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# Spectrum of placental changes in Toxemia of pregnancy: A case series study

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**Abstract**
**Background:** Toxemia of pregnancy is the leading cause of maternal mortality and is an important factor in fetal wastage. The incidence is high in developing countries with malnutrition, hypoproteinemia, and poor obstetric facilities.
**Objectives:** The present study was undertaken to analyze placental changes in the preeclampsia-eclampsia syndrome with a view to assess the significance of villous abnormalities by histopathological methods because these changes serve as a guide to the duration and severity of disease. Gross abnormalities noted were the placental infarcts, retroplacental hematoma, and calcification.
**Results:** The striking villous abnormalities observed in the study group were cytotrophoblastic proliferation (80%), thickening of the villous basement membranes (70%), increase in syncytial knots (82.5%), villous stromal fibrosis (72.5%), fibrinoid necrosis (77.5%), endarteritis obliterans (15%), decreased villous vascularity, and paucity of vasculosyncytial membranes (2.5%).
**Conclusions:** The gross abnormalities and villous lesions in the preeclampsia ($P<0.001$) and eclampsia syndrome ($P<0.05$) were significant.

**Keywords:** Calcification, eclampsia, infarction, preeclampsia, villous abnormalities

## Introduction
The placenta is the most accurate record of infant's prenatal experiences. Generally physicians are uncomfortable with the task of examining the placenta, but according to Benirschke [1] it is a task they should willingly undertake because submitting this organ to a knowledgeable look and touch can provide much insight into prenatal life. Toxemia of pregnancy, a multi system disorder, peculiar to pregnancy is characterised by gestational hypertension, proteninuria and activation of coagulation cascade with associated abnormalities in renal and hepatic function[9].Structural and functional derangement of placenta, evoke a considerable interest, as these may be the only yardsticks to measure adequacy of the foetal environment. Hypertensive disorders complicating pregnancy are common and form one of the deadly triads along with haemorrhage and infection, which result in large number of maternal deaths and thereof foetal deaths [2].
Maternal hypertension is diagnosed in 7% of all deliveries and is associated with 22% of all perinatal deaths and 30% of all maternal deaths [3]. In some mysterious way, in certain women, the presence of chorionic villi, with or without a foetus incites vasospasm and hypertension [4]. As a consequence of this vasospasm, villi in these placentas are subjected to a reduced maternal utero-placental blood flow [5]. Conflicting findings have been reported regarding the placental abnormalities, both gross and microscopic in hypertensive pregnancies. A number of microscopic abnormalities in the villi like decreased villous vascularity, basement membrane thickening, stromal fibrosis, cytotrophoblastic proliferation, syncytial knot formation and villous fibrinoid necrosis have been reported [6]. These are thought to represent a response, often of a compensatory nature to disturbances in blood flow. It has been emphasized that the most striking changes are cytotrophoblastic proliferation and thickening of basement membrane [7]. As the placenta is the direct link between mother and foetus, the examination of placenta gives the clear idea of what had happened with it, when it was in the mother's womb and what is going to happen with the foetus in the future. With this objective the present study was carried out. In fact there is very limited data available on the relationship between placental pathology and perinatal outcome [8].

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It was therefore, proposed to undertake a detailed study of placental histopathology in pregnancies complicated by pregnancy induced hypertension (PIH) to assess the spectrum of placental changes and to correlate these findings with the foetal outcome.

The present study was undertaken to analyze the quantitative placental changes in toxaemia of pregnancy which include mild pre-eclampsia, severe pre-eclampsia and pre-eclampsia superimposed on essential hypertension.To compare and to correlate with the severity of maternal disease, the study of placentae from uncomplicated pregnancies were taken as control.

**Material and Methods**

The present study was carried over a period of three years to undertaken to analyze placental changes in the preeclampsia-eclampsia syndrome with a view to assess the significance of villous abnormalities by histopathological methods because these changes serve as a guide to the duration and severity of disease. Gross abnormalities noted were the placental infarcts, retroplacental hematoma, and calcification. The study comprised of 50 cases clinically diagnosed as pre-eclampsia (12cases), severe pre-eclampsia (10cases), eclampsia (14cases), pre-eclamsia superimposed on essential hypertension (4cases) and normal uncomplicated pregnancies (10cases) obtained from the Department of O&G at our institution. The "study group" compised placenta of pateints having blood pressure >140/90 mmHg after 28 weeks of gestation, with or without edema, and/or proteinuria and convulsions. The "control group" comprised placentas from uncomplicated full term deliveries.

**Results**

**Table 1:** Macroscopic Placental Leisons

| Group | Placental Infraction | Calcification | Retro placental Hematoma |
|---|---|---|---|
| | | | |
| Gr.II (10) Severe PET | 9 | 3 | 5 |
| Gr.III (14) Eclampsia | 10 | 4 | 4 |
| Gr.IV (4) PET Superimposed on essential hypertension | 3 | - | 1 |
| Total(40) | 29 | 10 | 13 |
| Toxemia Cases | 72.5% | 25% | 32.5% |
| Control | 3 | 4 | - |
| 10cases | 30% | 40% | - |

**Table 2:** Microscopic Villous Variant

| Groups | Cyto proliferation | | VSM | | TBM Thickening | | Syncytial Knotting | | Stromal Fibrosis | | Fibrinoid Necrosis | | Villous Vascularity | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≤20% | ≥20% | ≤5% | >5% | ≤3% | >3% | ≤30% | >30% | ≤3% | ≥3% | ≤3% | >3% | Nor. | Hypo | Hyper |
| I(12) Mild PET | 6 | 6 | 4 | 8 | 7 | 5 | 5 | 7 | 8 | 4 | 6 | 6 | 8 | - | 4 |
| II(10) Severe PET | 2 | 8 | 8 | 2 | 3 | 7 | 2 | 8 | 2 | 8 | 2 | 8 | 6 | 1 | 3 |
| III(14) ECLAMPSIA | - | 14 | 10 | 4 | 2 | 12 | - | 14 | 1 | 13 | 1 | 13 | 10 | - | 4 |
| IV(4) Super-imposed on essential Hypertension | - | 4 | 4 | - | - | 4 | - | 4 | - | 4 | - | 4 | 2 | - | 2 |
| Total(40) | 8 | 32 | 26 | 14 | 12 | 28 | 7 | 33 | 11 | 29 | 9 | 31 | 26 | 1 | 13 |
| | 20% | 80% | 65% | 35% | 30% | 70% | 17.5% | 82.5% | 27.5% | 72.5% | 22.5% | 77.5% | 65% | 2.5% | 32.5% |
| Control | 10 | - | - | 10 | 2 | - | 8 | 2 | 8 | 2 | 8 | 2 | 8 | - | 2 |
| (10) | 100% | - | - | 100% | 20% | 0% | 80% | 20% | 80% | 20% | 80% | 20% | 80% | - | 20% |

**Table 3:** Statistical analysis of counts of villous variants in placenta

| Grades of Toxaemia | | Cyto. Prol. | VSM | TBM Thickening | Syncytial Knotting | Stromal Fibrosis | Fibrinoid Necrosis |
|---|---|---|---|---|---|---|---|
| Gr.I(12) | Range% | 14-40% | 5-22% | 1-5% | 20-50% | 1-5% | 2-6% |
| | Mean±SD | 25.4±9.12 | 12±6.71 | 3.4±1.24 | 37.5±10.9 | 3.08±1.24 | 3.8±1.46 |
| Gr.II(10) | Range% | 18-60% | 4-10% | 2-12% | 22-70% | 5-14% | 2-16% |
| | Mean±SD | 44.3±14.62 | 5.1±1.6 | 6.5±3.4 | 45.7±16.06 | 8.7±3.26 | 10.0±4.47 |
| Gr.III(14) | Range% | 25-70% | 2-15% | 2-15% | 35-70% | 3-20% | 2-20% |
| | Mean±SD | 48.5± | 5.8±3.81 | 7.7±3.85 | 52.6±13.65 | 14.1±5.21 | 12.07±5.49 |
| Gr.IV(4) | Range% | 30-47% | 2-4% | 7-30% | 50-70% | 5-10% | 6-20% |
| | Mean±SD | 38.5±8.73 | 2.9±0.95 | 18.0±9.62 | 60±18.16 | 8±2.4 | 12.9±6.07 |
| Control(10) | Range% | 5-20% | 20-40% | 1-30% | 10-35% | 1-5% | 1-5% |
| | Mean±SD | 9.5±4.32 | 30±5.7 | 1.7±1.15 | 21.8±7.96 | 1.9±1.52 | 2±1.69 |

**Table 4:** Significance of the result

| Grades of toxemia | Cyto Prol. | VSM | TBM Thickening | Syncytial Knotting | Stromal Fibrosis | Fibrinoid Necrosis |
|---|---|---|---|---|---|---|
| Gr.I Mild PET | $P<0.001$ | $P<0.001$ | $P<0.01$ | $P<0.001$ | $P>0.05$(NS) | $P<0.05$(SS) |
| Gr. II Severe PET | $P<0.001$ | $P<0.001$ | $P<0.001$ | $P<0.001$ | $P<0.001$ | $P<0.001$ |
| Gr.III Eclampsia | $P<0.001$ | $P<0.001$ | $P<0.001$ | $P<0.001$ | $P<0.001$ | $P<0.001$ |
| Gr IVPET Superimposed on essential Hypertension | $P<0.001$ | $P<0.001$ | $P<0.001$ | $P<0.001$ | $P<0.001$ | $P<0.05$(SS) |

NS       - Not Significant
$P<0.05$     - Statistically Significant (SS)
$P<0.01$     - Moderately significant
$P<0.001$    - Highly significant.

## Discussion
## Pathology of placenta in pre eclampsia [10, 11, 12, 13].
### Gross abnormalities of the placenta
Placentas from pre eclamptic women tend, on average to be smaller than those from uncomplicated pregnancies, but the decrease is only slight and a proportion of such placentae are unusually large. The feto placental ratio is generally decreased.

The incidence of placental infarction ranges from about 33% in cases of mild pre-eclampsia to approximately 60% in patients with severe form of the disease.

Extensive infarction (involving more than 10% of the parenchyma) is found in about 30% of placentae from cases of severe pre eclampsia, but not a feature of the milder forms of this disease.

A fresh placental infarct is well demarcated, dark red and moderately firm. As the infarct ages, it becomes progressively hard and its colour changes successively to brown yellow and white. An old infarct thus appears as a hard white plaque, with a smooth or slightly granular, amorphous cut surface.

Histologically, the early infarct is characterized by aggregation of villi in the affected area, with marked narrowing and often obliteration of the intervillous space. As the infarct ages, the syncytial nuclei eventually disappear and there is a progressive coagulative necrosis of the villi. The fetal erythrocytes trapped in the vessels of the infarcted villi, undergo heamolysis and the endothelium of these vessels degenerates. The old infarct simply consists of crowded ghost villi, without any fibrosis or cytotrophoblastic proliferation.

Infarction is the dramatic and easily recognized visible sign of maternal uterop lacental vascular insufficiency. Infarcts are more significant when they are central and greater than 3 cm in greatest dimension. Infarction is associated with significant perinatal mortality and morbidity, including IUD, fetal hypoxia, and neonatal mortality and morbidity.

Thus extensive infarction occurs only against a background of markedly abnormal maternal vasculature and a restricted maternal blood flow to the placenta and it is these factors, rather than the loss villi due to infarction, which are the real cause of the fetal complications. The true significance of extensive placental infarction is therefore that it is the visible hallmark of a severely compromised circulation to the placenta.

### Retro Placental Hematoma
Retroplacental hemotomas are found unduly frequently, occurring in about 12-15% all cases.This is a hematoma which is in between and separates the basal plate of the placenta and the uterine wall. It is apparent on the maternal aspect of the placenta and bulges up towards the fetal surface. An old hematoma is firmly adherent to the placenta and although a fresh one may become detached during delivery, it has a characteristic crater like depression on the maternal surface.They are found in approximately 5% of all placentas. Large lesions, in which 40% or more of the villous population is acutely deprived of the blood supply, are associated with high incidence of fetal hypoxia, death.Sub amniotic hematoma, Marginal hematoma, Massive sub chorial thrombosis, intervillous thrombosis are of not much clinical significance.

### Miscellaneous Macroscopic Abnormalities
These include subchorionic fibrin plaques, septal cysts and grossly visible calcification. Placental calcification, often regarded as evidence of either placental senescence or degeneration is of no pathological or clinical importance and not associated with any fetal complication.

### Histological abnormalities of the placenta
### Intervillous Fibrin Deposition
Some degree of fibrin deposition around villi occur in almost all placentas but in a proportion is sufficiently more to be macroscopically visible. It is seen either as a firm white plaque, often but not invariably in the marginal angle or as an area of irregular whitish mottling.

Histologically these lesions consist of widely separated villi entrapped in fibrin which fills in and obliterates the intervillous space. The syncytiotrophoblast of the entrapped villi degenerates and disappears but the villous cytotrophoblast persists and may proliferate not only to form a cellular mantle around individual villi but also to spread out into the surrounding fibrin. The stroma of the included villi becomes markedly fibrotic while their fetal vessels undergo sclerosis and eventual obliteration. There can be little doubt that fibrin deposition occurs as a result of turbulence, eddy currents and stasis of maternal blood within the intervillous space.

The outstanding significance of perivillous fibrin plaques is that, the placenta can withstand the loss of 30% of its functioning villous population without any evidence of physiological embarrassment. Very occasionally, however, there is a truly massive perivillous deposition of fibrin with 80-90% of the villous parenchyma being incorporated into fibrinous masses, the placenta can clearly not withstand a loss of villous tissue of this magnitude and very exceptionally fetal death can ensure from perivillous fibrin deposition of this degree.

### Clubbing of chorionic villi
### Accelarated villous maturation
Completely mature villi are found in a small proportion of placenta from immature, prematurely delivered infants and this form of feto-placental asynchrony is known as maturitas praecox placentae. Accelarated maturation is described in placenta from women with preeclampsia. This has been thought as compensatory mechanism to counter the effects of an inadequate uteroplacental blood flow.

Excessive number of syncytial knots: (Tenny Parker change):

Syncytial knots are focal clumps of syncytial nuclei that protrude into the intervillous space from the surface of the villi. Syncytial knots start appearing in the later stages of pregnancy and their number increases until term, at which time, knots are normally present on between 11 to 30% of the villi. Formation of knots on more than a third of the villi is considered excessive. They are most frequent at the periphery of cotyledons. Excessive formation of syncytial knots is a feature of placenta from pregnancies complicated by preeclampsia. They are formed due to the reduced fetal perfusion. In preeclampsia the tendency towards an increased formation of knots, is a consequence of the obliterative changes in the fetal stem arteries which are a characteristic feature of such placentas.

### End Artery Changes
The terminal villi of the mature placenta usually contain between two and six capillary vessels, which are sinusoidally dilated so as to occupy most of the cross sectional area of the villus. Three possible deviations from this norm can be envisaged, namely avascularity, hypovascularity and hypervascularity.

Avascular villi is noted in placenta from babies of low birth weight, this occurs as a consequence of fetal artery thrombosis.

The term villous hypovascularity indicates that the vessels present are small and non dilated vessels of this type are a

characteristic, defining feature of the immature villus and hence villous hypovascularity in the term placenta may be simply one facet of a delay in villous maturation. Diminished vascularity in mature villi is often secondary to an obstructive lesion of the fetal stem arteries such as a thrombus, an obliterative endarteritis or a fibromuscular sclerosis.

## Obliterative Endarteritis

There is a marked increase in the incidence of obliterative endarteritis in placenta from women with pre-eclampsia, there appears to be a direct relationship between the severity of the complicating hypertension and incidence of obliterative endarteritis.

In placenta from hypertensive women the vascular changes may represent a reactive change to an altered haemodynamic state which occurs in the fetal circulation as a response to uteroplacental ischemia. Constriction of the fetal stem arteries is an indirect response to diminished maternal uteroplacental blood flow and is part of an attempt by the deprived fetus to divert blood to the cerebral and coronary circulation.

## Hydropic changes of villi

The only abnormality of the trophoblastic basement membrane recognizable on light microscopy is increase in its thickness which is best appreciated when stained with PAS. Occasional villi with a thickened trophoblastic basement membrane are found in about one third of term placentas. A striking increase in the proportion of villi with unduly thick trophoblastic basement membrane is common feature in placenta from women with pre eclampsia. Fetuses whose placenta contain a marked excess of villi with abnormally thick trophoblastic basement membranes have a much higher incidence of clinical hypoxia than do those in which these changes are absent. The high incidence of fetal hypoxia found in association with this abnormality is due, not to basement membrane changes but to the ischemia, which is responsible both for the histological changes and fetal complications.

## Villous Oedema

It has been widely appreciated that villous oedema may also be found in placenta from women with pre-eclampsia.The cause of villous oedema is unknown, it has been attributed to functional insufficiency of the fetal circulation. Increased size of the oedematous villi may decrease the capacity of the intervillous space and thus limit the maternal flow through the placenta.

## Fibrinoid degeneration of villi

The first stage in the evolution of this lesio n is the appearance of a small nodule of homogeneous, acidophilic, PAS positive material at one point in the villous trophoblast. This nodule progressively enlarges as fresh fibrinoid material is laid down on its deep aspect so as to form a mass which gradually bulges into and compresses the villous stroma; this process continuing until the whole villous is converted into a fibrinoid nodule. The incidence of villous fibrinoid necrosis is found to be moderately increased in placenta from pre-eclampsia. The lesion has been variously attributed to an immunological reaction within villous tissue and to amyloid deposition, as an ageing change. The pathologist noting an excess of villi showing fibrinoid necrosis in a placenta is therefore not, at the moment in a position to arrive at any valid conclusion from this finding, though the possibility that it represents an immune attack on trophoblastic tissue cannot be totally discarded and should be borne in mind.
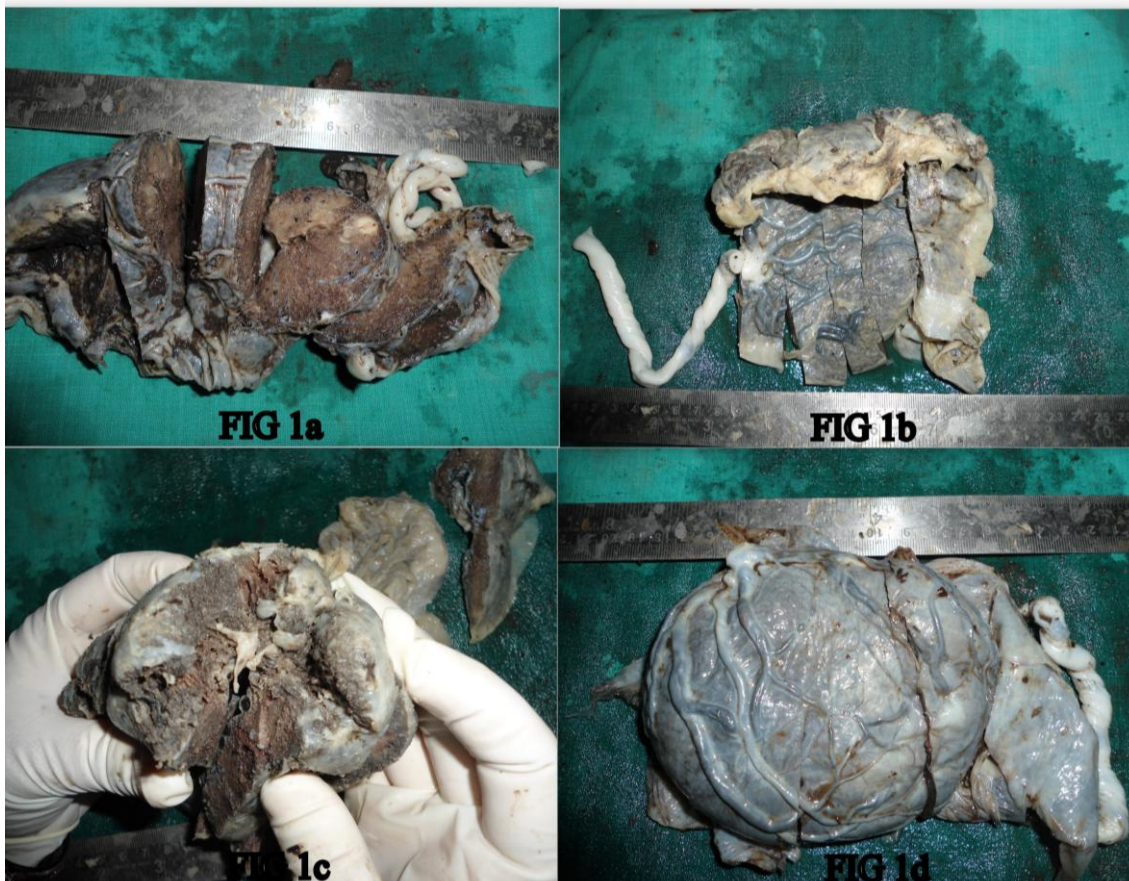


**Fig 1:** Gross Photograph of placenta showing (a) retroplacental haematoma, (b) eclamptic placenta, (c) placental infarction, (d) surface showing engorged vessels.
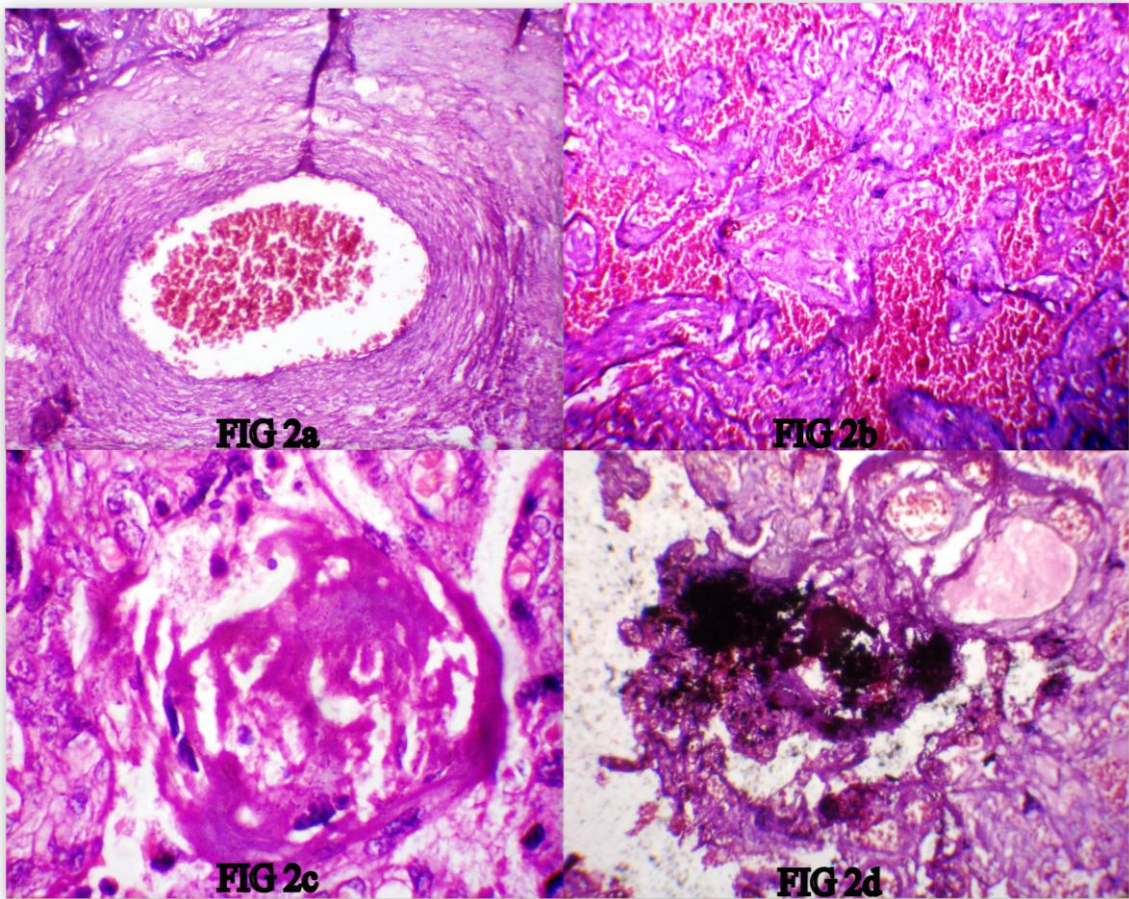
**Fig 2:** Microphotograph of villi showing (a) Obliterative endarteritis of fetal stem artery, (b) Extensive hemorrhage (c) Fibrinoid Necrosis (d) Calcification. H&E X40.
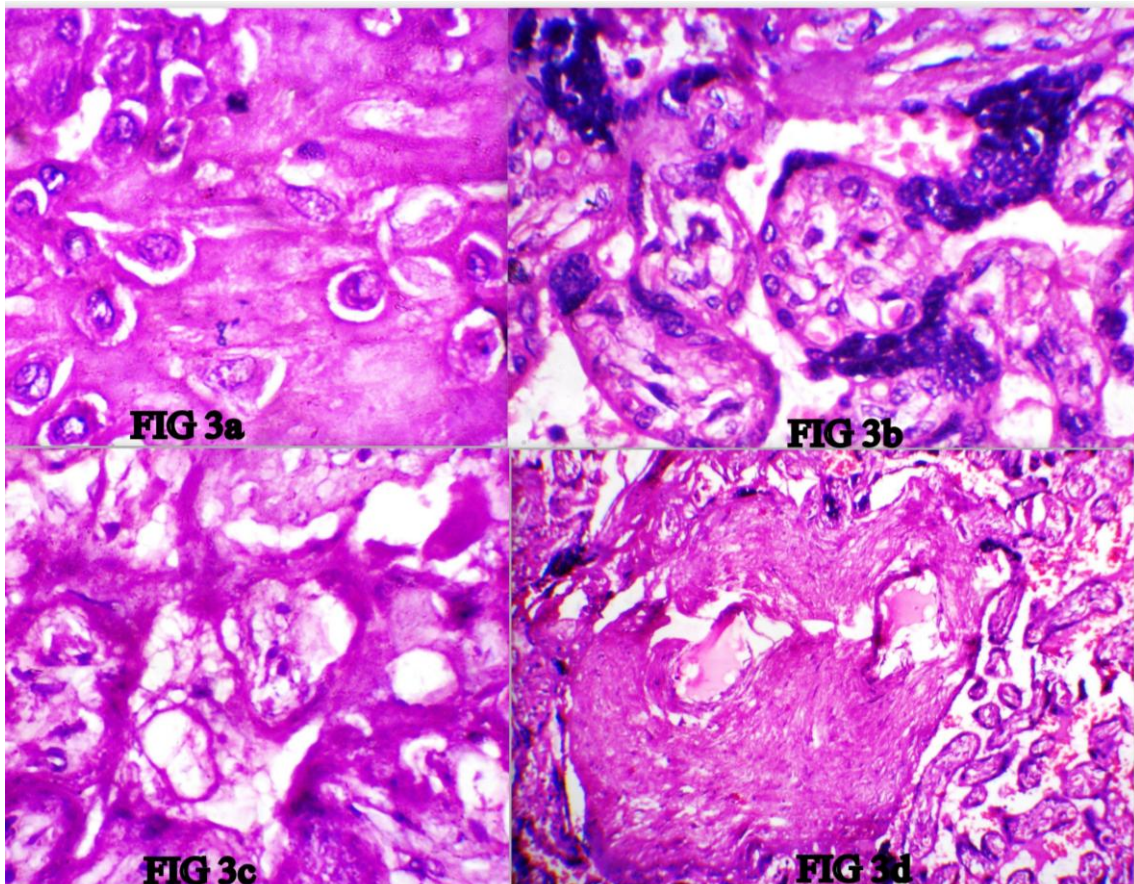


**Fig 3:** Microphotograph showing (a)extra-villous cytotrophoblastic cells (X-Cells), (b) prominent syncytial knotting, (c) Thickening of Trophoblastic basement membrane, (d) stromal fibrosis. H&E X 40.

**Conclusion**

In the present study of placental pathology, the incidence of infarction, calcification, intervillous thrombus, and perivillous fibrin deposit was high in toxemia of a pregnancy as compared to normal.

The striking villous lesions seen in placentas were from cases of the preeclampsia-eclampsia syndrome, and correlating well with the increasing severity of the toxemic process were cytotrophoblastic cell proliferation, increased syncytial knot formation, stromal fibrosis, altered villous vascularity (hypovascularity), paucity of vasculosyncytial membranes, and endarteritis obliterans. Basement membrane thickening, fibrinoid necrosis, and intervillous hemorrhage were significantly increased in toxemia of a pregnancy. These changes can be attributed to the reduced uteroplacental blood flow which occurs in toxemic cases.

To conclude, the gross abnormalities and villous lesions in the preeclampsia-eclampsia syndrome were significant ($P<0.001$ and $P<0.05$, respectively). Further studies have to be undertaken to ascertain the statistical significance of microscopic villous abnormalities among eclamptic patients.

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