

Original article:

HISTOPATHOLOGICAL CHANGES IN PLACENTA- A STUDY OF 50 CASES OF PREGNANCY INDUCED HYPERTENSION

Dr Onkar Kaur* , Dr Jaskaran Singh , Dr Karandeep Kaur

ESIC Model Hospital, New Delhi

Corresponding author*

ABSTRACT-

Pregnancy induced hypertension is a common syndrome involving 7-10% of pregnancies labelled by clinical criteria BP>140/90, edema and proteinuria .This study is done to analyse PIH changes in gross morphology of 50 placentae examined in ESI-PGIMS Hospital Basaidarapur delhi . Gross morophological changes were studied and abnormalities foundwere retroplacental clots , infarcts,edema where p value was found significant while other features like partial membranes ,abnormal weight and abnormal vessels in descending order were not significant. For the findings of microscopic examination, test of significance was calculated in our study and only cytotrophoblastic proliferation was found statistically significant with P value <0.05 while VSM deficiency , basement membrane thickening ,syncytial knots , stromal fibrosis and fibrinoid necrosis all had P value >0.05.

KEYWORDS- Placenta ,Pregnancy induced hypertension ,histopathological.

INTRODUCTION-

Pregnancy induced hypertension (PIH) is an important cause of maternal morbidity and mortality throughout the world and its incidence is particularly high among underprivileged women of developing countries (Dawn 1982). Almost 13% of maternal deaths in India have been attributed to PIH and its complications (Park 2001). PIH is defined clinically as hypertension with BP \geq 140/90mmHg at two occasions 6 hrs apart that develops as a consequence of pregnancy and regresses post partum (Cunningham et al 1997). It has been divided into three broad categories: hypertension alone, preeclampsia (hypertension, proteinuria and edema) and eclampsia (convulsions precipitated by rise in blood pressure). Out of these three categories, eclampsia is the most dreaded one associated with significant foeto maternal mortality.

Preeclampsia is a common syndrome involving 7-10% of all primigravida, characterized by increased blood pressure, edema and proteinuria. Unpredictable in its onset and progression, clinical manifestations may come about slowly or occasionally, explosively. If untreated, preeclampsia may result in eclampsia, that is convulsions, which is most dreaded of all manifestations and is associated with very high foetomaternal mortality. The disease is much more common in first pregnancy, in very young gravida and in multipara. While the clinical features of PIH and its complications are well known, its exact etiology still remains an enigma (Menon et al 1994). The various theories that have been formulated for its genesis includeimmunological basis, genetic predisposition, dietary deficiencies, vasoactive factors and endothelial dysfunction (Cunningham et al 1997). There is no specific diagnostic test. It is

recognized by pregnancy induced changes that regress after delivery. As PIH has high maternofoetal mortality, most maternal deaths due to PIH are preventable, provided an early diagnosis is made and the treatment constituted at the earliest (Cunningham et al 1997). The foetus is commonly growth retarded because of fairly characteristic alterations that result from a disturbed interaction between trophoblast and maternal uterine blood vessels. Placental delivery nearly always terminates the illness abruptly. However the preeclamptic syndrome is more polymorphic than the conventional definition, involving maternal liver, nervous system, coagulation (Redman 1990) and is associated with many serious complications such as placental infarction, abruptio placenta and foetal demise.

The clinical signs and symptoms of PIH are however notoriously subtle in the early disease and thus there is need to develop screening tests and criteria for early detection of PIH in antenatal period. The placenta (term designed from Latin that translates as “flat cake”), an organ of metabolic interchange between foetus and mother, provides oxygen, nourishment and protection to foetus, has excretory and endocrinal functions too. It has been described as the mirror of the maternal and perinatal mortality. Histopathological examination of placenta as an organ has been difficult as there is an overlap between the findings in normal and abnormal placenta and quantitative studies applied in practice are generally lacking. There are also the questions of who bears the cost of placental examination and of reducing the cost of medical care.

However, the results of placental examination in certain cases do explain perinatal morbidity or mortality and have an impact on management of mother and foetus. In 1989, The College of American Pathologists convened a conference entitled “Examination of placenta, patient care and risk management”. Pathologists with expertise in placental pathology, obstetricians, neonatologists and attorneys were invited to participate. The proceedings were published in July 1991 issue of Archives of Pathology and Laboratory Medicine. PIH is associated with variable degree of placental morphological and histopathological changes like infarcts, retroplacental bleeds, decidual vasculopathies, villous syncytial knotting and rarely molar changes (Lewis et al 1990). The study of these changes can provide an insight into the etiology of PIH

METHODS AND MATERIAL-

This was a prospective study of fifty patients conducted in Department of Pathology at our Hospital admitted further in the labour room in the Department of Gynae & Obstetrics. A detailed clinical history was obtained including headache, epigastric pain, nausea, vomiting, visual symptoms, respiratory symptoms, past history and other relevant history. General examination was done including Pulse, B.P., Pallor, cyanosis, pedal edema. Systemic examination, antenatal and fundus examination were done in all patients as relevant to PIH.

Laboratory investigations were performed including Hb, complete haemogram and blood group, urine (albumin), blood urea, serum creatinine, uric acid, LFT, Platelet count.

Criteria for selection of the patients in our study was:

1. Pregnant females followed up from the first trimester and who developed B.P. more than 140/90mmHg at two occasions six hours apart (with previous normal B.P.) after 20 weeks.
2. No previous or any present kidney disease
3. No H/o primary or previous hypertension in the past.
4. With normal functioning of liver, cardiovascular system and other systems.

5. In addition, a control group of 50 pregnant females was also studied. This control group consisted of patients with normal BP throughout their pregnancy. Their placentae were also studied for histopathological changes.

The selected females were followed up in antenatal clinic and delivery was performed vaginally or by caesarean section. Placentae were collected and sent to histopathology lab, examined fresh and fixation was done to evaluate further. Any gross abnormality was observed, photographed and noted. Weight was taken in the fresh specimen. Gross features were noted like cord length measurement, membranes knots, retroplacental clot, any infarct in the fresh specimen itself.

Examination of foetal placenta was done for any abnormality. Maternal surface was examined for completeness, tears, plaques, adherent clot for any missing cotyledon, membrane.

Placental tissue was put in 10% neutral buffer formalin solution for three days and kept for fixation. The several sections of placenta leaving the tissue attached at the foetal surface were made at 0.5 -1cm intervals, examined for septal cysts, intervillous thrombosis, subchorionic fibrin, plaques of perivillous fibrin, recent infarct or old infarct. The cut surface of the placenta was equally divided into subchorionic /foetal intermediate and maternal zone. The villi were best assessed for maturity and other features in the section taken to include the central part of the maternal zone.

Following histological sections were made as described by Altshuler and Fox.

1. Two rolls of membranes were placed in one cassette (each roll was prepared in such a way that the margin of it was in the centre of the roll). It was essential to include both amnion and chorion in the histological section.
2. Two sections of the central part of the placenta including maternal surface placed in the second cassette.
3. One section from the middle segment of the cord were placed in the 3rd cassette .
4. More section were taken required from the desired sited in individual case depending upon the pathology of the case .
5. H&E,PAS, Masson trichrome stains were done all sections taken.

Grading and scoring of placenta

Microscopic examination was done from the stained slides by two observers and following standards were followed. One hundred villi were counted from each sections and histological changes were expressed as percentage.

Cytotrophoblastic proliferation Villous cytotrophoblast cells are those that form a complete mantle around the immature villi and diminish in number with advancing pregnancy. Only few flattened cytotrophoblastic cells are seen in mature villi. Cytoplasm of syncytiotrophoblast is PAS

+ve that of cytotrophoblast is PAS negative in mature placentae. Cytotrophoblastic proliferation was seen in 20-40% of the villi. >20% proliferation was considered significant for PIH.

Vasculosyncytial membrane deficiency A distinct thick basement membrane separates the trophoblast from the villous stroma. In some areas syncytium between knots is thin and without nuclei. In the areas where dilated villous capillaries lie under neath such thin areas, the anuclear thin portion of the syncytium appears to fuse with the vessel wall to form vasculosyncytial membrane. Vasculosyncytial membrane deficiency was considered significant when it involved

>5% of the villi.

Fibrinoid necrosis Homogenous fibrinoid material seen beneath syncytiotrophoblast and external to basement membrane.

- About >3% villi showing fibrinoid necrosis was considered abnormal.

Thickened basement membrane

Assessment of basement membrane thickening was taken as subjective criteria and was examined in PAS stain slide.

Thickened basement membrane found in >3% villi was considered abnormal.

Syncytial knots

Syncytial knots in >33% of villi were considered excessive, the extent of knots was assessed by counting 100 villi in the histological sections of the placenta taken from the central portion of the maternal zone.

Stromal fibrosis

<3% of villi show fibrosis (Fibrotic villi) in term placenta. >3% of fibrotic villi were considered significant.

Villous vascularity

This parameter was purely subjective.

OBSERVATIONS AND RESULTS

In the present study, histopathological examination of placentae of PIH cases were carried out. In our study, maximum cases (46%) were seen in age group 29-33 yrs followed by 34% in 19-23 yrs, 16% in 24-28 yrs, and 4% in 34-38 yrs group with mean age 26.66 and standard deviation 4.885. Parity ranged from P1 to P6 in our study. Maximum percentage of cases were primipara (P1) i.e. 32% with mean 2.22 and SD 1.130

Most prominent symptom in our study was nausea and vomiting (60%) followed by headache (58%) epigastric pain (54%) and visual symptoms (28%) in descending order 6% cases had positive family history while 94% were found negative.

B.P. was most important criteria for selection of cases. BP >140/90mmHg was considered as PIH group, so this was 100% followed by pedal edema 62% and fundus changes in 14%. The cases with raised BP were further subdivided into mild and severe (>160 /110mmHg) categories. 40 cases were in mild PIH group (BP more than 140/90mmHg but less than 160/110mmHg) while 10 cases were in severe PIH group (BP more than 160/110mmHg)

In our study percentage of cases showing positive urine albumin was 74%, raised LFT was 50%, raised KFT was 20% and abnormal platelet count was 22%.

Histopathological Findings

In the present study, histopathological examination of placenta was done. Weight between 345- 617gm was taken as normal. 6% placentae had weight less than 345gm. 34% cases showed retroplacental clot. Infarct involving >5% area was taken as abnormal and 32% cases had significant placental infarct. Partial membranes were seen in 14%.

Umbilical cord examination was done and features observed were cord vessels; one case (2%) had 1A/V rest had 2 A/V, 6% cases showed umbilical cord knots while cord edema was seen in 11% cases.

Gross Pathology	No. of cases	Percentage
Weight	3	6%
Retroplacental clot	17	34%
Infarcts	16	32%
Membranes (partial)	7	14%
<i>Umbilical cord</i>		
Vessels	1	2%
Knots	3	6%
Edema	11	22%

Microscopic examination of placenta showed cytotrophoblastic proliferation (>20% villi showing cytotrophoblastic proliferation) in 31 cases i.e. 62% with mean 24.82 and S.D. 7.819. Vasculosyncytial membrane deficiency (villi showing VSM >5% was abnormal) was found in 68% with mean 6.38 and S.D. 4.025. B.M thickening is a subjective criteria (3% villi showing

B.M. thickening was considered significant), seen in 64% cases mean 4.68 and S.D. 2.896. Syncytial knots (>30% were taken abnormal) were present in 46%, Mean 2.8 with S.D. 3.025 stromal fibrosis (>3% was taken as abnormal) was seen in 68% with mean 6.92 and standard deviation 4.53. Fibrinoid necrosis (found in >3% was considered abnormal) was present in 70% cases with mean 7.26 and S.D. 4.7233. In villous vascularity, hypervascular and hypovascular cases were 14% each while the rest were normo vascular. Most common histopathological change in microscopic examination was fibrinoid necrosis (70%) followed by VSM deficiency and stromal fibrosis in 68% while abnormal villous vascularity was least common feature amongall.

Microscopic Examination	No. of cases	Percentage
Cytotrophoblastic proliferation	31	62%
Vasculosyncytial membrane deficiency	32	64%
B.M. thickening	32	64%
Syncytial knots	23	46%
Stromal fibrosis	34	68%
Fibrinoid Necrosis	35	70%
Villous Vasculature		
Cases Hypervascular	7	14%
Cases Hypovascular	7	14%
Cases Normovascular	36	72%

DISCUSSION –

Pregnancy induced hypertension is an important cause of maternal morbidity and is a disease of particularly underprivileged women of developing countries. Incidence of pre-eclampsia was reported 10% in rural India, Mudaliar and Menon 1972 and 3-10% by Lewis in 1965. High incidence in developing countries with low socioeconomic status is attributed to the lack of antenatal care. This study was conducted in Departments of Pathology, Gynae and Biochemistry, ESI (Employees State Insurance) hospital in Basaidarapur, New Delhi. ESI corporation is a social security scheme which provides comprehensive medical care as one of its benefits to the factory workers; this hospital mostly caters to many factory workers who have low socioeconomic status. The present study was a prospective study of pregnant females attending antenatal clinics in OPD, followed up in antenatal clinics and those who developed hypertension (PIH) were selected for the study. The number was confined to 50 and 50 cases were taken as control group. Age ranged from 19 years to 38 years in this study with mean age 26.66, SD 4.886. Maximum number of cases were found in 29 to 33 years group. Cuesley 1985 studied PIH and concluded that it more frequently affects teenagers or those older than 35 years, and pre-eclampsia in older women is more likely pregnancy aggravated hypertension. Parity ranged from P1 to P6 in our study. Maximum number of cases were primipara (32%) with mean parity 2.22±1.130. Lewis 1965, Mudaliar and Menon 1972, Dawn 1974 have also concluded that pre-eclampsia is more common in primigravidae (70%).

In our study the most prominent symptoms were nausea, vomiting 60% followed by headache 58%, pain abdomen 54% and least were visual symptoms 4%. Family history of high BP in parents was found in 6% cases only.

50 cases were taken in the study which showed high BP >140/90 after 20 weeks of gestation on two occasions 6 hrs apart with or without edema and proteinuria. 40 were labelled as mild PIH 140/90mmHg but <160/100mmHg and 10 cases as severe PIH (BP >160/110mmHg). Cases with eclampsia were not included in the study. Pedal edema was seen in 62% followed by fundus changes in 14% cases.

Biochemical parameters found abnormal in the study were albuminuria in 74%, impaired LFT in 50% cases, impaired KFT in 20% and low platelet count in 22% cases. Test of significance was calculated for cases with high blood urea, S. creatinine, high serum uric acid and low platelet count in severe PIH group, was <0.05 , which is in conformity with other workers (Simon Shehav et al 2002, Dunlop and Donaldson 1977, Radman et al 1976).

Histopathological examination of placenta was done. 6% cases had weight less than normal (345-617gms) in severe PIH group. 34% cases showed retroplacental clot. Infarct area involving $>5\%$ was taken abnormal and 32% cases had significant placental infarct. Partial membranes were seen in 14% cases only. Test of significance was calculated and P value was <0.05 for retroplacental clot, cord edema and infarct which is consistent with other workers who studied placental morphology in PIH (Mathews et al 1973, Maqueo et al 1964, Ker AU et al 1981

CONCLUSIONS

The most common histological change in placenta in the study was fibrinoid necrosis. The other histopathological changes were stromal fibrosis, BM thickening, VSM deficiency, cytotrophoblastic proliferation, syncytial knots and abnormal villous vascularity in descending order.

REFERENCES

1. Acker D, Sach BP, Tracyy KJ, et al: Abruptio Placental associated with cocaine use. *Am J Obstet Gynecol* 1983;146: 220-221.
2. Aladjem, S., Lueck J. and Brewer, J.J. Experimental induction of a toxemia like syndrome in the pregnant beagle. *Am J Obstet. Gynecol* 1983; 145:27-38.
3. Alanen A., Kekomaki, R., Kero, P., Lindstrom, P and Wager O: Circulating immune complexes in hypertensive disorders of pregnancy. *J. Reprod. Immunol* 1984; 6:133-140.
4. Ali, K.Z.M.: Serological study of the effect of attitude on the trophoblastic cell population of human term placental villi. *Placenta* 1997;18: 447-450.
5. Altshuler G.: Placenta within the medicolegal imperative. *Arch Pathol. Lab. Med.* 1991; 115 : 688-695.
6. Alvarez H, Benedelti W.L., Moral R.L. et al: Trophoblast development gradient and its relationship to placental hemodynamics. *Am. J. Obstet. Gynecol.* 1970;106:416-420.
7. Alvarez H, Benedelti WL and De Leons, V.K. Syncytial proliferation in normal and toxemic pregnancies. *Obstet Gynecol* 1967;29: 637-643.
8. Anderson W.R. and Mckay D.G.: Electron microscope study of the trophoblast in normal and toxemic placenta. *Am. J. Obstet Gynecol* 1966; 95: 1134-1148.
9. Anonymous: Pregnancy and the arachidonic acid cascade. *Lancet* 1982; 1:997-998.
10. Aquilina J, Maplethorpe R. Ellis P, Harrington K: Correlation between second trimester maternal serum inhibition. A and human chorionic gonadotrophin for the prediction of pre- eclampsia. *Placenta* 2000;21: 487-492.
11. Arnhokit H, Meisel F., Fardrey R. et al: Proliferation of villous trophoblast of human placenta in normal and abnormal pregnancies.

12. Ayala, A.R., De La Fuente, F.R., Loyola F.D., Gonzalez, E. and Kunhardt, J.: Evidence that a toxemia related organism (*Hydatoxy lualba*) is an artifact. *Obstet. Gynecol.* 1986;67: 47-50.
13. B.N.J. Wallters, Terence lao and Valeric Smith. □-fetoprotein elevation and proteinuric pre-eclampsia. *British Journal of Obstetrics and Gynecology* 1985;92: 341-344.
14. Balasch, J., Mirapeix, E., Borche L., Vives, J and Gonzalez Merlo J.: Further evidence against preeclampsia as an immune complex disease. *Obstet. Gynecol* 58: 435-437, 1981.
15. Barkal G., Ben Bamli G: The use of aspirin to prevent pregnancy induced hypertension and the ratio of thromboxane A2 to prostacyclin in relatively high risk pregnancies. *N Engl. J Med.* 1989; 321: 351-356.
16. Bartholomew, R.A., Colvin E.D., Grimes, W.H, Fish, J.S., Lester, W.M. and Galloway, W.H.: Facts pertinent to the etiology of eclamptogenic toxemia. *Am. J. Obstet. Gynecol* 74: 64-68, 1957.
17. Bartholomew, R.A.: Hemorrhages of late pregnancy. With emphasis on placental circulation and the mechanism of bleeding. *Postgrad. Med.* 30: 397-406. 1961
18. Beauflis, M., Uzan S., Donsimoni R, and Colau J.C., Prevention of preeclampsia by early antiplatelet therapy. *Lancet* 1: 840-842, 1985.
19. Benigni, A., Gregorini G., Frusca T, Chiabrando, C., Ballerini, S, Valcamonico A., Orisio S., Piccinelli A., Pinciroli V., Fanelli R., Gastaldi A., and Remuzzi G.: Effect of low-dose aspirin on fetal and maternal generation of thromboxane by platelets in women at risk for pregnancy induced hypertension. *N. Engl. J. Med.* 321:357-362, 1989.
20. Benirschke K: The placenta in the context of history and modern medicine practice are pathology. *Arch Pathol lab. Med.* 1991;115: 663-667.
21. Bhatia A, Sharma SD, Jalanwalla SF and Sagreiya K: A comparative study of placental pathology and foetal outcome. *Indian J Pathol Microbiol* 1981;24: 277.
22. Brosens I, Dixon H.G., and Robertson, W.B., : Prostaglandins and pre-eclampsia. *Lancet* II: 412-413, 1974.
23. Budilger, H: Plazentarver andernogen and ihre Benziehung Zur Spaltoxikase and perinatalen Kindlichen sterblichkeit. *Fortschr. Geburtstilfe Gynakol.* 17:86-110, 1964.
24. Burstein A., Berns AW, Hirata y et al: A comparative histologic and immunopathological study of the placenta in diabetes mellitus and in erythroblastosis fetalis. *Am J Obstet Gynaecol* 1963;86: 66-76.
25. Castellucci, M., Kaufman P. and Bischof P., : Extra cellular matrix influences hormones and protein production by human chorionic villi. *Cell Tissue Res.* 1990;262: 135-142.
26. Chalmers, I.: Salt, Pregnancy, hypertension – and literature searches. *Lancet* II: 1146, 1988.
27. Chan Dong H.S.U., M.D, MPH Daniel W. Chan et al: Elevated serum human chorionic gonadotropin an evidence of secretory response in severe preeclampsia. *Am. J. Obstet Gynecol.* 1994;170: 1135-1138.
28. Chesley LC: Diagnosis of Pre-eclampsia. *Obstet Gynaecol* 1985;65: 423.
29. Colbern G.T., Chiang, M.H. and Main E.K: Expression of the nonclassic histocompatibility antigen HLA-G by preeclamptic placenta. *Am. J. Obstet Gynecol* 170: 1244-1250, 1994.
30. Crosignani PG, Trojsi L, Attanasio A.E., and Combuoso Finzi GC: value of HCG and hCS measurement in clinical practice. *Obstet Gynecol.* 1974; 44, 673-681.

31. Cunningham F.G. and Lindheimer, M.D.; hypertension in pregnancy. *N. Engl. J. Med.* 326: 927-932, 1992.
32. Daunter B: Immunology of pregnancy: towards a unifying hypothesis *Eur J. Obstet Gynecol. Reprod Med.* 43: 81-95, 1992.
33. Dawn C.S.: Textbook of Obstetrics, 6th Edition, Dawn books, Calcutta, 1974; PP. 178-206.
34. Demers, L.M. and Gabbe S.G.: Placental prostaglandin levels in preeclampsia. *Am J. Obstet Gynecol* 126: 137-139, 1976.
35. Duda J.: Preeclampsia. Still an enigma. *West J. Med.* 164: 315-320, 1996.
36. Editorial: Systemic lupus erythematosus in pregnancy. *Lancet* 338: 87-88, 1991.
37. Erskine, K.J., Iversen S.A. and Davies R., An altered ratio of 18: 2(9,11) to 18:2(9,12) linoleic acid in plasma phospholipids as a possible predictor of preeclampsia. *Lancet I:* 554-555, 1985.
38. Fagan E.A.: Diseases of liver, biliary system, and pancreas. In, *Maternal fetal medicine. Principles and Practice.* R.K. Creasy and R. Resnik, eds. Saunders, Philadelphia, pp. 1054-1081, 1997.
39. Fitzgerald, D.J., Rocki W., Murray, R., Mayo G and Fitzgerald Hypertension. *Lancet* 335: 751-754, 1990.
40. Fix H: Calcification of the placenta. *J Obstet Gynaec Brit C' Wealth* 1964;7: 759.
41. Fox H., : Effect of hypoxia on trophoblast in organ culture. *Am. J. Obstet Gynecol.* 1970;107: 1058-1064.
42. Fox H.: Pathology of the placenta. Saunders Philadelphia 1978.
43. Fox H: Basement membrane changes in the villi of the human placenta. *J Obstet Gynaec Brit C Wealth* 1968;75: 302.
44. Fox H: Fibrosis of placental villi. *J Path Bact* 1968;95: 573.
45. Fox H: The incidence and significance of vasculosyncytial membrane in the human placenta. *J Obstet Gynaec Brit C Wealth* 1967;74: 28.
46. Fox H: The villous cytotrophoblast as an index of placental ischaemia. *J Obset Gynaec Brit C Wealth* 1964;71: 885.