

Prognostic Implication Of Thyroid Stimulating Hormone And Free Thyroid Hormones In The Advancement Of Severity Of Hypertension In Pregnancy

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Abstract: Background: Hypertensive disorders of pregnancy also known as gestational hypertension (GH) is the blood pressure (BP) of at least 140/90 mmHg at the onset of second trimester (14th week of gestation or beyond) with proteinuria ≤ 15 mg/dl in previously known normotensive women. It is the major risk factor for hypertensive complications during pregnancy commonly known as pre-eclampsia and eclampsia. In spite of its high maternal and perinatal morbidity and mortality rate, the pathogenesis of GH have not been fully elucidated.

Objective: This study was designed to evaluate the prognostic importance of thyroid stimulating hormone (TSH) and free thyroid hormones (fT3 and fT4) in the advancement of hypertension in pregnancy.

Materials and method: A total of 150 (43 mild, 58 moderate and 49 severe) hypertensive pregnant women aged between 22 and 40 years as test subjects and 150 age-matched normotensive individuals as controls were recruited for this study. The serum concentrations of TSH, fT3 and fT4 were determined using enzyme linked immuno-sorbent (ELISA) assay technique.

Results: The mean value of TSH was significantly higher in hypertensive subjects (3.9 ± 23.1) when compared with the control (2.0 ± 1.5) ($P < 0.05$). Whereas the mean serum level of fT3 was significantly decreased in hypertensive subjects (3.2 ± 2.0) when compared with the normotensive subjects (5.1 ± 2.3) ($P < 0.05$). More so, the serum level of TSH increased significantly ($P < 0.05$) from mild (3.1 ± 2.8) to moderate (3.8 ± 2.2) and to severe GH (4.5 ± 3.4); and also correlated negatively with the serum levels of fT3 ($r = -0.595$, $P = 0.000$) and fT4 ($r = -0.365$, $P = 0.000$) respectively.

Conclusion: We observed that consistent serum elevation of TSH and significant decrease of fT3 are associated with gestational hypertension, most especially with the progression of gestational hypertension as shown by the significant negative relationship between serum TSH and fT3 in GH and the consistent significant serum elevation of TSH in mild, moderate and severe GH, in the presence of consistently decreased serum fT3 in hypertensive pregnant mothers. Therefore, a hypothyroidism state could be an integral factor that predisposes hypertensive pregnant women to its associated complications.

Keywords: Hypertension, Pregnancy, Thyroid Stimulating Hormone, Free Thyroid Hormones.

I. INTRODUCTION

Hypertension during pregnancy (gestational hypertension (GH) is one of the important cause for maternal morbidity and

mortality in Nigeria (World Health Organization, 2014). This is because, it is the major risk factor for hypertensive complications associated with pregnancy such as pre-eclampsia and eclampsia. Among hypertensive disorders of pregnancy

pre-eclampsia is the leading cause and complicates 5%–10% of pregnancy. Pre-eclampsia is a multi-system disorder characterized by reduced renal perfusion and damage to glomerular basement membrane resulting in leakage of proteins in urine. Irrespective of the cause of hypertension, management of the health of both mother and fetus is important not only by making diagnosis, but also by predicting maternal and fetal outcome. Also, 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 and an increase in peripheral vasoconstriction (Omole and Ashimi, 2008; Olatinwo *et al.*, 2009).

Considering these issues, assessment of underlying factors or disease states that could predispose pregnant mothers with hypertension to its super imposed complications in pregnancy may be of good value. Thyroid associated endocrinopathies are among the most common endocrine disorders affecting 30-40% of most pregnancies. In most thyroid dysfunction also, impaired vascular smooth muscle relaxation leads to increased systemic vascular resistance. These effects can promote the rise in blood pressure and the severity of hypertension in pregnant mothers (Klein and Danzi, 2007). Therefore, pregnant women with untreated thyroid dysfunction could be at risk for the development of GH and its complications including heart failure (Wilson *et al.*, 2012). Thus, thyroid hormones could play a critical role during pregnancy both in the development of a healthy baby and in maintaining the health of the mother (Forrest, 2004, Morreale *et al.*, 2004, LaFranchi *et al.*, 2005). This is because, thyroid hormones increases or decreases basal metabolic rate in almost every tissue and organ system in the body and the increased or decreased metabolic demands leads to changes in cardiac output, cardiac contractility, systemic vascular resistance (SVR) and blood pressure. As a result, early and appropriate detection of thyroid dysfunction and timely interventions may improve maternal-fetal prognosis (Morreale *et al.*, 2004).

However, pregnant women with thyroid disease do not always develop symptoms, and when they do, these symptoms can sometimes be attributed to the pregnancy itself (LeBeau and Mandel, 2006). In these situations, accurate laboratory assessment of the changes in thyroid activity that may occur during gestational hypertension assumes an even greater importance. But due to the significant alterations associated with total thyroxine (T4) and tri-iodothyronine (T3) in pregnancy, the American Thyroid Association (ATA) have advocated for the use of free thyroid hormones (Ft3 and Ft4) and trimester specific intervals in the screening, diagnosis and monitoring or thyroid dysfunction in pregnancy, hence the need for this survey.

II. MATERIALS AND METHODS

Enzyme linked immune-sorbent assay (ELISA) machine (Statfax-2400) was used during the analysis.

RESEARCH DESIGN

This was a cross sectional study designed to assess the prognostic implication of TSH, fT3 and fT4 in the progression of severity of hypertension in hypertensive pregnant women in Nnewi Local Government Area of Anambra State, Nigeria. A total of 300 participants were selected for this study. The test participants were made up of 150 (43 mild, 58 moderate and 49 severe) hypertensive pregnant women (aged 22-40 years) and 150 age-matched normotensive pregnant women as controls. The gestational age of each participant was established based on last menstrual period.

STUDY SITE

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

INCLUSION CRITERIA

Subjects with hypertension diagnosed after 15 weeks (2nd and 3rd trimesters) of gestation with proteinuria ≤ 15 mg/dl and apparently healthy age and trimester-matched normotensive pregnant women were used in this study.

EXCLUSION CRITERIA

Subjects with hypertension predating the index pregnancy, subjects with diabetes mellitus, antenatal booking weight greater than 90 kg, those with proteinuria ≥ 0.3 gm, those with history of smoking and alcohol intake as well as those who refuse to consent were also excluded.

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.

SAMPLING TECHNIQUE

A total of 5 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. The anthropometric parameters such as blood pressure, height, weight and body mass index were determined using standard methods as described by National Institutes of Health (2006 and 2014). For example, the 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. Also, the urinary protein of each participant was quantified using urine dipstick test as described by Sapna *et al.*, (2014). Using the seventh

National Institute for Health criteria, the hypertensive participants were further classified as mild (n=43), moderate (n=58) and severe (n=49).

III. RESULTS

Table 1 Anthropometric characteristics of the study participants.

The demographic and anthropometric parametric analysis shows that the mean value of age in hypertensive pregnant women (27.5±4.9 years) was not significant compared with the normotensive subjects (26.9±4.4 years) (P=0.306). There was also no significant differences in the mean 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 systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly elevated in hypertensive subjects (159.9±15.2 mmHg and 93.1±10.0 mmHg) compared with the controls (115.6±9.1 mmHg and 68.5±3.5 mmHg) respectively (P<0.05).

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	0.100
SBP (mmHg)	159.9±15.2	115.6±9.1	30.578	0.000*
DBP (mmHg)	93.1±10.0	68.5±3.5	28.505	0.000*

Keys: SD = Standard deviation, BMI = Body mass index, SBP = Systolic blood pressure, DBP = Diastolic blood pressure. Mean difference is significant when P is <0.05. * = mild significance and ** = marked significance.

Table 1: Anthropometric characteristics of the study participants

Table 2 (Mean ± SD) of the serum levels of TSH, fT3 and fT4 in hypertensive and normotensive pregnant women.

The mean value of TSH was significantly higher in hypertensive pregnant women (3.9±3.1 µIU/ml) compared with the normotensive pregnant women (2.0±1.5 µIU/ml) (P=0.000). Conversely, the serum mean level of fT3 was significantly lower in tests subjects (3.2±2.0 pg/ml) when compared with the control subjects (5.1±2.3 pg/ml) (P=0.000). However, there was no significant difference in the mean value of fT4 in hypertensive pregnant women (2.1±1.3 pg/dl) compared with the normotensive pregnant women (2.3±2.1 pg/dl) (P=0.517).

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±1.5	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±2.1	-0.049	0.517

Keys: TSH = Thyroid Stimulating Hormone, fT3 = Free Tri-iodothyronine, fT4 = Free Thyroxine. Mean difference is significant when P is <0.05. * = mild significance and ** = marked significance.

Table 2: (Mean ± SD) of TSH, fT3 and fT4 in hypertensive and normotensive pregnant women

Table 3 Variations of the serum levels of SBP, DBP, TSH, fT3 and fT4 in mild, moderate and severe hypertension.

The SBP and DBP showed significant elevations from mild (146.6±6.8, 89.9±6.4 respectively) to moderate hypertension (165.2±5.5 and 103.2±3.1 respectively) and also from moderate (165.2±5.5 and 103.2±3.1 respectively) to severe hypertension (184.5±4.3 and 112.7±3.2 respectively) (P<0.05). Both SBP and DBP were also significantly elevated in mild, moderate and severe hypertension when compared to control (115.6±9.1 and 68.5±3.5 respectively) (P<0.05). The serum level of TSH was significantly lower in mild hypertension (3.1±2.8) when compared to moderate hypertension (3.8±2.7) and similarly when compared to severe hypertension (4.5±3.4) (P<0.05). Serum TSH was also significantly elevated in mild (3.1±2.8), moderate (3.8±2.7) and severe hypertension (4.5±3.4) when compared to control subjects (2.0±1.5) (P<0.05). Whereas the serum level of fT3 showed significant decrease in mild (3.1±1.9), moderate (3.3±1.7) and in severe hypertension (3.5±2.4) when compared to the control (5.1±2.3) (P<0.05), and also increased significantly (P<0.05) when compared between mild (3.1±1.9) and severe GH (3.5±2.4) respectively. Also, there was no significant difference in the mean value of fT4 when compared across the hypertensive groups (mild 2.1±1.3; moderate 2.4±1.6 and severe 1.7±1.2) and between the control subjects (2.3±2.1) (P>0.05) respectively.

Stages of GH	Mild (Mean±SD) n=43	Moderate (Mean±SD) n=58	Severe (Mean±SD) n=49	Control (Mean±SD) n=150	P-value
Parameters					
SPB (mmHg)	146.6±6.8 _{a,b}	165.2±5.5 _{a,b}	184.5±4.3 _{a,b}	115.6±9.0 _a	0.000*
DBP (mmHg)	89.9±6.4 _{a,b}	103.2±3.1 _{a,b}	112.7±3.2 _{a,b}	68.5±3.5 _a	0.000*
TSH (µIU/ml)	3.1±2.8 _{a,b}	3.8±2.7 _{a,b}	4.5±3.4 _{a,b}	2.0±1.5 _a	0.000*
fT3 (pg/ml)	3.1±1.9 _{a,c}	3.3±1.7 _a	3.5±2.4 _{a,c}	5.1±2.3 _a	0.000*
fT4 (ng/dl)	2.1±1.3	2.4±1.4	1.7±1.2	2.3±2.1	0.360

Keys: SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, TSH = Thyroid Stimulating Hormone, fT3 = Free Tri-iodothyronine, fT4 = Free Thyroxine. Mean difference is significant when P is <0.05. * = mild significance and ** = marked significance. a = significant difference between

hypertensive stages and control, b = significant difference across the hypertensive stages, c = significant difference between mild and severe GH only.

Table 3: Variations of the serum levels of SBP, DBP, TSH, fT3 and fT4 in mild, moderate and severe hypertension

IV. DISCUSSIONS

Gestational hypertension (GH) is a hypertensive disorder in pregnancy that is characterized by new onset of blood pressure (BP) elevations after 14 weeks of gestation in the absence of accompanying proteinuria (ACOG task force in hypertension, 2013). Outcomes in women with GH usually are quite successful; although some of these women experience BP elevations to the severe level with outcomes similar to women with hypertensive complications such as pre-eclampsia (Klein and Danzi, 2007). The cause of this BP elevation and its complications are unclear with those affected presenting with severe maternal-fetal morbidity and mortality (ACOG task force in hypertension, 2013). Herein, we aim to evaluate the prognostic implication of thyroid stimulating hormone and the free thyroid hormones in the advancement of hypertension in pregnancy.

The results indicate that there were no significant differences in the demographic and anthropometric parameters (BMI, age and gestational age) of the hypertensive and normotensive pregnant women studied. However, there were significant increase in the mean values of SBP and DBP of hypertensive pregnant women when compared with the normotensive pregnant women respectively. This imply that the test subjects were uniformly distributed between the groups and was in accordance with the findings of studies conducted in India, Ibadan, Benin and Kano (Qublan *et al.*, 2005, Rubinna and Tabassum, 2008, Ebeigbe and Aziken 2010, Irinyenikan *et al.*, 2012 and Abdusalam and Yahaya, 2015). However, the findings of this study were at variance with the findings of a similar study conducted among Ghanaian gestational hypertensive mothers and their normotensive counterparts (Turpin *et al.*, 2008).

The mean value of TSH was significantly higher in hypertensive pregnant women than normotensive subjects. The significant elevation of TSH in hypertensive pregnant women may be attributed to the inhibitory mechanism of gestational hypertension on the endothelium of the thyroid follicles through the activation of anti-angiogenic factors such as isoketals (Kirabo *et al.*, 2014). Also, gestational hypertension was postulated to have anti-placental growth factor signaling through its inhibitory effect on the vascular endothelial growth factor (Sabitha *et al.*, 2014). However, the vascular endothelial growth factor is often required for constitutive expression of the health and function of the thyroid capillaries (De-Cherney *et al.*, 2012). Therefore, the reduced level of vascular endothelial growth factor may reduce the functional capabilities of the thyroid capillaries thereby increasing the secretion TSH concentration as seen in the study. This finding is similar to related studies conducted in Australia, India and Kano, Nigeria (Gilbert *et al.*, 2008, Hardeep *et al.* 2015 and Abdusalam and Yahaya, 2015 respectively) 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.*, (2009).

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 of hypertensive subjects when compared with 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. Thyroperoxidase is 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 (Brent, 2016). More so, T3 is converted as required in the tissues by iodothyronine deiodinase (Brent, 2016). Therefore, the relative non significant difference in the 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 significant decrease of fT3 in GH than in normotensive individuals may be due to the relative inhibition of iodothyronine deiodinase in hypertensive pregnant women. According to Stella *et al.* (2002), T3 represents the metabolically active thyroid agent that possibly has a vasodilatory effect on the vascular muscle cells. Therefore, its significant decrease in hypertensive pregnant women than in normotensive mothers could be as a result of the inhibitory effect of GH on T3 producing enzyme thereby causing the significant elevation of TSH in hypertensive pregnant women. This is because GH as an autoimmune disorder could cause impaired production of vasodilators which has also been implicated in reduced thyroid function (Schiffirin, 2013). Therefore, the significant decrease in the serum level of fT3 could be due to the relative inhibition of T3 secretion; a resultant effect of endothelia dysfunction associated with increased peripheral vasoconstriction which is also implicated in blood pressure elevation. This finding is in line with the findings of Gilbert *et al.* (2008), Swati *et al.* (2014) and Abdusalam and Yahaya (2015). The observed values were in variance with the values reported by Pasupathi *et al.* (2009) among Indian pregnant women.

Furthermore, the serum level of TSH increased significantly as the severity of gestational hypertension increased (from mild to moderate and to severe gestational hypertension) while the serum level of fT3 decreased significantly as the severity of GH increased when compared across the hypertensive cases. Conversely, the serum level of fT4 showed no significant variation as the severity of hypertension in pregnancy increased. This may infer that inflammation could be the underlying disease state that predisposes hypertensive pregnant mothers to multiple organ dysfunctions thereby promoting them to hypertensive complications such as pre-eclampsia, eclampsia and even cardiovascular diseases. This is because, inflammation causes endothelial dysfunction, possibly by decreased capacity of the endothelium to generate vasodilatory factors such nitric oxide (NO) and the demonstrated T3 which in turn promotes vasoconstriction and then blood pressure elevation (Shafi *et al.*, 2010). This finding may also imply that hypothyroidism

could be the underlying disease state that predisposes hypertensive pregnant mothers to multiple organ dysfunctions thereby promoting the progression of severity of hypertension in gestational hypertension and also predisposing them to hypertensive complications such as pre-eclampsia and eclampsia as recorded in this study. This is because, the hypo-metabolic state of hypothyroidism can cause an increased arterial stiffness which is an important determinant and a major underlying cause of elevated blood pressure (Schiffrin, 2013). More so, 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) (Dernellis and Panaretou, 2002, Kirabo *et al.*, 2014).

Therefore, high level of TSH and low level of fT3 may promote vasoconstriction through the decreased function of vasodilators as demonstrated by T3 thereby enhancing the contraction of the muscle wall and the manifestation of blood pressure elevation. These changes could trigger hypertensive disorder in pregnancy and may promote hypertensive complications also. This is substantiated by several studies (LI Jian-jun, 2006; Pauleto and Rattazzi 2006, Nanda *et al.*, 2013). In the light of these findings and from several other studies we hypothesize that hypothyroidism may be the underlying disease condition that causes gestational hypertension and may also be the factor that predisposes them to hypertensive complications through its implication in vascular endothelial dysfunction.

V. CONCLUSION

Our results therefore suggest that consistent serum elevation of TSH and decrease of fT3 are associated with gestational hypertension, most especially with the progression of gestational hypertension. Thus estimation of thyroid function using TSH and free thyroid hormones can be potential tools for early identification of pregnant mothers at risk of hypertensive complications associated with pregnancy such as pre-eclampsia and eclampsia.

Inclusion of thyroid function in antenatal screening for those with established hypertension might be helpful in predicting the occurrence of severe hypertension in pregnancy and timely interventions for effective management of gestational hypertension and its superimposed complications, thereby reducing the maternal and perinatal morbidity and mortality associated with pregnancy induced hypertension.

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