Comparative Analysis of the Villous Abnormalities of Placentae in Pregnancy Induced Hypertension with that of Normal Pregnancy

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Authors’ contributions

This work was carried out in collaboration between both authors. Author MJ Professor of Pathology, designed the study, wrote the protocol and wrote the first draft of the manuscript. Author JS asst. professor of pathology, managed the literature searches, analyses of the study and performed the analysis. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Hypertension is one of the common complications seen in pregnancies in the developing countries which contribute significantly to the maternal and fetal morbidity and mortality.

Objective: The present study was undertaken to analyse the histomorphologic changes of the placenta in pregnancy induced hypertension by looking for any significant differences in the villous abnormalities between the PIH group and the control group.

Study Design: Placentae from fifty mothers with uncomplicated pregnancy and fifty mothers with pregnancy induced hypertension (PIH) were divided as control and study group respectively. The microscopic features were compared between the control and PIH group.

Place and Duration of study: Department of Pathology, MVJ Medical College and Research Hospital, Bangalore, between 2011 and 2013.

Methodology: The microscopic features such as syncytial knots, vasculo-syncytial membrane (VSM), fibrinoid necrosis, basement membrane thickening and villous stromal fibrosis were compared between the placentae of the control and the PIH group. About four hundred villi were...
counted for each placenta and the mean was calculated for all the microscopic features. A ‘p’ value less than 0.05 was taken to be statistically significant. Gross abnormalities such as infarction and calcification were noted.

**Results:** The villous abnormalities observed in the study (PIH) group were increased syncytial knots (66%), paucity of vasculo-syncytial membrane (80%), fibrinoid necrosis (100%), basement membrane thickening (76%) and villous stromal fibrosis (90%). A ‘p’ value <0.001 of statistical significance was noted in the microscopic abnormalities of the villi in the placentae of the PIH group.

**Conclusion:** A highly significant increase in the villous abnormalities in the PIH group was found as compared to full term placenta which could attribute towards reduced uteroplacental flow.

**Keywords:** Villous abnormalities; pregnancy induced hypertension; histomrphologic changes in placenta.

1. **INTRODUCTION**

Placenta is the most important and vital organ of intrauterine life. It is the fountain head of human existence. Normal fetal growth and survival depends on the proper development and function of the placenta, which serves to maintain a maternal-fetal interface for the exchange of blood gases, nutrients and waste. It also gives the most accurate record of the infant’s prenatal experience [1,2].

Hypertension is one of the common complications seen in pregnancy and contributes significantly to maternal and fetal morbidity and mortality. In developing countries, with uncared pregnancies, this entity on many occasions remains undetected till major complications supervene.

After delivery if the placenta is examined minutely it provides an insight into the prenatal health of the baby and the mother. Pregnancy associated complication like pre-eclampsia influence the morphology of placenta which adversely affect the perinatal outcome such as fetal growth restriction, neonatal respiratory difficulties and increased frequency of admission to neonatal ICU [3]. Despite the intuitive importance of placental dysmorphology in pregnancy induced hypertension, a systematic approach to the description and quantification of the placental changes has been lacking [4].

This study was undertaken to assess the morphology of placentae in pregnancy induced hypertension and to compare the same with that in normal pregnancy. This study will provide an insight into the various changes in the villi of the placenta which could be of clinical relevance for the morbidity and mortality of the fetus as well as the mother. So a diagnosis and management of PIH is necessary.

2. **MATERIALS AND METHODS**

This study was carried out after the approval from the Institute Ethics committee and obtaining an informed consent. Fifty mothers with uncomplicated pregnancy and fifty mothers with pregnancy induced hypertension were selected randomly from the in-patients of Obstetrics and Gynaecology Department. They were divided into two groups as Control group and PIH (Pregnancy induced Hypertension) group respectively.

The Control Group comprised of pregnant women with normal blood pressure and without proteinuria or edema. PIH Group comprised of pregnant women with blood pressure at or above 140/90 mm Hg on at least two occasions, six or more hours apart after 20 weeks of present pregnancy together with or without proteinuria, edema, convulsions and coma. Cases with a history of hypertension prior to this pregnancy and hypertension secondary to other causes were excluded. Also cases of associated diabetes mellitus, anaemia and multiple gestations were excluded.

Clinical data were collected from the case records along with laboratory investigations and weights of the newborn were taken.

The placentae were collected immediately following delivery and washed in tap water and blotted to remove the blood clots. The gross examination of the placentae was done noting the weight, diameter, thickness, number of cotyledons on the maternal surface, calcification, infarction and the umbilical cord for true or false knots and colour. The whole placenta was left for fixation in 10% formal saline for 24-48 hours. After recording the macroscopic features the placenta was cut into vertical strips (bread loaf manner) of 0.5 cms thickness and the gross
lesions were re-examined. The membranes were trimmed and a strip was taken as “swiss roll” for histopathological examination. The cord was cut at about 4cms from its insertion and examined for number of blood vessels. Two sections each from central and peripheral areas were taken. Additional sections were taken from grossly abnormal lesions. Tissue sections of $5 \mu m$ thicknesses were cut from paraffin embedded blocks and stained by conventional haematoxylin and eosin stain. One hundred villi were counted from each of the four sections obtained and histological changes expressed as percentage. Special staining techniques like PAS (Periodic Acid Schiff) for basement membrane thickening and Van Gieson for stromal fibrosis, were employed.

The different histological findings were observed against the background of normal standards of histology of placentae as described by Fox H and Peterson et al. [5,6].

2.1 Statistical Analysis

All the histological and various gross features were compared between the placentae of control group and PIH group. The mean and standard deviation or incidence was calculated for different parameters. Student t test was used for quantitative variables. In all the tests ‘p’ value less than 0.05 was taken to be statistically significant and a value less than 0.001 was taken as highly significant.

2.2 Observations

A total of 100 placentae were studied. Out of which 50(50%) placentae were from normal term mothers (BP<140/80) which formed the control group and 50(50%) placentae were from mothers with PIH (BP >140/80) who formed the PIH group. In the PIH group 41 cases were of preeclampsia, 6 cases of gestational hypertension and 3 cases of eclampsia. The microscopic features were compared between the control and PIH group.

The age range of women in both the control and PIH group was between 18-33 years and the gestational age in both the groups was 27-41 weeks. In the PIH group 33(66%) were primigravida and 17(34%) were multigravida. The mean blood pressure in the control group was 113/73 mmHg and 156/100 mmHg in the PIH group. The mean birth weight and the placental weight were 2855 gms and 497 gms respectively for the control group whereas 2055 gms and 390 gms respectively for the PIH group which was statistically highly significant. Also the mean diameter of the placenta in control group was 16.5 cms and that of PIH group was 14 cms which was very significant statistically. The incidence of infarction involving more than 5% of the parenchyma was found in 12(24%) of PIH group.

The gross features in the present study between the control and PIH group are shown in Table1.

Different histological features were quantified as described in methodology. Thus, in each placenta four hundred villi were counted and mean calculated. The mean number of villi showing syncytial knots (SK), vasculo-syncytial membrane (VSM), fibrinoid necrosis, basement membrane thickening and villous stromal fibrosis was determined.

The percentage of the characteristic histological features of normal placenta has been shown in Table 2.

Syncytial knots: These were seen as focal aggregates of syncytial nuclei forming a multinucleated protrusion from the villous surface. The number of villi with SK was recorded and the result expressed as a percentage of the total. A true SK was only accepted as such if it was visible on low power magnification and the actual counts were carried out using the high power magnification.

SK were present on more than 30 percent of the villi in 33/50 (66%) placentae of the PIH group. The difference of proportion of placentae showing high villous SK counts (>30% of the villi) between the two groups was statistically highly significant (p<0.001). On the basis of an aggregation around the terminal villi (TV), the SK in the present study was grouped into type 1, 2a, 2b, and 3 [7].

In type 1, SKs were found to accumulate to any one side of the TV leaving back the rest of the circumference of villi allowing free perfusion through VSM (Fig. 1a).

In type 2a, SKs accumulate almost half of the circumference of the TV and only a minimum area related to VSM was left for perfusion. In type 2b, the SKs were collected in two or three small groups surrounding the TV (Fig. 1b,c).

In type 3, three fourth of the circumference of TV was covered with SKs thus having the less chances of perfusion (Fig. 1d).
2.3 Vasculo-Syncytial Membranes

Vasculo-syncytial membrane was seen in villi as attenuated areas of syncytiotrophoblast, which overlie and appeared to fuse with the wall of the adjacent dilated fetal capillary [8]. The number of villi in which vasculo-syncytial membranes were present was expressed as a percentage of the total.

The incidence of vasculosyncytial membrane deficiency i.e ≤5 percent of the villi was seen in 40/50 (80%) placentae of the PIH group where the deficiency was nil in the control group (Fig. 2a).

2.4 Fibrinoid Necrosis

Fibrinoid necrosis was seen as small nodules of homogenous eosinophilic material within the villi. At places this fibrinoid material involved the entire villi (Fig. 2b). The number of villi showing fibrinoid necrosis was noted and the total of such villi was then expressed as a percentage incidence.

Fibrinoid necrosis was seen in >3 percent of the villi in 38/50 (76%) placentae of the control group and 50/50 (100%) placentae of the PIH group.

2.5 Fibrotic Villi (Increase in Villous Stromal Fibrosis)

Stromal fibrosis was observed in sections stained with Van Gieson as pink colored collagen fibers within the core of the villi (2c). The number of fibrotic villi was noted and this figure was expressed as a percentage incidences.

Increase in villous stromal fibrosis, involving more than 6% of villi was seen in 14/50 (28%) placentae of the control group and 48/50 (96%) placentae of the PIH group.

Table 1. Incidence of gross features in the present study between the control and PIH group

| Parameters                  | Control group (n=50) | PIH group (n=50) |
|-----------------------------|----------------------|------------------|
|                             | No. of cases (%)     | No. of cases (%) |
| Shape of placenta           |                      |                  |
| Circular                    | 29 (58)              | 24(48)           |
| Oval                        | 21 (42)              | 21(42)           |
| Irregular                   | Nil                  | 5                |
| Foetal surface              | Normal               | Normal           |
| Membranes                   | Normal               | Normal           |
| Umbilical cord insertion    |                      |                  |
| Central                     | 40 (80)              | 19(38)           |
| Eccentric                   | 9(18)                | 24(48)           |
| Marginal                    | 1(2)                 | 7(14)            |
| Velamentous                 | -                    | -                |
| Single umbilical artery     | Nil                  | Nil              |
| Mean umbilical cord length  | 25.6±6.5             | 22.2±7.9         |
| in centimetres              |                      |                  |
| Knots in umbilical cord     | Nil                  | Nil              |
| Maternal surface            |                      |                  |
| Mean number of cotyledons   | 19±2.52              | 15.86±3.05       |
| Calcification               | 23(46)               | 35(70)           |
| Infarction of >5% area      | 0                    | 12(24%)          |
| Retro placental hematoma    | Nil                  | Nil              |
| Mean placental weight       | 497.5                | 390.8            |
| ( grams)                    |                      |                  |
| Mean diameter (centimetres) | 16.5                 | 14.15            |

Table 2. The percentage of the characteristic histological features of normal placenta

| Sl. no | Parameters                           | Characteristics                             |
|--------|--------------------------------------|---------------------------------------------|
| 1      | Syncytial knots                      | Present in 11-30% of terminal villi         |
| 2      | Vasculo-syncytial membrane           | Present in 6-30% of terminal villi          |
| 3      | Villous syncytial membrane           |                                              |
| 4      | Fibrinoid necrosis                   | Present in 0-3% of terminal villi           |
|        | (Intra villous fibrinoid)            |                                              |
| 5      | Basement membrane thickening         | Present in 0-3% of terminal villi           |
Fig. 1. Photomicrograph of a villous showing: (a) Type 1 syncytial knot. (H&E, 40x); (b) Type 2A syncytial knot. (H&E, 40x); (c) Type 2B syncytial knot. (H&E, 40x); (d) Type 3 syncytial knots. (H&E, 40x)

Fig. 2. Photomicrograph showing: (a) Villous without vasculo-syncytial membrane. (H&E, 40x); (b) Villi with Fibrinoid necrosis. (H&E, 10x); (c) Villi with stromal fibrosis (pink). (Van Gieson, 40x); (d) Villous with basement membrane thickening (magenta). (PAS, 40x)
2.6 Basement Membrane Thickening

It was seen under high power in PAS stained sections as magenta colored membrane separating the trophoblastic mantle from the mesenchymal core (Fig. 2d).

Basement membrane thickening in >3 percent of the villi was seen in 1/50 (2%) placentae of the control group and 38/50 (76%) placentae of the PIH group.

The difference in the incidence of the placenta showing various villous abnormalities between the control group and the PIH group are compared in Table 3 and (Fig. 3). The villous abnormalities in the PIH group are shown in (Fig. 3b).

3. DISCUSSION

Placenta is an organ of vital importance because of its direct relation to the growth and development of the fetus in the uterus [9]. As per the literature much work has been done by the Pathologists and the Obstetricians to study the mysterious structure of the placenta. [9,10,11]. A systematic approach to the description and quantification of the placental changes has been lacking [4]. This study therefore contributes towards understanding the morphological changes in the chorionic villi of the placenta in pregnancy induced hypertension by comparing with that of the normal pregnancy.

Pregnancy induced hypertension is defined as the hypertension that develops as a direct result of the gravid state. It includes Gestational hypertension, Preeclampsia and Eclampsia as per the recommendation of The Working Group of National High Blood Pressure Education Program (2000) [12]. Hypertensive disorder may complicate in about 3-10% of all pregnancies with variable incidence among different hospitals and countries. [13] With this background a study was undertaken to assess the spectrum of the histopathological changes in placenta in pregnancy in PIH.

All the cases meeting the criteria for pregnancy induced hypertension were included in the study. However, the incidence of eclampsia (3/50) was low in the study population of the area possibly due to good obstetric care.

As per the literature, a reduced placental weight has been recorded in mild and severe cases of preeclampsia [9]. In this study, the average weight of normal placenta was 497.5 gm whereas the average weight in the PIH group was 390.8gms with a very significant 'p' value of <0.001.

![Fig. 3. Photomicrograph showing: (a) Terminal villi from normal placenta.(H&E, 40x) Note the absence of syncytial knots, fibrinoid necrosis and stromal fibrosis and presence of vasculo-syncytial membranes (red arrows) in all the villi; (b) PIH group. (H&E, 10x) Note the excessive number of syncytial knots (red arrows), fibrinoid necrosis (blue arrows), stromal fibrosis (black arrow) and absent vasculo-syncytial membrane](image-url)
Table 3. Comparison of the incidence of various villous abnormalities in both groups

| Villous lesions                          | Control group (50 cases) No. of cases | PIH group (50 cases) No. of cases | %     | P value |
|------------------------------------------|---------------------------------------|-----------------------------------|-------|---------|
| % of villi with syncytial knots          |                                       |                                   |       |         |
| < 30%                                    | 45                                    | 17                                | 90    | 34      | <0.001  |
| >30%                                     | 05                                    | 33                                | 10    | 66      |         |
| Vasculosyncytial Membrane                |                                       |                                   |       |         |
| < 5%                                     | 0                                     | 40                                | 0     | 80      | < 0.001 |
| >5%                                      | 50                                    | 100                               | 100   | 20      |         |
| Fibrinoid necrosis                       |                                       |                                   |       |         |
| <3%                                      | 12                                    | 0                                 | 24    | 0       | <0.001  |
| >3%                                      | 38                                    | 76                                | 50    | 100     |         |
| % of villi with stromal fibrosis         |                                       |                                   |       |         |
| <3%                                      | 10                                    | 03                               | 20    | 06      | <0.001  |
| 4-6 %                                    | 31                                    | 02                               | 62    | 04      |         |
| >6%                                      | 09                                    | 45                               | 18    | 90      |         |
| % of villi with Basement membrane thickening |                                 |                                   |       |         |
| <3 %                                     | 49                                    | 12                               | 98    | 24      | <0.001  |
| >3 %                                     | 01                                    | 38                               | 02    | 76      |         |

Placental infarction of more than 5% surface area is considered pathological and is seen more frequently in toxaemia of pregnancy due to thrombotic occlusion of maternal uteroplacental vessels [9]. Our study showed a placental infarction on gross in 12/50 (24%) of PIH cases which was not statistically significant probably because of either less number of toxemic cases in the study population or the infarction was seen only under microscope. The incidence of calcification was 70% in the study group as compared to 46% of the control group. Retroplacental haematoma was not seen in both the groups.

The microscopic lesions were assessed and quantified as percentage of placenta in control and PIH groups showing syncytial knots in more than 30% of villi, vasculo-syncytial membrane in ≤ 5% of villi, fibrinoid necrosis, stromal fibrosis and basement membrane thickening in more than 3% of villi. These were compared with two other studies as shown in Table 4 [6,9].

Syncytial knot counts were found to be significantly higher in PIH group including cases of eclampsia as compared to controls. Increases in the number of villi showing syncytial knots in conditions like toxaemia of pregnancy have been described [6,14]. The syncytium depends upon the maternal blood supply for its oxygen requirements and reduction of villous vascularity in no way impairs the oxygenation of the syncytium [15].

Table 4. Comparison of microscopic lesions in present study with that of studies

| Microscopic lesions                        | Percentage of placenta showing the microscopic lesions (%) |
|--------------------------------------------|-----------------------------------------------------------|
|                                            | Present study  | Narasimha et al. [9]  | Navbir et al. [6]  |
|                                            | Control (n=50) | PIH (n=50)  | Control (n=37)  | PIH (n=63)  | Control (n=30)  | PIH (n=30)  |
| Syncytial knots >30%                       | 10            | 66          | 45            | 90.47       | 6.67         | 66.67       |
| Vasculo-syncytial membrane ≤ 5%           | 0             | 90          | 0             | 93.65       | 0            | 56.67       |
| Fibrinoid necrosis >3%                    | 76            | 100         | 29.72         | 97.82       | 73.33        | 90          |
| Stromal fibrosis >3%                      | 80            | 94          | 81            | 92          | 80           | 93.33       |
| Basement membrane thickening >3%         | 2             | 76          | 0             | 49.25       | 0            | 70          |
Table 5. Comparison of percentage of microscopic lesions in the eclamptic placentae of the present study with that of other studies in literature

| Microscopic lesions                          | Present study (n=3) | Kurdukar et al. [20] (n=10) | Narasimha et al. [9] (n=9) | Navbir et al. [6] (n=6) |
|---------------------------------------------|---------------------|-----------------------------|---------------------------|------------------------|
| Syncytial knots >30%                        | 100                 | 100                         | 100                       | 100                    |
| Vasculo-syncytial membrane ≤ 5%             | 100                 | 70                          | 83.33                     | 100                    |
| Fibrinoid necrosis >3%                      | 100                 | 100                         | 100                       | 100                    |
| Stromal fibrosis >3%                        | 100                 | 50                          | 100                       | 100                    |
| Basement membrane thickening >3%           | 100                 | 100                         | 100                       | 100                    |

Vasculo-syncytial membranes (VSM) are focally attenuated anuclear syncytiothrophoblast which is in close opposition to, a sinusoidally dilated vessel. Placentae in which 6 to 30 percent of the villi show vasculo-syncytial membranes are said to have a normal count [16]. Vasculo-syncytial membrane counts measure the approximation of the villi to optimal maturity and hence give a good indication of the ability of the placenta to supply oxygen to the fetus. It was hypothesized that placenta responds to a decreased oxygen supply by increasing the number of vasculo-syncytial membrane for transfer purposes but it has not been established. The incidence of VSM deficiency (<5%) was 80% in the study group of PIH whereas none of the control showed this abnormality which is comparable to other studies [5-7,9,15-19].

Fibrinoid necrosis has been considered as a hallmark of an immunological reaction within the trophoblastic tissue. In an earlier report villous fibrinoid necrosis was considered to evolve from a degenerative change in villous cytotrophoblast. But still it is considered to be an enigma as its pathogenesis and significance is not known [6,9,20]. Villous fibrinoid necrosis (involving >3 % of villi) which is considered abnormal was seen in all the cases of the PIH group in this study [9].

In term placenta ≤ 3 percent of villi may be fibrotic and if more than 3 percent of villi in a placenta are fibrotic it is considered as abnormal. Increase in villous stromal fibrosis (>3% of villi) in the PIH group has been reported in literature. [6,9] The stromal fibrosis was seen in >6% of villi in 90% of PIH group which is of significance. The two factors responsible for the formation stromal fibrosis are a normal aging process and a reduced uteroplacental blood flow [9].

The basement membrane thickening is secondary to placental ischemia and that the cytotrophoblast secretes basement membrane material. Hence, cytotrophoblastic proliferation is seen as basement membrane thickening in placental ischemia of PIH group [14]. This study showed an increased basement membrane thickening in villi of 76% of PIH group as comparable to studies in the literature [6,9,20].

The microscopic lesions in the eclamptic cases were also quantified as percentage of placenta showing syncytial knots in more than 30% of villi, vasculo-syncytial membrane in ≤ 5% of villi, fibrinoid necrosis, stromal fibrosis and basement membrane thickening in more than 3% of villi.

As the severity of the disease increased like in eclampsia, the microscopic lesions were seen in increased number of villi (100%) in the present study. The percentage of various histomorphological changes in the eclamptic placentae of our study is compared with other studies in the literature in Table 5 above [6,9,20]. PIH induces various histological changes which significantly affect the birth weight [21].

4. CONCLUSION

Pregnancy induced hypertension alters the placental morphology as significant microscopic changes were observed in placenta of PIH group when compared to controls such as increased syncytial knots, fibrinoid necrosis, villous stromal fibrosis, basement membrane thickening and paucity of vasculo syncytial membrane (p<0.001). These changes can be attributed to a reduced uteroplacental blood flow. Therefore early recognition of pregnancy induced hypertension and proper management may be critical to normal placental function. Such studies will provide an insight to the obstetricians as well to the radiologists for an early detection of placental insufficiency in order to have a better perinatal outcome.
COMPETING INTERESTS

Authors have declared that no competing interests exist.

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