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## Urinary Serotonin and 5-Hydroxyindolacetic Acid Levels in Preeclampsia

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**Abstract:** The role of serotonin in the pathogenesis of hypertension which is one of the main symptoms of preeclampsia is of growing importance. The levels of serotonin (5-Hydroxytryptamin or 5-HT) and its metabolite, 5-Hydroxyindolacetic acid (5-HIAA) in twenty-four hour urine samples taken from severe preeclamptic and normotensive pregnant women were determined by colon chromatography and spectrophotometry. In preeclamptic pregnant women there was a significant increase in

5-HT levels ( $P<0.01$ ), a decrease in 5-HIAA levels ( $P<0.001$ ) and decrease in the 5-HIAA-serotonin ratio ( $P<0.001$ ). These changes indicate that the serotonin metabolism is influenced to a great extent by preeclampsia or this opposite change may have an important role in the pathogenesis of preeclampsia.

**Key Words:** Preeclampsia, Serotonin (5-HT), 5-Hydroxyindolacetic acid (5-HIAA).

### Introduction

Pregnancy may be complicated by elevated blood pressure or may exacerbate preexisting hypertension. Even the real etiology of pregnancy induced hypertension is unknown, and many pathophysiologic mechanisms like increased sensitivity against vasopressors and increased vasospasm (1), an imbalance in the synthesis of vasoactive prostaglandins (1, 2), increased thrombocyte activation and aggregation (2, 3), and endothelial cell dysfunction (4) are blamed. While serotonin is found at a maximum level of 90% in enterochromaffin cells in the gastrointestinal system, increased release of serotonin in the central nervous system and thrombocyte causes widespread vasospasm through 5-HT<sub>2</sub> receptors (5). The serotonin content of platelet rich plasma (PRP) is mainly of thrombocyte origin since thrombocytes are sensitive cells, they are easily destroyed once aggregated (6). Endothelial cell dysfunction causes relaxation of serotonin and vasoconstrictor thromboxane A<sub>2</sub> (TxA<sub>2</sub>) by triggering thrombocyte activation and aggregation.

This study was carried out to determine the role of serotonin in the pathogenesis of preeclampsia and the urine levels of serotonin and its metabolite 5-HIAA.

### Materials and Method

In Istanbul Medical Faculty, Gynecology and Obstetric Department, 24 women with severe preeclampsia (Study group) and 12 normotensive pregnant women without any disease (Control group) were enrolled in the study. The clinical findings of the Study and Control groups are given in Table 1. Severe preeclampsia was defined as a blood pressure of  $\geq 160/110$  mmHg after 30 minutes of rest on two separate readings at least 6 hours apart with proteinuria (more than 300 mg/day), and pathologic edema. Preeclamptic and normotensive pregnant women were nulliparas, the gestational age was  $33.25\pm 4.20$  and  $31.7\pm 5.76$  weeks, and the median age was 25 (range 18–32) and 27 (range 20–35) respectively. All women (Study and Control groups) had not had any medications for at least 10 days before the urine collection. Patients who had a history of hypertension before the twentieth week of pregnancy and diabetes mellitus were excluded from the study. All pregnant women had the same diet 24 hours before urine samples were taken. Twenty-four hour urine collections were taken from both the Study and Control groups in bottles containing hydrochloric acid. The urine containers were kept at  $-20^{\circ}\text{C}$  so that the urine was frozen immediately after the patient voided.

	Preeclamptic Pregnant Women (n: 24)	Normotensive Pregnant Women (n: 12)
Gestational age at sampling (week)	33.25±4.20	31.7±5.76
Systolic blood pressure (mmHg)	184.79±23.56	117±0.65
Diastolic blood pressure (mmHg)	125±15	77±5.4

Table 1. Clinical characteristics of preeclamptic and normotensive pregnant women.

The levels of urinary serotonin and 5-HIAA were determined with colon chromatography (Biosystems 5-HIAA kit-Barcelona, Spain). The products of the tryptophan metabolism were absorbed on a neutral resin; the serotonin and 5-hydroxytryptophan (5-HTP) were eluted together in the first place and then, the 5-HIAA. These metabolites were quantified spectrophotometrically by means of the product formed in the reaction with 1-nitroso-2-naphtol. The accuracy of the kit was 98%, intra-assay variations were 3% and inter-assay variations were 4%. The results were evaluated with Student's t test with average ± standard deviation.

**Results**

The average ± SD of urinary serotonin concentrations in preeclamptic pregnant women was found to be 5.75±0.90 mg/L while in normotensive pregnant women it was 4.94±0.68 mg/L (Table 2). A significant increase in urinary serotonin concentrations in preeclamptic pregnant women was found (P<0.01). 5-HIAA levels in preeclamptic pregnant women were 3.10±0.66 mg/L and in normotensive ones they were 4.90±1.46 mg/L. A significant decrease in 5-HIAA levels was found in preeclamptic pregnant women (P<0.001). When urinary serotonin and 5-HIAA levels were evaluated according to

urinary creatinine, a significant increase (P<0.05) in serotonin values and a significant decrease (P<0.02) in 5-HIAA levels were found in preeclampsia. While the 5-HIAA-serotonin ratio in pregnant women with toxemia was 0.54±0.11, it was 0.97±0.3 in normotensive pregnant women. A significant (P<0.001) decrease in the urinary 5-HIAA-serotonin ratio was found in preeclamptic women.

**Discussion**

Preeclampsia, seen in 6-8% of all pregnancies, is an important cause of maternal perinatal morbidity and mortality. One of the proposed hypotheses for the etiopathogenesis of preeclampsia includes endothelial cell dysfunction, abnormal thrombocyte activation and activation of coagulation mechanisms (2-7). Endothelial cell dysfunction causes the aggregation and activation of thrombocytes. Increased thrombocyte aggregation causes the release of vasoconstrictive thromboxane A<sub>2</sub> (TxA<sub>2</sub>), serotonin (5-HT) and adenin nucleotides. The main source of serotonin in blood is thrombocytes (4, 8). Serotonin release causes vasoconstriction via smooth 5-HT<sub>2</sub> receptors (5). The observations that ketanserin, a 5-HT<sub>2</sub> receptor antagonist, undoes vasoconstriction related to thrombocyte activation and successful therapy obtained by nimodipin, a serotonin inhibitor in causes of

	Preeclamptic Pregnant Women (n: 24)	Normotensive Pregnant Women (n: 12)	Student's t test
Serotonin (mg/L)	5.75±0.90	4.94±0.68	P<0.01
Serotonin/creatinine (mg/g)	6.76±2.47	5.16±0.72	P<0.05
5-HIAA (mg/L)	3.10±0.66	4.90±1.46	P<0.001
5-HIAA/creatinine (mg/g)	3.67±1.76	5.15±1.72	P<0.02
5-HIAA/serotonin ratio	0.54±0.11	0.97±0.3	P<0.001

Table 2. Urinary serotonin, 5-HIAA, serotonin/creatinine and 5-HIAA/creatinine levels and 5-HIAA/serotonin ratio in preeclamptic and normotensive pregnant women.

widespread ischemia supports the idea that serotonin causes the widespread vasospasm and hypertension in preeclampsia (9). Serotonin, a neurotransmitter, is metabolized to 5-HIAA by monoamine oxydase (MAO) and is excreted in urine. Serotonin concentration in plasma poor platelets (PPP) obtained from preeclamptic women is reported to be higher than in normotensive pregnant women (4, 6). Serotonin and 5-HIAA levels in umbilical cord plasma of fetuses of preeclamptic women are high when compared with fetuses of normotensive women whereas 5-HIAA/5-HT ratios are lower (10). In preeclamptic women, thrombocyte serotonin concentration is reported to be low (8). Increased plasma serotonin concentration is proposed to be related to increased embolic tropholastic fragmentation seen in the blood circulation of preeclamptic women (11). Like endothelial cell dysfunction, trophoblastic fragmentation causes thrombocyte activation and deprivation and thus causes serotonin release and a rise in blood pressure. In our study, we compared normotensive pregnant women with preeclamptic pregnant women, and found a significant increase in the urine serotonin levels, a

significant decrease in 5-HIAA levels, and a significant decrease in the 5-HIAA-serotonin ratio.

We encountered no research about urine serotonin levels in preeclampsia in the literature. Increased urinary serotonin levels may be due to the significant increase in the tropholastic fragmentation and increased blood serotonin levels. Decreased urinary 5-HIAA levels may be due to the decrease in monoamine oxydase activity. Many studies have shown a decrease in the placental MAO activation (12, 13). Filshie et al. showed the increase in the urinary 5-HIAA levels in preeclamptic pregnant women by using gas chromatography and mass spectrophotometry (11). In our study we found a decrease in the urinary 5-HIAA levels and an increase in the urinary serotonin levels. The increase in the serotonin is probably due to the decrease in the MAO activation and the decrease in its metabolism.

In conclusion, increased serotonin levels may play a role in the development of preeclampsia and hypertension. Future research about the 5-HIAA and serotonin may reveal this.

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