ORIGINAL ARTICLE

Association of Placental Risk Factors and Birth Weight of Newborn: A Case–Control Study

Balasubramanian R[1], Sulakshana Shridhar Baliga[2], Ranjit Kangle[3], Kamal P Patil[4], Karthik Srevatsa[5]

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Abstract

Introduction: The global incidence of low birth is 15%, and in India, it is 18%. Together with gestational maternal age and size, placental factors contribute to 32% of low-birth weight. Various factors influence the fetal growth such as the factors originating from fetus itself, maternal factors, placental factors, and the factors due to interaction of all these factors.

Materials and methods: The placenta was collected from 30 mothers of low-birth-weight babies and 60 placentas from mothers of normal-birth-weight babies in the Department of Obstetrics and Gynecology from October 2020 to December 2020. Information regarding maternal characteristics, placental morphometry, and newborn parameters were recorded.

Results: Mean of placental weight is significantly less in case group (420 + 7 gm) compared with control (560 + 100) group. Mean of placental length, breadth, surface area, diameter, and thickness is significantly less in the case group compared with the control group (p <0.05). The presence of hard areas, focal avascular villi, syncytial knotting, focal hyaline degeneration, and fibromuscular sclerosis was seen more in low-birth-weight babies when compared with normal-birth-weight babies (p <0.05).

Conclusion: Placental factors such as placental weight, placental length, breadth, diameter, surface area, thickness, and volume were less in low-birth-weight babies. All the microscopic and gross findings like the presence of hard areas, focal avascular villi, syncytial knotting, focal hyaline degeneration, and fibromuscular sclerosis were seen more in low-birth-weight babies.

Keywords: Low birth weight, Maternal risk factors, Newborn, Placental morphometry, Placental risk factors, Placental weight.

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Introduction

Placenta is an organ that facilitates exchange of gases and metabolic products (nutrients, electrolytes, and maternal antibodies) between maternal and fetal blood and produces hormones that sustain the pregnancy and prepares the mother and baby for postnatal period. Placental morphological changes such as length, breadth, weight, and shift in the insertion of umbilical cord on the chorionic plate may affect the vasculature of placenta, which is required to meet the requirement of nutrients and oxygen to the fetus. The placental weight also serves as a marker for the surface area available for maternal fetal nutrient exchange.[1]

The global incidence of low birth is 15%, and in India, it is 18%.[2] Together with gestational maternal age and size, placental factors contribute to 32% of low birth weight.[3] Various factors influence the fetal growth such as the factors originating from fetus itself, maternal factors, placental factors, and the factors due to interaction of all these factors. Low birth weight is usually associated with uterine malnutrition due to mother–placenta–fetus interchanges. Addressing the placental factors is of utmost importance since existing national programs address obstetric and neonatal care, but placental risk factors are neglected. So, we need to identify early changes in the placenta that helps in predicting and prevention of adverse fetal outcomes.[4]

Various studies have shown the association of maternal disorders, congenital anomalies, and chromosomal anomalies with low birth weight. This study highlights the association of placental risk factors such as changes in placental morphology, histological changes in the placenta, and low birth weight in the newborn. Hence, the present study was conducted to know the association between placental risk factors and birth weight of newborn.

[1,2]Department of Community Medicine, KAHER's Jawaharlal Nehru Medical College, Belagavi, Karnataka, India

[3]Department of Pathology, KAHER's Jawaharlal Nehru Medical College, Belagavi, Karnataka, India

[4]Department of Obstetrics and Gynecology, KAHER's Jawaharlal Nehru Medical College, Belagavi, Karnataka, India

[5]Department of Pathology, CIMS, Chikkaballapur, Karnataka, India

Corresponding Author: Sulakshana Shridhar Baliga, Department of Community Medicine, KAHER's Jawaharlal Nehru Medical College, Belagavi, Karnataka, India, Phone: +91 9342611358, e-mail: baliga1983@rediffmail.com

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Conflict of interest: None

Objectives

- To know the association between placental risk factors and birth weight of newborn.
- To know the association between maternal risk factors and birth weight of newborn.

Materials and Methods

Source of Data

Registered pregnant women undergoing normal or cesarean delivery at a Tertiary Care hospital in Belagavi.

Method of Collection of Data

Study design: Case–control study.

Study period and sample size: The placenta was collected from 30 mothers of low-birth-weight babies and 60 placentas from mothers of normal-birth-weight babies in the Department of Obstetrics and Gynecology from October 2020 to December 2020.

Study population: 90 newborn babies – 30 term low-birth-weight babies (cases) and 60 normal-weight term babies (controls).

- *Selection of cases:* Term low-birth-weight (<2.5 kg) babies who were delivered at a Tertiary Care hospital in Belagavi in the period from October 2020 to December 2020.
- *Selection of controls:* Term normal-birth-weight (2.5–4 kg) babies who were delivered to a Tertiary Care hospital in Belagavi in the period from October 2020 to December 2020.

  Two consecutive normal-birth-weight babies born after the birth of a low-birth-weight baby were chosen as controls (1 case: 2 control).

  In case they came under exclusion criteria, the next immediate normal-birth-weight baby was taken as control.
- *Matching:* Controls were matched for gestational age at delivery and sex of the baby. Group matching of the cases and controls was done.

Study tool: Pretested and predesigned questionnaire.

Study variables: Information regarding maternal characteristics, placental morphometry, and newborn parameters was recorded.

Method of Collection of Placenta

- The placenta was collected along with cord and membranes after delayed cord clamping within 1 hour of delivery. The placental clots if any were removed, washed thoroughly in running water to remove excess blood, the cord was cut at 5 cm from the insertion site, membranes were cut, and the weight of the trimmed placenta was measured within 10 minutes of collection of the placenta using a digital baby-weighing scale calibrated to 2 decimal points (10 gm).
- The placental volume was calculated by water displacement technique using standardized measuring apparatus.[5]
- Placenta was then examined for type of placenta, type of insertion of umbilical cord into the placenta, and presence of meconium staining on fetal surface by the investigator.
- The placenta along with the membranes and cord was cut into multiple longitudinal slices and transported in a container with 10% formalin, tagged with numbers for identification, and was sent to a histopathology lab attached to the medical college. Further gross analysis including dimensions of the placenta, was done using a Vernier caliper calibrated to 10 mm.
  - The maximum horizontal dimension of placenta was considered as length.
  - The dimension perpendicular to the length was considered as breadth.
  - Thickness was measured using a needle passed at the level of insertion of umbilical cord and then the thickness was measured using Vernier calipers.
  - Surface area of placenta was calculated using $\frac{3.14 \times ds \times dl}{4}$

  Where *ds* – smallest diameter (placental breadth) and *dl* – largest diameter (placental length)
  - Feto placenta ratio was calculated using the formula:[6]

$$\frac{\text{Weight of fetus}}{\text{Weight of placenta}}$$

  - Placental coefficient was calculated using the formula:[6]

$$\frac{\text{Weight of placenta}}{\text{Weight of fetus}}$$

- Placenta was dissected according to Amsterdam criteria 2016.[7]
- Placenta was cut into 1 cm slices extending just short of cutting through to look for abnormal areas.
- A minimum of 6 bits were given which included:
  - Umbilical cord 2 cm from site of insertion.
  - Umbilical cord at the site of insertion.
  - Membranes were rolled into a swiss roll model and cross section was taken.
  - Maternal surface of placenta.
  - Fetal surface of placenta.
  - Edge of placenta.
  - Abnormal areas, if any.
- The 5-cm wide section of membrane starting at the point of rupture of membranes extending till insertion of placenta at the margin was taken. The membrane was rolled with amniotic surface inward via Swiss roll model, and 1 cm cuts were made.
- The bits were processed to make slides of 4-micron thickness with Hematoxylin and Eosin stain.

Inclusion Criteria

- Singleton delivery of live neonate born to mothers of any parity at or after 37 weeks till 42 weeks of the period of gestation.
- Small for gestation and fetal growth restriction babies.

Exclusion Criteria

- Those not willing to be part of the present study.
- Congenital anomalies of baby detected antenatally or suspected postnatally.
- Twin or multiple gestations.
- RVD positive cases (increased risk of chorioamnionitis).
- Those who do not remember their last menstrual period.

Informed Consent

Written informed consent was taken from each participant prior to the study.

Statistical Analysis

Data were analyzed using statistical software R version 4.1.1 and Microsoft Excel. Continuous variables were represented by mean ± SD/median (range), and categorical variables were represented by frequency and percentage. To check the association between categorical variables, Chi-square test was used. To check the normality of variables, Shapiro–Wilk's test was used. To compare the mean between groups, two-sample *t*-test was used. *p*-value less than or equal to 0.05 indicates statistical significance. Logistic regression analysis was used to find the association between placental and maternal risk factors and birth weight of the newborn.

Ethical Clearance

Institutional ethical committee clearance was obtained vide reference number: MDC/DOME/147 dated 19/9/2019.

Results

Table 1 shows the maternal characteristics of the study participants. The mean maternal age was 23.6 + 3.71 years and 24.37 + 3.53 years in cases and controls, respectively. However, in our study, it was seen that maternal age was not a contributing factor for low birth weight (p = 0.4933). Our study did not show any significant difference in the mean of maternal age between the groups by two-sample t-test. By Mann–Whitney test, there was a significant difference in the distribution of registration of pregnancy between the groups wherein controls registered their pregnancy earlier (6 weeks) as compared with cases (9 weeks). One-tailed two sample t-test showed that mean of prepregnancy weight (p = 0.003033), weight at delivery (p = 0.000241), prepregnancy BMI (p = 0.01449), and BMI at delivery (p = 0.002444) were significantly less in case group compared with control group.

Table 2 shows the neonatal characteristics of study participants. There was no significant difference in the distribution of sex of the child. There was no significant difference in the distribution of Apgar scores between the groups. Mean placental weight was significantly less in case group (420 + 7 gm) compared with control (560 + 100)

Table 1: Maternal characteristics of study participants (n = 90)

Maternal characteristics	*Cases (n = 30)*	*Controls (n = 60)*	*Total (n = 90)*	*p-value*
Maternal age (in years)				
<20	3 (10%)	2 (3.33%)	5 (5.56%)	0.4933[MC]
20–25	17 (56.67%)	31 (51.67%)	48 (53.33%)	
25–30	8 (26.67%)	23 (38.33%)	31 (34.44%)	
≥30	2 (6.67%)	4 (6.67%)	6 (6.67%)	
Maternal age (in years)	23.6 ± 3.71	24.37 ± 3.53	24.11 ± 3.59	0.3424[t]
Registration of pregnancy	9 (4, 20)	6 (4, 20)	8 (4, 20)	0.0424[*MW]
Gestational age (in weeks)	38.87 ± 1.32	39.24 ± 1.04	39.11 ± 1.15	0.1485[t]
Prepregnancy weight (in kgs)	40.57 ± 7.58	46.18 ± 9.53	44.31 ± 9.27	0.003033[*t]
Weight at delivery (in kgs)	51.3 ± 7.97	58.83 ± 9.86	56.32 ± 9.9	0.000241[*t]
Prepregnancy BMI (in kg/m^2)	17.67 ± 2.64	19.6 ± 4.38	18.96 ± 3.98	0.01449[*t]
BMI at delivery (in kg/m^2)	22.37 ± 2.65	24.93 ± 4.47	24.08 ± 4.12	0.002444[*t]
Hemoglobin at 1st trimester (g/dL)	10.57 ± 1.49	10.15 ± 1.66	10.29 ± 1.61	0.8602[t]
Hemoglobin at 2nd trimester (g/dL)	10.6 ± 1.36	10.03 ± 1.15	10.4 ± 1.22	0.5321[t]
Hemoglobin at 3rd trimester (g/dL)	11.19 ± 1.77	11.26 ± 1.4	11.24 ± 1.52	0.4148[t]

[MC]Monte-Carlo simulation used in Chi-square test; [t]t-test; [MW]Mann–Whitney test, [*]p <0.05

Table 2: Neonatal characteristics of study participants (n = 90)

	Cases	*Controls*	*Total*	*p-value*
Sex of baby				
Female	14 (46.67%)	28 (46.67%)	42 (46.67%)	1
Male	16 (53.33%)	32 (53.33%)	48 (53.33%)	
Birth weight (in kg)	2.19 ± 0.26	2.98 ± 0.38	2.72 ± 0.51	<0.00001[*t]
Apgar	7 (7, 8)	7 (6, 9)	7 (6, 9)	0.9638[MW]
Fetal distress				
Absent	25 (83.33%)	46 (76.67%)	71 (78.89%)	0.465
Present	5 (16.67%)	14 (23.33%)	19 (21.11%)	
Placental weight (grams)	0.42 ± 0.07	0.56 ± 0.1	0.51 ± 0.11	<0.00001[*Wt]
Placental length (in cm)	14.64 ± 2.2	16.83 ± 2.89	16.1 ± 2.86	0.000222[*t]
Placental breadth (in cm)	12.57 ± 1.79	13.88 ± 1.96	13.44 ± 1.99	0.001424[*t]
Surface area (in cm^2)	145.85 ± 37.43	186 ± 52.84	172.62 ± 51.67	0.000177[*t]
Thickness (in cm)	2.12 ± 0.61	2.66 ± 0.93	2.48 ± 0.87	0.000734[*t]
Placental diameter	13.61 ± 1.71	15.35 ± 2.18	14.77 ± 2.19	0.00011[*t]
Placental volume	305.15 ± 87.21 344.54 (162.57, 495.14)	499.75 ± 225.47 476.15 (113.04, 1329.79)	434.89 ± 211.4 380.01 (113.04, 1329.79)	<0.00001[*MW]
Feto-placental ratio	5.3 ± 0.7	5.45 ± 0.77	5.4 ± 0.75	0.1947[t]
Placental coefficient	0.19 ± 0.03	0.19 ± 0.02	0.19 ± 0.03	0.8256[t]

[t]t-test; [MW]Mann–Whitney test; [Wt]Welch's t-test, [*]p <0.05

group (p <0.00001). Mean placental length, breadth, surface area, diameter, and thickness were significantly less in the case group compared with the control group (p <0.05). However, there was no difference observed in the mean of feto-placental ratio and placental coefficient between the groups by two-sample t-test. Feto-placental ratio was observed as 6:1 in case and 5:1 in controls. Placental volume was less in low-birth-weight babies when compared with normal-birth-weight babies (p <0.00001).

Table 3 shows the gross and microscopic examination of the placenta. Presence of hard areas (Fig. 1), focal avascular villi, syncytial knotting (Fig. 2), focal hyaline degeneration, and fibromuscular sclerosis was seen more in low-birth-weight babies when compared with normal-birth-weight babies (p <0.05).

Table 4 shows logistic regression for maternal risk factors for low birth weight. The model was finalized using stepwise regression method, and we can observe that only prepregnancy weight is affecting low birth weight. In this study, it was seen that with unit increase in the prepregnancy birth weight, log odds of having low birth weight decreased by a factor of 0.08.

Table 5 shows logistic regression for placental risk factors of low birth weight. The model was finalized using stepwise regression method, and we can observe that placental weight and focal hyaline degeneration is affecting low birth weight. With unit increase in the placental weight, log odds of having low birth weight decreased by a factor of 19.3282. Log odds of having low birth weight are 2.0164 times more for the subjects who had focal hyaline degeneration

Table 3: Gross and microscopic examination of placenta of study participants

	Cases	*Controls*	*Total*	*p-value*
Hard areas				
<10%	19 (63.33%)	50 (83.33%)	69 (76.67%)	0.03445*
>10%	11 (36.67%)	10 (16.67%)	21 (23.33%)	
Type of placenta				
Bidiscoidal	2 (6.67%)	0 (0%)	2 (2.22%)	0.1159MC
Circumvallate	0 (0%)	1 (1.67%)	1 (1.11%)	
Normal	28 (93.33%)	59 (98.33%)	87 (96.67%)	
Type of insertion of umbilical cord into placenta				
Central	6 (20%)	20 (33.33%)	26 (28.89%)	0.1454MC
Eccentric	18 (60%)	34 (56.67%)	52 (57.78%)	
Marginal	4 (13.33%)	6 (10%)	10 (11.11%)	
Velamentous	2 (6.67%)	0 (0%)	2 (2.22%)	
Meconium staining				
No	4 (13.33%)	8 (13.33%)	12 (13.33%)	1
Yes	26 (86.67%)	52 (86.67%)	78 (86.67%)	
Calcification				
No	13 (43.33%)	33 (55%)	46 (51.11%)	0.2966
Yes	17 (56.67%)	27 (45%)	44 (48.89%)	
Focal avascular villi				
No	15 (50%)	50 (83.33%)	65 (72.22%)	0.000874*
Yes	15 (50%)	10 (16.67%)	25 (27.78%)	
Syncytial knotting				
Mild	8 (26.67%)	31 (51.67%)	39 (43.33%)	0.0004998*MC
Moderate	9 (30%)	5 (8.33%)	14 (15.56%)	
Nil	4 (13.33%)	12 (20%)	16 (17.78%)	
Severe	9 (30%)	1 (1.67%)	10 (11.11%)	
Focal hyaline degeneration				
No	21 (70%)	55 (91.67%)	76 (84.44%)	0.0004998*MC
Yes	9 (30%)	4 (6.67%)	13 (14.44%)	
Hypertrophic vessels				
No	28 (93.33%)	60 (100%)	88 (97.78%)	0.1044MC
Yes	2 (6.67%)	0 (0%)	2 (2.22%)	
Thickened vessel wall				
No	30 (100%)	57 (95%)	87 (96.67%)	0.5502MC
Yes	0 (0%)	3 (5%)	3 (3.33%)	

Intervillous hemorrhage				
No	25 (83.33%)	55 (91.67%)	80 (88.89%)	0.2274[MC]
Yes	5 (16.67%)	4 (6.67%)	9 (10%)	
Infarction				
No	24 (80%)	56 (93.33%)	80 (88.89%)	0.073436[MC]
Yes	6 (20%)	4 (6.67%)	10 (11.11%)	
Fibrinoid necrosis				
No	24 (80%)	56 (93.33%)	80 (88.89%)	0.07096[MC]
Yes	6 (20%)	4 (6.67%)	10 (11.11%)	
Fibromuscular sclerosis				
No	27 (90%)	60 (100%)	87 (96.67%)	0.03998*[MC]
Yes	3 (10%)	0 (0%)	3 (3.33%)	

[MC]Monte-Carlo simulation used in Chi-square test, *p <0.05

Fig. 1: Gross examination of cut-slice placenta during dissection showing hard area

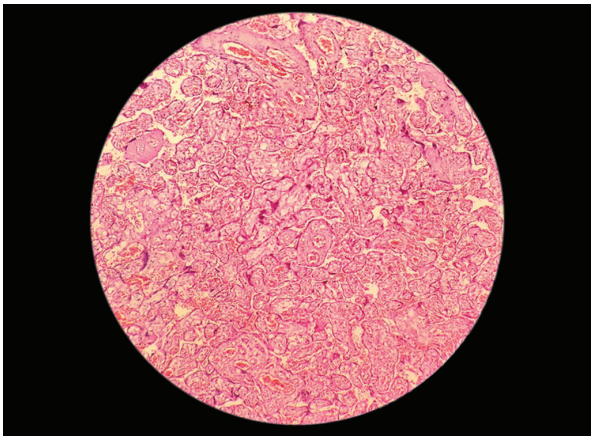

Fig. 2: Microscopic examination of placenta with H&E staining showing excessive syncytial knotting

Table 4: Logistic regression for maternal risk factors of low-birth weight

	Beta estimates (CI)	*p-value*
(Intercept)	−0.9694 (−5.259, 3.4491)	0.6589
Registered pregnancy	0.0713 (−0.0573, 0.2005)	0.2725
Prepregnancy weight (in kgs)	−0.0846 (−0.164, −0.0186)	0.0209*
Hemoglobin at 1st trimester	0.3088 (−0.0122, 0.6526)	0.066

*p <0.05

Table 5: Logistic regression for placental risk factors of low-birth weight

	Beta estimates (CI)	*p-value*
(Intercept)	7.5701 (3.271, 13.1303)	0.002165
Placental weight (in kg)	−19.3282 (−31.9028, −10.0619)	0.000402*
Syncytial knotting		
None	–	–
Mild	0.4774 (−1.3483, 2.5002)	0.619652
Moderate	1.5842 (−0.3929, 3.7575)	0.128046
Severe	2.2547 (−0.0589, 5.4578)	0.084992
Focal hyaline degeneration		
No	–	–
Yes	2.0164 (0.3107, 4.0539)	0.030415*

*p <0.05

Table 6: Correlation between placental parameters and birth weight over groups

	Cases		*Controls*	
	r-value	*p-value*	*r-value*	*p-value*
Placental weight (grams)	0.62761	0.00020*	0.67226	<0.00001*
Placental length (in cm)	0.32482	0.07989	0.3629	0.004375*
Placental breadth (in cm)	0.31787	0.08693	0.22457	0.08452
Surface area (in cm^2)	0.35870	0.05159	0.35144	0.00589*
Placental diameter	0.37517	0.04106*	0.340973	0.007676*
Placental volume#	0.46176	0.01021*	0.58756	<0.0001*
Thickness (in cm)	0.26386	0.1589	0.44946	0.00031*

#Indicates Spearman's correlation applied for the particular variable, *p <0.05

when compared with the subjects who do not have focal hyaline degeneration.

Table 6 shows the correlation between placenta parameters and birth weight between the groups. By Pearson's correlation test, there is strong positive correlation observed between placental weight and birth weight in both cases and controls. By Pearson's correlation test, there is moderate positive correlation observed between placental diameter and birth weight in both groups. By Spearman's correlation, there is moderate positive correlation observed between placental volume and birth weight in both groups (Figs 3 and 4).

Discussion

In our study, mean maternal age of cases and controls was 23.6 + 3.71 years and 24.37 + 3.53, respectively, which was similar to studies done in India.[8,9] In the present study, maternal age was not associated with placental weight that differed from other studies.[8,9] However, several studies have shown that teenage mothers had higher incidence of giving birth to low-birth-weight babies, which could be attributable to prematurity.[10,11] In our study, mean pregnancy weight, weight at delivery, prepregnancy BMI, and BMI at delivery were significantly less in mothers who had given birth to low-birth-weight babies, which could be attributed to poor nutritional status of the mother which was similar to other studies.[9,12]

Gender of the baby did not affect the birth weight of the baby in our study, whereas many studies have shown that male babies had higher birth weight than female babies.[13] Apgar score at 5th minute was similar in both groups unlike other studies.[14,15] It was probably similar in cases and controls in our study due to better neonatal resuscitation care and equipment availability in the tertiary care center. Fetoplacental ratio and placental coefficient were similar between the two study groups in our study, whereas several studies have shown that these could be less for small-for-gestational age and adverse pregnancy outcomes.[6,16–18] In the present study, mean placental weight was significantly lower in low-birth-weight babies, which were similar to other studies.[19–23] Low mean placental weight in low-birth-weight babies in our study could be due to decompensatory changes in the placenta.[19–23]

In our study, we could see changes in the placenta on gross and microscopic examination, such as the presence of hard areas, focal avascular villi, syncytial knotting, focal hyaline degeneration, and fibromuscular sclerosis which was more among low-birth-weight babies when compared with normal-birth-weight babies, which was similar to other studies.[24,25] Having diffuse hyaline

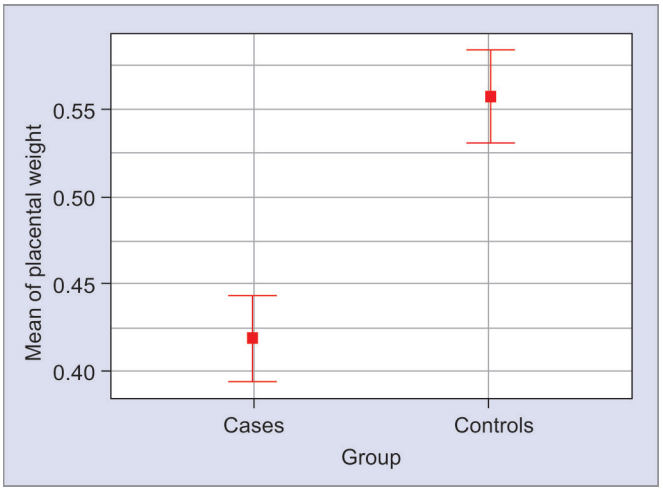

Fig. 3: Comparison of mean placental weight between the cases and controls

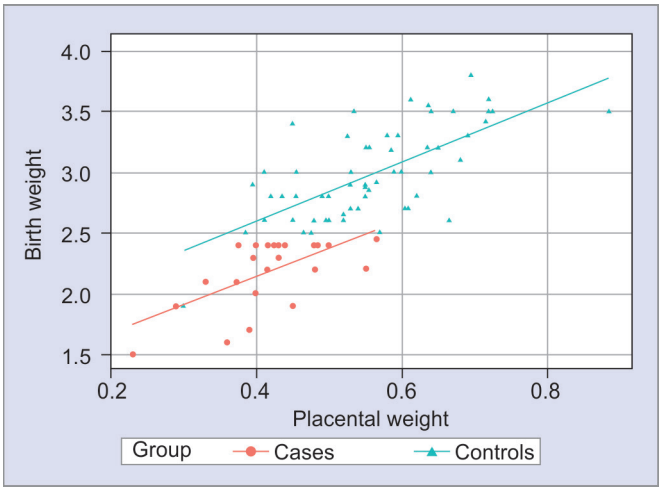

Fig. 4: Positive correlation plot between placental weight and birth weight

degeneration could be physiological. However, in our study, focal hyaline degeneration was seen, which could be due to vascular obliteration of stem villous vessel of noninflammatory cause that could predict the possibility of low birth weight.[24,25] Increased syncytial knotting was seen in the placenta of low-birth-weight

babies. This could be explained by the fact that there is higher vascular endothelial growth factor (VEGF) expression in patients with maternal stress as a part of placental adaptation to procure more nutrition. Vascular endothelial growth factor causes angiogenesis and more villous pattern of placental vessels that appears as syncytial knotting in low-birth-weight placentae.[26,27] Focal avascular villi, which is a predictor of low birth weight, were seen higher in our cases compared with controls.[28] Fibromuscular sclerosis is seen more in patients with GDM, however, our study showed a higher incidence in mothers who give birth to low-birth-weight babies.[29] Our study showed focal hyaline degeneration, focal avascular villi, increased syncytial knotting, and fibromuscular sclerosis to be significantly associated with low-birth-weight babies, however, in a study conducted in Uttar Pradesh showed that placental ischemia, placental infarction, fibrinoid necrosis, stromal fibrosis, and calcification were significantly associated with low-birth-weight babies.[8]

In our study, the placental diameter and volume had a moderate positive correlation with birth weight of the baby in both case and control groups similar to other studies conducted in Karnataka.[23,30] In our study, surface area and thickness had a positive correlation only with the control group and were significantly higher in the control group similar to other studies conducted in Karnataka.[23,30]

Strengths

This study was done on "term" babies, which enables us to study the reason why some babies are low birth weight, despite reaching term.

This study elucidates the importance of the placenta as a predictor for low birth weight.

Limitations

In this study, placentae were examined after delivery of the baby, thereby losing valuable preventive time that was available during the period of gestation.

This study does not correlate the postnatal gross and microscopic findings with antenatal ultrasonography (USG) or magnetic resonance imaging (MRI) of placenta.

Conclusion

- Placental factors such as placental weight, placental length, breadth, diameter, surface area, thickness, and volume were less in low-birth-weight babies.
- All the microscopic and gross findings like the presence of hard areas, focal avascular villi, syncytial knotting, focal hyaline degeneration, and fibromuscular sclerosis were seen more in low-birth-weight babies when compared with normal-birth-weight babies.
- Maternal factors such as prepregnancy weight, prepregnancy BMI, weight, and BMI at delivery were less in mothers of low-birth-weight babies, and were statistically significant.

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Orcid

Balasubramanian R https://orcid.org/0000-0002-9496-4294
Sulakshana Shridhar Baliga https://orcid.org/0000-0001-7165-4974
Ranjit Kangle https://orcid.org/0000-0003-2165-6634
Kamal P Patil https://orcid.org/0000-0003-3942-9245
Karthik Srevatsa https://orcid.org/0000-0002-2036-4309

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