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# Evaluation of pregnancy outcome in cases of intrauterine growth restriction in relation to placenta apoptosis and doppler indices of the umbilical and uterine arteries

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***Abstract*---**Objective: To assess apoptotic changes in trophoblastic cells in normal term placentae and term placentae complicated by either preeclampsia or intrauterine growth restriction (IUGR). Additionally, we aim to examine the correlation between these apoptotic changes and the Doppler velocity of the umbilical and uterine arteries. Methods: This prospective observational study was conducted on 150 pregnant women, including 100 cases with preeclampsia and 50 controls. Placentas were collected at delivery, and apoptotic changes were examined using light microscopy and immunohistochemical staining. Doppler velocimetries were performed to assess umbilical and uterine artery resistance indices. Pregnancy outcomes and neonatal data were recorded. Results: The incidence of apoptosis in placentae was significantly higher in the preeclampsia group compared to the control group ($p<0.001$). The umbilical and uterine resistance indices were also significantly higher in the preeclampsia group ($p<0.001$). There was a positive correlation between the incidence of apoptosis and Doppler resistance indices in the preeclampsia group. Fetal birth weight, Apgar scores at 1 and 5 minutes, and gestational age at delivery were significantly lower in the

preeclampsia group (p<0.001). Conclusions: Increased placental apoptosis and abnormal Doppler indices are associated with preeclampsia and adverse pregnancy outcomes. The findings suggest that placental apoptosis may contribute to impaired placental blood flow and compromised fetal well-being in preeclampsia. Early detection and management of pre-eclampsia are crucial to optimize pregnancy outcomes.

***Keywords*---**Apoptosis, Preeclampsia, Intrauterine Growth Restriction, Doppler Indices, Placenta.

## Introduction

In primigravidae, the incidence of preeclampsia ranged from 3.5% to 7.7%. In the same study, preeclampsia in multiparae occurred at a rate of 0.8% to 2.6%. Vasospasm, which impairs blood flow to various organs, particularly the uterus and placenta, is the primary pathological characteristic of preeclampsia [1]. Preeclampsia can be triggered solely by a placenta; no fetus is required. For instance, preeclampsia can develop from a hydatidiform mole, and it can also occur in abdominal pregnancies where a uterus may not be present. These abnormalities in placental blood flow hinder fetal oxygenation and growth. Uteroplacental ischemia is now considered to be the cause of preeclampsia [2]. Numerous clinical, biochemical, and physical tests have been developed and used for prediction, including uterine Doppler velocimetry, second-trimester serum screening, and homocysteine levels. However, none of these assays have demonstrated reliable accuracy [3].

In a study by Harrington et al., the utility of second-trimester uterine artery Doppler in predicting complications related to uteroplacental insufficiency was investigated in low-risk and high-risk multiparous women. They found that in high-risk multiparous women (those with a history of preeclampsia, gestational hypertension, stillbirth or abruption; delivered liveborn fetus with weight below the 5th centile, diabetes, and renal disease), persistent bilateral notches with a mean resistance index (RI) > 0.55 and unilateral notches with a mean RI > 0.65 at 20 weeks gestation identified the majority of women who would develop complications secondary to uteroplacental insufficiency [4]. In a 2019 study by Sezik et al., it was found that newborns with absent or reversed end-diastolic umbilical artery Doppler flow (AREDF) had an increased frequency of hypoglycemia and polycythemia [5].

Apoptosis, also known as "programmed cell death" or "cell suicide," is a fundamental biological phenomenon that can occur in various physiological and pathological conditions. Apoptosis is characterized by the condensation of nuclear heterochromatin, initially forming a crescent in opposition to the nuclear membrane and later consolidating into one or more dense masses. This can be observed using standard oil immersion light microscopy after staining cells with hematoxylin and eosin. Electron microscopy remains the most reliable method for identifying apoptosis [6].

In the human placenta, trophoblasts consist of two cell layers: cytotrophoblasts (c-cells) and syncytiotrophoblasts (s-cells). Human term placentas affected by preeclampsia or intrauterine growth retardation exhibit increased apoptosis in syncytiotrophoblasts [7]. Increased placental apoptosis may be a significant pathological event in preeclampsia and intrauterine growth restriction, leading to higher rates of placental apoptosis in preeclampsia [8].

Therefore, this study aimed to assess apoptotic changes in trophoblastic cells in normal term placentae and term placentae complicated by either preeclampsia or intrauterine growth restriction (IUGR). Additionally, we aim to examine the correlation between these apoptotic changes and the Doppler velocity of the umbilical and uterine arteries.

**Patients and Methods**

This prospective observational study was carried out on a total of 150 pregnant women, including 100 cases with preeclampsia and 50 controls who presented to the Gynecology Clinic. The study protocol was approved by the Human Research Ethics Committee of Banha Faculty of Medicine, and written informed consent was obtained from all individual patients prior to their participation. The study was done over a period of one year, from March 2020 to February 2021.

**Patient Groups**

**The study group** comprised 100 cases meeting the inclusion criteria. Preeclampsia was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, and proteinuria on catheterized urine specimen of at least 1+ on dipstick.

**The control group** consisted of 50 cases with gestational age after 34 weeks, a single viable baby, no obstetric or medical complications of pregnancy, blood pressure below 140/90 mmHg, and no proteinuria on dipstick. Participants in both groups did not receive any medication during the current pregnancy apart from tonics and iron.

**Data Collection**

**Before labor,** a detailed history was taken, and a complete physical examination was performed. Laboratory investigations included complete urine analysis, complete blood count, random blood sugar, and liver and renal function tests. Ultrasonography was conducted to estimate gestational age, fetal weight to detect any evidence of intrauterine growth retardation, and Doppler velocimetries for both umbilical and uterine arteries.

**During labor,** placentas were collected at delivery after 34 weeks of pregnancies complicated by preeclampsia and after 34 weeks of age-matched uncomplicated pregnancies. Only singleton pregnancies were studied. Placentas were sampled immediately after delivery, with samples taken randomly from apparently normal areas while avoiding obvious areas of infarction. Placental specimens for light microscopy were fixed in 10% neutral saline and processed to prepare 5 μm thick

paraffin sections for hematoxylin and eosin (H & E) stains. Placental specimens for electron microscopy were immediately fixed in 2.5% glutaraldehyde buffered with 0.1 M phosphate buffer at pH 7.4 for 2 hours at 4°C and prepared for immunohistochemical staining.

**After labor,** data on mode of delivery, neonatal outcomes, gestational age at delivery, birth weight, Apgar score at 1 and 5 minutes, and admission to the Neonatal Intensive Care Unit (NICU) were recorded.

**Statistical analysis**

The statistical analysis was performed using SPSS v25 (IBM©, Armonk, NY, USA). For quantitative parametric data, the mean and standard deviation (SD) were used to present the results. Qualitative variables were described using frequency and percentage (%), and the Chi-square test was utilized for their analysis. A two-tailed P value of less than 0.05 was considered statistically significant, indicating a significant difference or association between variables.

**Results**

Table 1 indicates that there were no significant differences (P>0.05) in the mean values of age and parity between the preeclamptic and control groups. However, significant differences were observed in the mean values of gestational age at delivery, systolic blood pressure, and diastolic blood pressure between the preeclamptic and control groups.

Table 1: Clinical characteristics of preeclamptic and control groups

| Characters | Preeclamptic Women (N=100) | Controls (N=50) | t | P |
|---|---|---|---|---|
| ***Age (years):**<br>Range<br>M±SD | <br>21-41<br>30.1±6.1 | <br>18-41<br>28.4±6.3 | 1.56 | > 0.05<br>N.S |
| ***Parity:**<br>Range<br>M±SD | <br>0-8<br>2.7±2.2 | <br>0-5<br>2.14±1.26 | 1.89 | > 0.05<br>N.S. |
| ***Gestational age (weeks):**<br>Range<br>M±SD | <br>34-40wks<br>37.0±2.05 | <br>37-41wks<br>38.7±1.31 | 5.3 | <0.001*<br>H.S. |
| ***S.B.P (mmHg)**<br>Range<br>M±SD | <br>140-200<br>165.6±9.4 | <br>105-125<br>119.9±6.3 | 17.6 | <0.001*<br>H.S. |
| ***D.B.P. (mmHg)**<br>Range<br>M±SD | <br>90-120<br>102.7±9.4 | <br>60-85<br>74.2±7.1 | 13.7 | <0.001*<br>H.S. |

S.B.P: systolic blood pressure, D.B.P: diastolic blood pressure. S.D: standard deviation. N.S. denotes non-significant results ($p > 0.05$), while S. indicates significant findings ($p < 0.05$). H.S. indicates highly significant results ($p < 0.001$).

Table 2 demonstrates that the umbilical and uterine resistance indices were significantly higher (P<0.001) in the preeclamptic group compared to the control group.

Table 2: Comparison between the doppler findings in the control and preeclamptic groups

| Doppler indices | Preeclamptic (N=100) | Controls (N=50) | t | P |
|---|---|---|---|---|
| ***Umb.R.I.** | | | | |
| Range | 0.60-0.85 | 0.51-0.65 | 8.9 | <0.001* |
| M±SD | 0.68±0.068 | 0.58±0.046 | | H.S. |
| ***Ut.R.I.:** | | | | |
| Range | 0.50-0.83 | 0.35-0.57 | 15.2 | <0.001* |
| M±SD | 0.64±0.072 | 0.45-0.069 | | H.S. |

R.I was considered ≥ o.65, Um.R.I. = umbilical artery resistance index, Ut.R.I= uterine artery resistance index

Table 3 reveals that the incidence of apoptosis was significantly higher (P<0.001) in the preeclamptic group compared to the control group.

Table 3: Comparison between the incidence of apoptosis in preeclamptic and control groups

| | Preeclamptic | | Controls | | $X^2$ | P |
|---|---|---|---|---|---|---|
| | No =100 | % | No =50 | % | | |
| Apoptosis (%) | 51 | (51%) | 9 | (18%) | 15.1 | <0.001 S. |

Table 4 displays that the mean values of uterine artery (R.I.) according to the incidence of apoptosis in the preeclamptic group were highly significant (P<0.001). Additionally, it shows that the mean values of uterine artery (R.I.) according to the incidence of apoptosis in the control group were not significant (P>0.05). Furthermore, the mean values of umbilical artery (R.I.) according to the incidence of apoptosis in the preeclamptic group were highly significant (P<0.001). Similarly, it shows that the mean values of umbilical artery (R.I.) according to the incidence of apoptosis in the control group were not significant (P>0.05).

Table 4: Means of uterine artery and umblical artery (R.I.) according to incidence of apoptosis in preeclamptic and control groups

| Apoptosis with relation to Means of uterine artery | Preeclamptic women | | Controls | |
|---|---|---|---|---|
| | No | X±SD | No | X±SD |
| Present<br>Absent | 51<br>49 | 0.68±0.071<br>0.60±0.05 | 9<br>41 | 0.45±0.071<br>0.45±0.070 |
| t<br>P | | 6.09<br><0.001<br>H.S.* | | 0.004<br>>0.05<br>N.S. |
| Apoptosis with relation to Means of umblical artery | Preeclamptic women | | Controls | |
| | No | X±SD | No | X±SD |
| Present<br>Absent | 51<br>49 | 0.71±0.069<br>0.64±0.042 | 9<br>41 | 0.58±0.056<br>0.58±0.045 |
| t<br>p | | 6.18<br><0.001<br>H.S.* | | 0.06<br>>0.05<br>N.S. |

Table 5 illustrates that fetal birth weight was significantly lower (P<0.001) in the preeclamptic group compared to the control group. Additionally, it demonstrates that the Apgar score at 1 minute was significantly lower in the preeclamptic group compared to the control group. Similarly, it shows that the Apgar score at 5 minutes was significantly lower in the preeclamptic group compared to the control group.

Table 5: Comparison between the preeclamptic and control groups according to the fetal outcome

| Fetal outcome | Preeclamptic (N=100) | Controls (N=50) | t | P |
|---|---|---|---|---|
| *** Fetal weight (Kg)**<br>Range<br>M±SD | <br>2.3-3.8<br>3.1±0.45 | <br>2.9-3.9<br>3.31±0.28 | t=2.8 | <0.001*<br>H.S. |
| ***Apgar score (1min)**<br>No (%)<br>7-10<br>4-6<br><4 | <br><br>52 (25%)<br>47 (47%)<br>1 (1%) | <br><br>45 (90%)<br>5 (10%)<br>0 | $X^2$=15.9 | <0.001*<br>H.S. |
| ***Apgar score (5min)**<br>No (%)<br>7-10<br>4-6 | <br><br>95 (95%)<br>5 (5%) | <br><br>50 (100%)<br>0 | $X^2$=4.78 | <0.05<br>S. |
| **SGA** | 57 57% | - - | 16.83 | <0.001<br>HS |
| **NICU admission** | 72 72% | 2 4% | 20.71 | <0.001<br>HS |
| **Neonatal death** | 13 13% | - - | 2.7 | <0.001<br>NS |

**Discussion**

The basic pathology in preeclampsia is vasospasm, which leads to increased peripheral vascular resistance. Therefore, measuring vascular resistance reflects the degree of the pathological process in the disease [9]. In this study, Doppler flow velocity waveform analysis was performed to identify pathologic waveforms in the umbilical and uterine arteries and correlate them with the severity of preeclampsia and fetal outcome.

Apoptosis is a natural mechanism through which the body eliminates potentially dangerous cells to maintain normal tissue function. It differs from necrosis, as apoptosis is an active form of cell death that depends on the internal machinery of the cell, whereas necrosis is accidental and caused by external factors [10]. In this study, various clinical, biophysical, and histologic parameters were examined in a group of 100 pregnant women with preeclampsia and a control group of 50 healthy pregnant women. The study primarily focused on Doppler flowmetric analysis of the umbilical and uterine arteries, the incidence of placental apoptosis, and fetal outcomes, including fetal birth weight and Apgar scores at 1 and 5 minutes.

In the current study, pre-eclamptic group had a significantly higher mean value of umbilical artery resistance index (UM RI) (0.68 ± 0.068) compared to the control group (0.58 ± 0.046). In the control group, none of the 50 cases had abnormal UM RI (>0.65), while 65% of the preeclamptic group (65 out of 100 cases) exhibited abnormal UM RI. The study showed a strong negative correlation between UM RI and fetal outcome parameters, including fetal birth weight, Apgar score at 1 minute, and Apgar score at 5 minutes ($r = -0.42$, $r = -0.60$, $r = -0.53$, respectively), indicating the impact of UM RI on fetal well-being.

These correlations with fetal outcomes are consistent with the results of Harrington et al. [4]. Additionally, these results align with Sezik et al., who observed adverse neonatal outcomes in preeclampsia associated with abnormal end-diastolic flow velocity in the umbilical artery [5]. The abnormality observed in the umbilical artery Doppler waveform analysis is correlated with adverse fetal outcomes due to progressive obliteration of the vascular bed. Severe forms of abnormal umbilical resistance, such as absent end-diastolic velocity, indicate extreme placental vasculopathy, resulting in poor fetal outcomes.

These findings differ from Berkowitz et al. [11] who observed abnormal Doppler waveforms but normal fetal outcomes in a significant number of fetuses. Hanretty et al. found no correlation with fetal outcomes except for birth weight [12]. The mean value of uterine artery resistance index (UT RI) in the preeclamptic group (0.68 ± 0.068) showed a positive highly significant correlation with systolic blood pressure (S.B.P) and diastolic blood pressure (D.B.P), highlighting the importance of uterine artery Doppler velocimetry as a severity parameter in preeclampsia. Among the control group, none of the 50 cases showed abnormal UT RI (<0.65), while 62% of the cases (62 out of 100) in the preeclamptic group exhibited abnormal UT RI. These results are consistent with previous studies [13].

In normal pregnancies, trophoblastic erosion occurs in the spiral arteries during placentation, stripping their musculoelastic coat and converting them into low-resistance vessels, leading to the development of low-resistance velocity flow in the uterine arteries [14]. While the flow pattern in individual radial placental bed channels may be normal, recordings from the main uterine trunk reflect the number of such channels. In the presence of poor placental stimulation for uteroplacental vascularization, as in preeclampsia, the number of channels and the extent of the placental bed decrease, resulting in high-resistance waveforms recorded in the main uterine trunk [15].

In the present study, the mean value of gestational age at delivery in the preeclamptic group was significantly shorter than that of the control group (37.0 ± 2.05 versus 38.7 ± 1.31). This can be explained by the fact that all 100 preeclamptic patients did not go into spontaneous labor and pregnancy termination was carried out (either by induction of labor or cesarean section) for maternal or fetal benefit.

In this study, the incidence of apoptosis in placentas from women with preeclampsia (51%) was higher than in the control group (18%). Similar findings were described by Diferderico et al. [16] in a smaller study on invading cytotrophoblasts. Smith et al. reported the presence of apoptosis in placentas throughout gestation using various techniques, including light microscopy, electron microscopy, and the TUNEL method [17].

Apoptosis has been detected in the trophoblast layer of placentas from uncomplicated pregnancies throughout gestation, suggesting constant cell turnover at the site of implantation necessary for placental growth and function. Additionally, the incidence of trophoblast apoptosis is higher in third trimester placentas compared to first trimester placentas in pregnancies complicated by preeclampsia or IUGR, indicating insufficient trophoblast invasion [7]. Crocker et al. also found differences in apoptotic susceptibility between cytotrophoblasts and syncytiotrophoblasts in normal pregnancy and those complicated by preeclampsia and IUGR in the third trimester [18].

The increased incidence of placental apoptosis observed in preeclampsia and fetal growth restriction (FGR) may be a result of the pathological process leading to the development of these disorders. Abnormal trophoblast invasion is considered a triggering point in the pathogenesis of preeclampsia, as inadequate trophoblast invasion is believed to initiate placental ischemia [19,20].

Defective trophoblast invasion leads to placental hypoxia and insufficient perfusion, causing damage and dysfunction of endothelial cells and ultimately resulting in preeclampsia [20]. A study found that placental apoptosis indicates abnormal trophoblast invasion and plays a role in endometrial decidualization and trophoblast invasion [9]. Selam et al. suggested that apoptosis initiated by the binding of FAS with FAS ligand (FASL) may be involved in trophoblast invasion and implantation processes [21]. Loke et al. associated preeclampsia with superficial invasion of cytotrophoblasts and enhanced apoptosis in trophoblasts, highlighting the role of HB-EGF in regulating trophoblast invasion [22].

Immunohistochemical analysis in this study revealed reduced Bcl-2 protein expression in severe preeclampsia compared to normal term placentas. Ishihara et al. found abundant expression of Bcl-2 protein in normal term placentas, protecting syncytiotrophoblasts from apoptosis. By contrast, reduced Bcl-2 protein expression in severe preeclamptic and IUGR placentas led to increased apoptosis in syncytiotrophoblasts [23].

In this study, the clinical characteristics of each group were presented. Preeclamptic women and controls were similar in age and parity. However, preeclamptic women had significantly lower gestational age at delivery and fetal birth weight compared to controls due to early termination of pregnancy (either by cesarean section or induction of labor) or fetal growth restriction associated with preeclampsia.

Allaire et al. reported that preeclamptic women delivered infants with significantly lower birth weights compared to controls. However, preeclamptic women and controls were similar in terms of age, gestational age at delivery, parity, smoking status, and race [24].

This study has several limitations. First, the sample size was relatively small. Additionally, the reliance on Doppler flowmetric analysis and histologic parameters may overlook other molecular and genetic factors involved in preeclampsia. Moreover, the study focused primarily on the umbilical and uterine arteries, potentially overlooking the influence of maternal factors or genetic predispositions. Lastly, the lack of a more diverse population and the absence of longitudinal follow-up restrict the comprehensive understanding of the disease.

## Conclusions

The study findings indicate a correlation between elevated placental apoptosis, atypical Doppler indices, and negative pregnancy outcomes in cases of preeclampsia. These results imply that increased placental apoptosis may contribute to impaired blood flow within the placenta and pose risks to fetal well-being in preeclampsia. Consequently, the timely identification and effective management of preeclampsia are of utmost importance in order to enhance the overall outcomes of pregnancies.

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