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Evaluation of Thyroid Hormones and Thyroid Antibodies in Nigerian Pregnant Women with Pre-eclampsia

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ABSTRACT
Objective: This study was aimed to evaluate thyroid function and thyroid antibodies in pregnant women with pre-eclampsia. **Method:** This was a case-control study and data were collected from a total of 140 women (aged 20 to 40 years) consisting of 60 pregnant women with pre-eclampsia (test) 40 age-matched normotensive pregnant women and forty (40) age-matched apparently healthy non-pregnant women with no history of hypertension (controls). Five milliliters (5ml) of blood was collected from each participant and their serum thyroid hormones, thyroid antibodies were measured by ELISA method. Kruskal Wallis test was used to check for any statistical difference among the study groups, Mann Whitney U test was carried out to check for any statistical difference between the study groups and data were presented as median. Level of significance was taken at $P<0.05$. **Results:** Thyroid hormones were significantly lower in pre-eclamptic women when compared with normotensive pregnant women, with the exception of T4 which was conversely higher ($p<0.05$). TG-Abs and TPO-Abs were significantly lower in pre-eclamptic pregnant women when compared with both normotensive pregnant women and non-pregnant women ($p<0.05$). **Conclusion:** The significantly higher level of T4, and lower levels of other thyroid hormones and antibodies could suggest poor conversion of T4 to the more active T3 in pre-eclampsia. The results also show that relatively low TG-Abs and TPO-Abs may be a consequence or cause of pre-eclampsia in pregnant women in Nigeria.

Keywords: Pre-eclampsia, Thyroid hormones and Thyroid antibodies

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Author's contributions:
This work was conducted and approved in collaboration between all the authors, who takes responsibility for its accuracy and integrity. MIC designed the study; none sourced for funding; ONT wrote the protocol; EMC contributed in literature search; ONT did the lab experiments; EMC did statistical analysis; EMC drafted the manuscript; MIC supervised the study; EMC Wrote the final manuscript; MIC proofread the manuscript for final publication.

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INTRODUCTION

Pregnancy, also known as gestation, is the state of carrying a developing embryo or fetus within the female body (1). About 10% of pregnant women suffer hypertensive disorders during pregnancy, with pre-eclampsia being seen in 2-8% of all pregnancies. Pre-eclampsia is a major complication of pregnancy and due to its frequency as well as its related maternal and prenatal morbidity and mortality, it is a major public health problem with a prevalence of 4.6% among pregnant women worldwide (2). Pre-eclampsia (PE) is a multi-systemic complication of pregnancy often characterized with the onset of hypertension and proteinuria after 20 weeks of gestation in previously normotensive women (3). Though the exact underlying mechanisms leading to pre-eclampsia still remain unknown, the pathophysiological mechanisms leading to pre-eclampsia may include impaired placentation, trophoblast invasion, and uterine spiral artery remodeling, followed by an adverse inflammatory, metabolic, and thrombotic response (4). Thyroid hormone, an important regulator of various metabolic and inflammatory processes plays a role in placental development, and overt gestational hyperthyroidism, is a known risk factor for pre-eclampsia (5,6,7). Most thyroid diseases affecting childbearing women are autoimmune. Van den Boogaard *et al*. (8) found that thyroid autoantibodies could be seen in 5–15% of women of reproductive age which may not necessarily be accompanied by thyroid dysfunction. This implies that thyroid autoimmunity (thyroid peroxidase (TPO) and thyroglobulin (TG) antibodies) could independently have a significant effect on the well-being of the pregnant mother as well as the fetus with no association of thyroid dysfunction (9,10). The aim of this study is to evaluate the relationship between thyroid hormones and antibodies in pregnant women with pre-eclampsia.

MATERIALS AND METHODS

The present study was carried out on a total of 140 women of which sixty were women with pre-eclampsia admitted to or attending the Outpatient Department of Obstetrics and Gynecology in Nnamdi Azikiwe University Teaching Hospital, Nnewi. Forty age & parity-matched normotensive pregnant women and forty age-matched, healthy non-pregnant women served as controls. Five milliliters of venous whole blood was collected aseptically from all subjects into well labeled plain tubes and kept to clot. Serum was obtained by centrifugation at 5000 rpm for 5 minutes and separated for assay for thyroid hormones and thyroid antibodies (T3,T4,TSH, TPO-Abs & TG-Abs) by Enzyme linked immunosorbent assay (ELISA). Kruskal Wallis test and Mann Whitney test were carried out to compare averages among and between groups of the study respectively. Associations between continuous variables were obtained using Pearson's correlation coefficients and level of significance was taken at P values <0.05. Inclusion criteria of pre-eclampsia were blood pressure of $\geq$ 140/90 mmHg on at least two occasions, six hours apart and/or proteinuria. Exclusion criteria were: history of chronic hypertension, any renal disease, any metabolic disorder or medication known to affect thyroid function. Ethical approval was obtained from the ethics committee of Nnamdi Azikiwe University Teaching Hospital with ethical reference number

NAUTH/CS/66/VOL11/005/2018/005. Informed consent was also obtained from the subjects before carrying out the study.

RESULTS

STable 1 showed the median levels of anthropometric variables of pre-eclamptic pregnant women, non-pre-eclamptic pregnant control, and apparently healthy non-pregnant control women. The median systolic blood pressure levels of the three groups were 160, 110, and 100 respectively. A Kruskal-Wallis H test showed that there was a statistical significant different in systolic blood pressure among the three groups ($\chi^2(2) = 101.601$, $p=0.000$). Systolic blood pressure of the pre-eclamptic pregnant women was significantly higher when compared with both the non-pre-eclamptic pregnant control, and apparently healthy non-pregnant control subjects ($p= 0.000$) but there was no significant difference in the systolic blood pressure of the non-pre-eclamptic pregnant control when compared with that of the apparently healthy non-pregnant control subjects ($p = 0.579$). The median diastolic blood pressure levels of the three groups were 100, 70, and 70 respectively. A Kruskal-Wallis H test showed that there was a statistical significant different in diastolic blood pressure among the three groups ($\chi^2(2) = 96.784$, $p = 0.000$). Diastolic blood pressure of the pre-eclamptic pregnant women was significantly higher when compared with both the non-pre-eclamptic pregnant control, and apparently healthy non-pregnant control subjects ($p = 0.000$) but there was no significant difference in the diastolic blood pressure of the non-pre-eclamptic pregnant control when compared with that of the apparently healthy non-pregnant control subjects ($p = 0.208$). There was no statistical significant difference in age and BMI of the three groups ($P = 0.471$, and $P = 0.368$, respectively).

Table 1: Anthropometric variables (median) of pre-eclamptic pregnant women, non-pre-eclamptic pregnant control and apparently healthy non-pregnant control subjects.

Groups	Age (years)	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)
Pre-eclamptic pregnant subjects (A)	31.50	32.53	160.00	100.00
Non- Pre-eclamptic pregnant subjects control (B)	29.50	30.09	110.0	70.00
Apparently healthy Non-pregnant control (C)	30.00	31.56	100.00	70.00
Kruskal Wallis test	1.507	1.999	101.601	96.784
p-value	0.471	0.368	0.000	0.000
A vs. B	0.368	0.172	0.000	0.000
A vs. C	0.740	0.938	0.000	0.000
B vs. C	0.223	0.283	0.579	0.208

BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure.

Table 2 shows thyroid hormones level of pre-eclamptic pregnant women, non-pre-eclamptic pregnant control, and apparently healthy non-pregnant control subjects. The median levels of TSH of the three groups were 0.950, 1.300, and 1.600 respectively. A Kruskal-Wallis H test showed that there was no statistical significant difference in TSH among the three

groups ($\chi^2(2) = 1.403$, $P = 0.494$). The median levels of T4 of the three groups were 33.200, 19.350, and 12.700 respectively. A Kruskal-Wallis H test showed that there was a statistical significant difference in T4 among the three groups ($\chi^2(2) = 52.385$, $P = 0.000$). T4 level of the pre-eclamptic pregnant women was significantly higher when compared with both the non- pre-eclamptic pregnant control, and apparently healthy non-pregnant control subjects ($p = 0.001$ and $p = 0.000$, respectively). T4 level was also significantly higher in non-pre-eclamptic pregnant control when compared with that of the apparently healthy non-pregnant control subjects ($p = 0.000$). The median levels of T3 of the three groups were 2.900, 3.500, and 3.050 respectively. A Kruskal-Wallis H test showed that there was a statistical significant difference in T3 among the three groups ($\chi^2(2) = 13.248$, $P = 0.001$). T3 level of the pre-eclamptic pregnant women was significantly lower when compared with non-pre-eclamptic pregnant control ($P = 0.000$). T3 was also significantly higher in non-pre-eclamptic pregnant control when compared with that of the apparently healthy non-pregnant control subjects ($p = 0.015$). There was no statistical significant difference in the median level of T3 of pre-eclamptic pregnant women when compared with apparently healthy non-pregnant control subjects ($p = 0.874$).

The median levels of FT4 of the three groups were 11.300, 13.500, and 15.500 respectively. A Kruskal-Wallis H test showed that there was a statistical significant difference in FT4 among the three groups ($\chi^2(2) = 23.485$, $P = 0.000$). FT4 level of the pre-eclamptic pregnant women was significantly lower when compared with both the non-pre-eclamptic pregnant control, and apparently healthy non-pregnant control subjects ($p = 0.022$ and $p = 0.000$, respectively). FT4 level in non-pre-eclamptic pregnant control was significantly lower when compared with that of the apparently healthy non-pregnant control subjects ($p = 0.005$).

The median levels of FT3 of the three groups were 7.000, 7.650, and 8.350 respectively. A Kruskal-Wallis H test showed that there was a statistical significant difference in FT3 among the three groups ($\chi^2(2) = 10.279$, $P = 0.006$). FT3 level of the pre-eclamptic pregnant women was significantly lower when compared with apparently healthy non-pregnant control subjects ($p=0.002$). The level of FT3 in non-pre-eclamptic pregnant control was significantly lower when compared with that of the apparently healthy non-pregnant control subjects ($p = 0.049$). There was no statistical difference in the level of FT3 of pre-eclamptic pregnant women when compared with the non-pre-eclamptic pregnant control ($P = 0.182$).

Table 2: Median levels of TSH, T4, T3, FT4, and FT3 in pre-eclamptic pregnant women, non-pre-eclamptic pregnant control, and apparently healthy non-pregnant control subjects.

Groups	TSH(µlU/ml)	T4(µg/dl)	T3(ng/dl)	FT4pmol/L	FT3pmol/L
Pre-eclamptic pregnant women (A)	0.950	33.200	290.00	11.300	7.000
Non- Pre-eclamptic pregnant women (B)	1.300	19.350	350.00	13.500	7.650
Apparently healthy Non-pregnant women (C)	1.600	12.700	305.00	15.500	8.350
Kruskal Wallis test	1.403	52.385	13.248	23.485	10.279
p-value	0.494	0.000	0.001	0.000	0.006
A vs B	0.377	0.001	0.000	0.022	0.182
A vs C	0.306	0.000	0.874	0.000	0.002
B vs C	0.640	0.000	0.015	0.005	0.049

TSH: Thyroid stimulating hormone, T4: Thyroxine, T3: Triiodothyronine, FT4: Free Thyroxine, and FT3: Free Triiodothyronine.

Table 3 shows the level of thyroglobulin antibody (TG-Abs) and thyroid Peroxidase antibody (TPO-Abs) in pre-eclamptic pregnant women, non-pre-eclamptic pregnant control, and apparently healthy non-pregnant control subjects. The median levels of TG-Abs of the three groups were 16.800, 20.700, and 24.150, respectively. There was statistical significant difference in TG-Abs among the three groups ($\chi^2(2) = 17.370$, $P = 0.000$). TG-Abs level of the pre-eclamptic pregnant subjects was significantly lower when compared with both the non-pre-eclamptic pregnant control, and apparently healthy non-pregnant control subjects ($p = 0.006$ and $p = 0.000$, respectively). The median levels of TPO-Abs of the three groups were 1.100, 1.950, and 3.050, respectively. There was statistical significant difference in TPO-Abs among the three groups ($\chi^2(2) = 34.688$, $P = 0.000$). TPO-Abs level of the pre-eclamptic pregnant women was significantly lower when compared with both the non-pre-eclamptic pregnant control, and apparently healthy non-pregnant control subjects ($p = 0.000$ and $p = 0.000$, respectively). There was no statistical significant difference in the median level of TG Abs and TPO-Abs of non-pre-eclamptic pregnant women when compared with apparently healthy non-pregnant control subjects ($p = 0.223$ and $p = 0.051$, respectively).

Table 3: Levels of TG-Abs and TPO-Abs in pre-eclamptic pregnant women, non-pre-eclamptic pregnant control, and apparently healthy non-pregnant control subjects

Groups	TG-Abs (IU/ml)	TPO-Abs (IU/ml)
Pre-eclamptic pregnant subjects (A)	16.800	1.100
Non- Pre-eclamptic pregnant subjects control (B)	20.700	1.950
Apparently healthy Non-pregnant control (C)	24.150	3.050
Kruskal Wallis test	17.370	34.688
p-value	0.000	0.000
A vs B	0.006	0.000
A vs C	0.000	0.000
B vs C	0.223	0.051

TG-Abs = Thyroglobulin antibody, TPO-Abs = Thyroid Peroxidase Antibody.

Table 4 shows the correlation coefficient (r) of thyroid hormones and antibodies with systolic and diastolic blood pressure in pre-eclamptic women. There were significant negative correlations between T3 systolic blood pressure (r = -0.249, p = 0.012) and between TG-Abs and systolic blood pressure (r = -0.261, p = 0.009) in the pregnant women studied

	Systolic blood pressure		**Diastolic blood pressure**	
Parameter	**r**	**p**	**r**	**p**
TSH	0.072	0.477	0.008	0.939
T3	-0.249	0.012*	0.053	0.600
T4	0.156	0.121	0.137	0.173
FT3	-0.124	0.220	-0.111	0.269
FT4	-0.156	0.122	0.004	0.972
TG-Abs	-0.261	0.009**	-0.164	0.104
TPO-Abs	-0.194	0.053	-0.156	0.121

r - Pearson Correlation Co-efficient, **Correlation significant at p<0.01; *Correlation significant at p<0.05; n – Number of subjects in the group; TSH – Thyroid Stimulating Hormone, T3 -triiodothyronine, T4-thyroxine, FT3- free triiodothyronine, FT4- free thyroxine, TG-Abs- thyroglobuline antibody, TPO-Abs- thyroid peroxidase

DISCUSSION

Pre-eclampsia may occur at second or third trimester of pregnancy, its etiology is not clearly known as many factors may play an important role in its development. (11,12). Several

studies showed that there are significant association between thyroid hormones and the development and severity of pre-eclampsia (13,14,15). In this present study, our findings showed a higher level of total thyroxine (T4), and lower levels of triiodothyronine (T3), free T3 (FT3), free T4 (FT4), thyroglobulin antibody (TG-Abs), and thyroid Peroxidase Antibody (TPO-Abs) but no significant difference in the level of thyroid-stimulating hormone (TSH) in pre-eclamptic women when compared to both non-pre-eclamptic pregnant women and healthy non pregnant women (control groups). Our findings of non significant difference in the level of TSH in pre-eclamptic women when compared to control groups is in agreement with the report of Qublan *et al.* (16), and Arash *et al.* (17) but disagrees with that reported by Sardana *et al.* (18). In the present study, T4 level was significantly higher in pre-eclamptic women when compared with the control groups. This result is not in agreement with that reported in Levin *et al.* (19) and Arash *et al. (*17). Thyroid dysfunction may have a great influence on the thyroid tissues thereby causing a change in the synthesis and secretion of the thyroid hormones which can significantly increase the level of T4 in severe pre-eclamptic women. These findings were not consistent with some studies (20,21). The result of this study revealed that the level of T_3 was significantly lower in pre-eclamptic women when compared with the non-pre-eclamptic pregnant women. This result is in agreement with that reported by Roncaglia *et al.* (22,23), but disagrees with the report of Arash *et al.* (17). This reduced level of T_3 could be as a result of failure of eostrogen production due to placental dysfunction and the loss of proteins and protein-bound hormones in urine during pre-eclampsia (13,24). The low level of T_3 could also be due to the decreased peripheral conversion of T4 to T3 due to the involvement of the renal and liver during pre-eclampsia (25,26). This present study showed that the level of FT4 in the pre-eclamptic pregnant women is significantly lower when compared with both the non-pre-eclamptic pregnant women and apparently healthy non-pregnant subjects but there was no significant difference in level of FT3 in the pre-eclamptic when compared with the non- pre-eclamptic pregnant women. Our finding of lower FT4 in the pre-eclamptic is in agreement with that reported by Raoofi *et al.* (15).The low levels of FT3 and FT4 could be as a result of iodine deficiency disorder due to low iodine and high dietary thiocyanates. Iodine is necessary in the production of the thyroid hormones so its deficiency could also affect or lead to a low production of the thyroid hormones (27). In the current study, TPO-Abs and TG-Abs were significantly lower in women with pre-eclampsia. Our findings of lower level of TG-Abs in the pre-eclamptic women is in agreement with the report of Elhaj *et al.* (28), but disagrees with the report of Männistö *et al.* (29). The significant lower level of TPO-Abs in pre-eclamptic pregnant women in this study is not consistent with the report of Elhaj *et al.* (28). During pregnancy, the plasma levels of estrogen, progesterone, and corticosteroids increases. While corticosteroids induces immune cell apoptosis and immunosuppression, estrogen produces negative regulation of B cell activity. This implies that B-cell production and activity are down regulated, and this leads to a reduction in antibody production. The degree of autoimmunity decreases with

advancing gestation (30). Since thyroid antibody titers decline due to the immuno-suppressive effect of pregnancy advancement, this could be the reason for the low level of these parameters (TG-Abs and TPO-Abs) found in this study as the pregnant women were in the third trimesters. We also studied the associations between thyroid hormones and antibodies with systolic and diastolic blood pressure levels in pregnant women. There were statistically significant negative associations between systolic blood pressure with T3 and TG-Abs in the studied pregnant women. The differences observed in the present study compared to some other reports could be as a result of differences in the geographical locations, race and/or diets of the study participants.

CONCLUSION

The study shows that the median T4 level in pre-eclamptic pregnant women is significantly elevated when compared to both the non pre-eclamptic pregnant women and apparently healthy non pregnant women. The study demonstrated lower level of T3 and FT4 in pre-eclamptic pregnant women compared to non pre-eclamptic pregnant women. Also, TG-Abs and TPO-Abs were lower in pre-eclamptic pregnant women compared to both non pre-eclamptic pregnant women and non pregnant women. Similarly, the antibodies are also lower in non pre-eclamptic pregnant women relative to their non pregnant counterparts. It could also be concluded that the increased T4 and low T3 levels in pre-eclamptic pregnant women may be as a result of poor conversion of T4 to T3 in pre-eclampsia due to renal and liver involvement, or could be as a result of failure of oestrogen production due to placental dysfunction seen in pre-eclampsia.

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