*Original Article*

# Histopathological Changes in Placenta in Cases of Intrauterine Growth Restriction

*Soma Ghosh[1], Shantanu Bhuniya[2], Dilip Kumar Biswas[3]*

## Abstract

***Background:*** Intrauterine growth retardation (IUGR) creates a significant worldwide public health burden being leading cause of perinatal mortality and morbidity. ***Objective:*** To determine correlation between placental pathology and IUGR, to assess pattern of placental histopathological changes in IUGR compared to uncomplicated pregnancy and to determine significant early neonatal outcome of IUGR baby in specific placental changes. ***Methods:*** A cross-sectional observational, descriptive study done in a study population of 100 placentae including 50 from uncomplicated pregnancy and 50 from IUGR cases. The histopathological, morphological changes of placentae in IUGR observed and compared with placentae of uncomplicated delivery for a period of eighteen months. All IUGR cases with time of delivery between 28 weeks and 40 weeks of gestation were included excluding multiple pregnancy and IUFD. ***Results:*** The mean gestational age in pre-term labor (PTL)was 30.4 weeks compared to 37.2 weeks in term population. Placental weight and diameter were reduced in PTL with decreased intervillous space, syncytial knot, terminal villous vascularity and stem villous fibrosis. Increased deposition of placental intervillous, perivillous fibrin; number of Hofbauer cells and fetal obstructive vascular lesions in PTL associated with different perinatal outcomes and mortality. Fetal Inflammatory Response was much higher in males. Increased stage, grade of infectious and ischemic changes of placentae were associated with more adverse outcomes. ***Conclusion:*** Adverse perinatal outcomes were more prevalent in preterm babies whose placentae showed infectious and ischaemic changes. An assessment of placental pathology is thus useful for resolving issues arising from pregnancy complications.

**Keywords:** IUGR, placenta, preterm birth, chorioamnionitis, obstructive vasculopathy

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## Introduction

Fetal growth is a complicated physiological process with contribution from both maternal and placental aspects.[1] Restricted growth is found with compromised placenta mediated foetal circulation. The perinatal morbidity and mortality are mostly caused by fetal growth restriction (FGR) encountered in 5-10% of all pregnancies.[2] Despite the latest diagnosing tools, false positive results are still in high frequency. Here, comes the importance of studying placental pathology that can be beneficial for early diagnosis and subsequent management of FGR. By definition, FGR is the failure of foetus to attain appropriate weight during a specific gestational age.[2]

Among the placental causes, uteroplacental insufficiency has been established as a predominant factor.[2] Foetal growth is mostly regulated by placental angiogenesis and circulation that carry oxygen to the growing foetus. The nutritional

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supply to fetus is greatly affected by retarded growth of the placental blood vessels resulting in retarded growth of fetus. This establishes the significance of angiogenesis in placenta both in normal condition and in growth restriction.[1,2] Chronic lung disease, hypothermia, chronic necrotizing enterocolitis, polycythemia, abnormal glucose metabolism and perinatal asphyxia are commonly observed in postnatal life of a foetus who experienced FGR.[3] Diseases appearing in adulthood are diabetes, hypertension, obesity .[3]

Identification of FGR can be done with the help of integrated prenatal screening tests comprising of low level of pregnancy associated plasma protein A (PAPP-A) with beta human chorionic gonadotropin (β-hCG), high levels of Alpha-fetoprotein (AFP) and inhibin coupled with vascular doppler study .[4] The pathophysiology of placenta is best assessed by histopathological examination amongst wide variety of investigations.[3.4]An elaborate examination of histopathological characteristics of the placenta is of help to evaluate pathogenesis of FGR , guiding to efficiently manage patient and eventually reducing the prevalence of FGR as well as unwanted future complications.

Hence, we proposed this study to determine correlation between placental pathology and IUGR, assess pattern of placental histopathological changes in IUGR compared to uncomplicated pregnancy and determine significant early neonatal outcome of IUGR baby in specific placental changes.

## Methods

A cross-sectional, observational, descriptive study was done in a teaching institute in West Bengal for a time period of eighteen months with written informed consent from the patient after completing case record and eventually collecting placentae from gynaecology labour room. All IUGR cases with time of delivery between 28 and 40 weeks of gestation during the study period were included (n=50), while similar numbers of placenta from uncomplicated pregnancy taken as control (n=50). The exclusion criteria were multiple pregnancy, IUFD, those born before 28 weeks and after 40 weeks of gestation .

The dependant variables were histopathological and morphological placental changes in IUGR. The independent variables were maternal factors associated with placental changes in IUGR and body weight of baby post-delivery. The study tools included case record form, routine histopathological reagents, slides, cover slip, hematoxylene & eosin (H&E) stain, 10 % formalin and microscope for histopathological processing, staining and observation. Formalin (10%) fixed placental specimens received from gynaecology department and grossing was done at pathology department. H&E staining of tissue done after preparing paraffin blocks and sectioning in Leica microtome. Histopathological examination of sections done under 4x,10x and 40x objectives. Placental parenchyma was examined for calcification, infarction and intervillous thrombosis. Microscopic study was performed on tissue sample taken from each placenta including at least six blocks of placental tissue which comprised of transverse section of umbilical cord, two tissue bits of parenchyma including villi and intervillous space from edge of placenta, free membrane bit , two sections of parenchyma from placental centre, one to two sections from abnormal gross pathological part.

The parameters included were post-delivery body weight of the baby; maternal gravida, age, weight,blood pressure, TSH,glucose level ; previous history of pregnancy with IUGR or infection or per vaginal bleed or eclampsia. History elicited of appropriate maternal intake of iron , folic acid supplements and socioeconomic status . The placental shape, size, weight, morphological and histopathological changes noted. The microscopical parameters included intervillous space (IVS), intravillous and perivillous fibrin (IVF, PVF), maternal inflammatory response (MIR), fetal inflammatory response (FIR), villitis, fetal obstructive vascular lesion (FOVL), infarction, syncytial knots(SK), calcification, stem villous fibrosis(SVF), hofbauer cells, vessel density(VD), villous maturity score (VMS). The specimens following routine tissue processing were stained by H&E method.

Statistical method: All numerical data was compared by using 2-tailed t-test and all categorical data was compared by using Chi-square for trend, Mann-Whitney U test and Binary logistic regression analysis. For statistical significance, P-value of less than 0.05 was considered. Statistical analysis was done by using Statistical Package for the Social Sciences (SPSS) software, version 24.0

## Results

In the present study, 50 preterm (case) and 50 term (control) placentae studied in a study population of 100 pregnant mothers. Their respective perinatal outcome was studied for duration of eighteen months. The study comprised of 68% primipara and 32% multiparous mothers without previous history of preterm birth. The mean maternal age was 20.6 years in preterm group and 22.2 years in term group.

The mean gestational age, body mass index (BMI) in pre-term labor (PTL) was 30.4 weeks and 19.2 $kg/m^2$ compared to 37.2 weeks and 20.9$kg/m^2$ in term population.(Table-1).The mean birth weight, mean of 1 minute and 5 minute Apgar score were low in cases compared to control (Table 1). The mean diameter and weight of placenta was also lower in PTL compared to term group. (Table 1).

Edematous umbilical cord was found in 50% of cases, battledore placenta in 6% and single umbilical artery in 2%. The differences between placental weight and diameter in cases and control were statistically significant; but not the difference between mean placental thickness .(Table :1) Among the preterm neonates, 54% were females and 46% males with higher perinatal mortality in males (37%). IVS was narrowed in 48% and widened in 24% of preterm placentae but normal in all term placentae. (Table:2a) VMS 22 (normal villous maturation pattern) was observed in 56% term and 20% preterm placenta.30% of preterm placenta showed VMS10; but no term placenta showed the score; which indicates less villous maturity in preterm placenta. Microscopy of preterm placentae showed SK count (Grade1,2), Hofbauer cells (Grade1-3),SVF (Grade1,2), VD(Grade1-3), calcification (Grade0-2), infarction (Grade 0-2), FOVL (Grade0-2) . The term placentae showed SK(Grade2); Hofbauer cell(Grade1); SVF,VD (Grade2); Calcification (Grade0,1); Infarction and FOVL(Grade0) (Table:2a,b) Association of MIR , FIR, Villitis and FOVL with PTL were statistically significant. The association of different stages and grades of MIR , FIR and villitis with PTL were statistically significant.(Table :3)

Increased stages and grades of MIR,FIR, villitis and FOVL were more frequently associated with gestational age<32 wks than 32.1-36 wks. They comprised of early neonatal sepsis (n=21), respiratory distress syndrome (RDS ,15) ,

**Table 1:** Differences in maternal and gestational age, BMI, birth weight of babies, 1 and 5min Apgar score, placental weight, diameter and thickness among case and control group

| Variable | Study Population | Mean | 2SD | P-value |
|---|---|---|---|---|
| Maternal age (years.) | Case 50<br>Control 50 | 20.6<br>22.2 | 2.6<br>2.7 | 0.001* |
| BMI ($kg/m^2$) | Case 50<br>Control 50 | 19.2<br>20.9 | 0.2<br>0.4 | 0.004* |
| Gestational age (weeks.) | Case 50<br>Control 50 | 30.4<br>37.2 | 2.9<br>0.8 | 0.003* |
| Birth weight of baby (gm.) | Case 50<br>Control 50 | 1692.3<br>2645.1 | 308.5<br>249.3 | 0.002* |
| 1min Apgar score | Case 50<br>Control 50 | 5.5<br>6.8 | 1.4<br>0.9 | 0.006* |
| 5min Apgar score | Case 50<br>Control 50 | 7.1<br>8.7 | 1.6<br>0.4 | 0.003* |
| Placental weight (gm) | Case 50<br>Control 50 | 310.7<br>422.5 | 25.7<br>29.9 | 0.005* |
| Placental diameter (cm) | Case 50<br>Control 50 | 17.7<br>18.2 | 0.6<br>0.8 | 0.002* |
| Placental thickness (cm) | Case 50<br>Control 50 | 2.2<br>2.4 | 0.1<br>0.1 | 0.854 |

hyperbilirubinemia (7) , bradycardia with apnoea (12), hypoglycemia (32), hypothermia (34), hypoxic ischemic encephalopathy (HIE ,17) and perinatal death (10) in PTL.However, the outcomes were favourable in term neonates with neither perinatal death nor late complication ( 96%). All adverse outcomes were more common in preterm newborns who were delivered before thirty two weeks of gestation, with birth weight less than 1.5 kg and low 1minute, 5 minute Apgar scores except RDS. Increased grade of PVF, IVF deposition was associated with poor perinatal outcomes.

**Table 2(a):** Placental microscopic changes

| Variable | Case (n=50) | Control (n=50) | P-value |
|---|---|---|---|
| Intervillous Space | Grade1 :24(48)<br>Grade2 : 16(32)<br>Grade3 : 12(24) | 0(0)<br>50(100)<br>0(0) | 0.004* |
| Intravillous fibrin | Grade 1: 7(14)<br>Grade2 : 20(40)<br>Grade3 : 25(50) | 42(84)<br>10(20)<br>0(0) | 0.009* |
| Perivillous fibrin | Grade1 : 19(38)<br>Grade2 : 22(44)<br>Grade3 : 9 (18) | 41(82)<br>11(22)<br>0(0) | 0.001* |
| Syncytial knot | Grade 1:34(68)<br>Grade2:18(36)<br>Grade3:0(0) | 0(0)<br>50(100)<br>0(0) | 0.006* |
| Hofbauer cell | Grade1 : 17(34)<br>Grade2 : 13(26)<br>Grade3 : 22(44) | 48(96)<br>4(8)<br>0(0) | 0.001* |
| Stemvillous Fibrosis | Grade1 :36(72)<br>Grade2 :14(28)<br>Grade3: 0(0) | 0(0)<br>50(100)<br>0(0) | 0.001* |
| Vessel density | Grade1 :15(30)<br>Grade2:35(70)<br>Grade3: 2(4) | 0(0)<br>48(96)<br>2(4) | 0.001* |

**Table 2 (b):** Placental microscopic changes

| Variables | Case (n=50) | Control (n=50) | P-value |
|---|---|---|---|
| Calcification | Grade 0 : 4(8)<br>Grade 1: 44(88)<br>Grade 2: 2(4) | 32(64)<br>18(36)<br>0(0) | 0.031* |
| Infarction | Grade 0: 31(62)<br>Grade 1: 13(26)<br>Grade 2: 6(12) | 50(100)<br>0(0)<br>0(0) | 0.005* |
| FVOL | Grade 0: 28(56)<br>Grade 1:10(20)<br>Grade 2: 12(24)<br>Grade 3: 0(0) | 48(96)<br>2(4)<br>0(0)<br>0(0) | 0.001* |

**Table 3:** Incidence of Chorioamnionitis (MIR, FIR), Villitis and FOVL in case and control group

| Variables | | Case | Control | P-value |
|---|---|---|---|---|
| MIR | Present | 47(94) | 1(2) | 0.001* |
| | Absent | 3(6) | 49(98) | |
| FIR | Present | 32(64) | 0(0) | 0.001* |
| | Absent | 18(36) | 50(100) | |
| Villitis | Present | 27(54) | 0(0) | 0.048* |
| | Absent | 23(52) | 50(100) | |
| FOVL | Present | 22(44) | 2(4) | 0.033* |
| | Absent | 28(56) | 48(96) | |

**Table 4(a):** Association of CA-MIR with perinatal outcomes

| **Variable** | **Association with perinatal outcome** | **Unadjusted Odd's ratio** | **95%CI** | | **Significance** |
|---|---|---|---|---|---|
| | | | **Lower** | **Upper** | |
| CA(MIR) | Neonatal Sepsis | 16.000 | 1.773 | 35.228 | 0.002* |
| | RDS | 5.289 | 1.158 | 24.086 | 0.039* |
| | Bradycardia,apnoea | 4.492 | 1.149 | 13.671 | 0.035* |
| | Hyperbilirubinemia | 3.448 | 1.163 | 13.641 | 0.028* |
| | Hypoglycemia | 8.749 | 1.228 | 14.154 | 0.002* |
| | Hypothermia | 5.229 | 1.171 | 24.132 | 0.044* |
| | HIE | 22.465 | 1.528 | 26.126 | 0.002* |
| | Perinatal death | 25.165 | 1.192 | 27.132 | 0.001* |

**Table 4(b):** Association of CA-FIR with perinatal outcomes

| Variable | Association with Perinatal outcome | Unadjusted Odd's ratio | 95% CI | | Significance |
|---|---|---|---|---|---|
| | | | Lower | Upper | |
| FIR | Sepsis | 12.000 | 1.915 | 46.117 | 0.009* |
| | RDS | 0.775 | 0.282 | 3.392 | 0.693 |
| | Bradycardia,Apnoea | 8.207 | 2.122 | 35.838 | 0.001* |
| | Hyperbilirubinemia | 0.506 | 0.745 | 6.836 | 0.099 |
| | Hypoglycemia | 13.533 | 3.418 | 46.228 | 0.001* |
| | Hypothermia | 0.619 | 0.259 | 2.731 | 0.682 |
| | HIE | 12.721 | 1.561 | 113.340 | 0.011* |
| | Perinatal death | 13.433 | 1.259 | 13.241 | 0.004* |

**Table 4(c):** Association of villitis with perinatal outcome

| Variable | Association with Perinatal outcome | Unadjusted Odd's ratio | 95% CI | | Significance |
|---|---|---|---|---|---|
| | | | Lower | Upper | |
| Villitis | Sepsis | 4.771 | 1.206 | 11.401 | 0.015* |
| | RDS | 0.701 | 0.298 | 3.196 | 0.661 |
| | Bradycardia, Apnoea | 0.759 | 0.707 | 4.182 | 0.551 |
| | Hyperbilirubinemia | 10.118 | 1.448 | 82.861 | 0.040* |
| | Hypoglycemia | 5.870 | 1.553 | 15.388 | 0.026* |
| | Hypothermia | 0.704 | 0.248 | 3.926 | 0.991 |
| | HIE | 5.114 | 1.83 | 18.461 | 0.033* |
| | Perinatal death | 5.896 | 1.227 | 4.376 | 0.046* |

**Table 4(d):** Association of FOVL with perinatal outcomes

| Variable | Association with Perinatal outcome | Unadjusted Odd's ratio | 95% CI | | Significance |
|---|---|---|---|---|---|
| | | | Lower | Upper | |
| FOVL | Sepsis | 0.692 | 0.153 | 1.826 | 0.388 |
| | RDS | 3.440 | 1.162 | 11.825 | 0.041* |
| | Bradycardia | 3.263 | 1.183 | 16.202 | 0.004* |
| | Hyperbilirubinemia | 0.829 | 0.274 | 4.791 | 0.773 |
| | Hypoglycemia | 5.393 | 1.715 | 19.496 | 0.019* |
| | Hypothermia | 3.338 | 1.161 | 13.214 | 0.016* |
| | HIE | 22.700 | 3.296 | 111.833 | 0.008* |
| | Perinatal death | 14.753 | 1.155 | 14.502 | 0.036* |

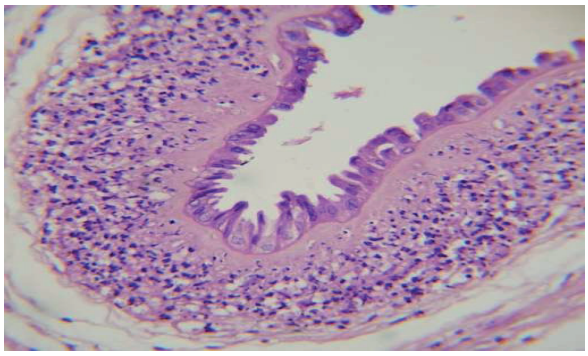

**Figure 1:** Photomicrograph showing maternal neutrophils migrating into connective tissue of chorion and amnion (CA-MIR grade 2); (H&E ×400).

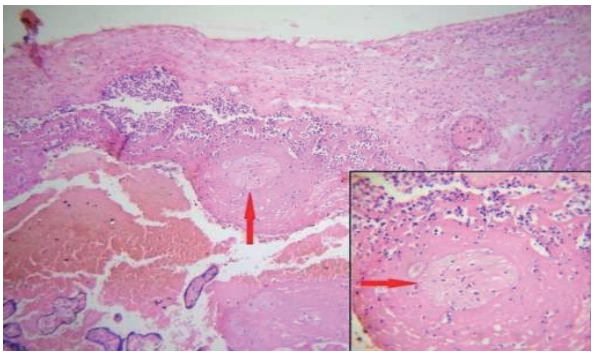

**Figure 2:** Photomicrograph showing chorionic vessel thrombi (inset) (H&E, ×400) FOVL (H&E, ×100).

## Discussion

Low maternal age and BMI representing low socioeconomic status was responsible for increased incidence of PTL. Several studies found positive correlation between low maternal age and BMI with PTL.[5-7] Owen et al. found increased incidence of spontaneous preterm birth (SPTB) in mothers having previous history of PTB. This indicates that there may be some unknown factors which induce PTL in those primi and multipara.[7]

PTL was associated with decreased placental weight and size; but increased edematous umbilical cord diameter which resemble findings of Mongia et al.[8] Mongia et al found increased IVF in hypoxia induced preterm labor.[8]Tang et al found large placenta (2.91%), short cord (4.85%) and velamentous cord insertion (3.88%) in preterm population (28-37 wks); whereas Vinograd et al found placenta accreta as an independent risk factor for late PTB.[9,10] But, these findings with respect to placental weight and diameter are obvious features of premature gestation but not significant with regards to perinatal outcome.[9,10]

Maternal immune reaction to fetal tissue was more common in male foetus than female, concluded from higher perinatal mortality in male babies. Waiker et al. noted preterm male neonate with increased risk of developing coronary artery disease.[11] Deborah et al. noted widened IVS in the preterm placenta;[12] but the present study found narrowed IVS with close approximation of villi in majority of the preterm placentae which may be due to prematurity and/or infection related pathological changes. Allaf et al. found increased IVF deposition in term placenta, whereas Mehta et al noted increased PVF deposition in preterm placenta along with disturbed fetoplacental blood flow.[13,14] Increased deposition of IVF, PVF in preterm placentae in present study was possibly due to vasculopathy related changes, aggravated by associated infection, resulting in PTL and poor perinatal outcome. Allaf et al. noticed decreased SK and increased Hofbauer cells in preterm placenta, resembling present study but contrary to Mongia et al., where they postulated increased SK count as a feature of hypoxia induced PTL.[8,13]

Reduced villous fibrosis with density and vascularity in underperfused preterm placenta in present study resemble findings of Mongia et al; but Allaf et al noted increased villous fibrosis in only 11.9% preterm placentae.[8,13] Andres et al and Salafia et al described the phenomena of infarction induced PTL which hampers fetal growth and even fetal death .[15,16]Low VMS being a normal feature of premature placenta is not directly related to poor perinatal outcome.The study indicated MIR, FIR and Villitis as significant risk factors for SPTB in asymptomatic patient with intact membrane as well as in early premature rupture of membrane.[15,16]

Defranco et al. noted 51.9% MIR , 35.4% FIR in SPTB despite absence of clinical evidence of CA. Risk of extreme PTB (<28 wks) was increased in presence of any grade or stage of MIR or FIR compared to late PTB (32–35 wks).[17] Üstün et al. found mild inflammation in 38% and severe grade in 31% of PTL.[18] Goldenberg et al found acute inflammation in 73.9% placentae of SPTB.[19] Perkins et al found increased inflammatory changes in placentae of SPTB with intact membranes than indicated preterm birth (IPTB); while Kovo et al noted just the reverse.[20,21] Salafia et al. found significant association between chronic villitis and PTL; whereas Kim et al noted concomitant CA with villitis in 38% of PTL.[22,23]

This study confirms that higher grades and stages of acute chorioamnionitis associated MIR, FIR and villitis were significantly associated with early SPTB (28-32weeks) compared to late (>32 weeks). FOVL was focally present in 20% preterm placentae and multifocal in 24%. Ischaemic vasculopathy may aggravate the incidence of PTL with poor perinatal outcome either alone or in association with infectious etiology.

Evidence showed a strong association between FOVL and increased incidence of PTL.[24,25] Germain et al found higher rate of PTB in infectious group (95.0%) compared to ischemic group (90.2%).[26] FOVL is thus, an obvious risk factor for PTL as well as poor perinatal outcome and must be considered in further management of subsequent pregnancy as well as in neonatal care unit(NICU).[26] (14)

No congenital abnormality was noted in newborns of both preterm and term deliveries in the present study. Among the preterm babies 42% cried immediately after birth, 40% had delayed and 18 % had poor cry. Germain et al had noticed high rate of low birth weight <1.5 kg (35%) and NICU admission (75%) in infection induced PTL, compared to ischemic group; while Salafia

et al noted decreased fetal growth with chronic villitis.[22,26]

Several researchers noticed strong association between CA and increased occurrence of early neonatal sepsis,[27-30] as like present study; but Strunk et al[31] observed reduced risk of late onset sepsis in neonate having CA. Therefore, it may be postulated that, though CA and FOVL both induced PTL, they had different pathogenesis to produce early neonatal sepsis and fatality. This study matches with the findings of Korraa et al. who observed strong association between CA and RDS,[32] but Bersani et al, Andrews et al, Liu et al, Dempsey et al, Elimian et al. found reduced incidence and severity of RDS which was due to increased use of antenatal steroid.[27,28,29,33,34]

Preterm babies in the present study had higher rate of RDS which may be due to increased incidence of obstructive vasculopathy with placental histologic CA. Bronchopulmonary dysplasia ( BPD) was not found resembling study of Rocha et al. and Masmonteil who could neither confirm decreased rate of RDS nor increased risk for BPD, in neonates with CA.[35,36]All perinatal adverse outcomes in the present study were due to prematurity, infection and ischemia leading to placental insufficiency. However, a large cohort study is necessary to establish the individual adverse effects of chorioamnionitis with MIR, FIR, villitis or placental vasculopathy on perinatal outcome. In this study, HIE induced preterm death was possibly sequel to obstructive vasculopathy as well as infection related pathological changes. Early neonatal sepsis progressing to multisystem failure who presented with low Apgar score, delayed and poor cry could be due to endothelitis. RDS along with toxaemia induced placental insufficiency is another possible etiology.

Kaukola et al. observed increased risk of intraventricular hemorrhage (IVH) and poor neurologic outcomes in preterm presenting with chorioamnionitis and placental perfusion defect.[37] Several research found strong association between CA and neonatal death;[29,30,32,33] however, Roescher et al. concluded neonatal mortality as combined result of placental underperfusion and CA.[38]

Dempsey et al. found no increased incidence of NEC or IVH in infection induced PTL similar to present study.[28] The association of FIR with increased perinatal mortality than MIR was unique in this study and the finding was similar to studies of Lau et al. and Mestan et al.[39,40] Perrone et al. concluded that low gestational age, CA, rather than placental vasculopathy, had negative impacts on adverse perinatal outcomes.[24,39,40] But, Lepais et al. observed that obstructive vasculopathy increased risk of fetal cardiopathy and neurodevelopmental complications respectively, which may be the outcome of chronic hypoxic damage induced by FIR.[25]

Ellis et al. found 11.4% positive and 99.9% negative predictive values of 1 min Apgar of ≤ 3 for neonatal encephalopathy;[41] whereas Brian et al. and Henry et al. noticed high mortality in preterm babies with 5 minute Apgar scores of 0-3.[42,43] This study had shown poor perinatal outcome in 1 minute Apgar score of 0-3 and 5 minute score of 4-6. The present study was limited by conducting study in a single institution not representing general population, non-blinding of pathologist to clinical history, low sample size and short duration of study.

## Conclusion

Histopathological examination of placenta must be considered mandatory for identifying infectious or obstructive vasculopathy to tailor neonatal therapy and to modify early neonatal care to prevent neonatal morbidity and mortality.

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**Author's contribution:** All authors were equally involved in conception, study design, data collection, statistical analysis, writing, editing, and final approval of the manuscript.

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