Original Article

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Pathology Section

Histopathological Changes of Placenta in Maternal Hypertensive Disorders and its Association with Birth Weight: A Case-control Study

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ABSTRACT

Introduction: One of the most common complications during pregnancy is hypertension. It leads to pathological changes which reduce the placental blood flow. Hypertensive disorders are strongly associated with foetal growth restriction, prematurity, lower foetal birth weights and contribute largely to perinatal mortality and morbidity.

Aim: To study the histomorphological changes of placenta in cases of maternal hypertensive disorders and compare it with normal controls as well as find out its association with neonatal birth weight.

Materials and Methods: A case-control study was conducted at the Department of Pathology of a Tertiary Care Hospital, Faridabad, Haryana, India. Duration of the study was two months from July to August 2018. This study is a part of Indian Council of Medical Research (ICMR) Short Term Studentship (STS) scheme for MBBS students. Control group was formed by 30 placenta of full term deliveries without any complications and 30 placenta of the females presenting with hypertensive pregnancies formed the case group. Specimens of placenta were studied in detail for morphological and histological changes. Neonatal Birth weight was recorded just after delivery of all the cases and controls. Analysis of statistical difference between the means of both groups was performed using student unpaired t-test. The data obtained was entered in Microsoft excel sheet and statistically analysed using Epi Info version 7.

Results: Mean maternal age for cases was 28.60 years and controls were 25.23 years. This association was found to be significant. Mean for gestational weeks at the time of delivery was 34.93 weeks in cases and 37.20 weeks in controls (p-value <0.0001). Average placental weight in cases was 410.20 grams and in controls was 480.80 grams (p-value <0.001). Histopathological changes comprised of syncytial knot formation, cytotrophoblasts proliferation, proliferation of endothelial lining of capillaries, stromal fibrosis, calcification, hyalinisation of villi and infarction were comparatively more frequent in cases (n=30). Mean neonatal birth weight was found to be 2809.67±128.32 grams in control group as compared 2427.67±152.22 grams in cases (p-value <0.001).

Conclusion: During pregnancy significant histomorphological changes in placenta are caused due to hypertensive disorders which lead to harmful and severe foetal outcomes. A valuable insight into the mechanism of placental dysfunction can be achieved through a detailed examination after delivery.

Keywords: Calcification, Hypertension, Infarction, Placenta, Pregnancy

INTRODUCTION

Hypertension is one of the common disorders encountered in pregnancy leading to significant morbidity and mortality [1]. Hypertension, hemorrhage and infection: this deadly triad results in large number of maternal and foetal deaths [2]. Chronic hypertension with superimposed Preeclampsia (PE) and gestational hypertension complicate up to 10% of deliveries and form most important cause of disease and mortality, according to the classification of the American College of Obstetricians and Gynaecologists (ACOG) [3].

Placenta plays a central role in pregnancy. It plays a vital role in the progress of the foetus in utero and thus known as the mirror of maternal and foetal status [4]. The pathology of the placenta gives the precise estimate of an infant's prenatal journey [5]. Examination of the placenta and umbilical line is important to recognise what is happening to the foetus [3]. A number of histological changes occur in preeclamptic/eclamptic placentas. Some of them are infarcts, increased syncytial knots, subchorionic fibrin deposition, calcification, hypo vascularity of the villi, cytotrophoblastic proliferation, thickening of the trophoblastic membrane, obliterative enlarged endothelial cells in the foetal capillaries, and atherosis of the spinal arteries in the placenta bed [3].

Pregnancy Induced Hypertension (PIH) has adverse effects on the health of foetus through its harmful effects on the placenta [5]. Poor placentation and endothelial dysfunction are the characteristic features of PE. It carries an increased risk of progression to eclampsia. Possibility of convulsion increases leading to complications, even mother and foetal deaths [6].

The present study was undertaken to analyse the histomorphological changes in the placentas of normal and hypertensive mothers and to study its association with birth weight.

MATERIALS AND METHODS

A case control study was conducted at the Department of Pathology of a Tertiary Care hospital in Faridabad, Haryana, India, from July and August 2018. This study was conducted under the Indian Council of Medical Research STS scheme for MBBS students and with the permission of the Institutional Ethics Committee of the College (134/A/11/16/Academics/MC/2016/104 dated 18.06.2018).

Control group was formed by 30 placenta of full term deliveries without any complications and 30 placenta of the females presenting with hypertensive pregnancies composed the case group (Blood Pressure ranged 140/90 mmHg or above with/without oedema and/or proteinuria and convulsions).

Inclusion criteria:

Cases: Placenta of Pregnant women presenting with hypertensive pregnancies, between 20-35 years of age, having one foetus (live)

in the duration of 34-40 weeks of gestation delivered only through caesarean section were included.

Control: Placenta of Pregnant women presenting with uncomplicated full term deliveries, between 20-35 years of age, having one foetus (live) in the duration of 34-40 weeks of gestation delivered only through caesarean section were included.

Exclusion criteria: Women suffering from hypertension before pregnancy, diabetes mellitus, hypothyroidism, anemia, cardiac disease, abruptio placentae, multiple pregnancies, jaundice and maternal malnutrition were excluded from the study.

Study Procedure

Immediately after delivery, the placenta including umbilical cord and membranes were collected. Specimen were submitted immersed in 10 % formalin from operation theatre and processed immediately.

Gross examination: Placenta was washed with water and weighed in grams after completely draining blood from it. Formalin fixation was done next. Measuring tape was used to record the placental diameter in centimeters. Physical features like general shape and gross abnormalities were recorded. Gross abnormalities were quantified using semi quantitative methods. This was further confirmed by microscopic examination. Placenta were cut in two equal halves along maximum diameter and then further cut in small pieces. One section from central area and one from peripheral area were taken. Some sections were taken from abnormal lesions. These sections were stained using Haematoxylin and Eosin (H&E) stain. From each section a hundred villi were counted and histological changes present in them were presented as percentage. Bedside blood pressure measurement and brief clinical history was taken of all the cases and controls. Neonatal birth weight was recorded just after delivery of all the cases and controls.

STATISTICAL ANALYSIS

The data obtained was entered in Microsoft excel sheet and statistically analysed using Epi Info version 7. The statistical analysis was done using student unpaired t-test. Statistical significance was set at p-value 0.05.

RESULTS

Data of females attending Outpatient Department (OPD) antenatal clinic during two months (research period) was collected. Analysis showed that out of 1780 females screened, 6.9% reported positive for PIH. Mean maternal age for cases was 28.60 years and controls was 25.23 years. This association was found to be significant. Mean for gestational weeks at the time of delivery was 34.93 weeks in cases and 37.20 weeks in controls (p-value <0.0001) which is statistically significant.

Both systolic and diastolic blood pressures measured were significantly associated in cases and the control group [Table/Fig-1].

Variables	Cases	Controls	t value, p-value
Mean Maternal Age (±2SD)	28.60 (3.70)	25.23 (3.75)	3.49, 0.001
Mean gestation age (±2SD) in weeks	34.93 (1.76)	37.20 (1.56)	-5.27 , 0.0001
Mean SBP (±2SD) mmHg	157.80 (9.64)	121.53 (7.11)	16.56, <0.001
Mean DBP (±2SD) mmHg	97.00 (5.55)	80.26 (3.81)	13.61, <0.001

[Table/Fig-1]: Baseline profile of Case and Control group (n=30).

Of the thirty cases, 53% were tested positive for proteinuria and 50% for oedema in extremities. None of the controls presented with these findings [Table/Fig-2].

Convulsions were observed among four cases which belonged to case group (4/30=13.3%). Eclampsia was diagnosed among 25% of cases with pre-eclampsia (4/16). Average placental weight in cases was 410.20 grams and in controls was 480.80 grams. This association was highly significant (p-value <0.001).

Parameters	Cases (n=30)	Controls (n=30)	Total (n=60)	Chi-square, p-value
Proteinuria				
Present n (%)	16 (53.3)	0	16 (26.7)	21.82, <0.001
Absent n (%)	14 (46.7)	30 (100)	44 (73.3)	
Oedema				
Present n (%)	15 (50)	0	15 (25)	20.00, <0.001
Absent n (%)	15 (50)	30 (100)	45 (75)	
Mean placental weight (±2SD) in grams	410.20 (24.67)	480.80 (32.78)		-9.424, <0.001
Gross abnormalities in placenta				
Absent n (%)	3 (10)	26 (86.6)	29 (48.2)	37.95, <0.001
Focal n (%)	18 (60)	4 (13.3)	22 (36.6)	
Extensive n (%)	9 (30)	-	9 (15)	
Mean Birth weight of foetus (±2SD) in grams	2427.67 (152.22)	2809.67 (128.32)		10.51, <0.001

[Table/Fig-2]: Distribution of signs and symptoms of hypertensive pregnancy among cases and controls and its outcome (in placenta).

Histopathological changes comprising of syncytial knot formation, cytotrophoblasts proliferation, proliferation of endothelial lining of capillaries, stromal fibrosis, calcification, hyalinisation of villi and infarction were comparatively more frequent in cases than in control [Table/Fig-3,4]. All the findings were statistically significant.

Histopathological characteristics of placenta	Cases (n=30)	Controls (n=30)	Total (n=60)	Chi-square, p-value
Syncytial knot formation				
Present (>50/100 Villi), n (%)	13 (43.3)	2 (6.7)	15 (25.0)	10.75, 0.002
Absent (0-50/100 Villi), n (%)	17 (56.7)	28 (93.3)	45 (75.0)	
Cytotrophoblasts proliferation				
Present (>10/100 Villi), n (%)	13 (43.3)	3 (10.0)	16	8.52, 0.007
Absent (0-10/100 Villi), n (%)	17 (56.7)	27 (90.0)	44	
Proliferation of endothelial lining of capillaries				
Present (>5/lpf), n (%)	10 (33.3)	0	10 (16.7)	12.00, 0.001
Absent (0-5/lpf), n (%)	20 (66.7)	30 (100)	50 (83.3)	
Stromal fibrosis				
Present, n (%)	3 (10.0)	2 (6.7)	5 (8.3)	0.218, 1.00
Absent, n (%)	27 (90.0)	28 (93.3)	55 (91.7)	
Calcification				
Present (>2/10 lpf), n (%)	11 (36.7)	1 (3.3)	12 (20.0)	10.42, 0.002
Absent (0-2/10 lpf), n (%)	19 (63.3)	29 (96.7)	48 (80.0)	
Hyalinisation of villi				
Present, n (%)	11 (36.7)	2 (6.7)	13 (21.7)	7.95, 0.01
Absent, n (%)	19 (63.3)	28 (93.3)	47 (78.3)	
Infarction				
Present, n (%)	10 (33.3)	0	10 (16.7)	12.00, 0.001
Absent, n (%)	20 (66.7)	30 (100)	50 (83.3)	

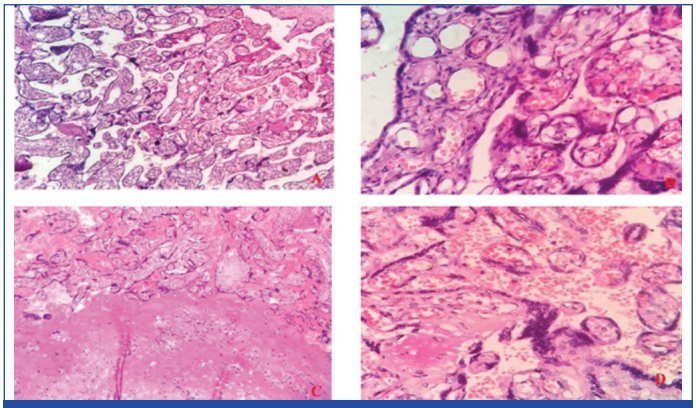
[Table/Fig-3]: Histopathological changes in cases and controls.

Mean neonatal birth weight [Table/Fig-2] was found to be 2809.67±128.32 grams in control group as compared 2427.67±152.22 grams in cases (p-value <0.001).

DISCUSSION

Placenta plays the role of a bridge between mother and foetus. Healthy placenta leads to a healthy pregnancy. Its histomorphological examination forms an essential role in determining etiopathogenesis and mechanism of toxaemic pregnancies. This helps the obstetrician to manage its consequences and fix the complication to great extent [7].

In the present study, mean maternal age for cases was 28.60 years and controls were 25.23 years. Gaur S et al., Sankar KD et al., and



[Table/Fig-4]: Photomicrograph showing; (a) Syncytial knot formation (H&E; 100X); (b) Syncytial knot formation (H&E, 400X); (c) Cytotrophoblasts proliferation, proliferation of endothelial lining of capillaries, stromal fibrosis (H&E; 40X); d) Calcification hyalinisation of villi and infarction (H&E; 400X).

Saleh RA et al., also noted similar findings [4,8,9]. Gaur S et al., and Saleh RA et al., did not find statistically significant correlation in their studies [4,9]; which is in contrast to findings of present study and study done by Sankar KD et al., where significant association was found [8]. The mean gestational age in the present study was 34.93 weeks in cases and 37.20 weeks in control group. Age in cases was lower than control group. Gestational age was reported to be 36.42±2.69 weeks in PE and 38.20±2.11 weeks in control group by Gaur S et al., [4]. Statistically significant association ($p<0.001$) in gestational age was reported in the present study and other studies [4,9,10]. Reduced uteroplacental circulation leading to foetal hypoxia can be one of the possible explanations [4].

The mean placental weight was less in cases (410.20 grams) when compared to control group (480.80 grams) in the present study. The mean placental weight of hypertensive pregnancies was observed to be 409±88.69 g whereas, 581±91.38 g in controls by Porwal V et al., [11]. Similar findings have been reported by Mallik GB et al., & Londhe PS et al., [12,13]. Salmani D et al., observed placental weight to be less in PE (395.15±63.40) and eclampsia (382.35±75.46) when compared with controls (519.80±59.23) [14]. Placental weight was found to be less in preeclamptic group in comparison to control group in study done by Samal R et al.,; Verma E and Kalra R [7,15]. Cibilis LA observed similar findings and concluded that an underlying pathological process was interfering with the normal growth of placenta [16]. Placentae were reported to be smaller in PE when compared to uncomplicated pregnancies by Fox H [17]. The placentae were lighter in PIH (405.2 gm) as compared to control (489.1 gm) and inverse relation was observed between weight and grade of PIH by Kambale T et al., [18].

In the present study, 13 cases (43.3%) had Syncytial knot formation when compared with controls. Syncytial knot formation in placental villi reflects maturity of the placenta. They may be due to placental insufficiency [11]. Syncytial knot density showed statistically significant difference between PE (16.78±2.42) and control group (8.95±0.79) in study done by Gaur S et al., [4]. Porwal V et al., found more number of syncytial knots in study group (93.33%) in comparison to controls (6.67 %) [11]. Eclampsia (100%) and severe PIH (84%) cases showed knot count increase in study done by Kurdukar MD et al., [19]. All cases of severe PIH and eclampsia revealed greater than 30% syncytial knots when viewed under low power in study done by Kambale T et al., [18]. Majumdar S et al., observed similar findings [20].

The purpose and development of syncytial knots is yet to become fully clear. They are thought to be part of a degenerative phenomenon i.e., change due to ageing, a syncytial hyperplasia and trophoblastic ischaemia or hypoxia. Reduced perfusion result in numerous syncytial knots [4]. Reduced foetal blood flow through the villi in toxaemia cases and normal aging process results in stromal fibrosis [4]. In the present study, stromal fibrosis was seen in 3 cases (10%) and 2 controls (6.7 %). Porwal V et al., found a higher percentage of stromal fibrosis (63.33%) in the study group [11].

Calcification is a sign of placental ageing or maturation [11]. In the present study, 11 cases (36.7%) and one control (3.3%) had presence of calcification. Porwal V et al., found 60% calcification in normal placenta [11]. Goswami P et al., observed 66% overall incidence of calcification in PIH cases [21]. Dutta DK et al., [22] observed presence of calcification in 12.5% cases of normal pregnancy (4 out of 32) and 44.3% of PIH group (26 out of 59 cases). Of the 50 cases of normal pregnancy 8% i.e., four cases and 14.3% i.e., 7 of 49 cases were observed with calcification in study done by Kurdukar MD et al., [19]. Fox H had included cases who delivered before term in his study and found the incidence of calcification was lower in PIH compared to normal group [17]. Kambale T et al., found 12 out of 45 (26.6%) placentae of PIH showed calcification out of this 4 (100%) cases belong to eclampsia, 5 (33.3%) cases belong to severe PIH, and 3 (11.5%) cases belong to mild PIH [18]. Hence, the authors concluded that the incidence of placental calcification increases as the severity of the hypertension increase.

Placental infarction denotes an area of ischemic villous necrosis secondary to thrombotic occlusion of the maternal uteroplacental blood vessels [11]. It is seen in pregnancies complicated by PIH. In the present study 10 cases (33.3%) had presence of infarction whereas no controls showed infarction. Major difference was observed while comparing presence of infarction in control and cases (p-value 0.001). Significant infarction was seen in hypertensive cases by Porwar V et al., (>5% surface area involved in 40% cases in study group), Kambale T et al., (increase in incidence of infarction in PIH group 28.8%), Das B et al., Udainia A et al.,; Narsimha A et al., [11,18,23-25]. Placental infarction was found among 46% of cases and 10% of controls in study done by Sammadar A et al., [26].

Mean neonatal birth weight was found to be 2809.67±128.32 grams in control group as compared to 2427.67±152.22 grams in cases (p-value <0.001) in our study. Gore CR et al., (2853±320 gm, 2516±385 gm) and Kambale T et al., (2739.7g, 2079.6 g) observed mean birth weight of babies in PIH group was lower when compared with control group [2,18]. Similar to our findings Majumdar S; Kurdukar MD et al., and Shevade S et al., found foetal birth weights were lower in cases of PE [19,20,27]. Mean birth weight of newborns to hypertensive and normotensive mothers was found to be 2464 g and 2847 g, respectively in study done by Sammadar A et al., [26]. In PIH, due to maternal vasospasm the blood flow from maternal utero-placenta is decreased. This results in indirect constriction of foetal stem arteries. Such babies are mostly small for date [2].

In the present study, cytotrophoblastic proliferation was observed more in cases when compared to controls i.e., 13 cases (43.3%) and 3 controls (10%). Findings of the present study are comparable to study done by Kambale T et al., who observed that the percentage of cytotrophoblastic proliferation of villi (>20%) increased in the placenta in all the severe PIH and eclampsia cases as compared to the normal group [18]. Kartheek BVS et al., recorded abnormal cytotrophoblastic proliferation in 36.36% of hypertensive pregnancies as compared to normal ones [28].

Limitation(s)

One of the major limitation of our study was its small sample size. This was due to time specification of two months to conduct the project by ICMR. Hence, the results cannot be generalised for larger population. To establish a clear association and assess the various parameters involved, studies need to be conducted on larger sample size. Hence, the earlier the disorder is diagnosed and confirmed, the better the foetal and maternal outcomes [29].

CONCLUSION(S)

During pregnancy significant histomorphological changes in placenta are caused due to hypertensive disorders which lead to harmful and severe foetal outcomes. The villous lesion in hypertensive placenta like cytotrophoblasts proliferation, proliferation of endothelial lining of capillaries, stromal fibrosis, calcification, hyalinisation of villi and infarction were found to be statistically significant in cases. A valuable insight into the mechanism of placental dysfunction can be achieved through a detailed examination after delivery.

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