



The spectrum of placental pathology in spontaneous preterm labor and its relationship to perinatal outcomes: A prospective cross-sectional study at a tertiary care hospital in Kolkata

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ABSTRACT

Background

Preterm birth is the leading cause of perinatal deaths worldwide and has a significant impact on public health. Numerous factors can lead to preterm birth, but frequently no cause is understood. This study was conducted with an objective to identify the various patterns of placental histomorphology in spontaneous preterm labour and the association of those findings with perinatal outcomes.

Method

This prospective comparative study was conducted at a tertiary care hospital in Kolkata from February 2022 to January 2023. The sample size was estimated with the Kelsey equation that showed 52 participants were required for each study group. Placentae of 104 uncomplicated spontaneous deliveries of term (37- 40 weeks) and preterm labor (28 - 36 weeks) were randomly collected along with evaluations of respective perinatal outcomes. Each specimen was studied by gross findings, and generous sections were taken from the fetal and maternal surfaces, membranes, and umbilical cords. Light microscopic examinations of 30 high-power fields of each section were evaluated by two independent pathologists using different histomorphological parameters and graded accordingly. Each parameter of placental pathology, identified in preterm labor was statistically compared with perinatal outcome, assuming the term placentae as control.

Result

Preterm placentas had reduced weight and diameter in respect to gestational age, and the majority showed decreased intervillous space, syncytial knot, terminal villous vascularity and stem villous fibrosis; but a significant increase in number of Hofbauer cells, perivillous and intravillous fibrin deposition, features of acute chorioamnionitis, villitis and fetal obstructive vascular lesions. In preterm labor chorioamnionitis (CA) was significantly associated with poor perinatal outcomes, like early neonatal sepsis [odds ratio (OR) 15; p=0.006], respiratory distress syndrome (OR 4.7; p=0.042), hypoxic-ischemic-encephalopathy (HIE, OR 23; p=0.001), cardiovascular complications and more so, when it is associated with villitis and fetal obstructive vascular lesions. A total of 68.7% of preterm newborns died of HIE, whereas the majority (94.23%) of the term newborns developed no complications.

Conclusion

There is a strong association between histologic chorioamnionitis, villitis, and placental vasculopathy with an increased risk of spontaneous preterm labor as well as adverse perinatal outcomes. Hypoxic-ischemic-encephalopathy is one of the major factors of perinatal mortality in preterm newborns.

Key words: Spontaneous preterm labor; histologic chorioamnionitis; fetal obstructive vascular lesions; perinatal outcomes

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INTRODUCTION

Preterm birth (PTB) poses a significant worldwide public health burden, and its importance lies in the fact that it accounts for 75% of perinatal mortalities and more than 50% of long-term infant morbidity, and when lethal anomalies are excluded, 85% of all neonatal deaths occur in preterm infants.² India has a substantially greater incidence of neonatal death than developed nations.³ Even though the rate of spontaneous PTB is rising, the precise etiology is still unknown, especially in cases of uncomplicated pregnancies.^{4,5}

The placenta is the vital organ that connects mother and fetus during pregnancy, and is essential for fetal growth and development as it facilitates the exchange of nutrients and oxygen with the fetus, eliminates waste elements, and acts as a barrier to toxins and infective organisms. Therefore, pathologic abnormalities that disrupt placental function may lead to morbidity or even mortality in both the mother and fetus.^{1,6-9}

An assessment of specific patterns of placental pathology in relation to gestational ages is useful for resolving issues arising from pregnancy complications, including poor fetal outcomes and perinatal loss.¹⁰ It will also guide the clinicians for future investigations and interventions relating to pre-pregnancy counselling, antenatal care, as well as modification of early treatment in neonatal intensive care units (NICU).^{11,29,32,33}

The correlation between placental lesions and unfavourable outcomes has been widely reported; however, currently, there is a lack of knowledge regarding the association between placental pathology in spontaneous preterm labor (SPTL) and perinatal outcomes. Therefore, this study was performed to provide new insights into the various histomorphometric patterns of placenta in uncomplicated SPTL and the relationship between those changes with perinatal outcomes in the Indian population.

Methodology:

A prospective cross-sectional study was performed on the placentae of 104 singleton uncomplicated pregnancies [52 preterm (28-36 weeks); 52 term (37-40 weeks)] with respective preterm and term neonates at the R.G. Kar Medical College and Hospital, a tertiary referral centre in Kolkata from February 1st, 2022 to January 31st, 2023. The sample size was estimated

using the formula $N_{\text{Kelsey}} = \frac{(\frac{Z_{\alpha}}{2} + Z_{\beta})^2 p(1-p)(r+1)}{r(p_0 - p_1)^2}$

assuming level of significance corresponding to 95% confidence level $Z_{\alpha/2} = 1.96$, power of study $Z_{\beta} = 0.84$, ratio of cases and control $r = 1:3$ that showed 52 participants were required for each study group to detect the correlations as per previous research by Ogunyemi et al³³. After obtaining approval from the institutional ethics committee and informed consent from the participants, this study was carried out. The placentae were selected by simple random sampling and collected from the labor room and operation theatre of the gynecology and obstetrics department. The preterm placentae of spontaneous preterm labor having an uncomplicated antenatal period were included in this study, while the cases having a previous history of PTB, premature rupture of membrane, incompetent cervix, uterine malformation, indicated PTB, any medical illness, multiple pregnancies, congenital malformation, and history of trauma or addiction were excluded. Findings of the clinical examination and history of the mothers were collected from individual bed-head tickets and antenatal cards. The preterm and term newborns were followed up for the first seven days after birth and their different clinical and laboratory parameters, including gross congenital anomalies, birth weight, Apgar score at 1 and 5 minutes, the necessity of mechanical ventilator support, and duration of NICU stay, were collected, respectively, from the NICU and postnatal ward. At the end of the early neonatal period, the outcomes of those neonates were also recorded and analyzed.

The placental specimens were fixed in 10% neutral buffered formalin overnight after being thoroughly examined. Full-thickness sections were taken from the fetal and maternal surfaces, membrane, and umbilical cord of each placenta and prepared for paraffin embedding. Sections of 5 μ thickness were obtained from each block and stained with a haematoxylin-eosin stain. Under the light microscope, 30 high-power-field (HPF) of each sample were examined by two independent pathologists, and the occurrence of different features like intervillous space (IVS), syncytial knot (SK), intravillous fibrinoid (IVF), perivillous fibrinoid (PVF), Hofbauer cells, vessel density, histologic chorioamnionitis (HCA) including maternal inflammatory response (MIR) and fetal

inflammatory response (FIR), villitis and fetal obstructive vascular lesions were graded and expressed with percentages. At the end, the

specific histopathological patterns of both term and preterm placentae were correlated with perinatal outcome.

Microscopically, the following placental parameters were noted and graded^{1,6,8}:

1. IVS (space between the chorionic villi)		
Grade 1	Narrowed	
Grade 2	Normal	
Grade 3	Widened	
2. IVF (Fibrin deposition within the villi)		
Grade 1	Normal deposition	
Grade 2	Mildly increased deposition	
Grade 3	Markedly increased deposition	
3. PVF (Fibrin deposition surrounding the villi)		
Grade 1	Normal deposition	
Grade 2	Mildly increased deposition	
Grade 3	Markedly increased deposition	
4. Acute chorioamnionitis: is maternal (MIR) and fetal inflammatory response (FIR) to infectious agents that have gained access to the gestational sac. Both parameters were graded as per the Perinatal Section of the Society for Paediatric Pathology ¹		
CA-MIR	Stage-0	Absent
	Stage-1	Acute subchorionitis/early chorionitis
	Stage-2	Chorionitis/chorioamnionitis
	Stage-3	Necrotizing chorioamnionitis
	Stage-4	Subchorionic microabscesses
CA-FIR	Stage-0	Absent
	Stage-1	Umbilical phlebitis/chorionic vasculitis
	Stage-2	Umbilical arteritis
	Stage-3	Necrotizing funisitis
	Stage-4	Intense chorionic vasculitis
5. Villitis (inflammation of villi, either within or surrounding it) was graded as per Fox and Sebire ¹		
Stage-0	Absent	
Stage-1	One or two foci of villous inflammation involving few villi per focus	
Stage-2	Upto six foci of inflammation involving up to twenty villi/focus	
Stage-3	Multiple inflammatory foci, each occupying half of the low-power microscopic field	
Stage-4	Large areas of villous inflammation in most or all of the four sections	
6. Syncytial knots are the aggregates of syncytiotrophoblast nuclei at the surface of terminal villi		
Grade 1	<5 / villous	
Grade 2	5-10 / villous	
Grade 3	>10/ villous	
7. Fetal vascular obstructive lesions are the vascular changes within the fetal circulation of the placenta ¹⁷		
Grade 1	No change	
Grade 2	Focal changes	

Grade 3	Multifocal changes
8. Hofbauer cells are fetal macrophages that present in villous stroma	
Grade 1	<5 / immature intermediate villi
Grade 2	5-10 / immature intermediate villi
Grade 3	>10/ immature intermediate villi
9. Vessel density¹	
Grade 1	<5 vessels/ 10 terminal villi/ 10 microscopic low-power-field (LPF)
Grade 2	5-10 vessels/ 10 terminal villi/ 10 microscopic LPF
Grade 3	>10 vessels/ 10 terminal villi/ 10 microscopic LPF
10. Stem villous fibrosis	
Grade 1	Fibrosis only around blood vessels and reticular peripheral stroma
Grade 2	Equal fibrosis throughout the villous
Grade 3	Increased fibrosis

Data analysis

We described the data through frequency, proportions, means, and standard deviations. The 2-tailed t-test was used to compare the numerical data and the categorical data were analysed by Chi-square for trend and Mann-Whitney U test using the SPSS 20 software. A binary logistic regression analysis was used to analyse the association between the placental histopathological variables and various perinatal outcomes. Results were presented as Odds ratio

(OR) with 95% confidence intervals (CI). Statistical significance was determined using a *p*-value cut-off of <0.05.

Result

In this study, placentae of a total of 104 pregnant mothers – 52 preterm (cases) and 52 term (controls) along with their respective perinatal outcomes were studied for one year.

Table I. Gross findings of term and preterm placentae.

Gross findings	Preterm placentae Mean±2SD	Term placentae Mean±2SD	p-value
Placental weight (gm)	316.50±31.29	438.65±9.61	0.001*
Placental diameter (cm)	17.03±0.82	18.97±0.25	0.001*
Placental thickness (cm)	2.31±0.04	2.34±0.12	0.405

**Statistically significant (2-tailed Mann-Whitney U test)*

Table I shows the differences in mean, 2 standard deviation, and significance of the placental weight, diameter, and thickness among cases and control groups. Placental mean weight and diameter in preterm labor were 316.50gm and 17.03cm, whereas in term delivery they were

438.65gm and 18.97cm, respectively, and the differences were statistically significant when compared with gestational age. The mean placental thickness in cases was 2.31cm compared to 2.34cm in controls, but this difference was not statistically significant.

Table II. Histological features of preterm and term placentae.

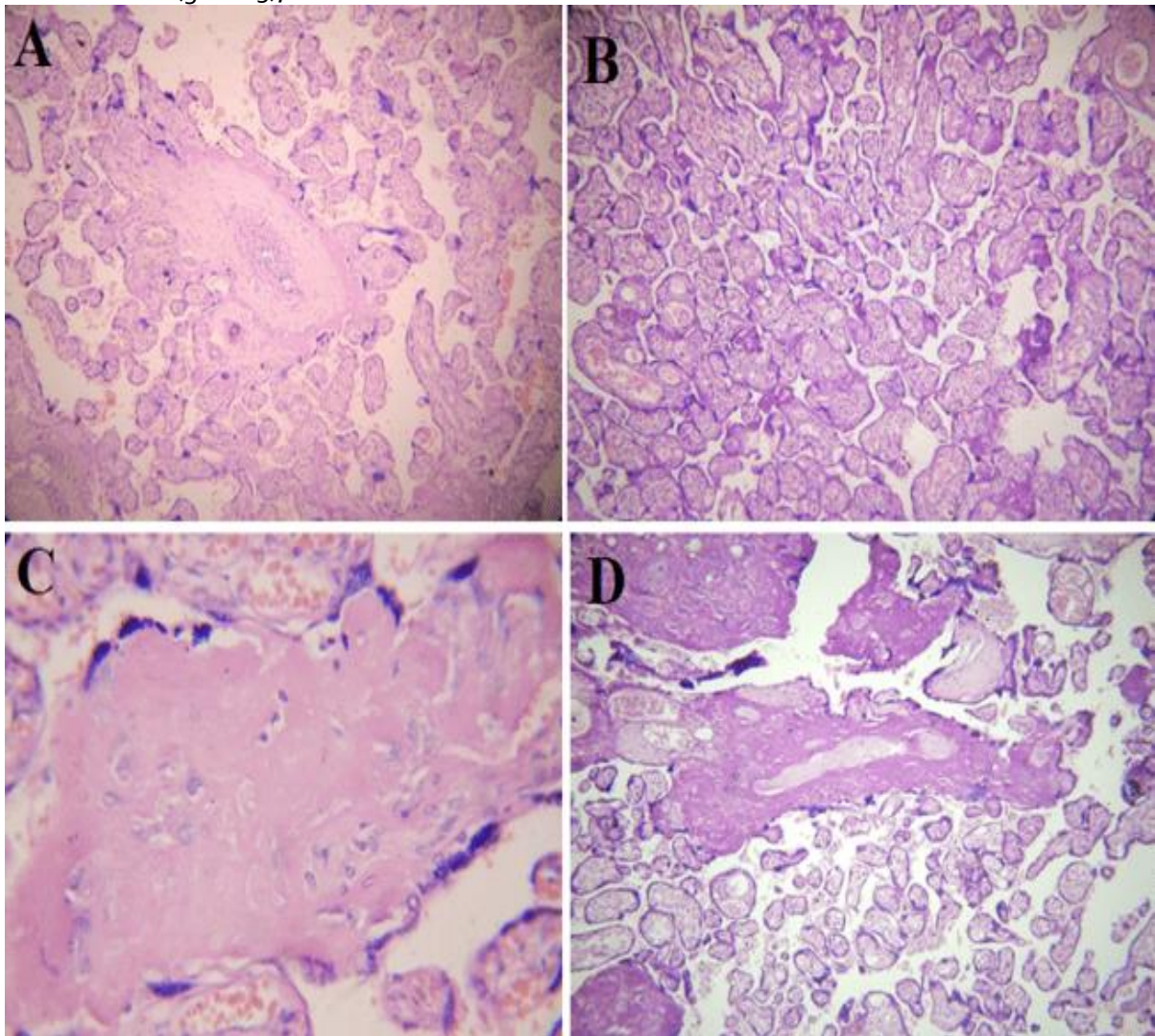
Variables/30 HPF	Cases (%) (n = 52)	Controls (%) (n = 52)	p-value
1. Intervillous space			
Grade 1	28 (53.85)	0 (0)	0.001*
Grade 2	11 (21.15)	52 (100)	
Grade 3	13 (25)	0 (0)	
2. Intravillous fibrinoid			
Grade 1	2 (3.85)	45 (86.54)	0.001*
Grade 2	26 (50)	7 (13.46)	
Grade 3	24 (46.15)	0 (0)	
3. Perivillous fibrinoid			
Grade 1	20 (38.46)	44 (84.62)	0.002*
Grade 2	21 (40.38)	8 (15.38)	
Grade 3	11 (21.15)	0 (0)	
4. Syncytial knots			
Grade 1	36 (69.23)	0 (0)	0.001*
Grade 2	16 (30.77)	52 (100)	
Grade 3	0 (0)	0 (0)	
5. Hofbauer Cells			
Grade 1	15 (28.85)	50 (96.15)	0.002*
Grade 2	16 (30.77)	2 (3.85)	
Grade 3	21 (40.38)	0 (0)	
6. Stem villous fibrosis:			
Grade 1	37 (71.15)	0 (0)	0.001*
Grade 2	15 (28.85)	52 (100)	
Grade 3	0(0)	0 (0)	
7. Vessels density:			
Grade 1	14 (26.92)	0 (0)	0.002*
Grade 2	32 (61.54)	50 (96.15)	
Grade 3	6 (11.54)	2 (3.45)	

*Statistically significant (Pearson's Chi-square test)

Table II shows the incidence of placental different microscopic changes with their significance. In our study, IVS was narrowed (Grade 1) in 53.85% and widened (Grade 3) in 25% of cases of preterm placentae; where it was normal (Grade 2) in all term placentae. Among the cases, IVF was mildly increased (Grade 2) in 50% and markedly increased in 46.15%; where the majority of the

term placentae (86.54%) showed normal IVF (Grade 1). In addition to that, PVF deposition was mildly (Grade 2) and markedly (Grade 3) increased respectively, in 40.38% and 21.15% cases of preterm placentae. However, the majority of the term placentae showed normal PVF (84.62%) deposition.

Figure 1. Different grades of IVS, IVF and PVF in cases and control: (A) Term placenta showing normal IVS (grade 2). Preterm placenta showing (B) decreased IVS (grade 1), (C) increased IVF (grade 3) and (D) increased PVF (grade 3); H&E x 100.



This study also revealed reduced syncytial knot count (Grade 1) in the majority (69.23%) of preterm placentae, whereas it was normal (Grade 2) in all term placentae. In addition to that, Hofbauer cells increased in number in 40.38% of the preterm placenta; while 96.15% of the term

placenta showed their normal count. In our study, stem villous fibrosis and vessel density were reduced respectively in 71.15% and 26.29% cases of preterm placentae; where both these findings were normal in the term placentae.

Figure 2. Different grades of syncytial knot, Hofbauer cell, villous fibrosis, and vessel density: (A) Term placental chorionic villi showing syncytial knot (grade 2; green arrow), vasculosyncytial membrane (red arrow), and (B) uniform stem villous fibrosis (grade 2); H&E x 400. (C) Immature chorionic villi of preterm placenta showing decreased vessel density (grade 1), increased number of Hofbauer cells (inset red arrow; grade 3), and (D) Fibrosis only around blood vessels with reticular peripheral stroma (grade 1); H&E x 400.

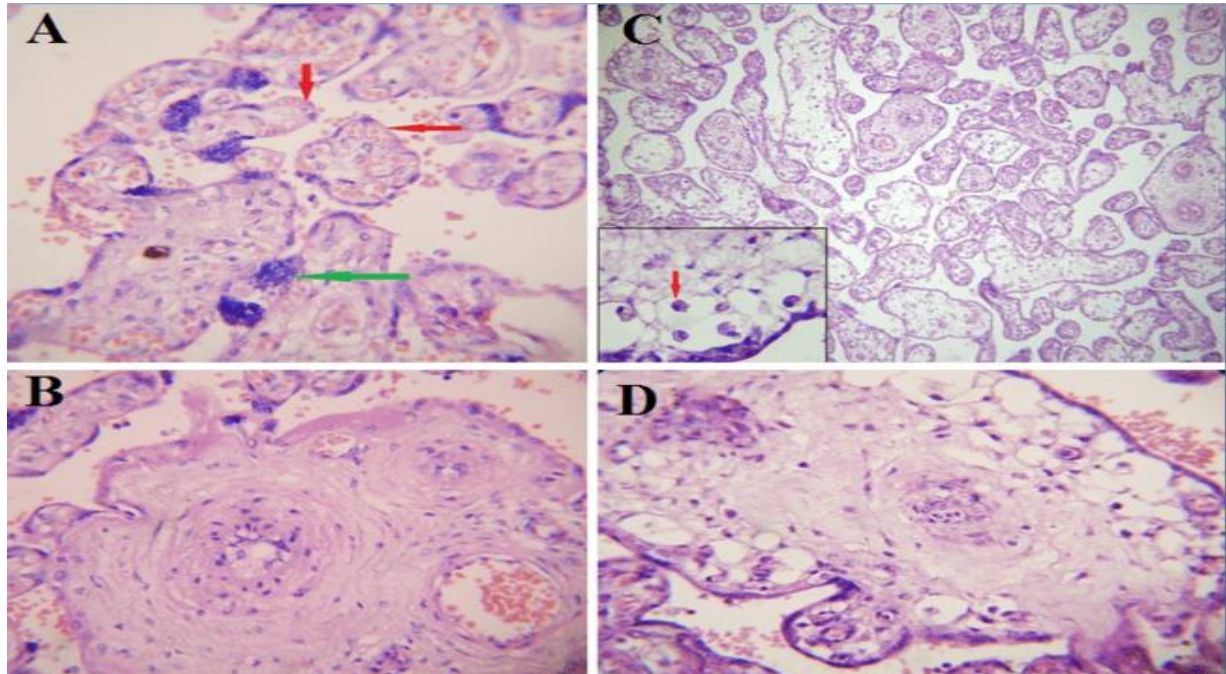


Table III. Incidence of different stages and grades of acute chorioamnionitis (MIR, FIR), villitis, and fetal obstructive vascular lesions in term and preterm placentae.

Variables	Cases (%) (n = 52)	Controls (%) (n = 52)	p-value
1. Chorioamnionitis (CA-MIR)			
Stage 0	2 (3.85)	4 (94.23)	0.002*
Stage 1	12 (23.08)	3 (5.77)	
Stage 2	23 (44.23)	0 (0)	
Stage 3	12 (23.08)	0 (0)	
Stage 4	3 (5.77)	0 (0)	
2. Chorioamnionitis (CA-FIR)			
Stage 0	18 (34.62)	52 (100)	0.003*
Stage 1	21 (40.38)	0 (0)	
Stage 2	9 (17.31)	0 (0)	
Stage 3	2 (3.85)	0 (0)	
Stage 4	2 (3.85)	0 (0)	
3. Villitis			
Grade 0	26 (50)	52 (100)	0.004*
Grade 1	17 (32.69)	0 (0)	
Grade 2	7 (13.46)	0 (0)	
Grade 3	1 (1.92)	0 (0)	
Grade 4	1 (1.92)	0 (0)	
4. Fetal Vascular Obstructive Lesions			
Grade 0	29 (55.77)	51 (98.08)	0.001*
Grade 1	10 (19.23)	1 (1.92)	
Grade 2	13 (25)	0 (0)	
Grade 3	0 (0)	0 (0)	

*Statistically significant (Pearson's Chi-square test)

Table III shows the incidence of different stages and grades of chorioamnionitis, including MIR, FIR, villitis, and placental fetal obstructive vascular lesions in term and preterm placentae, and their statistical significance with the occurrence of SPTL. We found an increased incidence of chorioamnionitis (96.15% MIR; 65.38% FIR and 50% villitis) in the preterm placentae; while the term placentae showed 5.77% MIR but absence of FIR and villitis. In our study, fetal obstructive

vascular lesions were present in 44.23% of preterm (19.23% had focal and 25% had multifocal lesions), but absent in the majority (98.07%) of the term placentae. The association of chorioamnionitis (both MIR, FIR), villitis, and fetal obstructive vascular lesions with preterm labor was statistically significant. Various grades of CA-MIR, CA-FIR and villitis in the preterm placentae are shown in Figure 3 and Figure 4.

Figure 3. Preterm placenta showing different grades of CA-MIR: (A) acute subchorionitis (grade 1), (B) chorioamnionitis (grade 2), (C) necrotizing chorioamnionitis (grade 3), and (D) subchorionic microabscesses (grade 4); H&E x 100.

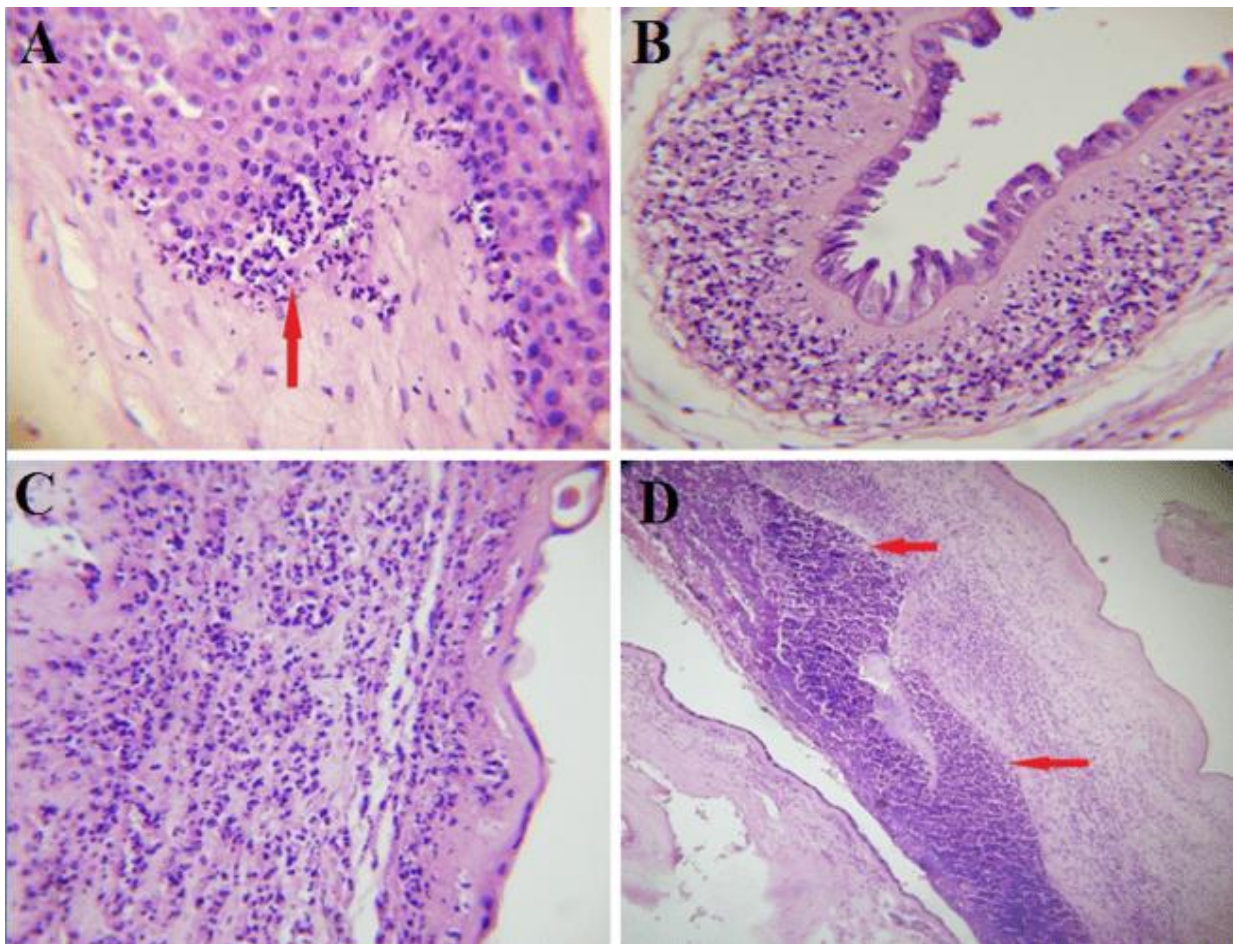


Figure 4. Preterm placenta showing various grades of CA-FIR and villitis: (A) umbilical arteritis (FIR grade 2), (B) necrotizing funisitis (FIR grade 3), (C) intense chorionic vasculitis (FIR grade 4), and (D) villitis (grade 2); H&E x 100.

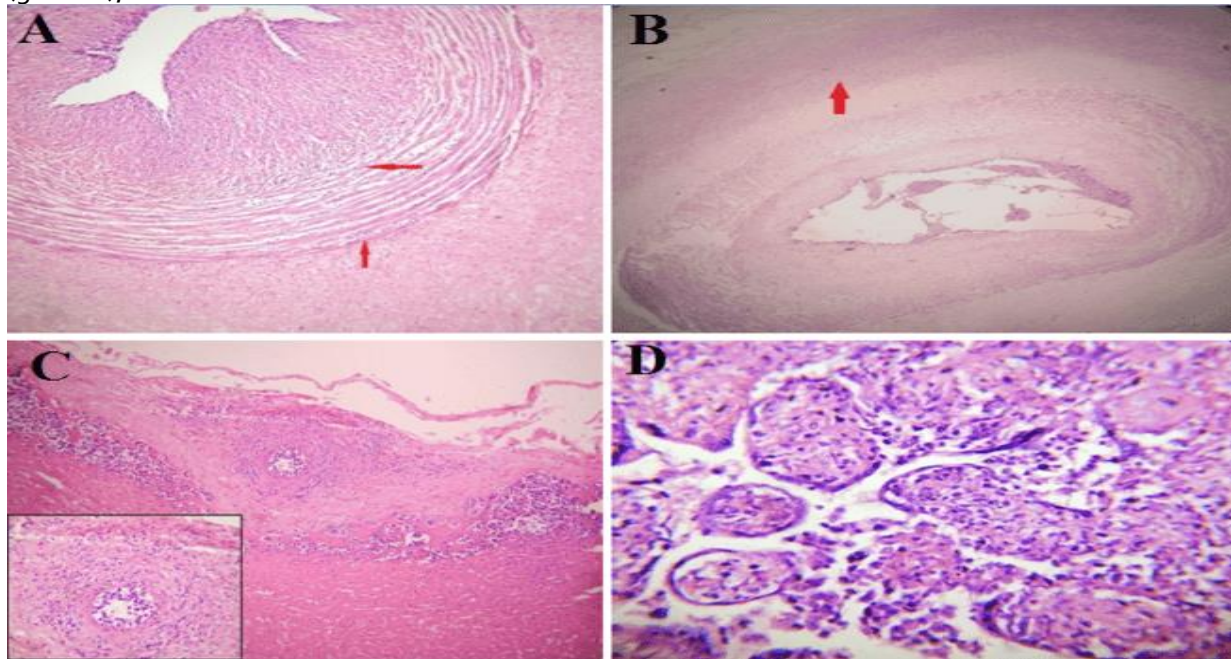


Table IV. Association of chorioamnionitis (MIR, FIR), villitis, and fetal vascular obstructive lesions with different perinatal outcomes.

Perinatal outcome	Adjusted OR (95% CI); p-value			
	CA-MIR	CA-FIR	Villitis	Fetal Obstructive Vascular Lesions
Early neonatal Sepsis	15 (1.52-34.35); 0.006*	9 (1.78-45.33); 0.008*	3.88 (1.17-12.84); 0.026*	0.53 (0.17-1.7); 0.29
RDS	4.76 (1.16-23.43); 0.042*	0.83 (0.24-2.84); 0.77	0.69 (0.21-2.27); 0.54	3.53 (1.17-12.7); 0.022*
Cardiovascular complications	3.88 (1.17-12.84); 0.026*	8.94 (2.14-37.33); 0.003*	0.8 (0.68-3.68); 0.45	2.53 (1.17-15.7); 0.029*
HIE	23.76 (1.54-27.42); 0.001*	13.42 (1.59-112.64); 0.017*	4.71(1.26-17.56); 0.021*	21(3.98-110.73); 0.001*
Hypothermia	4.76(1.16-23.43); 0.042*	0.83(0.24-2.83); 0.771	0.69(0.21-2.27); 0.54	3.53(1.17-12.78); 0.022*
Hypoglycemia	9(1.52-12.35); 0.008*	12.13 (3.12-47.12); 0.002*	4.9(1.41-16.98); 0.012*	5.08(1.38-18.69); 0.014*
Hyperbilirubinemia	3.88(1.17-12.84); 0.026*	0.46(0.78-5.33); 0.082	9.21(1.04-81.36); 0.046*	0.72(0.15-3.39); 0.678
Perinatal death	24.76(1.16-26.43); 0.002*	12.83(1.24-12.84); 0.001*	4.69(1.21-3.27); 0.054*	13.58(1.17-12.7); 0.022*

*Statistically significant (Binary logistic regression analysis).

The association of chorioamnionitis (MIR, FIR), villitis, and fetal vascular obstructive lesions with different perinatal outcomes is shown in Table IV. Chorioamnionitis (either MIR or FIR or both) was significantly associated with all adverse perinatal complications like early neonatal sepsis (MIR OR 15, $p=0.006$; FIR OR 9, $p=0.008$), respiratory distress syndrome (RDS; MIR OR 4.7, $p=0.042$), cardiovascular complications (MIR OR 3.8, $p=0.026$; FIR OR 8.9, $p=0.003$), HIE (MIR OR 23,

$p=0.001$; FIR OR 13.4, $p=0.017$), hypothermia (MIR OR 4.7, $p=0.042$), hypoglycemia (MIR OR 9, $p=0.008$; FIR OR 12.13, $p=0.002$), hyperbilirubinemia (MIR OR 3.8, $p=0.026$) and perinatal mortality (MIR OR 24.7, $p=0.002$; FIR OR 12.8, $p=0.001$; villitis OR 4.6, $p=0.054$) in preterm newborns and these were aggravated in presence of villitis and fetal obstructive vascular lesions; whereas majority (94.23%) of the term baby developed no complication (Table V).

Table V. Incidence of Perinatal Outcomes in term and preterm neonates.

Perinatal outcome	Cases (n=52)	Controls (n=52)
No late complication	13 (25%)	49 (94.23%)
Early Neonatal Sepsis	20 (38.46%)	0 (0%)
RDS	15 (28.85%)	1 (1.92%)
Hyperbilirubinemia	8 (15.39%)	1 (1.92%)
Bradycardia with apnea	13 (25%)	0 (0%)
Hypoglycemia	33 (63.46%)	0 (0%)
Hypothermia	33 (63.46%)	1 (1.92%)
HIE	16 (30.77%)	0 (0%)
Perinatal death	11 (21.15%)	0 (0%)

Table V shows increased percentages of all adverse perinatal outcomes were associated with preterm labor (case), and they developed in

various combinations, whereas the majority (94.23%) of the term neonates developed no complication.

DISCUSSION

We found a significant reduction in the preterm placental mean weight and diameter than the term, when compared with their gestational age but without any significant alteration of placental thickness and these findings were equivalent to other studies where conclusions were made that PTL was associated with decreased placental weight and size but an increase in umbilical cord diameter.^{8,10} But, Tang et al.¹¹ found large placenta (2.91%), short cord (4.85%), and velamentous cord insertion (3.88%) in the preterm population (28-37 weeks); however, Vinograd et al.¹² concluded that placenta accreta is a distinct risk factor for late PTB.

In our study, IVS was narrowed in 53.85% and widened in 25% of preterm placentas, whereas it was normal in all term placentas (Table II). Widened IVS in PTL was also noted in several previous studies.^{1,5,6,10,33} However, we found narrowed IVS in the majority of the preterm placentas, and it may be due to infection-related pathological changes and/or effects of late-onset intrauterine growth retardation.

We found increased deposition of both IVF and PVF in the preterm placentae, which matches other studies⁸. But Zaidi et al.¹⁰ had described an increased IVF deposition in the term placenta. In our research, increased depositions of both IVF and PVF were possibly due to vasculopathy-related changes, which may be aggravated by associated infection, resulting in SPTL.

We observed reduced villous fibrosis, vessel density, and decreased number of syncytial knots in the majority of the preterm placenta, but an increase in the number of Hofbauer cells, and these findings were similar to other previous studies.^{1,8,10}

In our research, chorioamnionitis, including MIR (96.15%), FIR (65.38%), and villitis (50%) were significant findings in placentas of SPTL with intact membrane, which is at par with other previous studies.¹³⁻¹⁵ In addition to that, we observed that increased stages and grades of MIR, FIR, and villitis were more frequent in newborns delivered at gestational age <32 weeks than 32-36

weeks.^{13,15} There was also a strong association between fetal obstructive vasculopathy (44.23%) with increased occurrence of SPTL ($p=0.021$), where it was absent in the majority (98.07%) of the term placentae.¹⁶⁻¹⁹

The major perinatal complications in the preterm neonates were early neonatal sepsis (38.46%), RDS (28.85%), hyperbilirubinemia (15.39%), cardiovascular complications (25%), hypoglycemia (63.46%), hypothermia (63.46%), HIE (30.77%) and perinatal mortality (21.15%) and these were more frequent in newborns delivered before 32 weeks than who delivered after 32 week,^{16,20,33} except RDS, which was more common in the later group and it may be due to increased use of antenatal steroids and/or increase mortality in the previous group. All these adverse outcomes might be the result of prematurity, infection, and toxemia-induced vasculopathy, which together lead to placental insufficiency. Increased occurrences of neonatal sepsis, RDS, cardiovascular and neurological disorders, and perinatal mortality were also observed in previous research.^{21-23,28-33}

In present study, the incidence of early neonatal sepsis was significantly associated with MIR (OR=15, CI=1.52-34.35, $p=0.006$), FIR (OR=9, CI=1.78-45.33, $p=0.008$) and villitis (OR=3.889, CI=1.17-12.84, $p=0.026$) similar to other studies²⁰⁻²³, but Strunk et al.²⁴ observed a reduced risk of late-onset sepsis in neonates having HCA.

In this study, increased incidence of RDS in the preterm newborns was significantly associated with the presence of placental features of MIR and fetal obstructive vasculopathy²⁵⁻²⁷, but there are studies where reduced incidence and severity of RDS were observed in preterm babies.^{20,28} The increased occurrence of RDS in our preterm newborns may be due to the concomitant presence of HCA with obstructive vasculopathy.

The preterm newborns of this study showed a higher incidence of HIE, hypoglycemia, and perinatal mortality, which were significantly associated with features of HCA (both MIR and FIR), villitis, and obstructive vascular lesions in placentas. An increased occurrence of hyperbilirubinemia was seen in association with CA-MIR and villitis, but not with CA-FIR and fetal

obstructive vascular lesions, whereas cardiovascular complications and hypothermia were significantly associated with CA-MIR and obstructive vasculopathy (Table IV).

We observed a large portion (30.77%) of the preterm babies died of HIE, possibly due to placental obstructive vasculopathy as well as infection-related pathological changes either alone^{22,25} or in combination.²⁹ Severe endotheliitis may arise out of overwhelming sepsis as well as due to hypoxic damage of the vessels in the early neonatal period, leading to multisystem failure. In addition, it may be due to severe RDS along with toxemia-induced placental insufficiency.

This study revealed an increased incidence and severity of MIR in association with adverse perinatal outcomes, which was aggravated in the presence of FIR, villitis, and/or fetal obstructive vasculopathy. But the association of FIR with increased perinatal mortality than MIR was unique in this study, and this finding was similar to other research.^{30,31}

The limitation of our study is that it was conducted on a small number of low-risk pregnant women attending a tertiary care teaching hospital; thus, the study population may not represent the general population. Therefore, a large cohort study covering moderate to high-risk populations with more parameters is necessary to establish the individual adverse effects of chorioamnionitis, villitis, or placental vasculopathy on perinatal outcome.

CONCLUSION

It may be concluded that there is a strong association between histologic chorioamnionitis, villitis, and placental vasculopathy with increased risk of spontaneous preterm labor as well as adverse perinatal outcomes. Hypoxic ischemic encephalopathy is one of the major causes of perinatal morbidity and mortality, which may be a terminal event in cases of overwhelming neonatal sepsis, leading to vascular damage, placental insufficiency, and hypoxia. Fetal obstructive vasculopathy is an associated risk factor for producing respiratory distress syndrome, particularly in later gestational age.



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