Placenta and Reproductive Medicine

ORIGINAL ARTICLE

Placental histopathology according to amsterdam criteria and correlation with maternal and neonatal outcomes: A case-control study

Jinal Dhruv[1], Nandita Maitra[1,*], Samiksha R. Shindegalwekar[2], Srilakshmi P. Hiryur[2], Pooja Shah[1], Twinkle Sara[1], Sheetal Parmar[1]

[1]Department of Obstetrics and Gynecology, Medical College and Government of Gujarat and Sir Sayaji General Hospital, Baroda 390001, India

[2]Department of Pathology, Medical College and Government of Gujarat and Sir Sayaji General Hospital, Baroda 390001, India

ABSTRACT

Objective: To assess the placental histopathology (as per the Amsterdam consensus criteria) with fetal placental Doppler and maternal and fetal outcomes in subjects with pre-eclampsia (PE) with severe features versus normotensive control group. **Methods:** A case control study was conducted over a period of 1 year at Medical college, Baroda which evaluated 40 women who were divided into case group (20 PE with severe features) and control group (20 normotensives) after matching chronological age, gestational age and parity. Parametric tests such as independent *t*-test and sensitivity, specificity and odds ratio were calculated. **Results:** Placentae of subjects with PE with severe features were significantly small and having less weight than control group. Mean thickness of umbilical cord (UC) in case group was 0.70 ± 0.23 cm and mean thickness in control group was 0.96 ± 0.10 cm (*P* value < 0.0001). No significant difference was seen in Feto-placental ratio. Infarction was present in 65% of case group and 5% of control group. Decidual vasculopathy was seen in 90% of case group and was not at all seen in control group. Increased syncytial knots were seen in 100% of case group and 65% of control group (*P* = 0.0040). Vascular sclerosis and stromal fibrosis were seen more in case group than in control group (*P* = 0.0196 and < 0.0001 respectively). **Conclusion:** The Amsterdam classification was useful in delineating histopathological findings such as syncytial knots, infraction, decidual vasculopathy and villous stromal vascular karyorrhexis which were found to correlate with abnormal Doppler velocimetry and adverse maternal and neonatal outcomes. However, it was found to be tedious and time consuming.

Key words: pre-eclampsia with severe features, histopathology of placenta, Amsterdam consensus, feto-placental Doppler

INTRODUCTION

Pre-eclampsia (PE) has been previously defined as the new onset of hypertension accompanied by significant proteinuria after 20 weeks' gestation.[1] Recently, the definition of PE has been broadened. Now the internationally agreed definition of PE is the one proposed by the International Society for the study of Hypertension in pregnancy (ISSHP).[2]

A number of histopathological changes of the hypertensive placentae have been described; namely placental infarcts, increased syncytial knots; hypovascularity of the villi, increased cytotrophoblastic proliferation, thickening of the subtrophoblastic basement membrane, obliterated enlarged endothelial cells in the fetal capillaries and atherosis of the spiral arteries in the placental bed. The volume of the intervillous space and the terminal villi are also decreased in proportion to the degree of preeclampsia.[3,4] The 2015 Amsterdam placental

***Corresponding Author:**
Dr. Nandita Maitra, Department of Obstetrics and Gynecology, Medical College and SSG hospital, Baroda, Anandpura, jail road, Vadodara 390001, Gujarat, India.
Email: n.maitra03@gmail.com. https://orcid.org/0009-0007-3116-9641

Received: 11 February 2023; Revised: 15 March 2023; Accepted: 8 February 2024
https://doi.org/10.54844/prm.2024.0341

workshop group consensus statement published in 2015 recommended a standardized approach to describe histopathological placental finding [5] which has been endorsed by several authors and is intended to reduce the variability of placental examination.[6]

Kartheek *et al.*[7] in his study proved that placental abnormalities correlate well with the factors causing high risk pregnancies and the subsequent maternal and foetal outcomes. Placental examination may help in better understanding of the mechanism of placental dysfunctions that may contribute to more effective therapeutic strategies in the future. Paules *et al.*[8] found out that PE is associated with different patterns of histopathological lesions in accordance with the clinical manifestation of the placental disorder. Fetoplacental doppler findings show an association with placental malperfusion lesions on the maternal side, supporting the use of abnormal Doppler as a surrogate for placental insufficiency.

The Amsterdam criteria have been assessed so far in pregnancies with fetuses that are small for gestational age (SGA) or fetal growth restriction (FGR). They have not been studied in subjects with PE with severe features as the primary underlying risk factor. This study will assess the placental histopathology as per the Amsterdam criteria and correlate these changes with fetal Doppler studies and maternal and neonatal outcome.

MATERIALS AND METHODS

This was a prospective case control study performed in the delivery ward of the department of Obstetrics and Gynecology, SSG Hospital and Medical College Baroda. The objective of the study was to assess the placental histopathology (as per the Amsterdam consensus criteria) with fetal placental Doppler and maternal and fetal outcome in patients with PE with severe features versus normotensive control group. Subjects were recruited as per the following inclusion and exclusion criteria. This project was approved by the Institutional Ethics Committee for Biomedical and Health Research (IECBHR) of Medical College & SSG Hospital (No. IECBHR/08-2002).

Inclusion criteria

Case group: Singleton pregnancies with PE with severe features. Preeclampsia with severe features will be defined as per the recommendations given in ISSHP guidelines.[2] Control group: Normotensive controls matched for maternal age, gestational age and parity.

Exclusion criteria

(1) Pregnant women with gestational or pre-existing diabetes mellitus, connective tissue disorders (e. g., systemic lupus erythematosus), thrombophillic disorders. (2) Multiple pregnancies. (3) Placental tumors. (4) Placental abruption. (5) Smoking.

Sample size

A minimum convenience sample of 40 subjects coming were recruited as case group and control group. Case group: Pregnancies complicated by PE with severe features (N = 20). Control group: 20 placentae from pregnant women with uncomplicated pregnancies whose gestational age, maternal age and parity will be matched with study group will be selected as control group. The study began with inclusion of pregnant women with severe PE and ended with delivery and sending of placenta for histopathological reporting and monitoring maternal and fetal outcome.

The Following clinical data was collected. (1) Measurement of systolic blood pressure (SBP), diastolic blood pressure (DBP) and calculation of mean arterial pressure (MAP) using formula (MAP = DBP + [SBP – DBP]/3). (2) Umbilical artery Doppler and middle cerebral artery (MCA) Doppler on admission. Doppler was carried out to obtain the pulsatility index (PI) and in consented females. The Doppler ultrasound was performed by a senior radiology resident using the Mindray Machine (DC-N3, Mindray, Shenzhen, China) available on the delivery suite and with a curvilinear low frequency transducer. Umbilical artery measurements were taken in a free umbilical cord (UC) loop with insonation angle maintained below 30 degrees. PI was categorized as abnormal if the values are above 95th percentile for the gestational age.

Placenta

Placental Grossing was done as per following criteria given by Khong *et al.*[5] in 2016: (a) Weight; (b) Disc dimension: length, width, breadth; (c) Description of UC, coiling, coiling index, handedness, presence of strictures and knots; (d) Description of membranes: color/opacity, completeness of membranes; (e) Description of Lesions: grossly identified lesions with a measurement of the two maximal dimensions. (f) Placenta was fixed in 10% buffered formalin solution and was sent for HP examination to the Department of Histopathology, Medical College, Baroda. Placenta was processed and slides were prepared and read by the senior pathologist as per the Amsterdam criteria.

Outcomes

Primary outcome: Correlation of placental histopathology according to Amsterdam criteria with feto-placental Doppler in patients with preeclampsia with severe features and normotensive control group. Secondary outcome: Correlation of placental histopathology with Doppler

findings and its association with maternal morbidity, mortality and neonatal outcome.

Statistical analysis

Data was entered in an excel sheet and it was analyzed using the SPSS 26.0 statistical software version. The data was presented using frequency tables and charts. The doppler indices were analyzed as mean ± SD and comparison of the outcome variables will be performed using student's *t*-test. *P* value < 0.05 was considered as significant. Correlation of feto-placental Doppler and histopathology of placenta according to Amsterdam criteria was analyzed.

RESULTS

Table 1 shows the comparison of blood pressure, birth weight, placental weight and feto-placental ratio (FPR) amongst the case group and control group. The differences in systolic and diastolic blood pressure, birth weight and placental weight was statistically significant.

Table 2 shows the dimensions of the placenta and UC in case group and control group. Mean diameter of placenta in case group was 12.70 ± 2.41 cm while in control group it was 17.20 ± 2.53 cm (*P* value < 0.0001). Mean thickness of placenta in case group was 0.71 ± 0.20 cm while in control group it was 1.02 ± 0.18 (*P* value < 0.0001). Mean length of UC in case group was 33.70 ± 5.21 cm and mean length of UC in control group was 41.90 ± 14.15 cm with *P* value of 0.0200 which suggests that there is significant difference in length of umbilical.

Table 3 shows presence or absence of maternal vascular related histopathological features on the maternal side of placenta in case group and control group. Infarction was present in 65% of case group and 5% of control group in this study. Decidual vasculopathy (DV) was seen in 90% of case group and was not at all seen in control group making the importance of this findings in placentae of patients with PE with severe features. Increased syncytial knots were seen in 100% of case group and 65% of control group (*P* = 0.0040). The histological features which were statistically significant were the presence of syncytial knots, infarction, villous stromal karyorrhexis and diffuse villous vasculopathy.

Table 4 shows presence or absence of histopathological features on the fetal side of placenta in case group and control group. Villous stromal vascular karyorrhexis as seen in 30% of the case group and 5% of control group (*P* = 0.0399). Vascular sclerosis and stromal fibrosis were seen more in case group than in control group with *P* value 0.0196 and < 0.0001 respectively. Stromal fibrosis in PE placentae might be associated with activation of stromal fibroblasts by the TGF-β1 signaling pathway.

Table 5 shows various neonatal parameters amongst case group, control group and those who had positive placental histopathology in the form of decidual vasculopathy, increased syncytial knots, infarction and villous stromal karyorrhexis. The mean birth weight in the group with positive HP findings was 1614.05 ± 724.08 g whereas mean birth weight amongst case group was much less 1325.90 ± 611.68 g. This mean BW in the patients with positive HP findings was higher than that of case group and lower than in the control group (*P* value of BW in case group *vs.* positive HP finding was 0.1497 and p value of BW in control group *vs.* positive HP finding was 0.17). This observation was not statistically significant between case group and control group. All the 6 neonates who developed retinopathy of prematurity (ROP) were having abnormal HP finding in placentae. There were 2 neonatal deaths in the case group and in both of the fetuses, placentae had abnormal HP finding.

According to the results of this study, there was overlap between case group and control group. The 6 (15%) neonates who developed ROP had positive histopathology findings out of which 5 (25%) were case group and 1 was control (5 % of 20 control placentae). Similar comparison has been done for neonatal death. Despite of overlap being present, the results were positively skewed towards cases with positive histopathology findings.

Table 6 shows that Uterine artery PI was > 95th centile in 55% of case group and was not abnormal in any of the control group. Umbilical artery PI was > 95th centile in 80% of the case group and 20% of control group again representing vasoconstriction in maternal circulation in patients of PE with severe features. MCA PI was < 5th centile in 70% of the case group and 10% of control group suggesting vasodilatation in the fetal cerebral circulation to compensate reduced blood flow to fetus *i.e.*, brain sparing effect in patients of PE with severe features. All observations were highly significant.

Table 7 shows the histopathologic findings of Amsterdam criteria, infarction and decidual arteriopathy showed same correlation in terms of maternal morbidity and mortality making them useful tools while doing histopathology of placentae.

Table 8 shows the diagnostic accuracy of the histopathology parameters that were significant for adverse maternal outcomes on univariate analysis. Sensitivity of increased syncytial knots to identify adverse maternal outcomes *i.e.*, calculating the probability of a positive test when truly being positive

Table 1: Comparison of blood pressure, birth weight, placental weight and FPR in case group *vs.* control group

Group	Systolic blood pressure	Diastolic blood pressure	Birth weight	Placenta weight	Feto-placental weight ratio
Case group (*N* = 20)	166.50 ± 20.07	110.50 ± 9.45	1325.90 ± 611.68	223.80 ± 88.62	5.94 ± 1.58
Control group (*N* = 20)	113.50 ± 10.89	73.00 ± 4.70	1902.15 ± 744.89	352.00 ± 112.00	5.32 ± 1.34
P value	< 0.0001	< 0.0001	0.011	0.0003	0.1887

Data were presented as mean ± stardard deviation. FPR: Feto-placental ratio.

Table 2: Dimensions of umbilical cord and placenta amongst case group and control group

Group	Dimension of umbilical cord		Dimension of placenta	
	Mean length (cm)	Mean thickness (cm)	Mean diameter (cm)	Mean thickness (cm)
Case group (*N* = 20)	33.70 ± 5.21	0.70 ± 0.23	12.70 ± 2.41	0.71 ± 0.20
Control group (*N* = 20)	41.90 ± 14.15	0.96 ± 0.10	17.20 ± 2.53	1.02 ± 0.18
P value	0.02	< 0.0001	< 0.0001	< 0.0001

Data were presented as mean ± stardard deviation.

Table 3: Histology findings in case group and control group

Group	Decidual vasculopathy	Increased Syncytial knots	Intervillous deposition	Infarction	Calcification	Accelerated maturation	Delayed villous maturation		Distal villous hypoplasia	
							Diffuse	Focal	Diffuse	Focal
Case group (*N* = 20)	18 (90)	20 (100)	9 (45)	13 (65)	11 (55)	5 (25)	2 (10)	0	4 (20)	8 (40)
Control group (*N* = 20)	0	13 (65)	8 (40)	1 (5)	9 (45)	1 (5)	0	1 (5)	0	5 (25)
P value	-	0.004	0.7521	0.0001	0.5323	0.0803	-	-	-	0.3173

Data were presented as *N* (%).

Table 4: Fetal vascular malformations in case group and control group

Group	Avascular villi			Intramural fibrin deposition		Villous Stromal-Vascular Karyorrhexis	Vascular Ectasia	Villous sclerosis	Stromal fibrosis
	Small	Intermediate	Large	Recent	Remote				
Case group (*N* = 20)	12 (60)	7 (35)	1 (5)	2 (10)	5 (25)	6 (30)	13 (65)	10 (50)	20 (100)
Control group (*N* = 20)	5 (25)	1 (5)	0	0	0	1 (5)	8 (40)	3 (15)	6 (30)
P value	0.552			-		0.0399	0.118	0.0196	< 0.0001

Data were presented as *N* (%).

Table 5: Comparison of perinatal outcome with significant placental histopathological features

Group	Birth weight (g)	NICU stay (d)	Retinopathy of prematurity	Neonatal death
Positive placental histopathology (*N* = 40)	1614.05 ± 724.08	12.00 ± 1.75	6 (15)	2 (5)
Case group (*N* = 20)	1325.90 ± 611.68	11.59 ± 1.72	5 (25)	2 (10)
Control group (*N* = 20)	1902.15 ± 724.08	12.64 ± 1.69	1 (5)	0

Data were presented as mean ± stardard deviation and *N* (%).

Table 6: Comparison of Doppler changes in case group versus control group

	Uterine artery–PI > 95th centile	Umbilical artery–PI > 95th centile	Middle cerebral artery–PI < 5th Centile
Case group (*N* = 20)	11 (55)	16 (80)	14 (70)
Control group (*N* = 20)	0	4 (20)	2 (10)
P value		0.0001	0.0001

Data were presented as *N* (%). PI: pulsatility index.

Table 7: Adverse maternal outcomes in abnormal histopathology

Abnormal histopathology	No complication	Eclampsia	PRES syndrome	HELLP syndrome	Maternal death	Acute respiratory distress syndrome	Disseminated intravascular coagulation	Postpartum hemorrhage
Accelerated villous maturation (*N* = 8)	1 (2.5)	2 (5)	0	1 (2.5)	0	1 (2.5)	2 (5)	1 (2.5)
Infarction > 5% (*N* = 26)	8 (20)	4 (10)	2 (5)	3 (7.5)	2 (5)	2 (5)	3 (7.5)	2 (5)
Decidual arteriopathy (*N* = 24)	5 (12.5)	4 (10)	2 (5)	3 (7.5)	2 (5)	2 (5)	3 (7.5)	3 (7.5)

Data were presented as *N* (%). PRES: posterior reversible encephalopathy syndrome; HELLP: hemolysis, elevated liver enzymes, low platelet count.

Table 8: Diagnostic accuracy of significant histopathology findings in relation to maternal adverse outcomes

Histopathology finding	Sensitivity	Specificity	AUC	OR with 95% CI	*P* value
Increased syncytial knots	45.56%	100%	0.727	22.78	0.037
Villous stromal vascular karyorrhexis	85.71%	72.73%	0.792	8.14	0.065
Villous infarct	83.33%	70.59%	0.770	6.33	0.108
Decidual vasculopathy	72.22%	90.91%	0.816	30.34	0.00003

AUC: area under the curve; OR: odds ratio; CI: confidence interval.

was 45.46%. Specificity of increased syncytial knots to identify mothers without adverse maternal outcomes correctly *i.e.*, ability of the test to correctly classify an individual as disease free was 100%. This means that if the placenta did not show features of increased syncytial knots, there were no mothers who were having adverse outcomes in our study. Odds ratio of increased syncytial knots was 22.78 which means that the finding was 22.78 times higher in case group than in control group. Odds ratio of Villous Stromal vascular karyorrhexis was 8.1429 which means that the finding was 8.143 times higher in case group than in control group.

Sensitivity of Decidual vasculopathy to identify adverse maternal outcomes *i.e.*, calculating the probability of a positive test when truly being positive was 83.33%. Specificity of Decidual vasculopathy to identify mothers without adverse maternal outcomes correctly *i.e.*, ability of the test to correctly classify an individual as disease free was 90.91%.

DISCUSSION

This case control study was undertaken to identify placental histopathology according to Amsterdam criteria and to correlate it with feto-placental Doppler, maternal and neonatal outcome in patients with PE with severe features *vs.* normotensive control group. Case group and control group were matched for maternal age, gestational age and parity.

There were significant different between case group and control group in terms of gross features of placenta and UC. These findings are in accordance with the studies of Tiruneh *et al.* [9] and Mehare *et al.* [10]

The histological features which were statistically significant in the present study were the presence of syncytial knots, infarction, villous stromal karyorrhexis and diffuse villous vasculopathy. Vascular sclerosis and stromal fibrosis were seen more in case group than in control group with *P* value 0.0196 and < 0.0001 respectively.

Pietro *et al.* [11] showed that large morphological changes were present in cases of early onset PE, such as hypoxia,

villous infarctions and hypoplasia, among others, in an attempt to stabilize the blood flow to the fetus. Minimal infarcts are not unusual findings in placentas delivered at term and are considered to be due to placental "aging". In preeclampsia/eclampsia, however, there is accelerated "aging", and widespread infarcts are common findings. Heider[12] showed that multiple histologic patterns of fetal vascular malperfusion have been described including thrombosis, avascular villi, villous stromal-vascular karyorrhexis, intramural fibrin thrombi, and stem villous vascular obliteration. Various underlying etiologies can be involved in fetal vascular malperfusion.

The fetal Doppler velocimetry was significantly abnormal in subjects with abnormal histopathological features in the placenta. This is in agreement with the studies of Adekanmi *et al.*[13] in 2019 and Khatri *et al.*[14] in 2021.

Several histopathologic findings of Amsterdam criteria, like infarction, decidual vasculopathy, villous stromal vascular karyorrhexis and increased syncytial knots showed positive correlation with adverse maternal and neonatal outcomes. All the 6 neonates who developed ROP and 2 neonates who died were having abnormal HP finding in placentae.

This study is different because the Amsterdam criteria checklist have been used to study the hispothological changes in the placenta and correlate these changes with clinical outcomes. Not many studies exist using these criteria. Moreover, the study has attempted to find the diagnostic accuracy (sensitivity and specificity) of significant histopathological findings in the prediction of adverse clinical outcomes. This study has also tried to postulate whether or not Doppler parameters of ultrasonography can be used as a surrogate marker instead of exhaustive Amsterdam Consensus. But to prove this point, studies on larger scale are required.

CONCLUSION

The Amsterdam classification was useful as an objective assessment tool in delineating histological characteristics such as infarction, syncytial knots, decidual vasculopathy and villous stromal karyorrhexis in subjects with severe PE as compared to normotensive control group. The findings of abnormal histopathology may not be specific to one disorder such as preeclampsia that was studied in this group. Since it is a post natal diagnosis, it is unlikely to serve as a management tool. Limitations of this study were a small sample size. This study did not consider any grading or staging of the lesions, as it focused on the presence/absence of the specific placental findings to reveal placental pattern according to the Amsterdam consensus.

DECLARATION

Author contributions

Dhruv J: Conceptualization and Writing original draft; Dhruv J, Shindegalwekar SR: Writing reviewing; Maitra N: Supervision.

Ethics approval

This project was approved by the Institutional Ethics Committee for Biomedical and Health Research (IECBHR) of Medical College & SSG Hospital (No. IECBHR/08-2002).

Source of funding

Not applicable.

Conflict of interest

The authors declare no competing interest.

Data availability statement

No additional data.

REFERENCES

1. Hypertension in pregnancy: diagnosis and management. London: National Institute for Health and Care Excellence (NICE);2019.
2. Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, *et al.* The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. *Int J Gynaecol Obstet* 2019;145(Suppl 1):1-33. Erratum in: *Int J Gynaecol Obstet* 2019;146:390-391.
3. Soma H, Yoshida K, Mukaida T, Tabuchi Y. Morphological changes in the hypertensive placenta. *Contrib Gynecol Obstet* 1982;9:58-75.
4. Pasricha N, Nagar A, Gupta A. Histological changes in placental in pregnancies complicated by pre-eclampsia and eclampsia and correlation with fetal outcome. *Int J Pharma Bio Sci* 2012;3:551-560.
5. Khong TY, Mooney EE, Ariel I, Balmly NC, Boyd TK, Brundler MA, *et al.* Sampling and definations of placental lesions: Amsterdam Placental Workshop Group Consensus Statement. *Arch Patholab Med* 2016;140:698-713.
6. Redline RW. Classification of Placental Lesions. *AM J Obstet Gynecol* 2015;213:521-528.
7. Kartheek BVS, Atla B, Prasad U, Namballa U, Prabhakula S. A study of placental morphology and correlation with colour doppler ultrasonography, maternal and neonatal outcome in high risk pregnancies. *Int J Res Med Sci* 2018;6:3364-3369.
8. Paules C, Youssef L, Rovira C, Crovetto F, Nadal A, Peguero A, *et al.* Distinctive patterns of placental lesions in pre□ eclampsia vs small□ for□ gestational age and their association with fetoplacental Doppler. *Ultrasound Obstet Gynecol* 2019;54:609–616.
9. Tiruneh ST, Bekele A, Guday E, Muche A. Macroscopic morphological variation of human placenta in normotensive and pre-eclamptic pregnant mothers, Northwest Ethiopia. *Eur J Anat* 2018;22:489-495.
10. Mehare T, Kebede D. Fetoplacental weight relationship in normal pregnancy and pregnancy complicated by pregnancy-induced hypertension and abruption of placenta among mothers who gave birth in Southern Ethiopia, 2018. *Obstet Gynecol Int* 2020;2020:6839416.

11. Pietro L, Guida JPS, Nobrega GM, Antolini-Tavares A, Costa ML. Placental Findings in Preterm and Term Preeclampsia: An Integrative Review of the Literature. *Rev Bras Ginecol Obstet* 2021;43:560-569.
12. Heider A. Fetal Vascular Malperfusion. *Arch Pathol Lab Med* 2017;141:1484-1489.
13. Adekanmi AJ, Roberts A, Akinmoladun JA, Adeyinka AO. Uterine and umbilical artery doppler in women with pre-eclampsia and their pregnancy outcomes. *Niger Postgrad Med J* 2019;26:106-112.
14. Khatri R, Jain B, Mhapankar S, Kumar S. A study of Doppler velocimetry in pre-eclampsia patients, and their perinatal outcome. *Clin J Obstet Gynecol* 2021;4:44-49.