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HISTOLOGICAL CHANGES IN PLACENTAE IN PREGNANCIES COMPLICATED BY PRE-ECLAMPSIA AND ECLAMPSIA AND CORELATION WITH FOETAL OUTCOME

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ABSTRACT

Pre eclampsia, the clinical state prior to full blown eclampsia (siezures), is one of the toxemias of pregnancy. The basic clinical definition is that it is a pregnancy specific condition of increased blood pressure accompanied by proteinuria, edema or both. Many phenomena have been investigated, but the recurring theme appears to be an abnormally low blood flow into the placenta. The present study was designed to determine the histological changes in pregnancies complicated by pregnancy induced hypertension and to correlate the changes with foetal outcome. A study of sixty placentae was done with the collaboration of Department of Obstetrics and Gynaecology, to find out the histological changes of placenta in 30 women suffering from pregnancy induced hypertension in comparison to 30 women with uncomplicated gestation. The main histological features noted were cytotrophoblastic proliferation, basement membrane thickening, vasculosyncytial membrane deficiency which correlated well with the foetal outcome. The other features noted were syncytial knot formation, fibrinoid necrosis and stromal fibrosis.

KEY WORDS

Pregnancy induced hypertension, placenta, cytotrophoblastic proliferation, basement membrane thickening

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. 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]

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.

MATERIAL AND METHODS

The present study was based on the observations made on the placentae of patients suspected to be the cases of pre-eclampsia - eclampsia syndrome. For the study, 60 placentae were selected at random from the women delivered at the Department of Obstetrics and Gynecology at Himalayan Institute of Medical Sciences, Jolly Grant, Dehradun. Thirty out of sixty placentae were from controls and thirty were from cases of PIH. The placentae were divided into four groups viz;

Group 1 – Eclampsia.
Group 2 – Moderate pre–eclampsia.
Group 3 – Mild pre–eclampsia.
Group 4 – Control group.

The criteria adopted for grouping of these cases were defined according to The International Society for the Study of Hypertension in Pregnancy Classification followed by the American College of Obstetrics and Gynecologists (ACOG)[9]. The diagnosis of

hypertension in pregnancy was made by any one of the following criteria:

1. A rise of 30 mm Hg or more in systolic blood pressure.
2. A rise of 15 mm Hg or more in diastolic blood pressure.
3. A systolic blood pressure of 140 mm Hg or more.
4. A diastolic blood pressure of 90 mm Hg or more.

These alterations in blood pressure were observed on at least two different occasions, at least six hours apart. The detailed menstrual and obstetric history and past history to exclude pre existing hypertension and diabetes mellitus was obtained. The weight of the foetus, still or live birth, presence of foetal distress, Apgar score (at 1 and 5 minutes after delivery of the entire body), sex and presence of any congenital malformation were recorded as parameters of foetal outcome.

The placentae were cut to obtain four samples of size 1cm X 1cm from each placenta, two from the peripheral part and two from the central part. The pieces were routinely processed for paraffin embedding and sectioning. The slides were stained with Haematoxylin- Eosin stain, Van Geison's stain and Periodic acid Schiff reagent. One hundred villi were examined from each of the four sections obtained from the placenta. Hence a total of 400 villi were studied from each placenta and the histological abnormalities were recorded as percentages. On examining the villi, the following features were noted viz. villous cytotrophoblastic cell proliferation, vasculosyncytial membranes, thickness of trophoblastic basement membrane, number of syncytial knots, stromal fibrosis and fibrinoid necrosis.

OBSERVATIONS AND RESULTS

Out of 30 patients of hypertensive pregnancies, there were 6 cases (20%) of eclampsia, 10 cases (33.33%) of moderate pre-eclampsia and 14 cases (46.67%) of mild pre-eclampsia. In the control group, there were 30 disease free women with uncomplicated gestations.

Cytotrophoblastic proliferation could be seen beneath the syncytiotrophoblast and external to the basement membrane as lighter stained nuclei, present in a single row (Fig 1). Cytotrophoblastic proliferation in significant percentage of villi (>20%) was observed in significantly higher proportion of cases of mild pre-eclampsia (64.29%), moderate pre-eclampsia (80%) and eclampsia (100%) as compared to controls, all of whom showed cytotrophoblastic cells in <20% of villi. The mean percentage of villi showing increased cytotrophoblastic proliferation in and mild pre-eclampsia, moderate, eclampsia and normal controls were 23.57 ± 8.05, 27.4 ± 5.62, 35.17 ± 3.19 and 11.53 ± 4.40 respectively. These observations were found to be highly statistically significant.

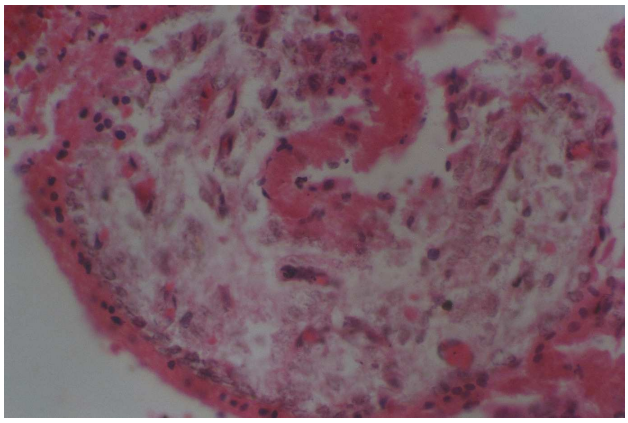

Figure 1

Cytotrophoblastic proliferation in study group (Haematoxylin and Eosin staining, 100X)

2. *Vasculosyncytial Membrane* was seen in the villous as attenuated areas of syncytiotrophoblast, which over lied and appeared to fuse with the wall of the adjacent dilated foetal capillary (Fig 2). These appeared to be deficient in the study group. Vasculosyncytial membrane in less than 5% of villi was considered significant and was observed in 5 out of 6 cases of eclampsia (3.17 ± 1.60) and 6 out of the 10 cases of moderate pre-eclampsia (5.00 ± 1.49) and in 6 out of 14 cases of mild pre-eclampsia (10.50 ± 6.05), while none of the control group of placentae (19.77 ± 6.98), showed significant vasculosyncytial membrane deficiency.

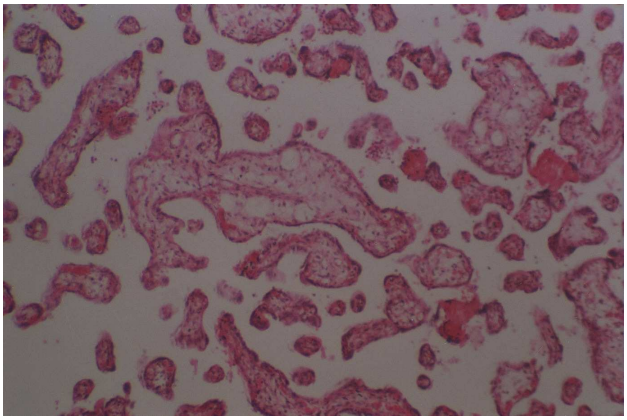

Figure 2
Vasculosyncytial membrane in control group (Haematoxylin & Eosin staining, 40X)

3) Basement membrane thickening:

The basement membrane was seen under high power in PAS stained sections as magenta coloured membrane separating the trophoblastic mantle from the mesenchymal core (Fig 3). An abnormal degree of basement membrane thickening (>3%) was observed in all the cases of eclampsia, 80% and 50% cases of moderate and mild pre-eclampsia respectively, while none of the controls revealed unusual basement membrane thickening. A direct correlation between the severity of pre-eclampsia-eclampsia syndrome and percent villi showing thickened basement membrane was observed. The mean values in mild pre-eclampsia were 3.64 ± 1.45, in moderate pre-eclampsia were 8.6 ± 3.37 and in eclampsia 12.33 ± 2.80 while in controls the mean value was 1.5 ± 0.90. There was statistically significant difference when study groups were compared with the control.

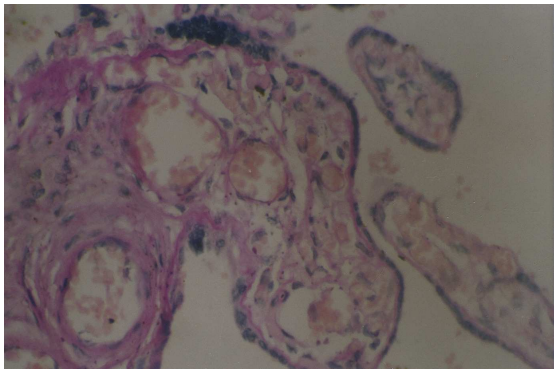

Figure 3

Basement membrane thickening in study group (PAS Staining, 100X)

4) Syncytial knots: Syncytial knots were seen as focal aggregates of syncytial nuclei forming a multinucleated protrusion from the villous surface (Fig 4). Excessive syncytial knot formation was seen in the study group. 93.33 % of the controls showed syncytial knots counts of less than 30% villi while higher percent of cases in the study group (35.71%-100%), depending upon severity of disease, revealed syncytial knot counts in excess of 30% of villi. The mean villous counts showing syncytial knot formation were found to be proportionally higher in eclampsia (54.67 ± 11.20), moderate pre-eclampsia (40.20 ± 9.78) and mild pre-eclampsia (27.36 ± 6.90) as compared to a mean value of 16.57 ± 6.52 in the controls.

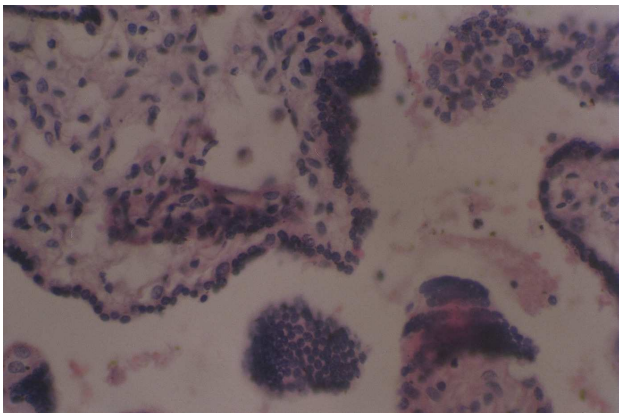

Figure 4
Excessive syncytial knotting in study group (Haematoxylin and Eosin, 100X)

5) Stromal fibrosis was observed in sections stained with Van Gieson's stain as pink coloured collagen fibers within the core of the villi (Fig 5). Stromal fibrosis in >3% of villi were observed in 85.71 to 100% of cases of hypertensive pregnancies. It was observed in 3-20% of the villi in these cases with progressively higher mean values correlating with the severity of the disease, being 18.83 ± 5.60 in eclampsia, 13.4 ± 3.20 in moderate pre-eclampsia, and 7.42 ± 2.65 in mild pre-eclampsia as compared to a mean value of 5.03 ± 2.01 in the control group.

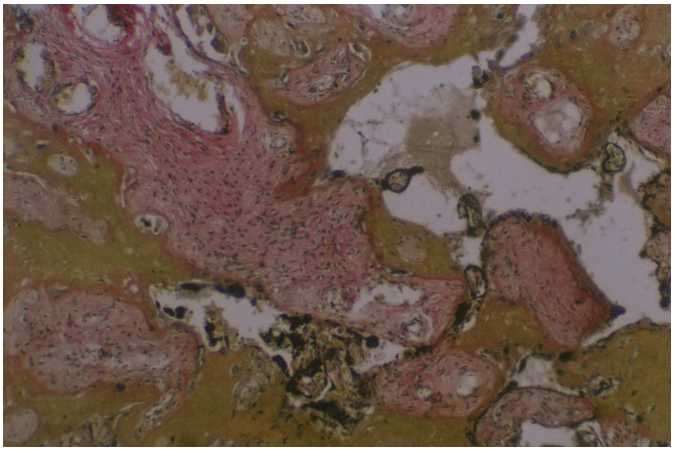

Figure 5
Stromal fibrosis seen in study group (Van Geison's stain, 40X)

Cases of eclampsia showed higher degree of stromal fibrosis of terminal villi as compared to controls and mild pre-eclampsia ($p<0.001$ each). Cases of moderate pre-eclampsia also revealed significantly more stromal fibrosis as compared to controls ($p<0.001$). However, mild pre-eclampsia cases did not show significantly different findings as compared to controls ($p<0.1$). Similarly there was significant difference in the findings between cases of eclampsia and moderate pre-eclampsia ($p<0.05$).

6) Fibrinoid necrosis

Fibrinoid necrosis was seen as small nodules of homogenous eosinophilic material within the villi. At places the fibrinoid material had enlarged pushing the basement membrane and compressing the entire villous stroma (Fig 7). Fibrinoid necrosis in 7 to 19% of villi was observed in all cases of eclampsia (mean 14.17 ± 4.36) and moderate pre-eclampsia (mean 10.8 ± 2.53), while this finding was observed in 78.57% cases of mild pre-eclampsia and 73.33% of the normal controls (mean 7.79 ± 3.33 and 5.20 ± 2.07 respectively).

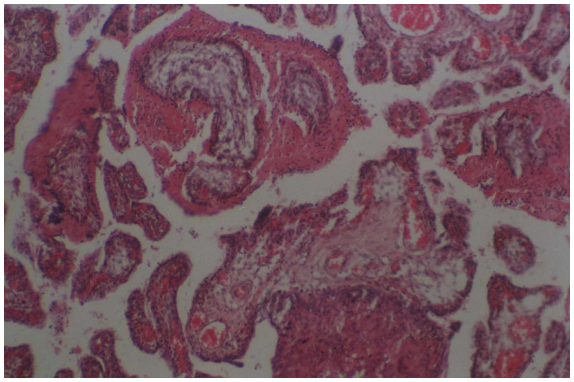

Figure 7
Fibrinoid necrosis in study group (Haematoxylin and Eosin, 40X)

Cytotrophoblastic proliferation in less than 20% villi, vasculosyncytial membrane formation in more than 5% villi and basement membrane thickening in less than 3% of villi were seen in all cases in the control group. In a majority of cases (70-80%) stromal fibrosis and fibrinoid necrosis in more than 3% of the villi were observed. Majority of the cases had syncytial knot counts in less than 30% villi and normal villous vascularity. In all the cases, there were live born babies, with an average weight 3.27kg and having normal Apgar scores.

TABLE 1
MICROSCOPIC FEATURES OF PLACENTAE IN STUDY GROUPS AND CONTROLS.

Villous variant		**Group 1 Eclampsia** N = 6	**Group 2 Mod.pre-Eclampsia** N = 10	**Group 3 Mild pre-Eclampsia** N = 14	**Group 4 Controls** N = 30
Cytotro-phoblastic Prolifer.	≤ 20%	---	2 (20%)	5 (35.71%)	30 (100%)
	>20%	6 (100%)	8 (80%)	9 (64.29%)	---
Vasculo-Syncytial Membrane	≤ 5%	5 (83.33%)	6 (60%)	6(42.86%)	--
	> 5%	1 (16.67%)	4 (40%)	8(57.14%)	30 (100%)

Basement Membrane Thickening	≤ 3%	--	2 (20%)	7 (50%)	30 (100%)
	> 3%	6 (100%)	8 (80%)	7 (50%)	--
Syncytial Knots	≤ 30%	--	1 (10%)	9(64.29%)	28(93.33%)
	> 30%	6 (100%)	9 (90%)	5(35.71%)	2(6.67%)
Stromal Fibrosis	≤ 3%	--	--	2(14.29%)	6(20%)
	> 3%	6 (100%)	10 (100%)	12(85.71%)	24(80%)
Fibrinoid Necrosis	≤ 3%	--	--	3(21.42%)	8(26.67%)
	> 3%	6 (100%)	10(100%)	11(78.57%)	22(73.33%)

TABLE 2
CORRELATION OF MICROSCOPIC PLACENTAL FOETAL CHANGES WITH FOETAL OUTCOME IN HYPERTENSIVE CASES AND CONTROLS

Villous lesion	Frequency	Foetal outcome Controls	Foetal outcome Study group
Cytotrophoblastic Proliferation	≤ 20%	28	5
	> 20	--	9
Vasculosyncytial Membrane	>5%	--	6
	≤ 5%	28	8
Basement membrane Thickening	≤ 3%	28	3
	> 3%	--	11
Syncytial Knots	≤ 30%	26	5
	> 30%	2	9
Stromal Fibrosis	≤ 3%	6	1
	> 3%	22	13
Fibrinoid Necrosis	≤ 3%	8	1
	> 3%	20	13

23 out of the 30 cases of hypertensive pregnancies had cytotrophoblastic cell proliferation and of these 8 cases (34.78%) had low birth weight, 6 (26.09%) had stillbirth, while four cases (23.53%) had low Apgar score at 1 minute.

Out of the 30-hypertensive cases, 15 cases (50%) had vasculosyncytial membrane ≤ 5%. Out of these six cases (40%) had low birth weight, three cases (20%) were associated with stillbirth and two cases (16.66%) had Apgar score at one minute below normal.

Out of the 30-hypertensive cases, 21 cases (70%) had basement membrane thickening in more than 3% of the villi. Of these, five cases had (23.81%) had low birth weight, four cases (19.05%) were associated with stillbirth and 14.29% had Apgar score at one minute below seven.

Out of the 30-hypertensive cases, 20 cases (66.67%) had syncytial knots in more than 30% of the villi. Out of these seven cases (35%) had low birth weight, four cases (20%) were associated with stillbirth and three cases (18.57%) had Apgar score at one minute below normal.

Out of the 30-hypertensive cases, 28 cases (93.33%) had stromal fibrosis in more than 3% of the villi. Out of these eight cases (28.57%) had low birth weight, six cases (21.43%) were associated with stillbirth and four cases (18.18%) had Apgar score at one minute below normal.

27 (90%) out of the 30 cases of hypertensive pregnancies had fibrinoid necrosis in more than 3% of villi, of these 8 cases (29.63%) had low birth weight, 6 (22.22%) had stillbirth while four cases (19.05%) had low Apgar score at 1 minute.

DISCUSSION

Wigglesworth[10], Maqueo et al[11], Kalra et al[12] & Kher and Zawar[13] have all reported the proliferation of villous cytotrophoblastic cells as a reaction to toxemia of pregnancy. In the present study it was apparent that there was a higher incidence of stillbirths(six), low birth weight (34.78%) babies and low Apgar scores (23.53%) in cases with high cytotrophoblastic cell count as compared with the non-proliferated group. Fox[14] reported a low vasculosyncytial membrane count (4.5-5.3%) in placentae from pregnancies complicated by pre-eclampsia and considered this as a manifestation of villous regression. Cases of hypertensive group showed significant vasculosyncytial membrane deficiency in 50% cases and the majority of cases belonged to higher grades of toxaemia. It was observed that babies born to hypertensive mothers with vasculosyncytial membrane deficiency had low birth weight in 40% and birth asphyxia in 16.67% cases as compared to those with normal vasculosyncytial membrane counts. Three stillbirths in the study group were associated with vasculosyncytial membrane deficiency. Fox[14], Kher and Zawar[13] & Mathews et al[15] have also commented upon an association of vasculosyncytial membrane deficiency and poor foetal outcome as observed in the present study.

The present study showed a direct correlation between the severity of maternal disease and the villous counts for basement membrane thickening. Fox[16] considered that the reason for higher percentage of villi with thickened basement membrane is due to the proliferation of cytotrophoblastic cells, which secrete the basement membrane as a response to placental ischaemia. Others like Sen and Langley[17] and Mirchandani et al[18] have shown a linear relationship between undue thickening of basement membrane and fibrinoid necrosis and both these findings have been considered as a manifestation of antigen antibody reaction in the body. Villous basement membrane thickening with high basement membrane counts (>3% villi) was seen in 70% (21/30) cases of hypertensive pregnancies. Of these 23.81% had low birth weight and 19.05% were associated with stillbirth. Of the live births 14.29% had low Apgar score at one minute. Fox[16], Kher and Zawar[13] & Mirchandani et al[18] have noted similar association of poor foetal outcome with high basement membrane counts.

Syncytial knot counts were found to be significantly higher in moderate and mild pre-eclampsia as compared to controls and in cases of eclampsia as compared to mild pre-eclampsia. Increased number of villi showed syncytial knots in conditions like toxaemia of pregnancy have been described by Benirschke[1], Maqueo et al[11], Kalra et al[12], Bhatia et al[19], Mathews et al[15], Masodkar et al[20] and Mehrotra et al[21]. Excess syncytial knot formation is attributed to decreased foetal perfusion of the villi. Out of the 66.67% (20/30) cases of hypertensive pregnancies with excess syncytial knot counts, 3 cases (18.75%) had infants with neonatal asphyxia and 5 cases (35%) had low birth weight babies. Fox[22] failed to demonstrate any relationship between variations in the incidence of syncytial knot formation and foetal parameters like foetal distress, birth weight and neonatal asphyxia.

In the study group, there was a higher percentage of stromal fibrosis correlating with increasing severity of disease and the highest villous counts (18.83±5.60) were noted in placentae from eclamptic women. It is thus evident that there was an increased incidence of fibrotic villi in cases of hypertensive pregnancies. Fox[23] and Kalra et al[12] have observed a higher incidence of stromal fibrosis in placentae from hypertensive women (92.3-100%) as well as in controls (76%) and their findings are almost comparable to our observations. From the observations in the present study it was concluded that villous stromal fibrosis, seen as frequently in the study group (93.33%), as in the controls (80%) did not appear to affect the foetal outcome. Kher and Zawar[13] have reported insignificant association between stromal fibrosis and foetal outcome

Results of the present study reveal a significant fibrinoid necrosis in 90-100% cases of the study group and quite common to the

tune of 73.34% in the control. Findings of Burstein et al[24] have found that fibrinoid necrosis is a form of senile amyloid due to immune attachment on trophoblastic cells, which because of ageing process contains mis-specified proteins. Since stromal fibrosis was seen quite commonly in controls as well as in the study group, the observation of poor foetal outcome with enhanced stromal fibrosis is of no consequence.

The present study thus shows a correlation between histopathological changes and severity of maternal disease, which is also documented by the study of Romero et al[25]. This study was also in concordance with Majumdar et al[26] who found that newborn babies of mothers with poorly controlled PIH were small for date and few of them had birth asphyxia; some of them were born prematurely.

CONCLUSION

In essence most of the important placental changes represent placental ischaemia, secondary to reduced maternal blood flow. The apparent ill effects on the foetus are the direct consequences of the mother to supply her foetus with inadequate amounts of oxygen and nutrients, because it has been well established by Stock et al[27] that a decreased maternal blood flow results in a marked reduction of foetal placental blood flow. Roberts et al[28] and Redman[29] have suggested that the maternal ill effects are due to the release of some substances into the circulation from the ischaemic placenta, which can be a topic for further research into this disease process.

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