

Relationship between Placental Pathology and Birth Weight of Newborns at a Tertiary Care Centre in Central Kerala, India: A Cross-sectional Study

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ABSTRACT

Introduction: Even minor changes in the placenta are associated with the mortality and morbidity of the growing foetus and mother, which may have long-standing effects on the foetus.

Aim: To study the relationship between placental pathological changes and the birth weight of newborn infants.

Materials and Methods: In this cross-sectional study conducted at Malankara Orthodox Syrian Church (MOSC) Medical College, Kolenchery, Ernakulam, Kerala, India, over a period of two months, all inborn neonates, irrespective of gestational age, were considered. The first 63 placental samples (with birth weight <2.5 kg) were taken as cases, and the immediately succeeding next 63 were taken as controls (birth weight >2.5 kilograms). At birth, neonatal details including birth weight, gestational age, placental weight, Small for Gestational Age (SGA)/ Appropriate for Gestational Age (AGA)/Large for Gestational Age (LGA), etc., were noted. The placentae were carefully removed, weighed before fixation, and subjected to pathological examination (including gross and microscopic examination). Data were

analysed using Statistical Package for the Social Sciences (SPSS) version 14.0 software by Chi-square test.

Results: A total of 126 placentae were examined. Increased fibrin deposition in the placenta (perivillous, intervillous, or subchorionic) was associated with Low Birth Weight (LBW) neonates (p -value=0.024), but infarcts were not. Increased fibrin deposition in the placenta (p -value=0.016) and infarcts in the placenta (p -value=0.02) were associated with SGA neonates. However, other findings like haemorrhage, thrombus, calcification, metaplasia, necrosis, vasculopathy, infections, fibrosis, vasculitis were not found to be associated with LBW or SGA neonates. There was a moderate positive correlation between placental weight and the birth weight of neonates (r -value=0.59).

Conclusion: Abnormal histopathological changes like infarcts and fibrin deposition in the placenta result in LBW infants. Therefore, proper antenatal screening of the mother for immunology-based rejection-like disorders, maternal coagulopathies, and imbalances between angiogenic or antiangiogenic pathways is necessary. Regular follow-up of infants with placental pathological changes are also essential.

Keywords: Fibrin, Haemorrhage, Infarcts, Placenta

INTRODUCTION

The placenta plays a vital role in the growth and development of a foetus. Even slight variations in the placenta and its circulation can result in the mortality and morbidity of the growing foetus, which may have immediate and long-term effects on the foetus [1]. Recent research on placental foetus lesions has led to a better understanding of placental functions. Suboptimal placental performance can interfere with foetal development; indeed, there are indications that placental lesions are the leading cause of foetal death. Impaired placental functioning can have significant implications for the live-born infant in various forms, especially regarding weight [2].

The response to alterations in maternal or foetal blood flow through the placenta results in significant histological abnormalities in the placental villi, and failure of the villous tree's maturation may cause defective trophoblastic differentiation. The clinical syndrome is due to inadequate transformation of the spiral arteries into uteroplacental vessels due to restricted supply of maternal oxygen and nutrients. This failure of placentation represents an abnormality in the relationship between foetal and maternal tissues at a relatively early stage of pregnancy and can lead to intrauterine growth retardation [3]. Impaired perfusion in the placental tissues leads to selective

suppression of protein synthesis and reduced cell proliferation, which can result in increased infarction and fibrin deposition.

Reduction in birth weight is observed in placentas with secondary changes involving dedifferentiation of smooth muscle cells that surround the foetal arteries within placental stem villi, and this correlates with absent or reversed end-diastolic umbilical artery blood flow. The changes are more severe in cases of growth restriction associated with preeclampsia than in those with growth restriction alone. In preeclampsia, there is a more significant degree of maternal vasculopathy with more extensive macroscopic placental damage, including infarcts, extensive fibrin deposition, and microscopic villous developmental defects, atherosclerosis of the spiral arteries, and non-infectious villitis [4]. Vasculopathy was associated with decreased birth weight and APGAR score at five minutes and had a high incidence of necrotising enterocolitis [5].

A baby born with LBW has a relationship with various histopathological changes in the placenta and their corresponding immediate effects on the foetus, which may aid in the intervention of long-standing neurological and other problems in the growing infant. By international agreement, an LBW infant has a birth weight of 2500 g or less, irrespective of gestational age [6].

Detailed investigation of intravascular fibrin deposition in pregnancy is necessary to address the broader issues that arise when intravascular coagulation is considered a component of pathogenesis in a range of associated conditions, there is a dynamic balance between coagulation and fibrinolysis, which is why fibrin deposition is looked for. When investigating the reasons for fibrin deposition, it could be due to immunologically based rejection-like disorders, maternal coagulopathies, and an imbalance between angiogenic/antiangiogenic pathways [7,8]. The significance of examining the placenta macroscopically and microscopically is not well-known among paediatricians and neonatologists. Therefore, a comprehensive study was conducted in Central Kerala to identify the relationship between various histopathological changes in the placenta and their corresponding immediate effects on the foetus. The objective of this study was to examine the relationship between placental pathological changes and the birth weight of newborn infants.

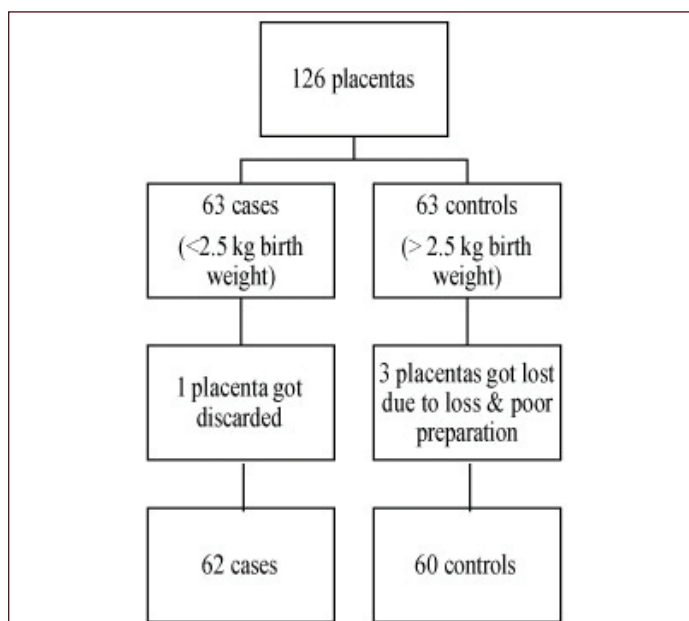
MATERIALS AND METHODS

The present study was as a cross-sectional study conducted over a two-month period (March 2015 to April 2015) at MOSC Medical College, Kolenchery, Ernakulam, Kerala, India. The study was approved by Institutional Ethics Committee (IEC) approval number is 60/2015. The fetoplacental units of all live deliveries from the centre were included in the study.

Inclusion criteria: Whenever LBW neonate was born, the immediately succeeding delivery where a neonate with a birth weight of >2.5 kg was born was taken as a control (63). In cases where two consecutive deliveries resulted in LBW neonates, the next two deliveries with birth weights >2.5 kg were taken as controls.

Exclusion criteria: Placentae of neonates with major congenital anomalies, lack of parental consent, and damaged placentae were excluded from the study.

Sample size: All neonates meeting the inclusion criteria were enrolled in the study. Though the sample size was 39 in each group, 63 samples from each group for the study was considered. The cases were the placentae of neonates with a birth weight <2.5 kg (LBW neonates), and the controls were those with a birth weight of ≥ 2.5 kg. One placenta from the LBW group and three from the other group had to be discarded, leaving behind 62 and 60 samples, respectively. Thus, the total number of samples was 122 [Table/Fig-1].



[Table/Fig-1]: Algorithm of sampling.

Methodology: During delivery, the placenta was carefully removed without causing damage. A gross examination of the placenta was conducted to identify any macroscopic lesions and anomalies. The placenta was then sent for histopathological examination using standard techniques by a qualified pathologist [9]. Relevant maternal and neonatal details, including birth weight, gestational age, SGA/AGA/LGA classification, and the baby's general condition and morbidities, were recorded. The birth weight and placental weight were measured using a standard digital weighing scale within one hour after birth. The placentae and their details were registered, labeled for identification, and subjected to the following procedures:

Grossing: The placental disc was cut into pieces, the membranes were rolled over, and the cord was cut. The pieces were then placed in formalin for fixation. After the sample was taken out, one section from the cord, one from the rolled-up membrane, one or two from the disc, and required samples from any other macroscopically abnormal area on any of these structures were cut out and deposited in plastic cassettes.

Tissue processing: The sample was dehydrated in a tissue processor, with one hour each of 50% alcohol, 60% alcohol, 70% alcohol, 80% alcohol, 90% alcohol, and 100% (absolute) alcohol. Then, alcohol was cleared with xylene.

Embedding: The tissue was embedded in molten wax and, after cooling, taken out of the cassette. Serial sections were taken using a microtome, and the thin film was put in water. These films were transferred onto a slide and kept in a hot air oven for 15 minutes to remove wax. Then, xylene, followed by absolute alcohol, 90%, 80%, 70%, 60%, and 50% alcohol, were applied, and then cleaned with water.

Staining: Haematoxylin stain was applied for five minutes, then washed. A 1% acid alcohol was applied, followed by ammonia, then eosin for one minute, followed by absolute alcohol thrice.

Mounting: The sample was mounted with a cover slip onto a microscope slide using Dextrene Phthallate Xylene (DPX) and labeled. Microscopic examination was conducted, and histopathological findings such as infarct, fibrin deposition, haemorrhage, thrombus, calcification, metaplasia, necrosis, vasculopathy, infections, fibrosis, and vasculitis were noted.

STATISTICAL ANALYSIS

The data was entered into Epi info 7 and transferred to SPSS 14 software for analysis. The histopathology of the placentae was compared to the birth weight numerically by correlation and divided into groups of LBW vs others and SGA vs AGA using the Chi-square test.

RESULTS

The mean birth weight (2014 \pm 441 g in cases and 3085 \pm 377 g in controls) and mean placental weight (407 \pm 114 g in cases and 529 \pm 150 g in controls) were higher in the control group. As the gestational age was not considered for categorising in the above two groups, the mean gestational age (and range) was higher in the control group (35.6 \pm 3 weeks in cases, and 38.7 \pm 1.3 weeks in controls) [Table/Fig-2].

In [Table/Fig-3], the different placental histopathological changes in LBW neonates were compared with the others. Any changes present in histopathology (microscopy) or in macroscopy or both were considered positive. Increased fibrin deposition in the

Parameter	Case (62)		Control (60)	
Gestational age <32 weeks	6 (9.7%)		0	
32-36 weeks	25 (40.3%)		3 (5%)	
>37 weeks	31 (50%)		57 (95%)	
Variables	Mean±SD	Range (case)	Mean±SD	Range (Control)
Birth weight (g)	2014±441	890-2480	3085±377	2550-4410
Placental weight (g)	407±114	110-720	529±150	320-1000
Gestational age (weeks)	35.6±3.0	27-40	38.7±1.3	33-40

[Table/Fig-2]: Descriptive statistics of cases and controls.

placenta (perivillous, intervillous, or subchorionic) was associated with LBW (p-value=0.024). Similarly, placental infarcts were also associated with LBW neonates, although the association was not statistically significant (p-value=0.08). However, other findings

Individual path findings (microscopic or microscopic or both)	SGA group (n=47)		AGA group (n=72)		p-value	Odd's ratio
	Pathological findings		Pathological findings			
	Absent (N)	Present (N)	Absent (N)	Present (N)		
Infarct	25%	22%	41%	31%	0.02*	0.40
Haemorrhage	29%	18%	39%	33%	0.66	1.18
Fibrin deposits	30%	17%	54%	18%	0.016*	0.34
Thrombus	43%	4%	69%	3%	0.52	0.59
Calcification	20%	27%	35%	37%	0.92	0.96
Metaplasia	40%	7%	62%	10%	0.75	1.18
Necrosis	47%	0	71%	1%	-	-
Vasculopathy	46%	1%	72%	0	-	-
Infections	45%	2%	69%	3%	-	-
Fibrosis	47%	0	71%	1%	-	-
Vacuclitis	47%	0	71%	1%	-	-

[Table/Fig-4]: Analysis of histopathological findings in the SGA/AGA groups. *p-value <0.05 statistically significant

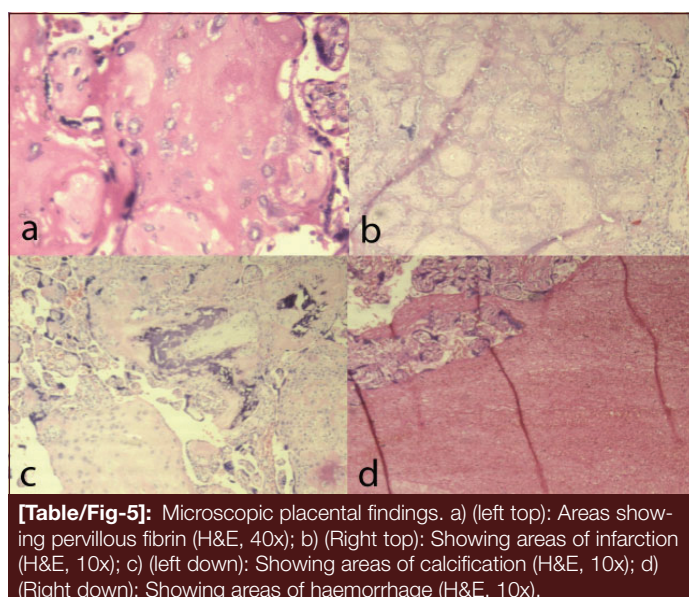
Individual pathological findings	Low birth weight (LBW) (n=62)			Birth weight > 2.5kg (n=60)			p-value	Odd's ratio
	Pathological findings			Pathological findings				
	Absent n (%)	Microscopic only n (%)	Macroscopic and microscopic n (%)	Absent n (%)	Microscopic only n (%)	Macroscopic and microscopic n (%)		
Infarct	30 (48)	23 (37)	9 (15)	38 (63)	15 (25)	7 (12)	0.08	0.34
Haemorrhage	36 (58)	4 (6)	22 (36)	34 (57)	3 (5)	23 (38)	0.87	1.46
Fibrin deposits	39 (63)	18 (29)	5 (8)	48 (80)	5 (8)	7 (12)	0.024	0.22
Thrombus	58 (94)	4 (6)	0	57 (95)	1 (2)	2 (3)	0.38	0.17
Calcification	28 (45)	33 (53)	1 (2)	27 (45)	32 (53)	1 (2)	0.99	0.97
Metaplasia	53 (86)	9 (14)	0	51 (85)	9 (15)	0	-	-
Necrosis	61 (98)	1 (2)	0	60 (100)	0	0	-	-
Vasculopathy	61 (98)	1 (2)	0	60 (100)	0	0	-	-
Infections	60 (98)	2 (3)	0	57 (95)	3 (5)	0	-	-
Fibrosis	61 (98)	1 (2)	0	60 (100)	0	0	-	-
Vacuclitis	62 (100)	0	0	59 (98)	1 (2)	0	-	-

[Table/Fig-3]: Analysis of histopathological findings in both the groups (LBW/others) (babies with birth weight >= 2.5 kg). (remaining were normal)

such as haemorrhage (p-value=0.87), thrombus (p-value=0.38), calcification (p-value=0.99), metaplasia, necrosis, vasculopathy, infections, fibrosis and vasculitis were not found to be associated with LBW.

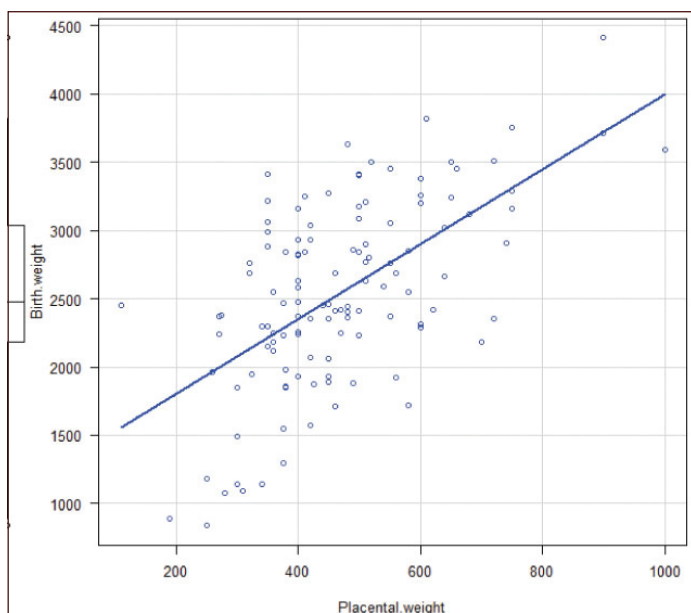
In [Table/Fig-4], the different placental histopathological changes in the SGA group were compared with the AGA group. The LGA category was avoided as there were only three cases. The histopathological findings of perivillous fibrin deposits [Table/Fig-5a] and infarcts [Table/Fig-5b] in the placenta are depicted. Comparing the SGA/AGA neonates, increased fibrin deposition in the placenta (perivillous, intervillous, or subchorionic) (p-value=0.016) [Table/Fig-5a] and placental infarcts (p-value=0.02) [Table/Fig-5b] showed an association with SGA neonates. The other histopathological changes such as calcification (p-value=0.92) [Table/Fig-5c], haemorrhage (p-value=0.66) [Table/Fig-5d], thrombus (p-value=0.52), metaplasia, necrosis, vasculopathy, infections, fibrosis, and vasculitis were not associated with SGA/AGA neonates.

In [Table/Fig-6], the placental weight was compared with the birth weight using the correlation method. There was a moderate positive



[Table/Fig-5]: Microscopic placental findings. a) (left top): Areas showing perivillous fibrin (H&E, 40x); b) (Right top): Showing areas of infarction (H&E, 10x); c) (left down): Showing areas of calcification (H&E, 10x); d) (Right down): Showing areas of haemorrhage (H&E, 10x).

correlation between placental weight and birth weight of neonates (p-value=0.001) (r-value=0.59). As the placental weight increased, the birth weight also increased.



[Table/Fig-6]: Correlation between the placental weight and birth weight.
*p-value- 0.001

DISCUSSION

This study highlighted the fact that placental histopathological changes are associated with changes in birth weight of the neonates, which might be a manifestation of pathological changes in different organs. The same cause (maternal, antenatal, or perinatal risk factor) that has affected the placenta (resulting in the changes) might also affect the baby's biochemical milieu and the organs themselves, and LBW might be the only visible change.

In this study, increased fibrin deposition in the placenta was associated with LBW neonates (37%) ($p=0.024$), which was lower than the study by Nigam JS et al., (75%) [10]. However, this study did not show any association of placental infarcts ($p=0.08$) and placental calcification ($p=0.99$), unlike Nigam J et al., which showed significant association with placental infarcts ($p\text{-value}<0.001$) and calcification ($p\text{-value}<0.01$). Kotgirwar S et al., also noted some histopathological changes associated with intrauterine growth retardation [11]. The percentage of LBW neonates having infarcts was comparable to the study by Magesh P (52% in the LBW group in both studies) [12]. In this study, increased placental infarcts (37%) ($p\text{-value}=0.02$) were found to be associated with SGA neonates, in addition to increased fibrin deposition (20%) ($p\text{-value}=0.016$). Kotgirwar S et al., also demonstrated increased fibrin deposition in intrauterine growth restriction (IUGR) neonates (16.7%) [11]. However, Redline RW demonstrated five chronic patterns of placental injury in placentae from neonates with IUGR, including maternal and foetal vascular obstructive lesions, high-grade villitis, perivillous fibrinoid deposition, and chronic abruption [13]. In this study, there was no association between placental histopathological findings such as haemorrhage ($p\text{-value}=0.66$), thrombus ($p\text{-value}=0.52$), calcification ($p\text{-value}=0.92$), metaplasia, necrosis, vasculopathy, infection, fibrosis, and vasculitis with birth weight. Some studies, like Ogunyemi D et al., had shown an association with various features associated with LBW, such as vasculopathy ($p\text{-value}=0.011$) [5]. Studies like Kotgirwar S et al., did not show the effect of vasculopathy, metaplasia, thrombosis, necrosis, and fibrosis on birth weight [11]. Placental calcification was not

found to be associated with neonatal morbidity in the study by Ramachandran A [14].

In this study, a moderate correlation was found between placental weight and birth weight of neonates ($p\text{-value}=0.001$) ($r=0.59$), which was comparable to the study by Ramachandran A where the fetoplacental weight was reduced in IUGR, SGA, and preterm neonates [14]. The knowledge gaps resulting from the present study include the biochemical and histological changes in the foetus and newborn that occur due to various maternal and perinatal insults. More studies on the placenta and stillborn neonates with more sophisticated techniques might give us more clues on these aspects.

Limitation(s)

A study with more samples might provide evidence of the association with other histopathological features as well. Additionally, long-term follow-up of the neonates could not be done as part of this study.

CONCLUSION(S)

Abnormal histopathological changes such as infarcts and fibrin deposition in the placenta were found to result in LBW infants. Therefore, prevention of these conditions should be targeted through proper maternal and antenatal screening. The neonates in present study should be further followed-up and monitored for long-term neurological and other disorders, which may help us in preventing them through early intervention in the mother or infant.

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