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Predictive Risks of Pre-eclampsia and Cardiovascular Diseases in Mild, Moderate and Severe Hypertensive Pregnant Women

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Received: 2 May 2017/ Accepted: 5 June 2017/Published online: 13 February 2018

Background: Gestational hypertension (GH), is a condition characterized by high blood pressure during pregnancy with proteinuria ≤ 15 mg/dl and can lead to serious complications such as pre-eclampsia, eclampsia and cardiovascular diseases if not managed properly.

Objectives: This study was designed to evaluate the factors predisposing mild, moderate and/or severe GH to pre-eclampsia and cardiovascular risks using thyroid function and the serum activity of C-reactive protein (CRP) in hypertensive and normotensive pregnant women.

Method: A total of 150 diagnosed hypertensive pregnant women classified into 43 mild, 58 moderate and 49 severe GH and 150 normotensive individuals serving as control were carefully selected for this study.The serum levels of thyroid stimulating hormone (TSH), free tri-iodothyronine (FT3), free thyroxine (FT4) and CRP were measured using enzyme linked immuno-sorbent (ELISA) assay procedure.

Result: The mean values of TSH and CRP were significantly higher ($P<0.05$) in hypertensive subjects (3.9±3.1 and 23.9±9.7) when compared with the control (2.0±1.1 and 5.5±2.1) respectively. The mean level of FT3 was significantly decreased in hypertensive subjects (3.2±2.0) when compared with the control subjects (5.1±2.3) ($P<0.05$). Furthermore, the serum levels of TSH and CRP were significantly elevated ($P<0.05$) as the severity of gestational hypertension became increased (mild (3.1±2.8 and 12.6±9.8); moderate (3.8±2.7 and 18.7±8.9); and severe (4.5±3.5 and 25.9±10.9) respectively. Also, the serum level of TSH correlated positively with the serum level of CRP ($r = 0.122$, $P = 0.000$), and negatively correlated with FT3 and FT4 ($r = -0.595$, $P = 0.000$ and $r = -0.365$, $P = 0.000$) respectively.

Conclusion: We observed that serum elevations of CRP and TSH (in the presence of significantly reduced metabolically active thyroid-hormonal agent (FT3) are consistently associated with the progression of gestational hypertension. Therefore, could be used as predictive markers for the occurrence of pre-eclampsia and cardiovascular diseases which are complications often associated with poorly managed mild, moderate and/or severe gestational hypertension.

Keywords: *Pre-eclampsia, Hypertension, Pregnancy, Thyroid function, inflammatory reaction.*

Highlights:

- There is progression of gestational hypertension (from mild to moderate and moderate to severe) in the presence of high TSH, low FT3 with normal FT4.
- There is significant progression of the severity of gestational hypertension in the presence of inflammatory reaction (high level of CRP).
- There is consistent progression of serum levels of TSH and CRP with the severity of gestational hypertension which could predispose hypertensive pregnant women to pre-eclampsia, eclampsia and cardiovascular risks.
- Free thyroxine (FT4) remains stable in the presence of a significantly decreased FT3, which is the metabolically active thyroid-hormonal agent that possibly has a vasodilatory effect on the vascular muscle cells and thus, could play a part in predisposing hypertensive pregnant mothers to hypertensive complications associated with pregnancy in the presence of elevated TSH and CRP.

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Introduction

Gestational hypertension (GH) is pregnancy induced hypertension (PIH) characterized by a blood pressure of at least 140/90 mmHg of onset or first recognition in a previously normotensive woman and with proteinuria ≤ 15 mg/dl in 24 hours urine collection.[1] According to the National Institute for Health, GH is classified into mild (140-159/90-99 mmHg), moderate (160-179/100-109 mmHg) and severe (≥180/110 mmHg) GH.[2] Being a multi-systemic disorder, GH can affect so many systems in the body if not properly managed and can lead to pre-eclampsia, impaired liver functions, affect the kidneys, pulmonary oedema, fetal growth restriction, placental abruption, cardiovascular diseases, premature delivery and maternal and perinatal mortality.[3] Despite being the leading cause of maternal death and a major contributor of maternal and perinatal morbidity, 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 increase in systemic resistance and vascular constriction.[3,4]

Thyroid hormones increase basal metabolic rate in almost every tissue and organ system in the body and the increased metabolic demands lead to changes in cardiac output, cardiac contractility, systemic vascular resistance (SVR) and blood pressure. In most cases, cardiovascular aberrations follow long-term exposure to excessive or decreased hormone levels.[5] Due to the profound biochemical changes in pregnancy associated with significant increase in both total thyroxine and tri-iodothyronine, the American Thyroid Association (ATA) and the British Endocrine Society (BES) advocate the use of free thyroid hormones and trimester-specific reference intervals in the screening, diagnosis and monitoring of thyroid function abnormalities in pregnancy and postpartum.[6-8] Also, in 2011, the Ministry of Health, New South Wales advocated the use of appropriate laboratory biomarkers such as inflammatory and cardiac testing in seeking a possible cause of gestational hypertension and to ascertain end-organ damage if present.[9] This is because gestational hypertension being a multi-systemic disorder, can affect so many systems in the body if not properly managed and can lead to the well known hypertensive complications in pregnancy such as pre-eclampsia, eclampsia, cardiovascular risks, maternal and perinatal mortality.[3,9]

C - reactive protein (CRP) is an acute phase protein which is synthesized in the liver. It is present in trace amounts in normal healthy persons and rises significantly following injury and inflammation.[10] In terms of clinical application, CRP seems to be a stronger predictor of cardiovascular events than LDL cholesterol, and it adds prognostic information at all levels of calculated Framingham Risk and at all levels of the metabolic syndrome.[11] Thyroid dysfunction is also associated with increased risk of pregnancy complications; including miscarriages, pre-eclampsia,[12] low birth weight or fetal growth restriction[13] and maternal cardiac dysfunction.[14] The relevance of elevated levels of thyroid and inflammatory biomarkers in predicting end-organ damage and cardiovascular risk is gaining increasing recognition[12,15] and in that respect, assessment of TSH, FT3, FT4 and CRP may be of good value in predicting elevated risk of pre-eclampsia in pregnant mothers with mild, moderate and severe hypertension and therefore elucidate on the implication of thyroid dysfunction and inflammation in pre-eclampsia and cardiovascular diseases. This study therefore was designed to evaluate the factors predisposing mild, moderate and/or severe gestational hypertension to pre-eclampsia and cardiovascular risks using thyroid function and the serum activity of C-reactive protein (CRP) in hypertensive and normotensive pregnant women.

Methods

Research design and sample size

This was a case-control study involving a total of 300 participants that were randomly selected through simple balloting, with sample size (N) obtained using the method of Niang *et al.*[16]:

$$N = Z^2 \times \frac{P(1-d)}{d^2}$$

where: N = sample size; Z= confidence interval = 1.96; P = prevalence rate of gestational hypertension in Nigeria 10.1%[17]; d = Desired level of significance = 5% (0.05); N = $(1.96)^2$ x 0.101 (1 - 0.05) / $(0.05)^2$ = 148.9; N = 148.9 approximately 150.

The participants were made up of 150 diagnosed hypertensive pregnant women (classified as mild (43), moderate (58) and severe (49) hypertensive pregnant women (aged 22-40 years) as test subjects and 150 age-matched normotensive pregnant women as controls. The gestational age of each

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participant was established based on last menstrual period.

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

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

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.

Data collection and analysis
The biodata of all study participants were obtained using a structured interviewer administered pretested questionnaire. Blood pressures of each participant were 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 after repeated measurements were considered abnormal. Using the seventh Joint National Committee (JNC VII) criteria, the hypertensive participants were further classified as mild (n=43), moderate (n=58) and severe (n=49).
Random sampling technique was used during sample collection. In this case, populations of pregnant mothers were asked to pick folded papers numbered from 1a to 500a for test and 1b to 500b for control subjects. The balloting was done until the study population was achieved for both test and control subjects using the selection criteria to either include or exclude from the study after simple balloting. 5 ml of venous blood was collected using a plain specimen container. The serum obtained after centrifugation was stored at 2-8°C until analyzed.

Enzyme linked immune-sorbent assay (ELISA)
ELISA test instrument (Statfax-2400) was used for the determination of thyroid stimulating hormone (TSH), free tri-iodothyroinine (FT3), free thyroxine (FT4) and C-reactive protein (CRP) as described by Tietz.[18]

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.

Statistical analysis
The data generated were presented as mean ± standard deviation. Variation of the serum levels of SBP, DBP, TSH, FT3, FT4 and CRP in mild, moderate and severe hypertension were assessed with a one-way analysis of variance (ANOVA), while differences between groups (Tables 1 and 2) were analyzed with student T-test. Relationship between serum levels of TSH, FT3, FT4 and CRP among the hypertensive pregnant women was described by Pearson's correlation coefficients. Significance was accepted at $P<0.05$. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), Version 20.0.

Results

Demographic and anthropometric parameters in hypertensive and normotensive pregnant women
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 were 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/kg^2) 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/kg^2 and 28.9± 5.3 weeks) ($p = 0.108$ and 0.1000) respectively. 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) compared with the controls (115.0±9.1 mmHg and 68.5± 3.5 mmHg) respectively ($p = 0.000$).

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

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(2.0± 2.0 µIU/ml, p < 0.001). The serum mean level of FT3 was also significantly lower in test subjects (3.2±2.0 pg/ml) when compared with the control subjects (5.1± 2.3 pg/ml, p < 0.001). However, there was no significant difference 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, p =0.517). The mean value of CRP in hypertensive pregnant women was significantly higher in hypertensive pregnant women (23.9±9.7 mg/L) when compared with the normotensive control subjects (5.5± 2.1 mg/L, p <0.001).) respectively.

Relationship between serum levels of TSH, FT3, FT4 and CRP among the hypertensive pregnant women

There were significant negative correlations between TSH and FT3 (r = -0.595), TSH and FT4 (r = -0.365, p <0.05) respectively. In contrast, the there was a significant positive association between TSH and CRP (r = 0.122, p <0.05). Also, the mean level of FT3 showed a significant positive correlation with the mean value CRP (r = 0.028) (p <0.05). However, there was a non significant positive association between the mean values of FT3 and FT4 (r = 0.412, p >0.05). The correlation between serum levels of FT4 and CRP (r = 0.002) showed no significant positive correlation (p >0.05).

Variations of the serum levels of SBP, DBP, TSH, FT3, FT4 and CRP in mild, moderate and severe hypertension

The SBP and DBP showed significant elevations from mild (146.6±6.8, 89.9±6.4) to moderate hypertension (165.2±5.5 and 103.2±3.1) and also from moderate (165.2±5.5 and 103.2±3.1) 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 (3.4±2.4), moderate (3.5±1.7) and in severe hypertension (3.1±1.9) when compared to the control (5.1± 2.3, p <0.05), but there was no significant difference when the mean value of FT3 was compared between mild (3.4±2.4) and moderate (3.5±1.7,p >0.05) but was significantly decreased in severe (3.1±1.9) when compared with both mild (3.4±2.4) and moderate (3.5±1.7, p < 0.05) 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.

The mean level of CRP in mild (12.6±9.8), moderate (18.7±8.9) and severe gestational hypertension (25.9±10.9) were significantly higher (p <0.05) than the mean value of the control subjects (5.5±2.1) respectively. The serum level of CRP also showed a significant increase from mild (12.6±9.8) to moderate (18.7±8.9) and to severe gestational hypertension (25.9± 10.9, p <0.05).

Table 1: Demographic and anthropometric characteristics of the study participants

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±9.1	30.578	0.000**
DBP (mmHg)	93.1±10.0	68.5±3.5	28.505	0.000**

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

Table 2: Mean values of TSH, FT3, FT4 and CRP in hypertensive and normotensive pregnant women

Parameters	*Test Subjects (Mean±SD) n=150*	*Control Subjects (Mean±SD) n=150*	*T-test*	*P-Value*

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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
CRP (mg/L)	23.9±9.7	5.5±2.1	8.354	0.000**

TSH = Thyroid stimulating hormone, fT3 = Free tri-iodothyronine, fT4 = Free thyroxine, CRP = C-Reactive Protein. Mean difference is significant when P is <0.05. * = less significance and ** = high significance.

Table 3: Relationship between serum levels of TSH, FT3, FT4 and CRP among the hypertensive pregnant women

Parameters	*r-value*	*P-value*
TSH Vs FT3	-0.595	0.000**
TSH Vs FT4	-0.365	0.009*
TSH Vs CRP	0.722	0.000**
FT3 Vs FT4	0.009	1.000
FT3 Vs CRP	-0.428	0.000**
FT4 Vs CRP	0.012	1.000

TSH = Thyroid stimulating hormone, fT3 = Free tri-iodothyronine, fT4 = Free thyroxine, CRP = C-Reactive Protein. Mean difference is significant when P is <0.05. * = less significance and ** = high significance

Table 4: Variations of the serum levels of SBP, DBP, TSH, FT3, FT4, CK-NAC, LDH and CRP in mild, moderate and severe hypertension

Parameters	*Mild (Mean±SD) n=43*	*Moderate (Mean±SD) n=58*	*Severe (Mean±SD) n=49*	*Control (Mean±SD) n=150*	*F-value*	*P-value*
SPB (mmHg)	$146.6\pm6.8_{a,b}$	$165.2\pm5.5_{a,b}$	$184.5\pm4.3_{a,b}$	$115.6\pm9.0_{a}$	1319.6	0.000**
DBP (mmHg)	$89.9\pm6.4_{a,b}$	$103.2\pm3.1_{a,b}$	$112.7\pm3.2_{a,b}$	$68.5\pm3.5_{a}$	2149.6	0.000**
TSH (µIU/ml)	$3.1\pm2.8_{a,b}$	$3.8\pm2.7_{a,b}$	$4.5\pm3.4_{a,b}$	$2.0\pm1.5_{a}$	14.419	0.000**
FT3(pg/ml)	$3.4\pm2.4_{a,d}$	$3.5\pm1.7_{a,e}$	$3.1\pm1.9_{a,d,e}$	$5.1\pm2.3_{a}$	17.132	0.000**
FT4 (ng/dl)	2.1±1.3	2.4±1.4	1.7±1.2	2.3±2.1	1.074	0.360
CRP (mg/L)	$12.6\pm9.8_{a,b}$	$18.7\pm8.9_{a,b}$	$25.9\pm10.9_{a,b}$	5.5±2.1a	172.5	0.000**

SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, TSH = Thyroid Stimulating Hormone, FT3 = Free Tri-iodothyronine, FT4 = Free Thyroxine, CRP = C-Reactive Protein. 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 moderate GH only, d = significant difference between mild and severe GH only and e = significant difference between moderate and severe GH only.

.Discussion

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.[19] Outcomes in women with GH usually are quite successful; although some of these hypertensive exposed pregnant women often present with complications such as pre-eclampsia, eclampsia and even cardiovascular diseases.[20] The cause of these complications is unclear and is often associated with severe maternal-fetal morbidity and mortality.[19] Thus, we aim to evaluate thyroid function and the activity of C-reactive protein in staged hypertensive and normotensive pregnant women using TSH, FT3, FT4 and CRP as markers, with the objective of assessing the role of TSH, free thyroid hormones and CRP in the occurrence of hypertensive complications (i.e. pre-eclampsia and cardiovascular diseases) in hypertensive exposed pregnant mothers.

The findings of this study showed that 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 implies 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.[21-25] However, the findings of this study were at variance with the findings of a similar study conducted among Ghanaian patients with gestational hypertension and their normotensive counterparts.[26]

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The mean value of TSH was significantly higher (above the reference range of 0.4-6.0 µIU/ml) in hypertensive pregnant women than normotensive subjects. The significant elevation of TSH in hypertensive pregnant women may be attributed to a state of thyroid dysfunction known as hypothyroidism. Hypothyroidism (elevated serum TSH) 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).[27-29] This finding is similar to related studies conducted in Punjab, India; Kano, Nigeria; and in Australia [25,30,31] respectively that reported significant mean values of TSH in hypertensive pregnant women in their respective locations. This finding is also in contrast to the findings of Pasupathi *et al*.,[32] that reported a non significant difference in Indian hypertensive and normotensive pregnant subjects.

In addition, the mean serum level of FT3 was significantly decreased (below the reference value of 1.8-4.2 pg/ml) in hypertensive pregnant women compared with 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 Tri-iodothyronine, 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.[33] More so, T3 is converted as required in the tissues by iodothyronine deiodinase.[33] This significant difference could be as a result of the dominant hypothyroidism state (elevated serum TSH in the presence of deceased serum FT3/normal FT4), evidently shown by the significant elevation in the mean value of TSH when compared with hypertensive and normotensive pregnant women ($P<0.05$). T3 represents the metabolically active thyroid agent that possibly has a vasodilatory effect on the vascular muscle cells.[34] 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.[28] 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 was in line with the findings of [25,31,] that reported significant decreased mean values in FT3 and FT4 in similar studies carried out in Australia and Nigeria respectively. The observed values were in variance with the values reported by Pasupathi *et al*.,[32] among Indian pregnant women.

The mean value CRP was found to be significantly increased (above the reference value of 0.2-10 mg/L) in gestational hypertensive women than the normotensive women. The reason may be due to the multi-organ dysfunction (vascular endothelial damage) associated with hypertensive disorders in pregnancy. C - reactive protein (CRP) is an acute phase protein which is synthesized in the liver. It is present in trace amounts in normal healthy persons and rises significantly following endothelial dysfunction and inflammation.[10] Its elevated serum level in gestational hypertension shows the extent of endothelial dysfunction associated with hypertensive complications of pregnancy. Therefore, gestational hypertension may stimulate the release of inflammatory cytokines and generation of reactive oxygen species and these attributes may be the main cause of hypertensive complications in pregnancy. This finding is supported by the hypothesis of formerly published studies.[21,22,35-39] However, the finding of our study was in contrast to the findings of McGrowder *et al*.,.[40]

The serum level of TSH correlated negatively with the serum levels of FT3 and FT4 and correlated positively with serum level CRP which had no significant association with the serum level of FT4 but negatively correlated with FT3. This implies that gestational hypertension is associated with hypothyroidism, endothelial dysfunction and inflammatory reaction. This is due to the fact that TSH has been an established marker for thyroid dysfunction so also CRP for endothelial dysfunction and inflammation. TSH also, has been documented to have a negative correlation with T3 and T4.[10,41] Therefore, the significant positive correlation between TSH and CRP shows their clinical importance in thyroid function and the occurrence of GH. However, the non-significant association recorded between FT4 and CRP may be due to the non-massive production or inhibition of serum level of FT4 as shown by the non significant difference between hypertensive and normotensive pregnant women. This may imply that in both hypertensive and normotensive pregnancy states, the T4 producing enzyme, thyroperoxidase is relatively functional therefore resulting in the neither non-inhibition nor significant production of FT4 as shown in this study. This is in accordance

with the research of Panag *et al.*,[37] that demonstrated a significant negative correlation between CK and FT3 in a similar study conducted in India.

Furthermore, the serum levels of TSH and CRP was significantly higher in severe gestational hypertension ($P<0.05$) when compared with mild and moderate cases. Therefore, the serum levels of TSH and CRP increases as the GH advances. This finding indicates that inflammatory reaction is associated with the progression of gestational hypertension. This may infer that there is an underlying inflammatory reaction that causes 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) thus, predisposing the hypertensive pregnant mothers to multiple organ dysfunctions as seen in pregnancies associated with hypertensive complications.[10] This finding may also imply that there is a hypothyroidism state that may be the intriguing factor in the progression of gestational hypertension. This is because, 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)[41] therefore allowing serum activities to rise hence, resulting in a marked release of TSH through the vascular endothelial cells. Nanda *et al.*,[42] reported a similar finding in a study conducted in Indian pregnant women with hypertension.

In the light of these findings and from several other studies we hypothesize that hypothyroidism being an autoimmune disorder may be the underlying condition that causes gestational hypertension and also predisposes hypertensive exposed pregnant mothers to pre-eclampsia and eclampsia through its implication in endothelial dysfunction, a major underlying factor in the pathogenesis of pre-eclampsia. Invariably also, we may infer that inflammation - per se may be the mitigating factor that predisposes hypertensive pregnant mothers to multiple end-organ dysfunction which in turn predisposes hypertensive exposed pregnant mothers to cardiovascular risks. According to Sinisalo *et al.*,[43] inflammation causes endothelial dysfunction, possibly by decreased capacity of the endothelium to generate vasodilatory factors, particularly T3 and nitric oxide (NO) which in turn raises blood pressure. This invariably triggers the release of the endothelial markers like the TSH as recorded in this study. Also, In an attempt to improve global cardiovascular risk prediction, considerable interest has focused on C-reactive protein (CRP), a marker of inflammation that has been shown in multiple prospective epidemiological studies to predict incident myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death. CRP levels have also been shown to predict risk of both recurrent ischemia and death among those with stable and unstable angina, those undergoing percutaneous angioplasty, and those presenting to emergency rooms with acute coronary syndromes,[11] thus, may be pertinent in pregnant mothers with mild, moderate or severe hypertension. This is substantiated by several studies which have shown inflammatory markers such as CRP as an independent determinant of endothelium dependent vascular dysfunction among patient with coronary heart disease (CHD) [16,44,45] and this situation may also exist in patients with gestational hypertension. CRP inhibits formation of vasodilators by endothelial cells which in turn promote vasoconstriction, leukocyte adhesion, platelet activation, oxidation and thrombosis. Moreover, high levels of CRP in conjunction with the high levels of TSH may upregulate angiotensin receptors and enhance expression of plasminogen activator inhibitor-1 by endothelial cells.[46] These changes could trigger hypertensive complications in pregnancy and may promote atherogenesis. Our findings are in agreement to the one reported by Sesso *et al.*,[47] who also have shown a link between elevated CRP and increased risk of developing hypertension in a cohort study, including people with baseline blood pressure in pre-hypertensive range.

There are some limitations in this study which have to be noted. The unequal classification of the mild, moderate and severe gestational hypertensive mothers may have impacted the study in one way or the other. More so, the study was a descriptive case-control study where the investigators had only one encounter with the study participants. Thus, continued follow up of these subjects would have been necessary to further clarify the conditions of these participants at the time of delivery or immediately after birth.

Conclusion

We observed that serum elevations of CRP and TSH (in the presence of significantly reduced metabolically active thyroid-hormonal agent (FT3) are consistently associated with the progression of gestational hypertension. Therefore, could be used as predictive markers for the occurrence of pre-eclampsia and cardiovascular diseases which are complications often associated with poorly

managed mild, moderate and/or severe gestational hypertension. Therefore, estimation of TSH and CRP levels may prove essential in early identification of hypertensive exposed pregnant mothers at risk for development of pre-eclampsia, eclampsia and cardiovascular diseases, since both elevated CRP and TSH in the presence of decreased FT3 are implicating factors for the progression of hypertension in pregnancy, which is a determinant for the occurrence of pre-eclampsia, eclampsia and even cardiovascular risks. Thus, the finding of this study may provide a rationale for pharmacotherapy, in a broader subset of women with gestational hypertension. Hence, strategies targeted to lower TSH and CRP levels may potentially provide increased clinical benefits.

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