

# The Pattern and Significance of Delivery Outcome in Anaemia-Induced Changes of the Placenta

Debjani Mallick<sup>1</sup>, Saswati Das<sup>2</sup>, Sonia Gon<sup>3</sup>, Sudipta Chakrabarti<sup>4\*</sup>, Mayukh Ray<sup>5</sup>, Prosun Gayen<sup>6</sup>

<sup>1</sup>Professor, Department of Pathology, ESIC Medical College, Bihta, Patna, Bihar, India

<sup>2</sup>Junior Resident, Department of Pathology, ESI PGIMS & ESIC Medical College, Joka, Kolkata

<sup>3</sup>Professor and Head, Department of Pathology, ESI PGIMS & ESIC Medical College, Joka, Kolkata

<sup>4</sup>Professor and Head of the department of Pathology, ESIC Medical College, Bihta, Patna

<sup>5</sup>Specialist and MPO cum Superintendent, Department of Gynaecology and Obstetrics, ESI Hospital, Manickatla

<sup>6</sup>Alumnus, Department of Applied Mathematics and Statistics, IIT Bombay, Powai, Mumbai

\*Corresponding Author:

Sudipta Chakrabarti, Professor and Head of the department of Pathology, ESIC Medical College, Bihta, Patna

E-MAIL: [sudiptach@gmail.com](mailto:sudiptach@gmail.com)



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## ABSTRACT

**Background:** Anemia is a clinical sign of the most prevalent nutritional deficiency in pregnant women worldwide. Histopathological study of the placenta provides valuable information on changes due to anemia in pregnancy. **Aim:** The present study was undertaken to evaluate the significance of macroscopic and histopathological changes in the placenta due to deficiency anemia in pregnancy consequently affecting the delivery outcome. **Material and methods:** An observational, prospective, cross-sectional study was conducted for one year. All the obstetric patients having hemoglobin (Hb) less than 11gm/dl were included in the study. After applying the exclusion criteria, 57 cases were included in the study. After delivery, the placenta was collected, fixed in formalin, weight measured, dimensions noted and volume was calculated. Gross features were noted and representative tissue was taken for histopathological study. **Results:** Term pregnancy was found commonly in mild anaemia (17 cases, 30%), preterm delivery in moderate anemia (14 cases, 25%), and Intrauterine fetal death (IUFD)/abortion in severe anemia (2 cases, 3%). The frequency of the presence of increased placental weight, decreased vascularity, increased fibrosis, and endarteritis are obliterans was found significantly higher in higher grades of anemia than in mild anemia. The same gross and histopathological features were significantly associated with poor obstetric outcomes (IUFD/abortion, preterm delivery) than good obstetric outcomes (term pregnancy). **Conclusion:** Studies of the placenta have a significant role in understanding the pathophysiology of anemia in pregnancy.

**KEYWORDS:** Delivery outcome, Anemia, Macroscopic and Histopathological changes of the placenta, Placenta

## INTRODUCTION

Anemia is a clinical sign of the most prevalent nutritional deficiency in pregnant women worldwide. Its prevalence varies from 14% in developed countries to 51% in developing countries. India also has a high prevalence ranging from 65% to 75%.<sup>[1]</sup> Pregnancy complicated with nutritional deficiency anemia has a high association with adverse maternal and fetal health outcomes. However, mild anemia is associated with better maternal and fetal survival and delivery outcomes.<sup>[2]</sup> Anemia influences the placenta's exchange along with hemodynamic processes resulting in morphological changes in the placenta.<sup>[3]</sup> Histopathological study of the placenta provides valuable information on changes due to anemia in pregnancy. Despite the remarkable reserve capacity of the placenta, anemia-associated adverse changes in the placenta result in a compromise in delivery outcomes.<sup>[4]</sup> Histopathological study of the placenta and its correlation with the severity of anemia will enable further understanding of the pathophysiology of the commonest risk factor of pregnancy and how it is associated with adverse fetal outcomes. The present study aimed to evaluate the significance of histopathological changes in the placenta due to deficiency anemia in pregnancy consequently affecting the delivery outcome. The importance of the study for primary care physicians is to provide a better understanding of pathophysiological changes of anemia in pregnancy for effective management and timely intervention for better fetal outcomes.

## MATERIAL AND METHODS

An observational, prospective, cross-sectional study was conducted for one year in a tertiary care hospital in the east-

ern region of India from 2021 to 2022. The present study was conducted on the placental specimens of anemic pregnant women whose histopathological features were studied and correlated with the severity of anemia and delivery outcomes. All the obstetric patients having hemoglobin (Hb) less than 11 gm/dl were included in the study. The placenta of such cases was studied irrespective of the outcome like abortion, Intrauterine fetal death (IUFD), preterm delivery, and term delivery. After the delivery/abortion, the placenta was received in the Department of Pathology. Exclusion criteria included specimens of the placenta of patients with Hb equal to or more than 11 gm/dl, anemia due to non-nutritional deficiency, other coexistent risk factors like pregnancy-induced hypertension and diabetes mellitus, which results in similar histopathological features to remove such confounding factors. The sample size was fifty-seven. The sampling technique was purposive sampling.

Data were collected regarding the mother's clinical history including age, current and past medical, obstetrics, and gynecologic histories. Horiba ABX Pentra XL 80 was used to estimate the hemoglobin level during antenatal visits with quality assurance maintenance. Cases were categorized by level of Hb as mild (10–10.9g/dl), moderate (7–9.9g/dl), and severe (<7g/dl). After delivery, the placenta was collected and kept in 10% buffered formalin for fixation for 24 hours. Placental weight was measured, the dimensions noted and the volume calculated. Gross features noted including any anomaly, insertion of cord, and membranes. Representative tissue from maternal surface (2 blocks), fetal surface (2 blocks), membranes (1 block), and umbilical cord (1 block) were taken for histopathological study. Additional sections were taken if any pathology is visible grossly. Tissues were processed in an automated tissue processor Leica ASP200S. Sections were taken 3–5  $\mu$ m, and stained with Hematoxylin and Eosin. Microscopy was done by two independent pathologists and their observations were noted. The histopathological features were noted and graded (villous vascularity, villous fibrosis, endarteritis obliterans, and others as found).

Data were compiled in Microsoft Office Excel and analyzed statistically. Association of different variables like age, placental weight, placental volume, vascularity, fibrosis, and endarteritis obliterans with grades of anemia and delivery outcomes were calculated. Birth weight was not considered a study variable as the data was not adequate. However, most (>95%) of the term deliveries had normal birth weight. The frequency of the presence of increased placental weight, increased placental volume, decreased vascularity, increased fibrosis, and endarteritis obliterans were compared between cases of higher grades (moderate and severe) of anemia with mild anemia. The occurrence of increased placental weight, and increased placental volume, decreased vascularity, increased fibrosis, and endarteritis obliterans were compared between cases of poor obstetric outcomes (IUFD/abortion, preterm delivery) and cases of good obstetric outcomes (term pregnancy). Statistical

significance was calculated by the Chi-Square test and  $p$ -value < 0.05 (Confidence limit 95%) was taken as positive using Stata software.

## RESULTS

Initially, 69 cases were evaluated for anemia. However, after applying exclusion criteria, the total number of cases was 57. Among these patients, the age was less than 20 years in 9 cases (16%), 20–35 years in 43 cases (75%), and more than 35 years in 5 cases (9%). Mild anemia (Hb10–10.9g/dl) was present in 20 cases (35%), moderate anemia (Hb7–9.9g/dl) was present in 30 cases (52.6%) and severe anemia was present in 7 cases (12.4%). Age group 20–35 years has the majority of cases (21 cases, 37%) of which 12 cases (21%) had mild anemia, 8 cases (14%) had moderate anemia, and 1 case (1.7%) had severe anemia. and severe anemia (5 cases, 9%) only. There were variable delivery outcomes. Term pregnancy was seen in 29 cases (50.8%) followed by preterm delivery (25 cases, 43.8%) and IUFD/abortion (3 cases 5.2%). Term pregnancy was found in 17 cases (30%) of mild anemia, preterm delivery was found in 14 cases (25%) of cases of moderate anemia, and IUFD/abortion was found in 2 cases (3%) case of severe anemia. In women under 20 years and 20–3, the most common delivery outcome was term pregnancy (13 cases, 23%) and (12 cases, 21%) respectively. In contrast, cases of more than 35 years of age had preterm pregnancy (13 cases, 23%). Table 1

Increasing grades of anemia showed increased placental weight and placental volume. Placental weight was increased in 11 cases (19.2%) of which 6 cases (10.5%) had moderate anemia and 5 cases (8.7%) had severe anemia. Placental volume was increased in 20 cases (35%) of which, 12 cases (21%) had moderate anemia and 8 cases (14%) had severe anemia. In women aged more than 35 years, preterm delivery and IUFD/abortion were found in 13 cases (22.8%) and 2 cases (3.5%) respectively.

Histopathology of placenta with anemia showed decreased vascularity, increased fibrosis, and the presence of end artery obliterans predominantly which varied with grades of anemia. Few cases included other changes like fibrinoid necrosis (8 cases, 14%), syncytial knots (4 cases, 7%), and hydropic changes (5 cases, 8.7%). Vascularity was decreased in the placentas of anemic patients, which varied with grades. Moderate anemia was associated with a mild decrease in vascularity (11 cases, 19%) whereas severe anemia was associated with a severe decrease in vascularity (6 cases, 11%). Fibrosis was increased in the placentas of anemic patients. 15 cases (26.3%) of moderate anemia cases showed a mild increase in fibrosis and 6 cases (10.52%) of severe anemia cases showed severe fibrosis. Similarly, the presence of endarteritis obliterans was also found in the placentas of 9 cases (15.7%) of moderate anemia and 6 cases (10.5%) of severe anemia.



Outcome	Anemia Percent (Number of cases)			Age		
	Mild	Moderate	Severe	<20 year	20-35 year	>35 year
IUDF/Abortion	0% (0)	2% (1)	3% (2)	0% (0)	2% (1)	3% (2)
Preterm delivery	12%(7)	25% (14)	5% (3)	5% (3)	14% (8)	23% (13)
Term	30% (17)	16% (9)	7% (4)	23% (13)	21% (12)	9% (5)

Table 1: Comparison of delivery outcome with anemia and age

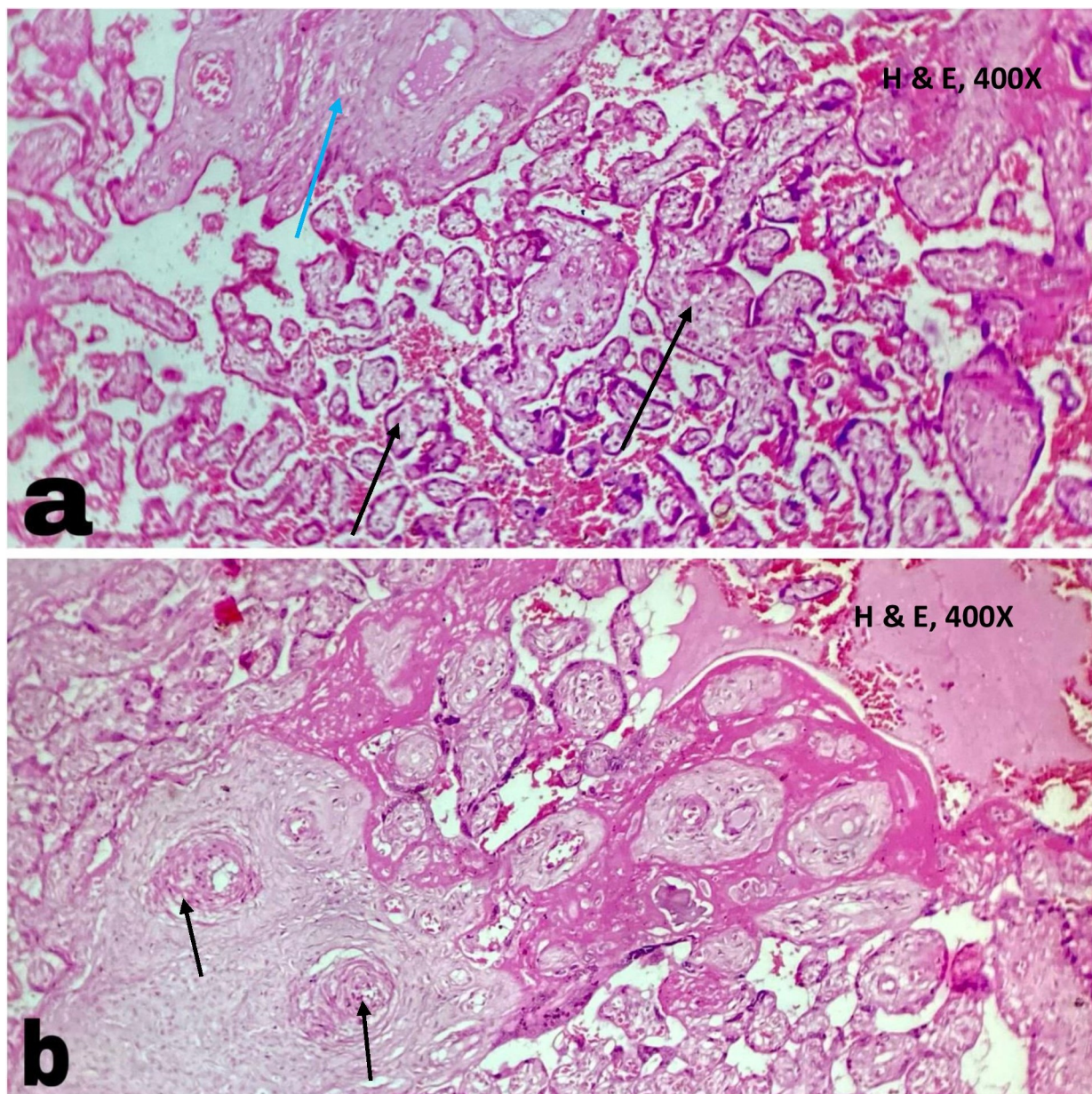


Figure 1: Figure 1a. The histological section showing decreased placental vascularity (black arrow) and increased stromal fibrosis (blue arrow)(H&E, 400X) Figure 1b. The histological section showing endarteritis obliterans (black arrow) and stromal fibrosis (H&E, 400X)



	Placental Weight Increased		Placental volume increased		Vascularity decreased		Fibrosis increased		End artery obliterations present	
Anaemia (moderate and severe)	91% (10/11)	p= 0.0068	75% (15/20)	p= 0.2684	77% (23/30)	p= 0.0012	71% (27/38)	p= 0.0022	79% (15/19)	p= 0.0114
Poor outcome (IUFD/ abortion, preterm delivery)	73% (8/11)	p= 0.0304	55% (11/20)	p= 0.1981	63% (19/30)	P= 0.0055	58% (22/38)	p= 0.0122	79% (15/19)	p= 0.0004

Table 2: Comparison of placental features with anemia and outcome

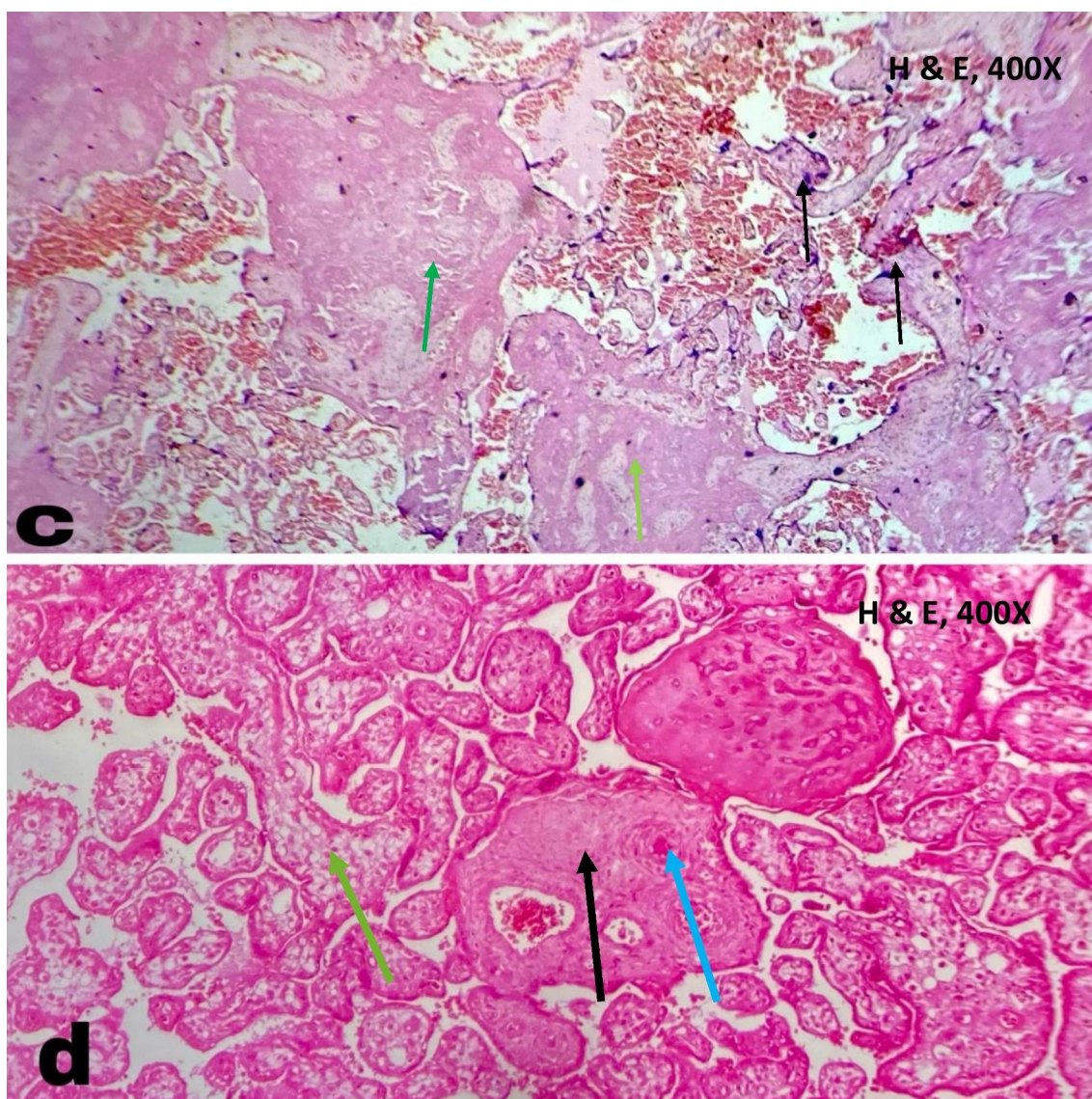


Figure 2: Figure 2c. The histological section showing fibrinoid necrosis (green arrow) and syncytial knots (black arrow)(H&E, 400X) Figure 2d. The histological section showing decreased vascularity (green arrow), stromal fibrosis(black arrow), endarteritis obliterans( blue arrow)(H&E, 400X)

The frequency of the presence of increased placental weight, increased placental volume, decreased vascularity, increased fibrosis, and endarteritis obliterans was compared between higher grades (moderate and severe) of anemia with mild anemia. The difference was found significant in all the variables except placental volume ( $p < 0.05$ ). Figure 1 The occurrence of increased placental weight, increased placental volume, decreased vascularity, increased fibrosis, and endarteritis obliterans was compared between cases of poor obstetric outcomes (IUFD/abortion, preterm delivery) and cases of good obstetric outcomes (term pregnancy, Figure 2 All the variables except placental volumes were found significantly ( $p < 0.05$ ) associated with higher grades of anemia and poor obstetric outcomes. Table 2

## DISCUSSION

The present study showed the maximum occurrence of anemia in 20-35 years (43 cases, 75%). Suryanarayana R et al. also found the prevalence of anemia in pregnant women common in 21-30 years (66.1%) similar to the present study.<sup>[5]</sup> Mild anemia was most prevalent (20 cases, 35%) followed by moderate anemia (30 cases, 52.6%) and severe anemia (7 cases, 12.4%) in the present study. Suryanarayana R et al. also found the most common cases of mild anemia (163 cases, 38.2%) followed by moderate anemia (55 cases, 12.9%) and severe anemia (10 cases, 2.3%).<sup>[5]</sup> They also found that the prevalence of anemia increased with the pregnancy duration, though not statistically significant.<sup>[5]</sup> Kaushal et al. found 5.8% of cases of anemia were in their first trimester, 20.93% were in the second trimester, and 73.25% were in the third trimester of pregnancy.<sup>[6]</sup> The present study also found most of the cases of anemia were in the third trimester (48 cases, 85%) of which mild anemia (22 cases, 39%) was followed by moderate anemia (21 cases, 37%) and severe anemia (5 cases, 9%).<sup>[6]</sup>

Sun Y et al. found that term delivery was inversely proportional to gestational anemia postulating the absence of anemia was correlated with favorable delivery outcomes.<sup>[7]</sup> The findings also indirectly indicate that gestational anemia might increase the risk of preterm birth. The present study also showed a majority of term pregnancies in mild anemia (17 cases, 30%), preterm pregnancy in moderate anemia (14 cases, 25%), and IUFD/abortion in severe anemia (2 cases, 3%)

Ramteke et al. found increased placental weight, which correlated with the severity of anemia.<sup>[8]</sup> Villous vascularity was decreased, fibrosis increased, increased fibrinoid necrosis and syncytial knots were found in anemic cases compared to the control group in their study. It has been proposed that diminished villous vascularity is an effect of an increase in stromal fibrosis. An attempt to form new villi causes the formation of increased syncytial knots so that the effective surface area for exchange is increased. Increased villous stromal fibrosis may be due to relative hypoxia in the periphery of the

placental lobule. The present case also found increased placental weight, decreased vascularity, increased fibrosis, and the presence of endarteritis obliterans in cases of moderate and severe anemia compared to mild cases which were statistically significant.<sup>[8]</sup>

Lelic et al.<sup>[9]</sup> showed that both placental mass and volume had not any statistical difference in the anemic and control groups. Hypoxia, depending on duration and time, results in hypertrophy but with advanced pregnancy placental growth restriction occurs with the development of small, hypertrophic placenta.<sup>[3]</sup> The present study showed increased placental weight in moderate and severe anemias which was statistically significant but the increase in placental volume was not statistically significant. The discordance may be due to variable gestational age.

Maternal anemia is considered a risk factor for poor pregnancy outcomes, and it threatens the life of the fetus.<sup>[10]</sup> In normal pregnancy due to physiological changes, there is a 50% increase in plasma volume leading to a decrease in hemoglobin resulting in iron deficiency anemia. However, pathological decreases in Hb can lead to adverse pregnancy outcomes such as preterm birth, low birth weight, and intrauterine growth retardation.<sup>[11]</sup> In gestational anemia, there is iron deficiency, which results in reduced Hb levels thereby decreasing oxygen-carrying capacity. The resultant state of chronic hypoxia compromises fetal growth and development.<sup>[12]</sup>

Ancillary studies like immunohistochemistry (IHC) can also be performed in placental studies. Camen et al. used Periodic Acid Schiff–Hematoxylin (PAS-H) as a special stain and IHC staining of CD34 and anti-vascular endothelial growth factor (VEGF) antibody. CD 34 was used to stain capillary endothelium signifying intravillous neoformation of blood vessels and anti-VEGF labeled proteins, which stimulates the vessel formation. PAS-H staining highlighted intra/extravillous vascular basement membranes and the fibrin deposits rich in glycosaminoglycans.<sup>[13]</sup> Gadhiraju et al. studied maternal nutritional anemia by IHC expression of FPN1 in the placenta and found that maternal iron deficiency increases placental FPN1 protein, thus facilitating increased maternal-to-fetal iron transport.<sup>[14]</sup> The present study did not include immunohistochemistry.

Very few studies have been done correlating macroscopic and histopathological changes of the placenta in anemic pregnancy with the delivery outcome. In the present study, the occurrence of increased placental weight, increased placental volume, decreased vascularity, increased fibrosis, and endarteritis obliterans was compared between cases of poor obstetric outcomes (IUFD/abortion, preterm delivery) and cases of good obstetric outcomes (term pregnancy). All the variables except placental volumes were found significantly ( $p < 0.05$ ) associated with higher grades of anemia and poor obstetric outcomes.

The histopathological features of increasing severity of anemia show significantly decreased vascularity and blood



supply to the fetus thereby resulting in poor fetal outcomes. Early correction of nutritional anemias and radiological follow-up for checking vascular compromise in severe anemia cases could prevent poor fetal outcomes through timely intervention. The findings of this study provide a better understanding of pathophysiological changes of anemia in pregnancy for primary care physicians to provide for effective management and timely intervention for better fetal outcomes.

## CONCLUSION

Anemia in pregnant women continues to be a major public health problem due to its high prevalence in India. Anemia in pregnancy adversely affects delivery outcomes. The present study showed the significance of the histopathological study of the placenta in anemic pregnancy. There were gross and histopathological changes in the placentas, which correlated with higher degrees of anemia and poor delivery outcomes. The study suggests further such studies of the placenta to understand the pathophysiology of changes associated with anemia in pregnancy.

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