ORIGINAL ARTICLE

Spectrum of changes in placenta in toxemia of pregnancy

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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 (86%), thickening of the villous basement membranes (95.23%), increase in syncytial knots (90.4%), villous stromal fibrosis (92%), fibrinoid necrosis (97.82%), endarteritis obliterans (53.96%), decreased villous vascularity, and paucity of vasculosyncytial membranes (93.65%). **Conclusions:** The gross abnormalities and villous lesions in the preeclampsia ($P < 0.001$) and eclampsia syndrome ($P < 0.05$) were significant.

KEY WORDS: Calcification, eclampsia, infarction, preeclampsia, villous abnormalities

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INTRODUCTION

Placenta is a unique and wonderful organ that arises de novo, directly related to the growth and development of the fetus in the uterus. Being an organ of vital importance for the continuation of a pregnancy and fetal nutrition, it has evoked great interest among the pathologists and the obstetricians as well, and much work has been done to understand the "unique biological status" of this complex organ.[1]

Irrespective of size and dimensions, few obstacles have yet proved unsurmountable before man's indomitable will and persistence. It is this hope alone which sustains our constant efforts to study the mysterious structure of the placenta, and every study, no matter how small contributes toward this goal.[2]

The hypertensive disorders complicating a pregnancy are quite common.

In India, the incidence of preeclampsia is 1.5%. In all earlier studies, gross abnormalities of placenta have received undue attention and undeserved status. Recently, morphological changes in the chorionic villi have proven a relationship between placental pathology and fetal well-being.[3]

The present study was undertaken to correlate the gross and villous abnormalities of placenta with the severity of toxemia of a pregnancy as well as to compare the incidence of villous abnormalities of placenta in the preeclampsia- eclampsia syndrome with that of normal pregnancies.

MATERIALS AND METHODS

The study comprised of 100 cases obtained from the Department of Obstetrics at our institution. Thirty-seven placentas from uncomplicated full term deliveries formed the "control group." Sixty-three placentas from toxemia of pregnancies formed the "study group." Toxemia of pregnancies were divided into mild, severe preeclampsia, and eclampsia based on the level of blood pressure >140/90 mmHg after 28 weeks of gestation, with or without edema, and/or proteinuria and convulsions.

The cases were divided into four groups, namely, control (group I), mild preeclampsia (group II), severe preeclampsia (group III), and eclampsia (group IV). The collected placentas were drained completely of blood, washed, weighed before formalin fixation, and after trimming cord and membranes,

examined for gross abnormalities. The gross abnormalities were quantified using semiquantitative methods as "absent" when no visible lesion was noticed, "+" when gross lesions were focally distributed, and "++" when the lesions were extensive. Infarction and perivillous fibrin deposits were quantified based on the surface area of involvement. These were further confirmed by histology. Two sections each from central and peripheral areas were taken. Additional sections were taken from grossly abnormal lesions. Sections were stained with the hematoxylin and eosin (H and E) stain. One hundred villi were counted from each of the four sections obtained and histological changes expressed as percentage. In addition, depending on the need, special stains like periodic acid Schiff (PAS), Van Geison, phosphotungstic acid hematoxylin (PTAH), and Masson's trichrome stains were used to highlight the membrane abnormalities and elastic tissue.

Statistical Analysis

The incidence of various gross and histological features was compared with that of normal pregnancies by using the unpaired-type Student '*t*' test.

Observations

The present study included 100 placentae of both control and study groups. The number of placentae in each of the four groups were 37 (group I), 27 (group II), 27 (group III), and 9 (group IV). This study included women with an age group of 20-35 years. Both primigravida and multipara were considered for the study. The placentae from severe pre-eclampsia weighed < 500 g, the least weight recorded being 150 g, whereas the placentae from normal pregnancies weighed >500 g, the heaviest being 800 g in the present study.

Gross features in the present study among various groups are compared in Table 1.

The diameter of the placenta was less in eclamptic patients. The cord length ranged from 17 to 55 cm. True and false knots and thrombosis of the cord were seen occasionally in severe preeclampsia whereas cord hematoma and thrombosis of fetal stem vessels were seen in eclamptic patients. Majority of the placentae were round, the incidence of bilobed placenta (placenta succenturiate) being 1% in the present study. The placentae from eclampsia are small in size when compared to normal placentae. The commonest mode of insertion of the umbilical cord into the placenta was central (57%), followed by eccentric (37%), and battledore insertion (6%) being the least common. Velamentous or membranous insertion was not observed in the present study.

Gross macroscopic lesions are highlighted in Table 2.

Subchorionic fibrin deposit 6 (16.2%) [Figure 1a] and calcification 23 (62.16%) were seen in a higher frequency in group I (normal controls) when compared to toxemic cases. The incidence of infarction 21 (77.7%) [Figure 1b], intervillous thrombus 17 (62.96%) [Figure 1c], and perivillous fibrin 20 (74%) [Figure 1d] was higher in group III (severe preeclampsia) followed by group IV (eclampsia).

Villous abnormalities in the present study among various groups are compared in Tables 3 and 4.

PAS highlighted basement membrane thickening and fibrinoid necrosis. Villous stromal fibrosis was highlighted using Van Vieson and Masson's trichrome stains.

Statistical analysis done using the unpaired-type Student's *t*-test gave the following results:

a. Gross abnormalities in the study groups were statistically significant ($P < 0.001$) when compared to normal.
b. Villous abnormalities in the mild preeclampsia group (group II) when compared to the normal were not significant ($P > 0.01$) – this implies that there is no significant difference in villous lesions between the mild preeclampsia and normal group.
c. Villous abnormalities in the severe preeclampsia group (group III) when compared to the normal group were statistically significant ($P < 0.05$).
d. The villous abnormalities in the eclampsia group (group IV) when compared to the normal group were not significant ($P > 0.05$). This is probably due to inadequate sample size.

DISCUSSION

The placenta has been described as the mirror of the perinatal mortality. A glance at the literature reveals that the preeclampsia-eclampsia syndrome exerts its deleterious effects on the placenta.

Table 1: Gross placental features in various groups

Gross features	*Group I (37 cases) No. of cases (%)*	*Group II* (27 cases) No. of cases (%)*	*Group III* (27 cases) No. of cases (%)*	*Group IV* (9 cases) No. of cases (%)*
Average diameter and placental thickness (cm)	20 × 17 × 2.5	17 × 13 × 2.5	17 × 15 × 3	15 × 14 × 2.5
Umbilical cord length				
<32 cm	15 (40.5)	16 (59. 2)	17 (62.9)	4 (44. 44)
>32 cm	22 (59.45)	11 (40.7)	10 (37)	5 (55.5)
True knots	–	–	2 (7.4)	–
False knots	–	–	2 (7.4)	–
Cord hematoma	8 (21.6)	4 (14.8)	1 (3.7)	6 (66.66)
Thrombosis of cord	–	–	2 (7.4)	–
Thrombosis of fetal stem vessels	1 (2.7)	–	1 (3.7)	5 (55.5)

**P* < 0.001 – highly significant.

Table 2: Gross placental changes in various groups

Gross features	*Group I (37 cases) No. of cases (%)*	*Group II* (27 cases) No. of cases (%)*	*Group III* (27 cases) No. of cases (%)*	*Group IV* (9 cases) No. of cases (%)*
Subchorionic fibrin deposit				
Absent	31 (83.78)	23 (85.18)	20 (74)	7 (77.7)
+	4 (10.8)	2 (7.4)	4 (14.8)	2 (22.2)
++	2 (5.4)	2 (7.4)	3 (11.1)	–
Infarction				
0–4%	8 (21.6)	–	–	–
5–9%	4 (10.8)	2 (7.4)	4 (14.8)	–
10–25%	–	3 (11.1)	6 (22.2)	1 (11.1)
>25%	–	6 (22.2)	11 (40.7)	4 (44.4)
Perivillous fibrin deposit				
0–4%	2 (5 .4)	2 (7.4)	–	–
5–9%	–	4 (14.8)	2 (7.4)	–
10–25%	–	5 (18.5)	8 (29.6)	5 (55.55)
>25%	–	3 (11.1)	10 (37)	1 (11.1)
Intervillous thrombus				
Absent	35 (94.5)	19 (70.3)	10 (37)	4 (44.4)
+	–	6 (22.2)	2 (7.4)	–
++	2 (5.4)	2 (7.4)	15 (55.5)	5 (55.5)
Calcification				
Absent	14 (37.8)	21 (77.7)	18 (66.6)	7 (77.7)
+	20 (54)	2 (7.4)	3 (11.1)	2 (22.22)
++	3 (8.10)	4 (14.8)	6 (22.2)	–
Retroplacental hematoma	–	–	5 (18.5)	2 (22.22)
Cysts	–	–	2 (7.4)	–

*$P < 0.001$ – highly significant.

Table 3: Villous lesions of the placenta in various groups

Villous lesions	*Group I (37 cases) No. of cases (%)*	*Group II* (27cases) No. of cases (%)*	*Group III** (27 cases) No. of cases (%)*	*Group IV*** (9 cases) No. of cases (%)*
Villous vascularity				
Normal	36 (97.2)	9 (33.33)	2 (7.40)	2 (22.22)
Increased	1 (2.70)	2 (7.40)	3 (11.1)	–
Decreased	–	16 (59.2)	22 (81.48)	7 (77.77)
Cytotrophoblastic proliferation				
<20%	37 (100)	9 (33.33)	–	–
20–40%	–	17 (62.96)	17 (62. 96)	–
>40%	–	1 (3.70)	10 (37)	9 (100)
Basement membrane thickening				
<3%	–	20 (74)	7 (25. 92)	–
>3%	–	4 (14.8)	20 (74)	9 (100)
Vasculosyncytial membrane				
<6%	–	23 (85.1)	27 (100)	9 (100)
6–30%	12 (32.43)	2 (7.40)	–	–
>30%	10 (27)	–	–	–
Endarteritis obliterans	–	4 (14.8)	21 (77.77)	9 (100)

*$P > 0.01$ – not significant. **$P < 0.05$ – statistically significant. ***$P > 0.05$ – not significant.

So, 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.

In the present study, the average weight of the normal placenta was 500 g and the weight was < 500 g in mild and severe cases of preeclampsia, the lowest recorded weight being 150 g. Mallik *et al.*[4] have reported five cases of toxemia with the placental weight less than 300 g. Nobis and Das[1] in their study have shown that the placental weight in toxemic cases varies from 279 to 407 g. Bhatia *et al.*[5] in their study have shown reduced placental weights in severe toxemia, the lowest weight recorded being 280 g.

The gross lesions of the placenta have attracted undue attention in the past.

The overall incidence of subchorionic fibrin deposit was 11% in controls as compared 20% in a study by Fox[6] and 9.52% in

Table 4: Villous lesions of the placenta in various groups

Villous lesions	*Group I (37 cases) No. of cases (%)*	*Group II* (27 cases) No. of cases (%)*	*Group III** (27 cases) No. of cases (%)*	*Group IV*** (9 cases) No. of cases (%)*
Syncytial knots				
<30%	20 (54)	6 (22.22)	–	–
30–50%	17 (45.9)	19 (70.3)	15 (55.55)	–
>50%	–	2 (7.40)	11 (40.7)	3 (33.33)
>90%	–	–	1 (3.70)	6 (66.66)
Villous stromal fibrosis				
<6%	30 (81)	17 (62.9)	4 (14.8)	1 (11.1)
>6%	–	6 (22.22)	22 (81.48)	8 (88.88)
Fibrinoid necrosis				
<3%	23 (62.1)	15 (55.55)	–	–
>3%	11 (29.72)	10 (37)	25 (92.5)	6 (66.66)
>10%	–	–	2 (7.40)	3 (33.33)
Intervillous hemorrhage	–	4 (14.8)	12 (44.44)	4 (44.44)
X-cells of Wilkin	6 (16.2)	6 (22.22)	12 (44.44)	2 (22.22)

*P > 0.01 – not significant. **P < 0.05 – statistically significant. ***P > 0.05 – not significant.

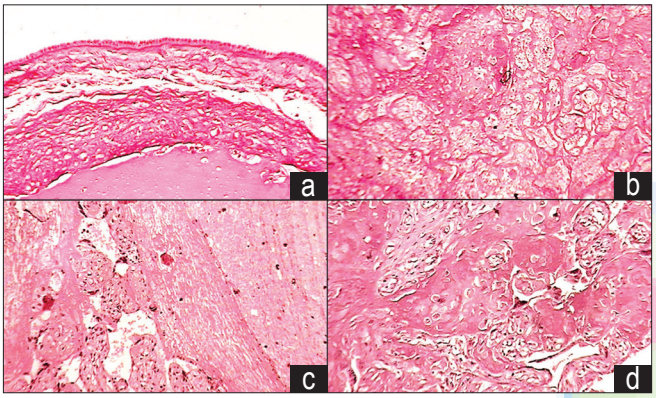

Figure 1: Photomicrograph showing (a) a chorionic plate with subchorionic fibrin deposition; (b) ghost-like appearance of villi in an old infarct with crowding of villi and obliteration of intervillous space; (c) aging intervillous thrombus with linear streaks of fibrin and degenerated red blood cells (H and E, ×100); (d) villi encased in perivillous fibrin deposits (H and E, ×450)

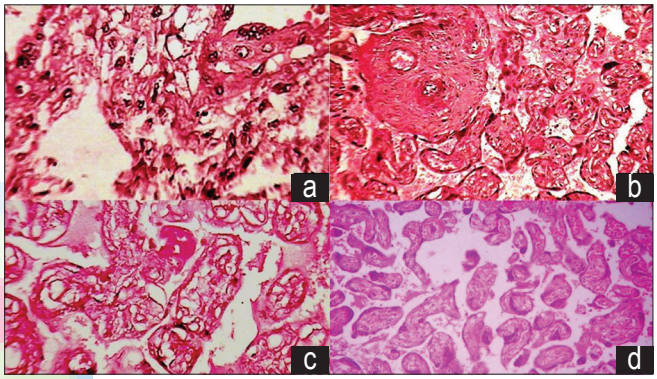

Figure 2: Photomicrograph of villi showing (a) cytotrophoblastic proliferation (H and E, ×600); (b) villous stalk showing obliterative endarteritis and stromal fibrosis (H and E, ×100); (c) markedly thickened trophoblastic basement membrane (PAS, ×200); (d) increased syncytial knots (H and E, ×100)

toxemic cases. This is due to stasis of the maternal blood in the subchorionic area of the intervillous space.[7]

Placental infarction of more than 5% surface area is considered pathological and more frequently seen in toxemia due to thrombotic occlusion of maternal uteroplacental vessels.[8] Infarction was seen in 41% of our cases in comparison with Mirchandani *et al*'s 37%[9] and Masodkar *et al.*'s 40.4%.[10]

The incidence of calcification in normal placenta in the present study was 62.1%. In toxemic cases, the overall incidence was 26.9%, 22.2% in mild preeclampsia and slightly higher (33.3%) in severe preeclampsia. Calcification is regarded as evidence of placental senescence or degeneration.[7] Cysts were noted in two cases of placentae from patients with severe preeclampsia in the subchorionic area as compared to the study of Nobis and Das[1] who found multiple chorionic cysts in two cases.

In the present study, the incidence of retroplacental hematoma

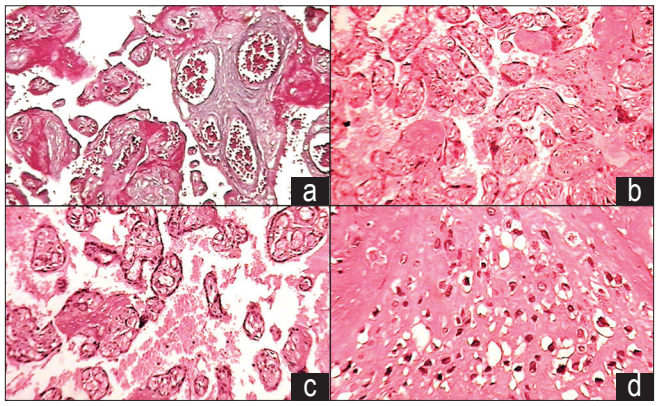

Figure 3: Photomicrograph of villi showing (a) stromal fibrosis (Masson's trichrome, ×200); (b) fibrinoid necrosis; (c) intervillous hemorrhage (H and E, ×100); (d) extra-villous cytotrophoblastic cells (X-cells) in the fibrinoid material of the basal plate (H and E, ×450)

(11.1%), calcification (26.9%), infarction (41.3%), intervillous thrombus (47.6%), and perivillous fibrin (63.49%) was observed in toxemic cases.

Wide spectrums of villous lesions were observed in toxemic cases in our study. The villous lesions were attributed to the decreased maternal uteroplacental blood flow in preeclampsia due to maternal vasospasm as proposed by Browne and Veall:[11]

a. Villous vascularity – hypovascular villi were observed in cases with severe preeclampsia (81.48%) and eclampsia (77.77%) as evidenced by Syed[2] and Kalra *et al.*[3]
b. Cytotrophoblastic proliferation – all the cases of the control group fell within the normal range of villi containing cytotrophoblastic cells (<20%); while 86% of cases of the study group had high villous counts of these cells, the rise in counts accompanied the increasing severity of the toxemic process [Figure 2a].
c. Endarteritis obliterans – is seen in placentae from patients with preeclampsia and eclampsia. In the present study, the incidence of endarteritis obliterans was 53.96% [Figure 2b]. Similar findings were observed by Kalra[3] and Davey.[12]
d. Paucity of the vasculosyncytial membrane is an index of fetal hypoxia. The incidence of vasculosyncytial membrane deficiency (<6%) was 93.65% in the study group, while none of the controls showed this abnormality. The paucity of the vasculosyncytial membrane was seen in higher grades of toxemia correlating with the severity of the disease.
e. Basement membrane thickening – the incidence of villi showing a thickened basement membrane more than 3% of the villous population is regarded as abnormal and is a common feature of placentae from toxemia. None of the placentae from the control group showed undue basement membrane thickening, while the incidence of basement membrane thickening in the present study is 95.23% [Figure 2c]. Basement membrane thickening is the byproduct of cytotrophoblast cell hyperplasia as the basement membrane protein is secreted by these cells. These findings concurred with those of other authors.[8,10,13]
f. Syncytial knots – they are seen with increased frequency in last weeks of pregnancy and more villi show these changes in toxemia.[4,9,14] It is an indication of excessive aging due to either postmaturity or a disease state causing placental insufficiency.[2] Syncytial knots were seen in all the placentas from the control group while the increased incidence of syncytial knots in toxemic cases in the present study was 90.47% [Figure 2d].
g. Villous stromal fibrosis – 81% placentae from controls and 92% cases of toxemia were fibrotic [Figure 3a]. There was an increased incidence of fibrotic placentae in pregnancies complicated by preeclamptic toxemia as studied by Fox,[15] Salvatore,[16] and Mehrotra *et al.*[17] The two factors responsible for the formation of stromal fibrosis are a normal aging process and a reduced uteroplacental blood flow.[2]
h. Fibrinoid necrosis – significant villous fibrinoid necrosis was noted in 97.82% cases of the preeclampsia-eclampsia syndrome of varying grades and equally often in cases of uncomplicated gestations (91%)[Figure 3b]. These findings were in accordance with those of other authors.[2,3,8,10]
i. Intervillous hemorrhages – they were observed in preeclamptic as well as eclamptic cases (44.44%) in the present study [Figure 3c].
j. X-cells of Wilkin – extra-villous cytotrophoblastic cells referred to as "X" cells of Wilkin, due to localized villous ischemia, were seen in 31.74% of toxemic cases in the present study [Figure 3d]. A similar finding was reported by Fox.[18] If the syncytiotrophoblast suffers ischemic damage, the cytotrophoblast proliferates in an attempt to replace the damaged tissue. The degree of cytotrophoblastic hyperplasia is related to the extent of syncytial damage and thus serves as a rough quantitative index of the severity of ischemia.[4]

The present study included all the cases meeting the criteria for preeclampsia and eclampsia. However, the incidence of eclampsia was low in the study population of the area where the study was conducted due to good obstetric care as most of these cases were booked cases. Hence the incidence of preeclampsia landing in eclampsia was less. The results have to be viewed with this background.

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.

REFERENCES

1. Nobis P, Das U. Placental morphology in hypertensive pregnancy. J Obstet Gynecol 1990;40:166-9.
2. Sayeed M,Chakrawarti RN, Devi PK. A comparative study of placental villous changes in normal and abnormal pregnancies. J Obstet Gynaecol India 1976;26:217-21.
3. Kalra VB, Aggarwal A, Sareen PM, Kalra R. Histopathological changes in placenta in toxaemia of pregnancy. J Obstet Gynaecol India 1985;35:86-90.
4. Mallik GB, Mirchandani JJ, Chitra S. Placenta in intrauterine growth retardation. J Obstet Gynaecol India 1979;29:805-10.
5. Bhatia A, Sharma SD, Jalnawalla SF, Sagreiya K. A comparative study of placental and fetal outcome. Indian J Pathol Microbiol 1981;24:277-83.
6. Fox H, Sebire NJ. Macroscopic abnormalities of the placenta. In: Houston M, editor. Pathology f the placenta. 3rd ed. Philadelphia:

Saunders Elsevier: 2007. p.100-3.
7. Fox H. General pathology of the placenta. In: Fox H, editor. Haines and Taylor Obstetrical and Gynecological Pathology. 4th ed. Edinburgh: Churchill Livingstone: 1995. p. 1480-2.
8. Kher AV, Zawar MP. Study of placental pathology in toxemia of pregnancy and its fetal implications. Indian J Pathol Microbiol 1981;24:245-51.
9. Mirchandani JJ, Mallik GB, Chitra S. Correlation of foetal outcome with some pathological changes of placenta. J Obstet Gynaecol India 1979;29:1131-9.
10. Masodkar AR, Kalamkar LR, Patke PS. Histopathology of placenta and its correlation with fetal outcome. J Obstet Gynaecol India 1985;35:294-7.
11. Browne JC, Veall N. The maternal blood flow in normotensive and hypertensive women. J Obstet Gynaecol Br Emp 1953;60:141-7.
12. Davey DA, Mac Gillivray I. The classification and definition of the hypertensive disorders. Am J Obstet Gynecol 1988;158:892-8.
13. Sodhi S, Mohan H, Jaiswal TS, Mohan PS, Rathee S. Placental pathology in pre-eclampsia eclampsia syndrome. Indian J Pathol Microbiol 1990;33:11-6.
14. Mirchandani JJ, Mallik GB, Chitra S. Villous fibrinoid necrosis and basement membrane thickening in toxemia of pregnancy and in intrauterine growth retardation. J Obstet Gynaecol India 1979;29:407-11.
15. Fox H. Basement membrane changes in the villi of the human placenta. J Obstet Gynaecol Br Commonw 1968;75:302-6.
16. Salvatore CA. The placenta in acute toxemia: Acomparative study. Am J Obstet Gynecol 1968;102:347-53.
17. Mehrotra VG, Mukherjee K, Pande M, Gurtu P, Mukherjee M. The histological study of placentae in normal and abnormal pregnancy. J Obstet Gynaecol India 1972;22:248-53.
18. Fox H. The villous cytotrophoblast as an index of placental ischaemia. J Obstet Gynaecol Br Common 1964;71:885-92.

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