THE ROLE OF ENDOTHELIN-1 AS A NEW INDICATOR OF PRE-ECLAMPTIC TOXAEMIA

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ABSTRACT

Endothelin is a potent vasoconstrictor released from injured endothelial cells. As the pathophysiology of the mechanisms of Preeclamptic toxaemia are not exactly known, the present study aimed at determining the level of Endothelin in normal & preeclamptic pregnant women. The study also aimed to postulate any possible relation between the severity of the Preeclamptic toxaemia & the levels of circulating Endothelin-1 (ET-1).

The study was carried out on 45 pregnant women at 37 - 40 weeks of gestation. They were classified into 3 groups, each 15 patients, namely: Control group (normal Pregnancy), Group of pregnant women with mild Preeclamptic toxaemia, and a third group of women with severe Preeclamptic toxaemia.

The results showed significant increase in the systolic and diastolic pressure & ET-1 levels in mild & severe Preeclamptic toxaemia, compared with control group (p<0.001). Also, a significant increase in systolic, diastolic blood pressure & ET-1 level in blood was observed between mild & severe Pre-eclamptic toxaemia group (p<0.001).
A positive linear correlation was recorded between ET-1 and each of the systolic blood pressure & diastolic blood pressure in the Pre-eclamptic groups ("r" = 0.437 & 0.495) respectively. This suggests that ET-1 may share in the pathogenesis of preeclampsia and in the severity of the disease.

**Introduction**

Pre-eclampsia is unique to human pregnancy. It complicates 6-8% of gestation exceeding 24 weeks (4). It develops mainly, but not exclusively in nulliparous women & resolves within several days after delivery (2). It appears to be the largest single cause of maternal death (3, 4). According to the World Health Organisation, it is the main cause of perinatal mortality & morbidity (5).

The aetiology of Preeclampsia, still, remains unknown. However during the past few years, major advances as regards pathogenesis, early detection, potential prevention and management have been achieved.

Pathophysiological abnormalities in preeclampsia includes: vascular spasm, activation of the coagulation system, abnormal hemostatic mechanisms, altered prostacyclin-thromboxane ratio (6).

Consequent to the injury of the endothelial cells, potent vasoconstrictor substances e.g. endothelins are released. The most potent constrictor of the three endothelins is Endothelin-1 (ET-1). Increased release of this vasoconstrictor is accompanied by decreased production of endothelial derived relaxation factor. The blood flow through various organs is thus disturbed (6). The disturbed blood flow includes the uteroplacental vascular bed.

The aim of the present study was to compare ET-1 levels in the plasma of patients with pre-eclamptic toxemia with that in normal pregnant women. Also, the present study is a trial to postulate whether there is a possible relation between the severity of pre-eclampsia and the levels of circulating ET-1.

**Subjects and Methods**

This study was carried out on patients from Benha University Hospital during the period from March 1995 to April 1996. The study included 45 pregnant women at 37-40 weeks of gestation as determined by the sure date of the last menstrual period & as confirmed by ultrasonographic scanning.

These subjects were classified into 3 groups. Each group included 15 patients.

1. The first group: This group which is served as a control group included 15 normal pregnant women
2. The second group: It included 15 pregnant women with mild preeclamptic toxemia (Blood pressure...
140 - 160/90 - < 110 mm Hg on two occasion 24 hours apart and proteinuria 500 - 1000 mg / L in 24 hours urine by combi kits, Boheringer Ingelheim).

3. The third group: It included 15 patients suffering from severe Preclampsia (Blood pressure ≥ 160 / 110 mm Hg and proteinuria > 1000 mg / L in 24 hours urine).

All patients participated in the present study were subjected to full history and clinical examination including the following: Age, weight, gravity, & measuring the blood pressure.

From every patient, a morning venous sample (4 ml) was collected into chilled syringe, & was transferred into polypropylene tube containing EDTA (1mg/ml) & Apotinin (500 KIU/ml). The blood samples were centrifuged at 3000 rpm for 15 minutes at 0°C. Plasma was separated and stored at -60°C for estimation of ET -1 by RIA (7 & 8).

The results of the present study were subjected to statistical analysis using the student “t” test (9). The results were considered significant when p < 0.05.

**Results**

Table 1 shows the mean, Standard Deviation (SD) & Standard Error (SE) of the results of the three investigated groups. It can be observed that there was no significant difference between the age of the three groups. Also no significant difference was observed between the weight gain in the control group and the mild preclampsia group: however a significant increase in the body weight was noted in the group with severe preeclampsia (P < 0.05).

As regards gravidity, a statistically significant difference was observed between the control group & the other two Preclampsic groups (P < 0.02) but no significant difference was noted between the two groups of Preeclampsia.

As observed from table 1, the systolic & diastolic blood pressures were significantly higher in the two Preclampsic groups (p < 0.001) as compared with control group. Also a significant increase in the systolic & diastolic blood pressure in the group with severe preeclampsia compared with group of mild preeclampsia (p < 0.001) was noted.

As regards ET -1 level in the plasma, it is shown from table 1 that there is a highly significant difference between the control group & the two groups of preeclampsia (p < 0.001) and between the two groups of mild & severe preeclampsia.

Figures 1 & 2 show that ET -1 level rises with the increase in systolic (figure 1) and diastolic (figure 2) blood pressures. This indicates a significant positive linear correlation between ET - 1 levels and the blood pressures. The correlation coefficients “r” = 0.437 & 0.495 respectively.
<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>Weight Gain</th>
<th>Gravida</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
<th>ET -1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Years</td>
<td>Kg</td>
<td></td>
<td>mm Hg</td>
<td>mm Hg</td>
<td>pg/ml</td>
</tr>
<tr>
<td>Control</td>
<td>mean</td>
<td>28.33</td>
<td>10.33</td>
<td>1.67</td>
<td>124.87</td>
<td>76.67</td>
</tr>
<tr>
<td></td>
<td>S.D. ±</td>
<td>5.8</td>
<td>1.28</td>
<td>0.9</td>
<td>9.9</td>
<td>4.83</td>
</tr>
<tr>
<td></td>
<td>S.E.</td>
<td>1.5</td>
<td>0.47</td>
<td>0.9</td>
<td>1.26</td>
<td>0.48</td>
</tr>
<tr>
<td>Mild</td>
<td>mean</td>
<td>28.67</td>
<td>13.60</td>
<td>2.6</td>
<td>145.09</td>
<td>92.00</td>
</tr>
<tr>
<td></td>
<td>S.D. ±</td>
<td>5.59</td>
<td>1.34</td>
<td>0.35</td>
<td>5.00</td>
<td>3.16</td>
</tr>
<tr>
<td></td>
<td>S.E.</td>
<td>1.44</td>
<td>0.34</td>
<td>0.35</td>
<td>0.82</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>p1</td>
<td>&gt; 0.4</td>
<td>&gt; 0.2</td>
<td>&lt;0.02*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>mean</td>
<td>28.27</td>
<td>16.40</td>
<td>3.07</td>
<td>165.44</td>
<td>115.33</td>
</tr>
<tr>
<td></td>
<td>S.D. ±</td>
<td>5.59</td>
<td>1.00</td>
<td>2.28</td>
<td>11.25</td>
<td>5.03</td>
</tr>
<tr>
<td></td>
<td>S.E.</td>
<td>1.59</td>
<td>0.26</td>
<td>0.59</td>
<td>3.63</td>
<td>2.91</td>
</tr>
<tr>
<td></td>
<td>p1</td>
<td>&gt; 0.2</td>
<td>0.05*</td>
<td>&lt;0.02*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>p2</td>
<td>&gt; 0.2</td>
<td>0.2</td>
<td>&gt;0.3</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

S.D. : Standard Deviation
S.E. : Standard Error
P1 : Comparison between mild or Severe Groups with control
P2 : Comparison between mild & Severe Groups
* Significance

Table 1 Mean, S.D., S.E of the clinical data & Plasma ET -1 level in the 3 groups investigated
Figure 1: Scatterplot showing serum Endothelin and systolic blood pressure in Preeclampsia patients.

Figure 2: Scatterplot showing serum Endothelin & diastolic blood pressure in Preeclampsia patients.
Discussion

Hypertensive disorders complicate up to 15% of all pregnancies depending on the population studied & diagnosis. criteria adopted. It is responsible for 1/6 of the maternal deaths in England & Wales. The commonest causes of death are cerebrovascular complications, cerebral oedema, Hepatic & renal failure and cardiac failure (10).

Pre-eclampsia is a pregnancy specific hypertensive disorder and is a major cause of maternal, foetal, & neonatal mortality & morbidity (11). Its prevention requires not only knowledge of pathophysiological mechanisms of the disease but also availability of its early detection (12). The exact cause of the disease is still unknown; however, several hypotheses are described:

1. Altered endothelial function
2. Immunological hypothesis
3. Activation of neutrophils
4. Increased atrial natriuretic peptide level in plasma
5. Mitochondrial dysfunction
6. Platelet activation coagulation

The clinical signs & symptoms of pre-eclampsia, supported by experimental evidences indicate that maternal vascular endothelial cell dysfunction is an important pathogenic feature of preeclampsia (13 & 14).

There is an evidence that endothelial cell injury results in impaired synthesis of vasodilators and an increase production of vasoconstrictors which is a basic pathogenic mechanism in preeclampsia (15). ET -1 is an endothelin derived peptide. It has a potent vasoconstrictor effect. Its plasma level rises in response to endothelial cell damage. The major site of the pre-eclampsia activity of ET -1 is the renal vascular bed (16). The venous capacitance vessels are also sensitive targets of ET -1 (17). As vasospasm of the glomerular & capacitance vessels is a hemodynamic hallmark of preeclampsia, it is possible that ET -1 may play an important role in the pathophysiology of the disease.

The results of the present study show that circulating levels of immunoreactive ET -1 are significantly higher in preeclamptic patients than matched normal pregnant women. At term, when pregnant patients can be distinguished clinically as normal or preeclamptic, plasma ET -1 levels correlate with high level of significance with both systolic & diastolic pressures. These results are consistent with the report of Roberts et al (18). Thus, we can suggest that ET -1 shares in the pathophysiology of the disease through its very potent vasoconstrictor action.

Increased plasma ET -1 levels have been reported in uraemic patients (19 & 20), but the levels were not correlated with blood urea nitrogen, or creatinine levels. Elevated ET -1 levels in the blood were also noted in patients with septic shock (21), acute myocardial infarction (22) and preoperatively (23).
Vascular endothelial cell injury is a common feature in these different clinical conditions & thus it is the most likely explanation for the rise of ET-1 level. However, a trophoblastic origin in pregnancy cannot be excluded (18).

Robert et al., (18) & Schiff et al. (24) suggested that serum levels of ET-1 decrease during normal pregnancy and that preeclamptic patients were associated with levels that were significantly higher than those of normal pregnancy. However, Robert et al (18) could not demonstrate a correlation of the circulating ET-1 levels to the severity of the disorder. This may be due to the small number of preeclamptic patients in their study (only 10 patients).

The levels of ET-1 in the present study are less than those reported by Yangisawa et al (7) to elicit a contractile vascular response in vitro (160 pg/ml). The lower levels of ET-1 in the plasma of preeclamptic patients in the present study compared with that reported in the in vitro studies of Yangisawa et al (7) is explained by the report of Bengui et al., (25) that preeclamptic serum may accelerate the degradation of ET-1. The authors also reported increased renal endothelin breakdown in preeclampsia.

In conclusion, the increased levels of ET-1 in preeclamptic patients together with the significant correlation between its levels and both systolic and diastolic blood pressures suggest that ET-1 may share in the pathogenesis of preeclampsia and in the severity of the disease through its very potent vasoconstrictor action.

REFERENCES


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Egyptian Society of Obstetrics & Gynaecology


Resolution Accepted by FIGO General Assembly, Montreal, Canada 1994

FEMALE GENERAL MUTILATION

The FIGO General Assembly.

CONSIDERING that Female Genital Mutilation (Female circumcision) is a harmful traditional practice which is still prevalent in over 30 countries of the world, including areas of Africa, Asia and the Middle East.

CONCERNED: about the serious adverse effects of this practice on the human rights, as harmful procedure performed on a child who can not give informed consent.

RECOGNIZING: that Female Genital Mutilation is a violation of human rights, as harmful procedure performed on a child who can not give informed consent.

RECALLING: the 1994 World Health Assembly Resolution WHA 47, 10 welcoming the policy declarations to the United Nations Special Rapporteur on traditional practices by governments in countries where female genital mutilation is practiced.

— INVITES: Member Societies to:

1. URGE: their governments to ratify the Convention on the Elimination of ALL Forms of Discrimination Against Women, if they have not already done so, and to ensure the implementation of the articles of the Convention, if the Convention has already been ratified.

2. URGE: their governments to take legal and/or other measures to render this practice socially unacceptable by all sectors and groups in society.

3. COLLABORATE: with national authorities, non-governmental and inter-governmental organizations to advocate promote and support measures aiming at the elimination of female genital mutilation.

— RECOMMENDS: that obstetricians and gynaecologists:

1. EXPLAIN: the immediate dangers and long-term consequences of female genital mutilation to religious leaders, legislators and decision makers.

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2. **EDUCATE**: health professionals, community workers and teachers about this harmful traditional practice.

3. **SUPPORT**: those men and women who want to end the practice in their families or communities.

4. **ASSIST**: in research for the documentation of the prevalence of the practice and its harmful consequences.

5. **OPPOSE**: any attempt to medicalize the procedure or to allow its performance, under any circumstances in health establishments or by health professionals.
LETTER TO THE EDITOR

Dear Prof. Sammour,


I would like to comment on the article written in the October, 1996 Journal (Vol. XXII No. 4) on female circumcision.

First, physicians should listen to the Fatwas of the religious scientist, they can quote it but should not issue their own.

Second, information in this article represents the personal opinions of the authors and not that of the Egyptian Society of Obstetrics and Gynaecology whose Board had outlined its viewpoint as regards female circumcision in a letter directed to the Egyptian Medical Syndicate. In this letter, the Society advised that the operation should not be performed because of its possible harmful effects.

I would not go into a scientific debate to criticize the information provided in this article, however, certain points need to be clarified:

— How can one explain to a girl aged 9 years the wrong information mentioned in the article?

— There are no references about the technique of circumcision. This operation is not taught in the medical curricula and is not part of the training in obstetrics and gynaecology. Everyone realizes the difficulties of removal of the prepuce of the clitoris particularly at that age without injury to adjacent organs. Even if this can be done, the resultant adhesions affect the physiological role of the clitoris.

— What is the use of retropubic injection of a local anesthetic while the patient is under general anesthesia? Can this obviate post-operative pain as mentioned. What are the dangers that can be encountered by that practice.

— The stated benefits of this operation has no scientific basis; on the contrary so many harms, physical, sexual and emotional can result from this practice.

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I attach the resolution that was unanimously adopted by all Societies of Gynaecology and Obstetrics all over the world during the Fourteenth World Congress of Gynaecology and Obstetrics organized by the International Federation of Gynaecology and Obstetrics (FIGO) held in Montreal, Canada in September 1994.

Prof. Ezzeldin Osman Hassan

Secretary General.

The Egyptian Society of Gynaecology and Obstetrics.