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Original Research

Prevalence and Pattern of Gestational Thyroid Dysfunction in a Population of South-East Nigerian Women.

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Abstract

Background: Pregnancy serves as a physiological stress test for the thyroid which often leads to dysfunction in women with limited thyroid reserves. The occurrence of gestational thyroid dysfunction is linked to unfavourable obstetric and foetal outcomes. Globally, iodine deficiency is a prominent causative factor for thyroid dysfunction. The study aimed to determine the prevalence and pattern of thyroid dysfunction among pregnant women in Enugu, South-east Nigeria.

Methodology: This hospital-based descriptive cross-sectional and observational study was conducted over six months on selected participants from pregnant women attending antenatal clinics at the study sites. Maternal clinical and demographic risk factors for thyroid dysfunction were evaluated in a cohort of 318 pregnant women. An analysis of variance (ANOVA) was performed to compare participants' thyroid status across different trimesters of pregnancy, and different thyroid and nutritional iodine states.

Result: The prevalence of thyroid dysfunction in the study population is 6.6%. Hypothyroidism was detected in 5.3% of the participants, consisting of 3.8% sub-clinical hypothyroidism and 1.6% overt hypothyroidism. Sub-clinical hyperthyroidism accounted for 1.3% of all participants; no overt hyperthyroidism was detected in this study.

Conclusion: There is a relatively high prevalence of gestational thyroid dysfunction in the study population with hypothyroidism being the predominant disorder. This highlights the need for region-specific considerations in antenatal care to facilitate early detection and effective management of gestational thyroid dysfunction, thereby mitigating potential adverse maternal and foetal outcomes.

Keywords: Hypothyroidism, Pregnancy, Prevalence, Nigerian, Nutritional Iodine Status, Thyroid dysfunction.

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Introduction:

Thyroid disease is the second most common endocrine disorder affecting women in their reproductive years after diabetes mellitus, and it is associated with an increased risk of adverse pregnancy outcomes when left untreated. [1–4] During normal pregnancy, the thyroid gland remarkably increases in size by about 10% and significantly more in iodine deficient women. This is because of an increase in demand of thyroxine from the foetus which drives increased thyroid hormone synthesis and iodine requirement. [5] Women who have low thyroid reserve or iodine deficiency are typically unable to meet up with the human chorionic gonadotropin (hCG) hormone mediated increased in the demand for thyroxine during the early stages of pregnancy. [4]

The prevalence of thyroid dysfunction in pregnant women is influenced by factors such as dietary iodine availability, environmental conditions, autoimmunity, and social background. Hypothyroidism accounts for 2.8% to 13.7%, while hyperthyroidism for 1.25% to 3.43% of cases globally.[7–13] In Africa, previous studies have documented hypothyroidism rates between 2.8% and 3.2% and hyperthyroidism between 1.3% and 3.4% in pregnancy.[11,12] A recent study in Zaria, Northwest Nigeria, reported an overall thyroid dysfunction prevalence of 5.3% during pregnancy, with hypothyroidism at 3.0% and hyperthyroidism at 2.3%.[13] These findings underscore the global variation in thyroid dysfunction prevalence among pregnant women, emphasizing the need for region-specific studies to inform healthcare strategies.

Thyroid dysfunction has been associated with the incidence of spontaneous abortion, pre-eclampsia, eclampsia, abruptio placentae, preterm delivery and low birth weight in pregnant women, as well as decreased IQ and motor development early in the life of their offsprings [2,14–16] with implications for both affected families and the healthcare system. Previous studies have shown that people residing in hilly and mountainous areas, like the study population, are at higher risk of thyroid dysfunction due to low iodine levels. [17,18] We hypothesized that this geographical vulnerability in the region may result in a high prevalence of gestational thyroid dysfunction. As such, there may be a need to implement routine screening for thyroid diseases in pregnant women in the area during antenatal visits. However, there is a notable paucity of data to support policy changes for such screenings in this population. This study, therefore, aims at contributing to the growing body of knowledge of thyroid disorders in pregnancy by determining the prevalence and pattern of the disease in the study population.

Materials and Methods:

Ethical consideration:

This study adhered to ethical standards in line with the Declaration of Helsinki. Ethical approval was obtained from the Health Research and Ethics Committee of UNTH Ituku-Ozalla. All participants provided informed and voluntary consent after receiving detailed information about the study's purpose, procedures, benefits, and potential risks. To ensure confidentiality, unique identification codes were assigned to participants, and their personal information and medical records were securely stored. The investigators prioritized the welfare and rights of participants throughout the research process, emphasizing the principles of autonomy, beneficence, and non-maleficence.

Study Design and Setting

This was a hospital-based descriptive cross-sectional and observational study which was conducted at the antenatal clinics of University of Nigeria Teaching Hospital (UNTH), Ituku-Ozalla and Enugu State University Teaching Hospital (ESUTH), Parklane, both in Enugu State, South-East of Nigeria between February2019, and August 2019 (a 6-month period).Both facilities serve the rural, suburban, and urban areas of Enugu State and receive referrals from neighboring states like Abia, Anambra, Ebonyi, Imo, Kogi and Rivers.

Pregnant women in their reproductive years (18 – 45 years), across all trimesters, from whom informed consent were obtained were considered to have met the inclusion criteria for the study. Exclusion Criteria

included individuals with known history of diabetes mellitus patients, hypertensive patients, acutely or chronically ill patients (associated with stress-induced derangement in thyroid hormone profile), patients on medications known to affect thyroid hormone metabolism like thyroid medications, amiodarone, lithium, interferon and heparin, those under the age of 18, those with previous neck surgery or neck irradiation, and non-consenting individuals.

Participants who met the inclusion criteria were selected by stratified random sampling technique from pregnant women attending antenatal clinic at the study sites after informed written consent had been obtained. The potential participants were first stratified by trimester, after which the required sample was selected from each stratum by using a computer-generated random number table. The minimum sample size was calculated based on the prevalence of5.3% previously reported in another Nigerian study, (13) a significance level of 0.05, and adjusted for a 10% non-response rate. Then the target minimum sample size was calculated to be 78 participants from each site. However, a total of 318 participants were recruited and completed the procedure. The formula used for the minimum sample size calculation was as follows:(19)

$n = Z^2(PQ/d^2)$
where:

- n = required sample size,
- Z = Z-score corresponding to the desired level of confidence (95%),
- P = prevalence thyroid dysfunction in pregnancy from a previous study,
- Q = 1 – P
- d= margin of error.

$n = (1.96)^2[(0.053\times0.947) \div (0.05)^2] = 77.23 = 78$

Data Collection:
Patient biodata and medical history were obtained using a validated and structured research proforma. Variables of interest included demographics (age, gender, etc.), clinical parameters (blood pressure measurements, parity, and gestational age, etc), and laboratory measurements (Thyroid function test (TFT) and Urine iodine concentration (UCI)).

Serum and Urine Sample Collection:
Five millilitres (5mLs) of venous blood samples were drawn from the median cubital vein into plain vacutainer tubes in the morning between 8am to 11am while maintaining ascetic measures. These samples were centrifuged at 3000 rpm for 10 min after clotting and retraction, separated, and stored frozen at a -20°C until assayed in monthly batches to minimize inter-run variations. Urine samples were also obtained using a wide neck universal container for iodine determination and stored at -20^{o}C until assayed in monthly batches. Temperature was closely monitored all through the storage period to ensure stability of both sample types.

Assessment of TSH, FT4, FT3 and UIC:
Serum TSH, FT4 and FT3 in picograms per millilitre (pg/mL) were assayed using quantitative sandwich enzyme-linked immunosorbent assay (ELISA) technique. The assay kits were the TSH, FT3 and FT4 AccuBind ELISA test system supplied by Monobind Inc, California, USA. (20–22) Commercially prepared quality control sera (Acusera, Randox) at levels 1, 2, and 3 were assayed alongside samples and standards to guarantee analytical precision. Nutritional Iodine Status (NIS) was assessed using Urine Iodine concentration (UIC) which was assayed using the modified Sandell-Kolthoff reaction as described by Pino (Ammonium persulfate method). (23)

Diagnosis of gestational thyroid dysfunction was made when values fall outside the recommended trimester specific reference intervals as recommended by the American Thyroid Association (ATA) (Table 1). (24)

Table 1: Trimester specific reference values as recommended by the ATA.

Subjects	TSH (μIU/L)	Free T4 (ng/mL)	Free T3 (pg/mL)
Normal	0.12 – 3.73	0.81 – 1.91	1.56 – 3.62
Pregnant	0.10 – 3.19	0.73 – 2.06	1.69 – 3.81
1st Trimester	0.03 – 2.41	0.84 – 2.06	1.92 – 3.56
2nd Trimester	0.14 – 3.55	0.76 – 2.08	1.65 – 3. 96
3rd Trimester	0.21 – 3.12	0.70 – 1.70	1.74 – 3.65

TSH – Thyroid Stimulating Hormone

Statistical Analysis:
Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) computer software version 23.0 for windows (IBM, Inc, USA). Descriptive statistics, including means, standard deviations, and frequencies, were used to summarize quantitative (age, parity, gestational age, TFT hormone levels, etc) and qualitative variables (Educational status, marital status, etc.). Univariate analysis was performed to compare the means of continuous independent variables like age, parity and serum TFT hormone levels in both euthyroid and non-euthyroid participants using the independent T-test, while the Chi square test was used for categorical independent variables like sex, marital status, educational status etc. An analysis of variance (ANOVA) was performed to compare participants thyroid status across different trimesters of pregnancy, and different thyroid and nutritional iodine states. Statistical significance was at probability value of < 0.05.

Results:

Out of a total 318 patients, 21 (6.6%) had deranged thyroid function, making the prevalence of thyroid dysfunction in the study population 6.6%. Hypothyroidism was detected in 17 (5.3%) of the participants consisting of 12 (3.8%) sub-clinical and 5 (1.6%) overt hypothyroidisms. Sub-clinical hyperthyroidism accounted for 4 (1.3%) of all participants and no overt hyperthyroidism was detected in this study.

The maternal clinical and socio-demographic characteristics of the study participants are shown in Table 2. Statistically significant differences were seen in the women with euthyroid pregnancies versus those with non-euthyroid pregnancies with regards to parity (primigravida n = 22 versus n = 8, multigravida n=275 versus n=13; p = 0.001), mean TSH (1.0 ± 0.4mIU/L versus 4.1 ± 2.1 mIU/L; p < 0.001), mean

FT4 (1.4 ± 0.3 ng/dL versus 1.1 ± 0.6 ng/dL; p < 0.001), mean FT3 (2.4 ± 0.3 pg/mL versus 2.1 ± 0.9 pg/mL; p < 0.001) and mean UIC (201.1 ± 36.4 µg/L versus 180.8 ± 64.7 µg/L; p = 0.021). No significant differences in mean age, BMI, gestational age, trimester, educational status, occupational status, religion, ethnicity, marital status and blood pressure were noted between euthyroid versus non-euthyroid participants. However, differences in the mean age across various thyroid states was significant with euthyroid participants (n=297) having a mean age of 32.7 ± 6.7 years, sub-clinical hypothyroid participants (n=12) with mean age of 23 ± 6.4 years, overt hypothyroid participants(n=5) with 39.2 ± 5.1 years, and sub-clinical hyperthyroid participants(n=4) with 39.8 ± 1.0 years (p-value < 0.001).

Table 2: Maternal clinical and socio-demographic characteristics in Euthyroid and Non-euthyroid pregnant women

Characteristic	Total (n=318) N (%) orMean±SD	Euthyroid Pregnancies (n=297) N (%) or Mean±SD	Non-euthyroid Pregnancies (n=21) N (%) or Mean±SD	p-Value
Age (years)	32.5 ± 7.0	32.7 ± 6.7	30.3 ± 9.8	0.129
BMI (kg/m^2)	31.0 ± 1.7	31.1 ± 1.7	30.8 ± 1.7	0.220
Gestational age (weeks)	20.8 ± 9.6	20.8 ± 9.6	20.0 ± 9.9	0.691
Parity:				
Primigravida	30 (9.4)	22 (7.4)	8 (38.1)	0.001*
Multigravida	288 (90.6)	275 (92.6)	13 (61.9)	
Trimester:				
First	107 (33.6)	99 (33.3)	8 (38.1)	0.650
Second	105 (33.0)	100 (33.7)	5 (23.8)	
Third	106 (33.3)	98 (33.0)	8 (38.1)	
Educational status:				
Primary	5 (1.6)	4 (1.3)	1 (4.8)	
Secondary	97 (30.5)	92 (31.0)	5 (23.8)	0.059
Tertiary	194 (61.0)	181 (60.9)	13 (61.9)	
Postgraduate	22 (6.9)	20 (6.7)	2 (9.5)	
Occupational status:				
Civil servants	80 (25.2)	72 (24.2)	8 (38.1)	
Unemployed	72 (22.6)	68 (22.9)	4 (19.0)	0.572
Self-employed	148 (46.5)	140 (47.1)	7 (33.4)	
Traders	18 (5.7)	17 (5.7)	2 (9.5)	

Religion:				
Christianity	316 (99.4)	295 (99.3)	21 (100.0)	0.701
Others	2 (0.6)	2 (0.7)	0 (0.0)	
Ethnicity:				
Igbo	306 (96.2)	286 (96.0)	20 (95.2)	0.434
Others	12 (3.8)	11 (4.0)	1 (4.8)	
Marital status:				
Married	310 (97.5)	290 (97.6)	20 (95.2)	0.124
Single	8 (2.5)	7 (2.4)	1 (4.8)	
SBP (mmHg)	110.0 ± 7.3	109.9 ± 7.5	112.4 ± 4.4	0.433
DBP (mmHg)	63.7 ± 4.8	63.6 ± 4.8	63.8 ± 5.0	0.280
TSH (mIU/L)	1.2 ± 1.0	1.0 ± 0.4	4.1 ± 2.1	< 0.001*
FT_4 (ng/dL)	1.4 ± 0.3	1.4 ± 0.3	1.1 ± 0.6	< 0.001*
FT_3 (pg/mL)	2.4 ± 0.4	2.4 ± 0.3	2.1 ± 0.9	< 0.001*
UIC (µg/L)	199.8 ± 39.1	201.1 ± 36.4	180.8 ± 64.7	0.021*

* Statistical significance level = 0.05; N = Number of observations; SD = Standard Deviation

A significantly greater proportion of non-euthyroid participants, 13 (61.9%), were multigravida compared to 8 (38.1%) who were primigravida ($p < 0.001$). When compared across the trimesters of pregnancy (Table 3), a significantly greater proportion of sub-clinical hypothyroidism (n=8) were detected amongst the first trimester participants while others including overt hypothyroidism and sub-clinical hyperthyroidism were distributed between the second and third trimesters ($p = 0.041$).

Table 3: Distribution of Thyroid status across the trimesters.

Thyroid Status	**Total (n=318) N (%)**	**First trimester (n=107) N (%)**	**Second trimester (n=105) N (%)**	**Third trimester (n=106) N (%)**	**p-value**
Euthyroid pregnancies	297 (93.4)	99 (92.5)	100 (95.2)	98 (92.5)	
Sub-clinical Hypothyroidism	12 (3.8)	8 (7.5)	2 (1.9)	2 (1.9)	
Overt	5 (1.6)	0 (0.0)	1 (1.0)	4 (3.8)	0.041*

Hypothyroidism				
Sub-clinical Hyperthyroidism	4 (1.3)	0 (0.0)	2 (1.9)	2 (1.9)

*p-value significant at 0.05; N = Number of observations; SD = Standard Deviation

The relationship between NIS and specific thyroid dysfunctions is presented in table 4. There was a statistically significant difference in the NIS with a higher proportion of the hypothyroid participants (n=13) with insufficient NIS while all the hyperthyroid participants (n=4) had NIS above required levels ($p < 0.001$). There was also a significant difference in the mean UIC across the various thyroid states with euthyroid participants having a mean value of 201.1 ± 36.5 µg/L, sub-clinical hypothyroid participants 158.7 ± 31.1 µg/L, overt hypothyroid 138.4 ± 18.8 µg/L, and sub-clinical hyperthyroid with 301.0 ± 4.0 µg/L ($p < 0.001$). When compared across the trimesters of pregnancy (Table 5), a significantly greater proportion of participants with insufficient NIS (n=16) were detected amongst the first trimester participants while those with NIS above requirement were distributed across all trimesters with a greater proportion (n=6) in the second trimester ($p = 0.009$). There were no significant differences in the mean UIC levels across the various trimesters of pregnancy.

Table 4: Nutritional Iodine Status amongst Euthyroid and Non-euthyroid pregnant women

Nutritional Iodine Status	**Total (n=318)**	**Euthyroid Pregnancies (n=297)**	**Sub-clinical Hypothyroid pregnancies (n=12)**	**Overt Hypothyroid pregnancies (n=5)**	**Sub-clinical Hyperthyroid pregnancies (n=4)**	**p-value**
	N (%) or Mean±SD	**N (%) or Mean±SD**	**N (%) or Mean±SD**	**N (%) or Mean±SD**	**N (%) or Mean±SD**	
Mean UIC (µg/L)	199.7 ± 39.1	201.1 ± 36.5	158.7 ± 31.1	138.4 ± 18.8	301.0 ± 4.0	< 0.001*
Insufficient (< 150 µg/L)	25 (7.9)	12 (4.0)	8 (66.7)	5 (100.0)	0 (0.0)	
Adequate (150–249 µg/L)	281 (88.4)	277 (93.3)	4 (33.3)	0 (0.0)	0 (0.0)	< 0.001*
Above requirement (250–499 µg/L)	12 (3.8)	8 (2.7)	0 (0.0)	0 (0.0)	4 (100.0)	

*p-value significant at 0.05; N = Number of observations; SD = Standard Deviation

Table 5: Nutritional Iodine Status across the trimesters

Nutritional Iodine Status	Total (n=318) N (%) or Mean±SD	First trimester (n=107) N (%) or Mean±SD	Second trimester (n=105) N (%) or Mean±SD	Third trimester (n=106) N (%) or Mean±SD	p-value
Mean UIC (µg/L)	199.8 ± 39.1	203.7 ± 33.8	203.3 ± 49.0	192.3 ± 31.7	0.054
Insufficient (< 150 µg/L)	25 (7.9)	16 (15.0)	5 (4.8)	4 (3.8)	
Adequate (150–249 µg/L)	281 (88.4)	87 (81.3)	94 (89.5)	100 (94.3)	0.009*
Above requirement (250–499 µg/L)	12 (3.8)	4 (3.7)	6 (5.7)	2 (1.9)	

*p-value significant at 0.05; N = Number of observations; SD = Standard Deviation

Discussion:

Thyroid dysfunction during pregnancy is a critical concern due to its potential impact on both maternal and foetal health. In this study, we observed a prevalence of 6.6% for thyroid dysfunction in pregnant women, with hypothyroidism being more prevalent than hyperthyroidism. These findings are consistent with the global variation in the prevalence of gestational thyroid dysfunction, emphasizing the importance of region-specific studies in informing targeted antenatal care strategies.[4,7–11,13,25–27] The variations in prevalence could be attributed to factors such as dietary iodine availability, environmental conditions, trimester-specific reference intervals used to define thyroid status, ethnic differences and social backgrounds, all of which influence thyroid function during pregnancy.[24,28]

Hypothyroidism, particularly subclinical hypothyroidism, was the predominant thyroid dysfunction observed in our study. This is consistent with previous research highlighting the association between hypothyroidism and adverse pregnancy outcomes, including spontaneous abortion, pre-eclampsia, eclampsia, abruptio placentae, preterm delivery, and low birth weight.[29–31] The increased demand for thyroxine during pregnancy, driven by human chorionic gonadotropin (hCG) hormone, may exacerbate pre-existing thyroid insufficiencies or iodine deficiencies, contributing to the observed prevalence of hypothyroidism in our study.[5,32]

The significant differences observed in maternal clinical and socio-demographic characteristics between euthyroid and non-euthyroid pregnancies in this study emphasize the importance of considering these factors in the management of thyroid disorders during pregnancy. Notably, the mean age differences across various thyroid states highlights age as a potential risk factor for thyroid dysfunction during pregnancy, with both hypothyroidism and hyperthyroidism associated with advanced maternal age. This is contrary to previous studies in larger cohorts which suggests that advancing maternal age was not

associated with a higher risk of thyroid diseases in pregnancy. [10,33,34] The exact reason for the association between advanced maternal age and gestational thyroid disease in our study is not known, but it may be due to the increased risk of autoimmune thyroid disease associated with increasing age in the general population, [35] hence the need for further studies.

The association between insufficient dietary iodine intake, as reflected by urinary iodine concentration (UIC), and specific gestational thyroid dysfunctions emphasizes the importance of addressing iodine deficiency in antenatal care. Our findings correspond with those of previous studies indicating that individuals residing in regions with low iodine levels, such as hilly and mountainous areas, are at higher risk of thyroid dysfunction [17,18]. This may in part explain the higher prevalence of gestational thyroid disease on our study compared to those from other regions in Nigeria [13,36] given that the city of Enugu, Nigeria is essentially a highland despite nationwide iodine supplementation. Therefore, implementing routine screening for thyroid diseases during antenatal visits, especially in areas vulnerable to iodine deficiency, may be crucial in preventing adverse outcomes associated with gestational thyroid dysfunction.

The observed distribution of thyroid disorders in pregnancy across parity and trimesters further emphasizes the dynamic nature of thyroid function during pregnancy. The higher prevalence of thyroid dysfunctions among multigravida participants has been attributed to increased autoimmune thyroid disease as a result increase foetal cell exposure and foetal microchimerism, [37] and this suggests the need for increased vigilance in monitoring thyroid function, especially in this category of women. The trimester-specific findings revealed a higher proportion of sub-clinical hypothyroidism in the first trimester, whereas overt hypothyroidism and sub-clinical hyperthyroidism were distributed mostly between the second and third trimesters. This temporal variation in thyroid dysfunction is consistent with the physiological changes that occur during pregnancy. The increased demand for thyroid hormones, particularly in the first trimester, may contribute to the higher prevalence of sub-clinical hypothyroidism during this period.[5,36,38] Similarly, the higher prevalence of insufficient nutritional iodine level observed in the first trimester is in keeping with that from a previous study which identifies the first trimester as the most vulnerable period of gestation responsible for organogenesis and foetal brain development.(39)These trimester-specific findings highlight the dynamic nature of thyroid function during pregnancy and the importance of considering these variations in clinical assessments.

The cross-sectional design of the index study limits the establishment of causality, and the relatively short duration does not provide adequate opportunity to capture longitudinal variations in thyroid functions during pregnancy. Furthermore, the study focused on a specific geographic region, so caution should be exercised when extrapolating the findings to other populations. As such, we recommend further studies with longitudinal design involving diverse populations to allow for a more comprehensive understanding of thyroid function dynamics and explore the influence of environmental factors, dietary habits, and socio-economic status on thyroid disorders in pregnancy for the development of targeted preventive strategies.

Conclusion:

There is a relatively high prevalence of gestational thyroid disease in the study population with hypothyroidism being the predominant disorder. This underlines the importance of region-specific considerations in antenatal care, emphasizing the impact of factors such as dietary iodine availability, environmental conditions, and trimester-specific variations on thyroid function. Early detection and management of thyroid disorders in pregnancy are crucial to mitigate potential adverse maternal and foetal outcomes.

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Conflict of interest:
Authors disclose no potential conflict of interests.

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