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Thyroid Function in Pregnant Women from a West-African Population

Bonaventure Awede[1], Mariane S. Hounnou[1], Christiane Tshabu-Aguemon[2], Grace Adehan[3], François Djrolo[4], Marcellin Amoussou-Guenou[3], Anatole Laleye[5]

[1]Unité de Physiologie, Faculté des Sciences de la Santé, Université d'Abomey-Calavi, Cotonou, Benin
[2]Unité de Gynécologie et d'Obstétrique, Faculté des Sciences de la Santé, Université d'Abomey-Calavi, Cotonou, Benin
[3]Unité de Biophysique et de Médecine Nucléaire, Faculté des Sciences de la Santé, Université d'Abomey-Calavi, Cotonou, Benin
[4]Unité d'Endocrinologie et de Nutrition, Faculté des Sciences de la Santé, Université d'Abomey-Calavi, Cotonou, Benin
[5]Unité de Biologie Humaine, Faculté des Sciences de la Santé, Université d'Abomey-Calavi, Cotonou, Benin
Email: bonawed@yahoo.com, hounnoulise@yahoo.fr, caguemon@yahoo.fr, asianatou@yahoo.fr, fdjrolofss@yahoo.fr, agkuassimarcellin@yahoo.fr, laleyec@yahoo.fr

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Abstract

Thyroid dysfunction is frequent in pregnant women and is often associated with an increased risk of adverse maternal and fetal outcome. In the present work, thyroid function of pregnant women from Benin republic was studied. Two hundred forty (240) pregnant women, without thyroid disease history, have been included in the study. A blood sample was drawn for measurement of TSH, free T3 and free T4 serum levels. From the first to the third trimester, plasma levels of free T3 and free T4 decreased when plasma levels of TSH increased. Using recommendations of the 2011 American Thyroid Association (ATA) guidelines, thyroid dysfunction was observed in 24.17% of subjects. Hypothyroidism was present in 22.50% of subjects with 19.17% of subclinical hypothyroidism, 0.83% of overt hypothyroidism and 2.50% of hypothyroxinemia and hyperthyroidism was observed in 1.67% of subjects. An increase from 15.52% to 28.07% was observed in the frequency of hypothyroidism from the first to the third trimester of pregnancy. When an upper cut-off value of 4 mU/L was used for TSH, as recommended in the 2017 ATA guidelines, prevalence of thyroid disorders was 14.58% with 12.91% of hypothyroidism but no hypothyroidism was observed in women in the first trimester of pregnancy. A rise in hypothyroidism frequency was observed when pregnant women age increased. Hypothyroidism was very common in pregnant women in Benin. To allow accurate assessment of thyroid status in pregnant women in Benin, pregnancy specific range for plasma level of TSH and thyroid hormones should be established.

Keywords

Pregnancy, Thyroid Function, Hypothyroidism

1. Introduction

Pregnancy is a physiological state in which significant changes in thyroid function occur. Several factors contribute to these changes. Indeed, since the beginning of pregnancy, the hCG (human chorionic gonadotrophin) secreted by the placenta, given its homology of structure with TSH (thyroid stimulating hormone), exerts a stimulatory effect on thyroid gland leading to an increase in the secretion of thyroid hormones (T3 and T4) and a decrease in TSH, especially during the first trimester. High levels of estrogen induce an increase in hepatic synthesis of TBG (thyroxin binding globulin), one of the thyroid hormone binding proteins resulting in an increase in the bound fraction of thyroid hormones, a trend to a decrease in free fractions of thyroid hormones and then an increased secretion of TSH which stimulates thyroid gland to produce more hormone [1] [2].

In addition, pregnancy induces increase in metabolic function and requires a higher production of thyroid hormone. Demand for iodine intake increases especially as there is a greater urinary excretion of iodine and a transfer of iodine to the fetus when his thyroid becomes functional [1] [2]. All these factors could contribute to thyroid dysfunction during pregnancy especially when a deficiency of iodine intake exists and when thyroid reserve is not sufficient.

Thyroid disorders prevalence therefore increases during pregnancy. Hyperthyroidism is observed in about 0.2% of pregnant women. Hypothyroidism is most common during pregnancy and its prevalence is generally estimated to 2% to 3% [2] [3] [4]. Higher prevalence of hypothyroidism has however been reported in many studies [5] [6] [7] [8]. These thyroid disorders have been shown associated with increased risk of preeclampsia, miscarriages, fetal death, pre-term delivery, hypertension [7] [9] [10] [11].

Benin is a west-African country where iodine intake in the general population is excessive according to the Iodine Global Network (available on http://www.ign.org/). However, two departments in the country are still considered as areas of endemic iodine deficiency [12]. Pregnancy complications that may be associated with hypothyroidism are also common in Benin women but evaluation of thyroid function is not often performed in Beninese pregnant women. In addition, no study evaluating thyroid status of pregnant woman in Benin has ever been performed. Our hypothesis is that thyroid dysfunction could be frequent in Beninese pregnant women. Therefore, the present work was carried out to study thyroid function in pregnant women living in Cotonou.

2. Materials and Methods

This is a cross-sectional, descriptive and analytical prospective study which was

conducted from May to December 2015.

2.1. Study Subjects

Pregnant women have been recruited in antenatal care at the University Clinic of Gynecology and Obstetrics of the National and University Hospital Hubert Koutoukou Maga of Cotonou, Republic of Benin. Only women, without history of thyroid disorder, who was not taking medication which could interfere with the metabolism of thyroid hormones and who gave written informed consent, were included in the study.

Sociodemographic and clinical data were collected during a clinical examination and using a questionnaire. A venous blood sample was drawn from each pregnant woman for the measurement of TSH, free T3 (FT3) and free T4 (FT4) serum levels.

2.2. Hormone Levels Measurement

Serum levels of TSH, free T3 and free T4 have been measured by radio-immunoassay. Blood samples were centrifuged at 4000 rpm for 10 minutes at room temperature and the sera were recovered and stored at −20˚C until use. Hormone levels measurement was performed using specific kits for TSH, free T3 and free T4 acquired from DEMEDITEC Diagnostics (Germany) according to the manufacturer instructions.

2.3. Thyroid Status Determination

American Thyroid Association (ATA) guidelines of 2011 have been used to determine the thyroid status of pregnant women [13]. Thus, normal range for TSH was in the first trimester 0.1 - 2.5 mU/L; in the second trimester, 0.2 - 3.0 mU/L and in the third trimester, 0.3 - 3.0 mU/L.

Overt hypothyroidism was defined as an elevated TSH (>2.5 mU/L) in conjunction with a decreased FT4 concentration. Women with TSH levels of 10.0 mU/L or above, irrespective of their FT4 levels, were also considered to have overt hypothyroidism. Subclinical hypothyroidism was defined as a serum TSH between 2.5 and 10 mU/L with a normal FT4 concentration in the first trimester. In the second and third trimesters, serum TSH levels between 3 and 10 mU/L have been considered as subclinical hypothyroidism.

Isolated hypothyroxinemia was defined as normal range of TSH associated with decreased FT4 levels. Normal range of free T4 was 9 - 24 pmol/L.

Thyroid status of pregnant women was also determined according to the 2017 guidelines of the American Thyroid Association (ATA) which recommend, when internal or transferable pregnancy-specific TSH reference ranges are not available to use an upper reference limit of approximately 4.0 mU/L [14].

2.4. Statistical Analysis

Data were analyzed using Excel, and GraphPath Prism V, software.

Data were expressed as means ± standard deviation or as proportions. Means were compared using the student's t-test and comparison of proportions has been made using the Chi-square test. Significant difference was set for a p-value < 0.05.

3. Results

3.1. General Characteristic of Subjects

Characteristics of subjects of the study are presented in Table 1. Two hundred and forty (240) pregnant women were included in the study: 58 women (24.2%) with a first trimester pregnancy (gestational age from 4 to 15 weeks), 68 women (28.3%) with a second trimester pregnancy (gestational age from 16 to 28 weeks) and 114 women (47.5%) with a third trimester pregnancy (gestational age from 29 to 41 weeks).

Mean pregnant women age was 29 ± 5.5 years. Mean gestational age was 25.27 ± 10.72 weeks. Mean gravidity was 2.89 ± 1.63 and parity was 1.33 ± 1.34.

3.2. Serum Levels of TSH and Thyroid Hormones

Mean serum levels of TSH in women in each trimester of pregnancy are shown in Figure 1. There was an increase in TSH mean serum levels from 1.39 ± 0.88 mU/L in the first trimester to 2.10 ± 1.28 mU/L in the second trimester and to 2.34 ± 1.78 mU/L in the third trimester.

Mean free T3 and freeT4 serum levels decreased progressively from the first to the third trimester of pregnancy. Thus, as shown in Figure 2, the mean serum concentration of free T3 was 2.99 ± 0.53pmol/L; 2.66 ± 0.49 pmol/L and 2.62 ± 0.39 pmol/L respectively in the first, second and third trimesters of pregnancy. The mean concentration of free T4 decreased from 14.4 ± 2.92 pmol/L in the first trimester to 12.46 ± 2.29 pmol/L in the second trimester and then to 11.41 ± 1.74 pmol/L in the third trimester. Mean serum levels of these hormones in the second and the third trimesters of pregnancy were significantly different from those in the first trimester.

Table 1. Characteristics of pregnant women.

Variable	Value
Age, years ± SD	29 ± 5.5
Gestational age, weeks ± SD	25.27 ± 10.72
First trimester, n (%)	58 (24.2%)
Second trimester, n (%)	68 (28.3%)
Third trimester, n (%)	114 (47.5%)
Gravidity	2.89 ± 1.63
Parity	1.33 ± 1.34

Values are expressed as means ± standard deviation (SD) or as number of subjects and percentage.

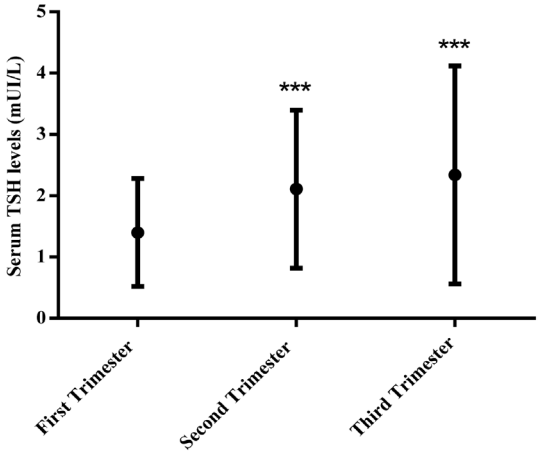
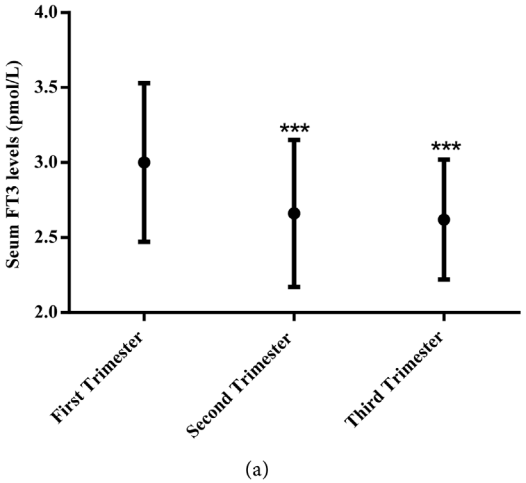
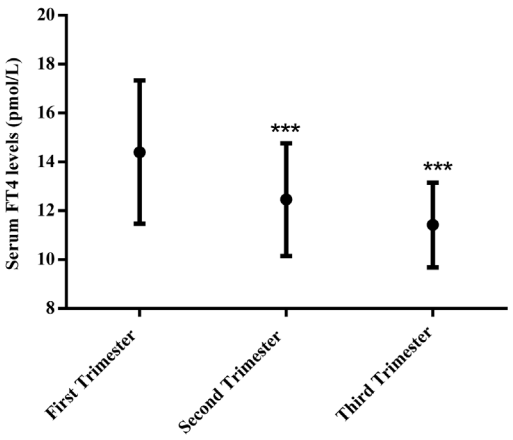


Figure 1. Thyroid stimulating hormone (TSH) levels in pregnant women. Values are means ± standard deviation, n = 58 for first trimester; 68 for second trimester and 114 for third trimester; ***significantly different from first trimester value with $p < 0.001$.



(a)



(b)

Figure 2. Serum Free T3 and T4 levels in pregnant women. (a) Serum Free T3 levels in pregnant women; (b) Serum Free T4 levels in pregnant women. Values are means ± standard deviation, n = 58 for first trimester; 68 for second trimester and 114 for third trimester; **significantly different from first trimester value with $p < 0.001$.

3.3. Thyroid Status of Pregnant Women

Thyroid status of pregnant women determined using 2011 ATA guidelines is represented in Table 2. Thyroid dysfunction was present in 24.17% of the pregnant women. Hypothyroidism was observed in 22.5% of subjects with 19.17% of subclinical hypothyroidism, 0.87% of overt hypothyroidism and 2.5% of hypothyroxinemia while hyperthyroidism was present in 1.67% of the subjects. From the first to the second and to the third trimester of pregnancy, the proportion of subjects with hypothyroidism increased from 15.52% to 19.12% and to 28.07%. An increase in hypothyroidism frequency was also observed with pregnant women age. This frequency was 17.6% in pregnant women under 30 years old, 26.41% in pregnant women aged 30 to 39 years and 44% in women over 39 years.

Table 3 presents the thyroid status of pregnant women using 2017 ATA guidelines (TSH upper reference limit of 4.0 mU/L). In this case, thyroid disorders were present in 14.58% of pregnant women. The frequency of subclinical hypothyroidism, overt hypothyroidism, hypothyroxinemia and hyperthyroidism were respectively 9.58%, 0.42%, 2.91% and 1.67%. Hypothyroidism was observed in 11.76% of women with second trimester of pregnancy and in 20.17% of women with third trimester pregnancy but no hypothyroidism was observed in women with first trimester pregnancy.

When a TSH upper reference limit of 4.0 mU/L was used, an increase in hypothyroidism frequency was also observed with pregnant women age. This frequency was 8% in pregnant women under 30 years old, 16.98% in pregnant women aged 30 to 39 years and 33.33% in women over 39 years.

Table 2. Thyroid status of pregnant women determined using TSH trimester ranges recommended by 2011 ATA guidelines.

	Euthyroid, n (%)	Hypothyroidism, n (%)	Hyperthyroidism, n (%)
All subjects (n = 240)	182 (75.83%)	54 (22.5%)	4 (1.67%)
First trimester (n = 58)	47 (81.03%)	9 (15.52%)	2 (3.45%)
Second trimester (n = 68)	53 (77.94%)	13 (19.12%)	2 (2.94%)
Third trimester (n = 114)	82 (71.93%)	32 (28.07%)	0 (0%)

Table 3. Thyroid status of pregnant women using TSH normal upper limit of 4 mU/L.

	Euthyroid, n (%)	Hypothyroidism, n (%)	Hyperthyroidism, n (%)
All subjects (n = 240)	205 (85.42%)	31 (12.91%)	4 (1.67%)
First trimester (n = 58)	56 (96.55%)	0 (0%)	2 (3.45%)
Second trimester (n = 68)	58 (85.30%)	8 (11.76%)	2 (2.94%)
Third trimester (n = 114)	91 (79.83%)	23 (20.17%)	0 (0%)

TSH value was > 4 mU/L in hypothyroidism and was between the lower normal value (0.1, 0.2 and 0.3 mU/L in respectively first, second and third trimester) and 4 mU/L in euthyroid. In hyperthyroidism, TSH was inferior to the lower normal value.

4. Discussion

In the present work, thyroid status of pregnant women as well as serum TSH, free T3 and freeT4 mean levels during each trimester of pregnancy has been determined. Although thyroid function in pregnant women is well documented, this is the first study carried out in the field in Benin.

An increase in the serum concentration of TSH and a decrease in those of free T3 and free T4 from the first to the third trimester of pregnancy were observed. These results are in agreement with several published data [1] [6] [15] [16]. The mechanisms of the decrease in free T3 and T4 are not clear but interactions between TSH, estrogens and TBG could be involved [1] [2]. The increase levels of TSH could be explained by the decline of the transient stimulatory effect of hCG on thyroid gland early in pregnancy, which could result in a decrease in thyroid hormones secretion and a reduction of their negative feedback on the hypothalamus-pituitary axis.

A high frequency of thyroid disorders was observed in this study. The most common dysfunction was hypothyroidism, especially subclinical hypothyroidism. In previous published data, an important variability in hypothyroidism prevalence in pregnant women has been reported. Hypothyroidism prevalence in pregnant women from 2% to 56% has been reported [3] [5] [6] [7] [8] [17]. This variability in thyroid disorders prevalence in pregnant women could be explained by the iodine status of study population, the references used to define thyroid status or by ethnicity specificity [18] [19] [20].

In our study, hypothyroidism prevalence in pregnant women, according to 2011 ATA guidelines, was 22.5%. Applying the European Thyroid Association recommendations, with a normal range of TSH of 0.3 to 3.5 mU/L in the third trimester [20], would lead to a hypothyroidism frequency of 19.85%, frequency which is not too different from that obtained with ATA recommendations. In previous studies, very high hypothyroidism prevalence of hypothyroidism has been reported when the trimester-specific ranges of TSH recommended by 2011 ATA guidelines were applied [8] [21] and it has been suggested that these guidelines lead to over diagnosis of hypothyroidism. Indeed, when data obtained following these TSH ranges were compared to those obtained by applying laboratory pregnancy specific TSH ranges, significant difference in thyroid disorders prevalence were observed. Thus, in China it has been shown that prevalence of subclinical hypothyroidism using laboratory trimester specific ranges for TSH was 4% in pregnant women during the first trimester whereas this prevalence was 27.8% when a diagnostic criterion of TSH > 2.5 mU/L was used [21]. Moreover, many reported trimester-specific reference intervals for TSH were different from those recommended by 2011 ATA guidelines [22] [23]. It is therefore probable that, in our study, hypothyroidism frequency determined following 2011 ATA guidelines was overestimated.

Using TSH normal upper limit of 4 mU/L, the hypothyroidism prevalence was reduced to 12.91% but no hypothyroidism was observed in women with first

trimester pregnancy. This result suggests that, with this TSH normal upper limit, many women suffering of subclinical hypothyroidism in the first trimester were not probably diagnosed and that the upper limit of normal TSH in the first trimester of pregnancy was probably lower than 4 mU/L. Although no trimester specific TSH range determined in a similar area and which could be used in Benin is available, in Sudan and in the North of Nigeria, upper normal limits of TSH established for the first trimester were even lower than 2.5 mU/L [16] [17]. Further studies should therefore establish laboratory trimester specific range of TSH and thyroid hormones in Beninese pregnant women to allow an accurate determination of their thyroid status.

The main causes of hypothyroidism are iodine deficiency and autoimmune thyroid diseases [19]. It has been shown that 55% of pregnant women with subclinical hypothyroidism and 80% of those suffering of overt hypothyroidism, were thyroid antibody positive [9]. Thyroglobulin and Thyroid peroxidase (TPO) antibodies positivity was not investigated in this study but although low prevalence of thyroglobulin and TPO antibody positivity has been reported in black women [18] [19], autoimmune thyroid disease could be involved in the hypothyroidism observed in some subjects. Hypothyroidism could also be related to iodine intake deficiency. Although iodine intake in Benin general population is considered as excessive, there is no available data on iodine intake in pregnant women. In addition, iodine supplementation is not often recommended to Beninese pregnant women. Iodine intake in pregnant women should therefore be evaluated in order to determine its involvement in thyroid disorders. Study of urinary excretion of iodide could help to appreciate this iodine intake. As urinary excretion of iodide reflects only recent iodine intake, measurement of thyroglobulin levels could therefore be useful as it has been suggested that thyroglobulin level was an indicator of iodine nutrition status [6] [24] [25].

An increase in the frequency of hypothyroidism with age, reaching 44% in pregnant women aged 40 years and over, was observed. This could be related to a decrease in thyroid reserve with age leading to a decrease in the ability of the thyroid gland to adapt to pregnancy. Special monitoring of thyroid function in pregnant women over 40 years should be performed.

In view of the high prevalence of thyroid disorders in pregnant women without thyroid disease history and the increased risk of adverse obstetrical and fetal outcome associated to thyroid disorders, systematic screening for thyroid disorders in Beninese pregnant women should be performed. In a recent study, carried out in Iran, it has shown that about 1/3 of pregnant women with thyroid disorders would be missed if targeted high-risk case finding approach was used instead of universal screening [26].

The present study has some limitations. Thyroid autoimmunity and the relationship between iodine status and thyroid function were not investigated. Thyroid function was not evaluated on the same group of women throughout the pregnancy. Laboratory pregnancy specific ranges for TSH were not used to

determine thyroid status. Further studies will take into account these aspects.

5. Conclusion

Thyroid disorders are frequent in Beninese pregnant women and are probably related to either iodine deficiency or thyroid autoimmunity. ATA 2011 and 2017 guidelines recommendations, when trimester specific TSH ranges were not available, seem not appropriate to determine with accuracy thyroid status in Beninese pregnant women. It is therefore of great importance to carry out appropriate studies to determine such trimester specific ranges.

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