsys	9–13 27–29 36–39	0.11-3.39 0.25-3.38 0.51-3.85	11.70-20 9.3-14.2 8.1-14.9	/ / /
Ortega Carpio 2018 Spain (26)	Roche Elecsys	9–11 26–28 34–36	0.25-4.68 0.62-4.83 0.76-4.57	12.30-20.2 12-16.9 9-16.3	/ / /
Kostecka-Matyja 2017 Poland (24)	Roche Elecsys	1st T 2nd T 3rd T	0.01-3.18 0.05-3.44 0.11-3.53	11.99-21.9 10.46- 16.6 8.96-17.23	3.63-6.55 3.29-5.45 3.1-5.37
Yuen 2020 China (25)	Roche Elecsys	12–13 16–20 32–36	0.06-3.14 0.15-3.78 0.31-4.54	11.2-22.2 10.1-19.4 9-17	3.47-5.06 3.25-5.2 2.94-4.56
Yuen 2020 China (25)	Siemens Centaure	12–13 16–20 32–36	0.03-2.5 0.08-2.95 0.25-3.9	11.9-20.2 11.3-18.7 10.1-16	3.63-5.73 3.99-5.26 3-4.52
Yuen 2020 China (25)	Beckman DXI	12–13 16–20 32–36	0.11-2.71 0.19-3.25 0.3-3.87	8.3-14.4 7.4-12.6 6.7-11	4.04-6.14 3.85-5.75 3.57-5.18
Yuen 2020 China (25)	Abbott architect	12–13 16–20 32–36	0.04-2.11 0.1-2.51 0.19-2.99	11.2-19 10.5-17.1 9.5-14.7	3.45-5.52 3.39-5.52 3.22-5.12
Ollero et al. 2019 Spain (28)	Abbott architect	9 15 36	0.13-4.16 0.31-3.73 0.58-4.36	10.94-15.9 10.55-15.4 8.62-13.64	/ / /

The analysis of our reference intervals shows partial concordance with the ATA recommended upper limit of 4 mIU/L, as our TSH upper limit was close to this threshold. Although some similarities are observed with ATA recommendations, discrepancies remain, highlighting the importance of population-specific RIs as the optimal reference standard.

For FT4 reference interval, analytical limitations significantly contribute to the wide variability in FT4 RIs reported across studies in pregnant populations. Given this heterogeneity, the ATA recommends establishing FT4 reference intervals that are both population and method-specific in order to ensure accurate assessment of thyroid function during pregnancy.

In our study, we observed a continuous decline in FT4 reference interval values across pregnancy, a trend that has been consistently documented in the literature. Measurements performed with reference methods, such as direct equilibrium dialysis and Liquid Chromatography–Tandem Mass Spectrometry (LC/MS/MS), also confirm this progressive decline with advancing gestational age [30]. This reduction is explained by physiological adaptations of the thyroid gland during pregnancy, particularly increased demand for thyroid hormones and iodine, as well as enhanced renal clearance, among other contributing factors.

Regarding FT3, RIs remained relatively stable throughout pregnancy, which is consistent with several previously published studies listed in Table 2. However, the FT3 upper reference limit of our population was slightly higher compared to that reported in other studies performed on Roche analyzers. This discrepancy may be attributed to inter-population differences.

Strengths of the Study

The main challenge in our work was the selection of apparently healthy pregnant women. This issue represents a major difficulty for clinical biologists worldwide when establishing biological reference intervals and explains the on-going efforts of scientific societies to develop alternative approaches. The principal strength of our study lies in the rigorous selection of participants, as demonstrated by the very low proportion of outliers, which did not exceed 5% of the study population. In addition, we applied additional criteria beyond those defined by the NACB, ensuring a more accurate and reliable selection of reference subjects.

Limitations of the Study

The limitations of our study regarding the establishment of RIs include, first, the absence of iodine status assessment among participants, which would have allowed us to exclude women with severe iodine deficiency. However, it is recognized that the Oran region is not considered an iodine-deficient area. Another limitation is the exclusive use of a Roche analyzer for measurements, whereas variations across different analytical platforms are well documented. Ideally, assessments should have been conducted across multiple analyzers to establish method-specific RIs. Nevertheless, our study provides valuable data for populations assessed on Roche platforms.

Conclusion

Thyroid dysfunctions during pregnancy constitute a major maternal–fetal health concern, requiring careful evaluation and tailored clinical management. In the absence of population-specific reference intervals for TSH and thyroid hormones in our country, establishing such values represents a significant advancement, enabling more accurate diagnosis and improved management of thyroid disorders. Our work therefore provides a basis for revising screening and monitoring protocols for thyroid disorders in Algeria, with the ultimate aim of promoting a more personalized and effective approach to care that reflects the specific characteristics of our population. This study represents a first step, and we intend to extend this work to include the entire country in the future.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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CRediT Author Statement

All authors contributed substantially to the development of this work: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft, Supervision.

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Data Availability Statement

The data supporting the findings of this study are available from the corresponding author.

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