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Assessment of Thyroid Function Among Hypertensive Pregnant Women: A Cross Sectional Study from South Eastern Nigeria

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Abstract

Background: Gestational hypertension (GH) is defined by an elevated blood pressure (BP) at or beyond 20 weeks gestation in the absence of proteinuria in previously known normotensive women. It is the most frequent cause of hypertensive complications during pregnancy ranging from 10% to 17% of all pregnancies. These complications include pre-eclampsia, eclampsia and death if not managed properly. Despite being a major contributor of maternal and perinatal morbidity and mortality, the mechanisms underlying the pathogenesis of GH have not been fully elucidated. This study was designed to evaluate thyroid function in hypertensive pregnant women.

Materials and methods: A total of 300 subjects aged between 22 and 40 years were recruited for this study. These comprised 150 hypertensive and 150 age-matched normotensive individuals as controls. Serum concentrations of thyroid stimulating hormone (TSH), free tri-iodothyronine (FT3) and free thyroxine (FT4) were measured using enzyme linked immunosorbent (ELISA) assay procedure.

Result: The mean value of TSH was significantly higher in hypertensive subjects when compared with the control ($P<0.05$). The mean level of FT3 was significantly decreased in hypertensive subjects when compared with the control subjects ($P<0.05$). There was no significant difference when the serum level of FT4 was compared between hypertensive and normotensive pregnant women ($P>0.05$). Furthermore, the serum level of TSH correlated

significantly (P<0.05) with both SBP (R=0.925, P=0.000) and DBP (R=1.191, P=0.000). Also, the serum level of TSH negatively correlated with FT3 (R= -0.595, P=0.000) and FT4 (R= -0.365, P=0.000) respectively.

Conclusion: Therefore, we observed that gestational hypertension is associated with decrease activity of thyroid hormones as indicated by the significantly lower FT3 and higher TSH levels. Also, there were significant positive correlation (P<0.05) between SBP and TSH, and between DBP and TSH, and significant negative correlations between TSH and FT3 and between TSH and FT4. Thus, estimation of TSH could provide an alternative prognostic tool for predicting the underlying cause of gestational hypertension.

Keywords: Assessment; Thyroid function; Pregnant women; Nigeria

1. Introduction

Foods Gestational hypertension (GH), is a condition characterized by high blood pressure during pregnancy and can lead to serious complications such as pre-eclampsia, eclampsia and death if not managed properly [1]. As a multi-systemic disorder, it is estimated to affect 10% to 17% of all pregnancies. Despite being a major contributor of maternal and perinatal morbidity and mortality, the mechanisms responsible for the pathogenesis of GH have not been fully elucidated. However, several factors have been postulated as contributory mechanisms to the rise in blood pressure during pregnancy. These factors include among others, an expansion in total plasma volume of up to 40%, an increase in the red cell mass of about 25%, and increase in the synthesis of thyroid hormones [2, 3].

In women generally, thyroid associated endocrinopathies are the second most common endocrine disorders after diabetes mellitus. These disorders are 4-5 times more prevalent in women during their reproductive ages and may likely be more frequent in those with other co-morbid conditions such as gestational hypertension [4]. Also, thyroid hormones exert their effect on all tissues and can modulate the rate of metabolic activity. Alterations in thyroid function can therefore affect the various organ system of the body and may be the leading cause of hypertensive complications in pregnancy [5].

Currently used tests for the assessment of thyroid function (thyroid-stimulating hormone (TSH), tri-iodothyronine (T3) and thyroxine (T4) are sometimes insufficient to clearly make out the diagnosis as T3 and T4 levels are affected by so many other non-specific conditions [5]. Thus, this present study is aimed to evaluate thyroid function among gestational hypertensive mothers attending antenatal clinic at Aguata Diocesan Hospital, Igbo-Ukwu and Nnamdi Azikiwe University Teaching Hospital, Nnewi using TSH, FT3 and FT4, as markers.

2. Materials and Methods

2.1 Research design

A total of 300 participants were randomly selected for this study. The participants were made up of 150 hypertensive pregnant women (aged 22-40 years) as test subjects and 150 age-matched normotensive pregnant women as

controls. The gestational age of each participant was established based on last menstrual period. The study was a cross sectional study designed to assess thyroid dysfunction among hypertensive and normotensive pregnant women in Aguata and Nnewi Local Government Area of Anambra state, Nigeria.

2.2 Study Site

This research work was carried out at Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Anambra State, Nigeria.

2.2.1 Inclusion Criteria:

- Subjects with hypertension diagnosed after 20 weeks (2nd and 3rd trimesters) of gestation were used in the study.
- Apparently healthy age and trimester-matched normotensive pregnant women attending antenatal clinic were selected as control subjects.

2.2.1 Exclusion Criteria:

- Subjects with hypertension predating the index pregnancy,
- Subjects with diabetes mellitus,
- Those with antenatal booking weight greater than 90 kg were excluded from the study.
- All patients with proteinuria $\geq$ 0.3 gm were equally excluded from the study.
- Patients with history of smoking and alcohol intake as well as those who refuse to consent were also excluded.

2.3 Ethical Consideration

Ethical approval for this study was obtained from the Ethics Committee of Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi. Informed written consent was obtained from the participants before the collection of data and blood samples.

2.4 Sampling Technique

Random sampling technique was used during sample collection. 3 ml of whole blood was collected using a plain specimen container. The serum obtained after centrifugation was stored at 2-8°C until analyzed. The biodata of all study participants were obtained using a structured interviewer administered pretested questionnaire. Blood pressure of each participant was measured using Accoson mercury sphygmomanometer. Korotkoff's sound phases I and V were used to determine the systolic and diastolic blood pressures (SBPs and DBPs) respectively. Values above 140 and 90 mmHg for the SBP and DBP respectively were considered abnormal.

Two reviewers independently screened the titles and abstracts to determine if a citation met the general inclusion criteria. The full text of citations classified as include or unclear was reviewed independently with reference to the predetermined inclusion and exclusion criteria. Finally, we hand-searched reference lists of any relevant conference

abstracts and of the included trials for potentially relevant citation. Non-English full text citations were excluded. Disagreements between the two reviewers were resolved through consensus and by third-party adjudication, as needed.

3. Results

The demographic and anthropometric parametric analysis shows that the mean value of age in hypertensive pregnant women (27.5 ± 4.9 years) was not significantly different when compared with the normotensive subjects (26.9 ± 4.4 years) (P=0.306). There was also no significant differences in the mean levels of height (1.62 ± 0.03 m), weight (68.9 ± 8.3 kg), body mass index (26.2 ± 3.4 m/kg2) and gestational age (29.5 ± 5.4 weeks) of hypertensive subjects when compared with the normotensive subjects (1.63 ± 0.03 m, 67.6 ± 8.5 kg, 25.9 ± 3.3 m/kg2 and 28.9 ± 5.3 weeks) respectively (P>0.05).

However, the mean values of systemic blood pressure (SBP) and diastolic blood pressure (DBP) in hypertensive subjects (159.9 ± 15.2 mmHg and 93.1 ± 10.0 mmHg) were significantly higher (P<0.05) when compared with the controls (115.0 ± 9.1 mmHg and 68.5 ± 3.5 mmHg) respectively.

Of the 139 citations identified through electronic and hand searches, we included 6 trials enrolling a total of 308 participants (Figure 1) 22-27. Trials were published between 2005 and 2015. The outcomes relevant to peripheral blood flow included: total peripheral resistance, flow mediated vasodilatation, forearm blood flow and blood pressure. Only two trials did not measure flow mediated vasodilatation (23,27). The key features of the included studies are outlined in Table 1.

Parameters	**Test Subjects (Mean ± SD) n = 150**	**Control Subjects (Mean ± SD) n = 150**	**T-test**	***P-Value***
Age (years)	27.5 ± 4.9	26.9 ± 4.4	1.026	0.306
BMI (kg/m^2)	26.2 ± 3.4	25.9 ± 3.3	2.941	0.108
Gestational age (weeks)	29.5 ± 5.4	28.9 ± 5.3	4.267	0.1
SBP (mmHg)	159.9 ± 15.2	115 ± 9.1	30.58	0.000**
DBP (mmHg)	93.1 ± 10.0	68.5 ± 3.5	28.51	0.000**

Table 1: Demographic and anthropometric characteristics of the study participants.

Mean difference is significant when P is <0.05. * =mild significance and ** = marked significance.

The mean value of TSH was significantly higher (P<0.05) in hypertensive pregnant women (3.9 ± 3.1 µIU/ml) compared with the normotensive pregnant women (2.0 ± 2.0 µIU/ml). The serum mean level of FT3 was also significantly lower (P<0.05) in test subjects (3.2 ± 2.0 pg/ml) when compared with the control subjects (5.1 ± 2.3 pg/ml). However, there was no significant difference (P=0.517) in the mean value of FT4 in hypertensive pregnant women (2.1 ± 2.3 pg/dl) compared with the normotensive pregnant women (2.3 ± 2.1 pg/dl) (Table 2).

Parameters	**Test Subjects (Mean ± SD)** **n=150**	**Control Subjects (Mean ± SD)** **n=150**	**T-test**	**P-Value**
TSH (µIU/ml)	3.9 ± 3.1	2.0 ± 1.1	6.279	0.000**
FT3 (pg/ml)	3.2 ± 2.0	5.1 ± 2.3	-7.435	0.000**
FT4 (ng/dl)	2.1 ± 1.3	2.3 ± 1.7	-0.049	0.517

Table 2: Mean and standard deviation of TSH, FT3 and FT4 in hypertensive and normotensive pregnant women.

Mean difference is significant when P is <0.05. * =mild significance and ** = marked significance.

The incidence rate of thyroid dysfunction was 19.3% in hypertensive pregnant mothers with subclinical hypothyroidism (8.7%) and overt hypothyroidism (5.3%) accounting for 14% while hyperthyroidism (both subclinical and overt) accounted for 5.3% (2.0% and 3.3% respectively). However, only the incidence rate of subclinical hypothyroidism showed a statistical difference (P<0.05) between the hypertensive and normotensive pregnant women while others showed no significant differences (P>0.05). The gestational hypertensive women with apparently normal thyroid function (euthyroid) accounted for 80.7% of the total prevalence rate (100%) of thyroid classification (Table 3).

Thyroid status	**Test subjects: n (%)**	**Control subjects: n (%)**	**P-Value**
Euthyroid	121 (80.7)	138 (92)	0.729
Subclinical hypothyroidism	13 (8.7)	6 (4)	0.005**
Overt hypothyroidism	8 (5.3)	3 (2)	0.235

Subclinical hyperthyroidism	3 (2)	1 (0.7)	0.764
Overt hyperthyroidism	5 (3.3)	2 (1.3)	0.832
Total	150 (100)	150 (100)	--

Table 3: Incidence of thyroid disorders among hypertensive and normotensive pregnant women.

The correlation coefficient showed a significant positive relationship between SBP and DBP (R=1.211a and P=0.000), SBP and TSH (R=0.925a, P=0.000). Also, there were significant negative correlations between TSH and FT3 (R= -0.595b, P=0.000), and between TSH and FT4 (R= -0.365b, P=0.000). However, there were non-significant positive relationship (P>0.05) between the mean values of SBP and FT3 (R=0.031), SBP and FT4 (R=0.019), DBP and FT3 (R=0.032), DBP and FT4 (R=0.016), and FT3 and FT4 (R=0.012) (Table 4).

Parameters	**SBP** mmHg	**DBP** mmHg	**TSH** (µIU/ml)	**FT3** (pg/ml)	**FT4** (ng/dl)
SBP (mmHg)	--	1.211_a	0.925_a	0.031	0.019
DBP (mmHg)	1.211_a	--	1.191_a	0.032	0.016
TSH (µIU/ml)	0.925_a	1.191_a	--	-0.595_b	-0.365_b
FT3 (pg/ml)	0.031	0.032	-0.595_b	--	0.012
FT4 (ng/dl)	0.019	0.016	-0.365_b	0.012	--

Table 4: Relationship between SBP, DBP, TSH, FT3 and FT4 among the hypertensive pregnant women.

Mean difference is significant when P is <0.05. a = marked positive significance and b = marked negative significance.

4. Discussion

Gestational hypertension being considered a transient condition is the most common form of hypertension in pregnancy [6]. Most researchers have focused their efforts on pre-eclampsia because of its implications for maternal-fetal health, whereas information about the implications of a diagnosis of GH is much more limited [6]. Some evidence shows that thyroid associated endocrinopathies are among the most common endocrine disorders in women of maternal age [5].

According to Klein et al. (2007), 30% of pregnant women diagnosed with GH present with pre-eclampsia and other hypertensive complications in pregnancy. As a result, thyroid dysfunction may be the underlying disorder in GH and other endothelial vascular diseases. Herein, we attempt to evaluate thyroid function among hypertensive disordered pregnant women in order to ascertain the most up to date information regarding the pathogenesis, etiology and implication of thyroid dysfunction in the development of GH.

The mean value of TSH was significantly higher (P=0.000) in hypertensive pregnant women than normotensive subjects. The significant apparent elevation of TSH in hypertensive pregnant women may be attributed to a state of thyroid dysfunction known as hypothyroidism. Hypothyroidism is predominantly an autoimmune disorder mostly characterized by the activation of antigen presenting dendritic cells by self-proteins. However, the activated antigen presenting dendritic cells can in turn stimulate the T-cells to produce cytokines that promote hypertension through vascular remodeling (increased peripheral vascular resistance) [7-9]. This finding is similar to related studies conducted in Australia, India and Kano, Nigeria and in Australia [10-12], that reported significantly increased mean values of TSH in hypertensive pregnant women in their respective locations. This finding however is in contrast to the findings of Pasupathi et al. [13] that reported a nonsignificant difference in Indian hypertensive and normotensive pregnant subjects. The mean level of TSH (3.9 ± 3.1) as obtained in this present study is still within the acceptable reference level (0.4–6.0 μIU/ml) for the study population. However, there is a significant incidence of subclinical hypothyroidism (P<0.05) in gestational hypertension than the normotensive pregnant women.

Conversely, the mean serum level of FT3 was significantly decreased in hypertensive pregnant women compared to the normotensive pregnant women, whereas there was no significant difference in the mean serum level of FT4 when compared with both hypertensive and normotensive cases. FT4 and FT3 are the free circulating thyroid hormones (Thyroxine, T4 and Triiodothyronine, T3) which are produced from thyroid follicular cells within the thyroid gland through thyroperoxidase, the enzyme responsible for the copulation of iodine to tyrosine residues to form the thyroid hormone, T4 which is believed to be the pro-hormone and a reservoir for the active and main thyroid hormone, T3 [14]. More so, T3 is converted as required in the tissues by iodothyronine deiodinase [14]. Therefore, the relative non significance difference in serum level of FT4 in both hypertensive and normotensive pregnant women may be due the normal functioning of the enzyme, thyroperoxidase in both subjects while the apparent decrease of FT3 in GH than in normotensive individuals may be due to the relative inhibition of iodothyronine deiodinase in hypertensive pregnant women. T3 represents the metabolically active thyroid agent that possibly has a vasodilatory effect on the vascular muscle cells [15]. It has also been documented that hypertension is an autoimmune disorder that leads to impaired production of vasodilators such as endothelin, nitric oxide (NO) and T3 inclusive [8]. Therefore, the significant decrease in the serum level of FT3 could be due to the relative inhibition of FT3 secretion; a resultant effect of thyroid dysfunction associated with increased peripheral vasoconstriction which is also implicated in blood pressure elevation. This finding is in line with the findings of Ref [10, 12, 16]. The observed values were in variance with the values reported by Pasupathi et al. [13] among Indian pregnant women. More so, the incidence rate of thyroid disorders among the study participants showed a significant difference in the

subclinical hypothyroidism ($P<0.05$) and non significant differences in euthyroid, overt hypothyroidism, subclinical hyperthyroidism and overt hyperthyroidism ($P>0.05$).

Furthermore, the serum level of TSH correlated significantly with SBP and DBP in hypertensive pregnant women. Serum levels of FT3 and FT4 showed no significant relationship with both SBP and DBP when correlated with each other. Therefore, the serum level of TSH increases as hypertension advances. This finding indicates that there is a state of hypothyroidism that is associated with the development of hypertension in pregnancy as demonstrated by the significant difference in subclinical hypothyroidism between hypertensive and normotensive pregnant women. According to [8], the hypo-metabolic state of hypothyroidism can cause an increased arterial stiffness which is an important determinant of vascular endothelial dysfunction and changes in arterial wall elasticity (the major underlying cause of elevated blood pressure), therefore resulting in the development of hypertension in pregnancy. Thus, subclinical hypothyroidism being an autoimmune disorder may therefore be the factor implicated in the vascular changes that promotes hypertensive disorder in pregnancy. Nanda et al. [17] reported a similar finding in a study conducted in India pregnant women with hypertension.

Therefore, the results obtained in this work can be explained at the level of thyroid hormonal activity which is associated with significant increases in peripheral vascular resistance, vasoconstriction and vascular endothelial dysfunction. The increased peripherial vascular resistance and vasoconstriction reflects the induction of TSH and the absence of demonstrated vasodilatory FT3 effect on vascular endothelial cells which invariably could be the reason behind the hypertensive disorder often seen in late pregnancies. The negative correlation between TSH, FT3 and FT4 implies that; with higher circulating levels of TSH and low or normal circulating levels of FT3 and FT4, there is a significant volume change (caused by increase in peripheral vascular resistance and vasoconstriction), initiating a volume-dependent, low plasma renin activity (PRA) which is the mechanism of blood pressure elevation [7, 15].

The key finding in the study is the significant positive correlation between SBP, DBP and TSH and the significant negative correlation between TSH, FT3 and FT4 which indicate that there is a state of thyroid dysfunction that is implicated in the development of hypertension in pregnancy. This is due to the fact that TSH has been an established marker for thyroid dysfunction and has also been documented to have a negative correlation between FT3 and FT4 [18]. Consequently, its significant elevation in increasing SBP and DBP in gestational hypertension could be help in predicting the occurrence of gestational hypertension.

5. Conclusion

We observed that gestational hypertension is associated with decrease activity of thyroid hormones as shown by the significantly lower FT3 and higher TSH levels, significant positive associations between SBP and TSH, and DBP and TSH. There were also significant negative correlations between TSH and FT3, and TSH and FT4. Thus, estimation of TSH could be a good predictor of the development of hypertension in pregnancy. This is due to the fact that TSH has been an established marker for thyroid dysfunction and was found to be significantly elevated as systemic and diastolic blood pressure progresses in pregnancy.

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