



## Detection of Relationship between Maternal Thyroid Hormones and Severity of Preeclampsia

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### ABSTRACT

**Background:** Preeclampsia is the most frequent medical complication of pregnancy and it is a multisystem disorder. Previous studies suggested a relationship between thyroid hormones levels and preeclampsia. **Objective:** To assess the relation of thyroid hormone and preeclampsia. **Method:** This was a case-control study conducted at the Department of OBG, Babylon Teaching hospital for Maternity and child complex from the 1<sup>st</sup> of Jan 2018 to the end of May 2018. **Results:** Total 200 respondents were included in this study, thyroid stimulating hormone TSH was increased in preeclamptic patients and were more than the other with significant association ( $p=0.02$ ). T3 was decreased significantly in preeclampsia than normal healthy women with a decrease from severe to mild (0.04). Thyroid hormone T4 was also decreased in preeclamptic pregnant women than normal pregnant but no significant association was found ( $p=0.06$ ). **Conclusion:** There is a significant relation between preeclampsia and thyroid hormone.

**Keywords:** Pregnancy, Thyroid function, Preeclampsia, Thyroid hormone

### INTRODUCTION

There are diseases that alter the normal function of pregnancy and produce high rates of morbidity and mortality maternal and perinatal health, adversely impacting the public health, as in the case of hypertensive diseases associated with pregnancy. The hypertensive states associated with pregnancy worldwide present a rate of maternal mortality of direct cause from 6% to 12% [1].

Preeclampsia (PE) is the most frequent medical complication of pregnancy and it is a multisystem disorder characterized by hypertension of recent onset and proteinuria [2]. The pathogenesis of PE is not yet well understood; however, different theories have been postulated. Physiopathological mechanisms of the hypoxic, metabolic, immune and genetic type have been postulated, with an increase in anti-angiogenic factors, placental oxidative stress due to an imbalance of pro-oxidants and maternal antioxidants and aberrant expression of cytokines, which causes an exaggerated systemic inflammatory response [2-4].

#### Diagnosis of Preeclampsia

Preeclampsia is only diagnosed in the presence of high blood pressure and protein in the urine. However, experts stated that PE is possible to present even in the absence of proteinuria. Hypertension is characterized by recent beginning and a value above 140/90 mmHg two times within 6 hours is abnormal in pregnancy, additionally, a protein excretion of almost 300 mg in 24 hours urine collection more than two (++) on a test strip. This development of hypertension occurs usually after the 20<sup>th</sup> week of gestation in previously normotensive [5-7]. The proteinuria is diagnosed with an excretion of proteins till 24 hours since the absence of proteins in some women does not correlate with the degree of severity of the disease. Hypertension with absence of protein should be considered preeclampsia when it is associated with persistent, epigastric brain symptoms, which is sometimes associated with nausea and vomiting, thrombocytopenia and elevation of liver enzymes [5,8].

Preeclampsia is classified as severe when represents tension figures of 160/110 mmHg, associated with proteinuria, or severe proteinuria that is >5 g of proteins in urine in 24 hours [9]. The working group of the National Blood Pressure Education Program (NHBPEP) classifies hypertensive disorders into four classes [5] (Table 1).

**Table 1 Classification of hypertensive status**

Classification	Hypertensive Status
Preeclampsia-eclampsia	Systolic BP>140 mmHg and/or diastolic BP>90 mmHg after the 20 <sup>th</sup> week, in a previously normotensive woman, proteinuria>300 ng in a 24-hour urine collection
Preeclampsia plus chronic hypertension	The appearance of proteinuria in a previously hypertensive patient
Chronic hypertension	Systolic BP>140 mmHg and/or diastolic BP>90 mmHg, documented before the 20 <sup>th</sup> week
Gestational hypertension	Systolic BP>140 mmHg and/or diastolic BP>90 mmHg after of the 20 <sup>th</sup> week of gestation in a previously normotensive woman. The absence of proteinuria hypertension will have to return to normal before week 12 after the obstetric resolution, otherwise, the patient will be classified as chronic hypertensive

Hypothyroidism has been recognized among the causes of elevated blood pressure [10]. In preeclampsia, there is a failure in the production of estrogens due to malfunction of the placenta leading to a reduction of TBG, TT3, and TT4 along with the growth retardation of the fetus [11]. Increasing evidence suggests that oxidative stress and altered endothelial cell utility may have a role in preeclampsia [12-14]. Also, oxidative stress has been proposed as another contributing source of the hyperuricemia noted in preeclampsia apart from renal dysfunction [15]. Nitric oxide has a significant value in controlling of blood pressure systematically. The synthase of endothelial nitric oxide (e-NOS) generates NO continuously, which diffuses into the underlying muscle and mediates vasodilation. It inhibits the activation of platelets and neutrophils and, if not formed, activates neutrophils; there will be vasoconstriction, adhesion and platelet aggregation and release of vasoconstrictor substances. In preeclampsia, an excess of superoxide anion increase in the superoxide anion, which may inactivate NO, leading to reduced relaxation and increased vasoconstriction [14,16,17].

#### PATIENTS AND METHODS

This was a case-controls study achieved in the Department of OBG, Babylon Teaching hospital for Maternity and child complex from the 1<sup>st</sup> of Jan 2018 to the end of May 2018, which included a total of 100, proved diagnosed PE woman patients and were assigned into 2 subgroups according to the severity of PE. Group I included 50 women with severe PE and Group II included 50 women with mild PE. Additionally, 100 apparently healthy normotensive pregnant women were enrolled as controls' group and they were almost matched to the cases of preeclampsia.

Women were excluded from the study if they had one or more of the following criteria:

- Any patients with a history of HT, cardiac disease, and renal disorders, RHD, epilepsy
- History of molar pregnancy, multiple pregnancies, congenitally malformed fetus
- History of metabolic disorders
- History of intake of any medication that might affect thyroid function like drugs, e.g. glucocorticoids, phenobarbitone, ferrous sulfate

Diagnosis of PE was based on the clinical picture of the patient in which blood pressure more than 140/90 mmHg on two or more occasions at least 6 hours apart and proteinuria of more than 300 mg/L in 24-hour urine collection was considered.

Laboratory investigations were performed for all PE patients and controls where a sample of venous blood of 2 ml was drawn under sterile techniques and was sent to the laboratory for analysis using chemiluminescence immunoassay system for the Thyroxine (T4), Triiodothyronine (T3) and Thyroid stimulating hormone (TSH). Other routine investigations were performed including urinalysis and 24 hours collection for proteins in the urine.

#### Ethics and Consent

The official agreement was obtained from the health authorizes, hospital administration office and the local committee for researches ethics in Babylon health directorate. Signed written consent was obtained from all participants prior to inclusion in the study; non-consenting women were excluded. Patients data were collected according to the declaration of Helsinki 2013 and the purpose and procedures were explained to all the participants and were informed that they have the right to participate or not, with the assurance that interprets gained will be kept confidentially and will not be disclosed to unauthorized personnel.

### Statistical Analysis

Data of the participants were checked for errors or inconsistency and then transformed into the computerized database with the Statistical package for social sciences (SPSS) software for Windows version 24.0. Descriptive statistics were presented as a mean, standard deviation, frequencies, and simple percentages. Continuous variables were tested for statistical normal distribution, and all followed the normal distribution. Statistical tests were applied accordingly; analysis of variances (ANOVA) was used to compare means (among more than two groups). In all statistical analysis, the level of significance was set at  $p \leq 0.05$ .

### RESULTS

No significant difference had been found in maternal age and parity among the 3 groups ( $p > 0.05$ ), while significant differences had been reported among the 3 groups in gestational age at labor, SBP, DBP, childbirth weight, serum albumin and serum uric acid ( $p < 0.001$ ) (Table 2).

**Table 2 Baseline characteristics of the studied group**

Variable	PE group (N=100)		Control (N=100)	p-value
	Mild PE (n=50)	Sever PE (n=50)		
Maternal age	25.1 ± 1.8	25.4 ± 2.1	25.0 ± 2.3	0.77
Gestational age at labor	38.8 ± 0.1	36.3 ± 1.1	39.1 ± 1.3	< 0.001
Parity	2.1 ± 1.3	2.05 ± 1.1	2.4 ± 1.4	0.3
SBP (mmHg)	145.2 ± 10.2	153.4 ± 20.5	105.6 ± 8.9	< 0.001
DBP (mmHg)	105.5 ± 8.1	109 ± 10.5	67.5 ± 6.7	< 0.001
Child birth weight (kg)	1.73 ± 0.4	2.2 ± 0.31	2.79 ± 0.1	< 0.001
Serum albumin (g/dL)	3.7 ± 0.1	3.4 ± 1.2	2.9 ± 0.8	< 0.001
Serum uric acid (mg/dl)	5.7 ± 0.9	7.88 ± 1.7	2.5 ± 1.1	< 0.001

Thyroid stimulating hormone (TSH) was higher in severe PE patients than in those with mild PE and controls, ( $p = 0.02$ ). The T3 level was significantly lower in PE than normal healthy women with a lower level of severity than mild PE (0.04). Thyroid hormone T4 were also decreased in PE women than normal pregnant but the differences did not reach the statistical significance ( $p > 0.05$ ) (Table 3).

**Table 3 Comparison of mean levels of thyroid hormones among the studied groups**

Thyroid hormones	PE group (N=100)		Controls (N=100)	p-value
	Mild PE (n=50)	Sever PE (n=50)		
TSH	3.23 ± 1.8	4.4 ± 2.2	2.1 ± 1.3	0.02
T3	2.3 ± 0.7	2.0 ± 0.9	2.7 ± 1.1	0.04
T4	1.46 ± 0.3	1.39 ± 0.7	1.79 ± 0.9	0.06

All values are mean ± standard deviation

### DISCUSSION

Many diverse factors may play an important role in the progress of preeclampsia. Etiology of preeclampsia is obviously unknown and it may occur at the second or third trimester of pregnancy [18,19]. The current study revealed that there is a significant association found between thyroid hormone (TSH and T3) and preeclampsia. These findings wasn't in accordance with that reported by Nayki, et al., where statistically significant difference was present in the levels of FT3, FT4 and TSH between the preeclamptic group and normotensive controls in the third trimester of gestation [20]. Moreover, it is not in agreement with Qublan, et al., study who reported that the thyroid function did not alter in severe preeclamptic women group when compared with normotensive controls group [21]. But it is in agreement with that mentioned by Rafeinia, et al., study, where the levels of TSH and T3 were higher in preeclampsia women compared to healthy pregnant women ( $p > 0.05$ ) [22]. Many studies revealed that there was a significant association between thyroid hormones and the development and severity of preeclampsia. Lower T3 level in PE patients in comparison to controls was observed in the current study with more lower levels in severe than mild PE, this is supported by previous studies and could be due to the kidney and liver involvement during pregnancy that may lead to the decreased peripheral conversion of thyroid hormone T4 to T3, and hence lead to a decrease in the level of T3 [22]. Similarly, Başbuğ, et al., reported low T3 levels in PE patients, the lower levels of T3 in PE, particularly in severe

form gives a good indicator that the PE is associated with level of TSH in the serum, and also the level of increment in this hormone depends on the severity of disease [23]. This is in accordance to that found in Sardana, et al., and Basbug, et al., studies who concluded that the increased level of TSH might be related to increased risk of PE and PE women may be more liable to give birth to low weight infants [23,24]. Furthermore, Kumar, et al., suggested that reduced concentration of thyroid hormones in preeclampsia may be due to the loss of protein-bound hormones in the urine [25]. Lao, et al., in his study mentioned that levels of T4 were decreased with elevated TSH levels in patients with PE [26]. These findings could be due to that hypothyroidism that can cause contraction of the smooth muscle in both systemic and renal vessels, which lead to elevated diastolic hypertension, peripheral vascular resistance and decreased tissue perfusion [27,28]. The current study revealed that severe PE women had higher uric acid levels and low serum albumin levels as compared to patients with mild preeclampsia ( $p < 0.001$  in both cases, Table 1). Also, the highly significant association was found between childbirth weight (gm) and patients with mild preeclampsia, this is in agreement with that found by Sardana, et al., [24].

### CONCLUSION

There was a significant association between preeclampsia and lower levels of thyroid hormones.

### DECLARATIONS

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#### Conflict of Interest

The authors have disclosed no conflict of interest, financial or otherwise.

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