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"CORRELATION BETWEEN CLINICAL AND HISTOPATHOLOGICAL FEATURES IN PRETERM AND TERM BIRTH PLACENTA USING HISTOCHEMICAL AND IMMUNO-HISTOCHEMICAL METHODS"

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ABSTRACT

Introduction: Preterm birth is a complex condition caused by multiple risk factors and can lead to long-term health problems in the child. Examination of the placenta provides valuable diagnostic information to help determine the underlying cause of preterm birth.

Aim: This study aimed to describe and compare the histo-morphological changes in preterm and term placentas, correlating gross and microscopic findings with maternal and fetal risk factors associated with preterm birth. Specific objectives included correlating gross and microscopic structural and vascular placental changes with coexisting maternal and fetal clinical features, and establishing a correlation between histological findings using special stains (PAS, Masson's trichrome, reticulin, and Congo red) and immunohistochemical markers (VEGF and CD34) in preterm placentas.

Materials and Methods: A case-control study was done on a total of 64 samples, which were collected in the study period of October 2024 to February 2026 in SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India, with 32 placentas from preterm delivery and 32 placentas from term placenta.. Histological changes in the placenta were assessed in both groups. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 28.0). For the data follows normal distribution and homogeneity of variance, we used Students t test for 2 groups. The data doesn't follow normality and homogeneity, so we have used the Nonparametric Mann-Whitney U test for comparing two groups. For the association between categorical data, we have used the chi-square test. Descriptive statistics were expressed as mean, standard deviation and percentage. A p-value <0.05 is considered statistically significant.

Results:A total of 64 placentas (32 preterm, 32 term) were analysed. Maternal age was comparable between groups ($p = 0.266$), while gestational age and birth weight differed significantly ($p < 0.001$ and $p = 0.009$). GHTN and hypothyroidism were the most prevalent comorbidities in the preterm cohort (21.9% each). Gross findings were more frequent in preterm placentas but did not reach statistical significance.

Histologically, syncytial knots (>50%) were the most significant finding (59.4% preterm vs. 6.3% term; $p < 0.001$), followed by stromal fibrosis (68.8% vs. 31.3%; $p = 0.003$) and perivillous fibrin deposition (57.4% vs. 42.6%; $p = 0.048$). On immunohistochemistry, VEGF expression was significantly elevated in preterm placentas ($p = 0.030$), while CD34 microvessel density was markedly reduced by 51.1% (82.93 vs. 169.79 vessels/HPF; $p < 0.001$).

Conclusion: The structural characteristics of the placenta play a crucial role in determining pregnancy outcomes. Preterm placentas exhibit distinct histological alterations that can influence neonatal development. Understanding these changes offers valuable insight for anticipating risks and potentially preventing specific morbidities in future pregnancies.

KEYWORDS: Faetomaternal insufficiency, Stromal fibrosis, Syncytial knots.

INTRODUCTION

Preterm birth (<37 weeks of gestation) is a global burden considered to be one of the main risk factors for neonatal mortality (aged under 5 years) and is associated with short-term and long-term effects, such as poor health and growth, intellectual and mental disabilities, and early onset of chronic diseases, among others.(1) Newborn babies born preterm have substantially higher risks of adverse outcomes compared with babies born at term. Risks of mortality and morbidity increase according to degree of prematurity, with babies born extremely preterm (<28 weeks of gestation) at the highest risk, followed by babies born very preterm (28 weeks to <32 weeks), then babies born moderate to late preterm (32 weeks to <37 weeks).[2,3,4].

Placental insufficiency manifests as reduced surface area of placenta that in turn affects foetomaternal transmission [5,6]. In case of poor pregnancy outcome, placenta should be examined [7]. Classification of pathological lesions of placenta

are as follows: Lesions causing foetal and neonatal morbidity, lesions causing preterm delivery, lesions changing immediate maternal management, lesions changing management in consecutive pregnancy [7].
This study compares gross and microscopic placental changes in preterm and term pregnancies, correlates these findings with maternal and fetal clinical features, and evaluates histological alterations using special stains and immunohistochemical markers (VEGF, CD34) in the preterm placenta.

MATERIALS AND METHODS

This case-control study was conducted in SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India between October 2024 to February 2026 after getting approval from Institutional Scientific and Ethical Committee (Ethical clearance number:SRMIEC-ST1124-1762).
Inclusion criteria: Placentas from term and preterm <37weeks, maternal age 18- 20 years, 21-25 years, 26-30 years,> 30 years.
Exclusion criteria: Inadequate clinical history, placenta <24 weeks, and autolysed sample.
After excluding the cases according to exclusion criteria, consecutive 32 placentas from preterm delivery and 32 placentas from term delivery were collected. Sample size was calculated using the formula n=4 pq/L2, p-prevalence, q-100-p, L-allowable error/precision. Placenta was placed on a flat surface with maternal surface facing upwards and parallel sections were made with a sharp knife at an interval of 5 cm. Tissue samples of 2 cm thickness were taken such that it included both maternal and foetal surface after fixing the specimen in 10% formalin for 24 hours. Three micron sections were taken after tissue processing. The Haematoxylin and Eosin (H&E) stained slides were used for studying histological features like syncytial knots, PVFD, chorioamnionitis, stromal fibrosis and calcification. Special stains like PAS,Massons trichrome,Reticulin and congo red stains were used. Additional sections(each 4µm thick) was taken for IHC staining of CD34,VEGF.

STATISTICAL ANALYSIS

All statistical analyses were performed using statistical package for social science (SPSS version 28.0). For the data follows normal distribution and homogeneity of variance, we used Students t test for 2 groups. The data doesn't follow normality and homogeneity we have used the Nonparametric Mann-Whitney U test for comparing two groups. For the association between categorical data, we have used the chi-square test. Descriptive statistics were expressed as mean, standard deviation and percentage. A p-value <0.05 is considered statistically significant.

RESULTS

A total of 64 placentas were examined during the study period, including 32 preterm and 32 term placentas, all fulfilling the inclusion and exclusion criteria.
Maternal and clinical characteristics
The mean maternal age was 26.09 ± 5.46 years in the preterm group and 25.47 ± 4.20 years in the term group, showing no significant difference between the groups. The mean gestational age of preterm deliveries was 32.09 ± 3.78 weeks, which was significantly lower than that of term deliveries (38.22 ± 0.83 weeks). The mean birth weight was also significantly lower in the preterm group (1.98 ± 0.55 kg) compared with the term group (2.83 ± 0.33 kg). Although placental weight was lower in preterm placentas (396.84 ± 181.74 g) compared with term placentas (449.22 ± 138.90 g), the difference was not statistically significant. The comparison of these parameters is summarized in Table 1.

TABLE :1 Mean comparison of maternal age, gestational age, birth weight and placental weight

Variable	Preterm placenta Mean ± SD	Term placenta Mean ± SD	P value
Maternal age (years)	26.09 ± 5.46	25.47 ± 4.20	0.094
Gestational age (weeks)	32.09 ± 3.78	38.22 ± 0.83	0.000
Birth weight (kg)	1.98 ± 0.55	2.83 ± 0.33	0.009
Placental weight (g)	396.84 ± 181.74	449.22 ± 138.90	0.921

Maternal risk factors
Among the 64 cases studied, 46 placentas were associated with at least one maternal risk factor. Maternal risk factors were present in 81.4% of preterm cases and 62.6% of term cases. The most common risk factors observed in the preterm group were gestational hypertension and hypothyroidism, each accounting for 21.9% of cases, followed by anemia and gestational diabetes mellitus. However, statistical analysis showed no significant association between maternal risk factors and preterm delivery (p = 0.410). The distribution of maternal risk factors is presented in Table 2.

TABLE :2 Comparison of maternal risk between preterm and term placenta.

Maternal risk factor	Preterm (n=32)	Term (n=32)	Total

Anemia	6 (18.8%)	7 (21.9%)	13
GDM	6 (18.8%)	3 (9.4%)	9
GHTN	7 (21.9%)	4 (12.5%)	11
Hypothyroidism	7 (21.9%)	6 (18.8%)	13
Nil	6 (18.8%)	12 (37.5%)	18
Total	32	32	64
P value = 0.410			

Figure 1.Histological findings in anaemia complicating pregnancy in preterm placenta

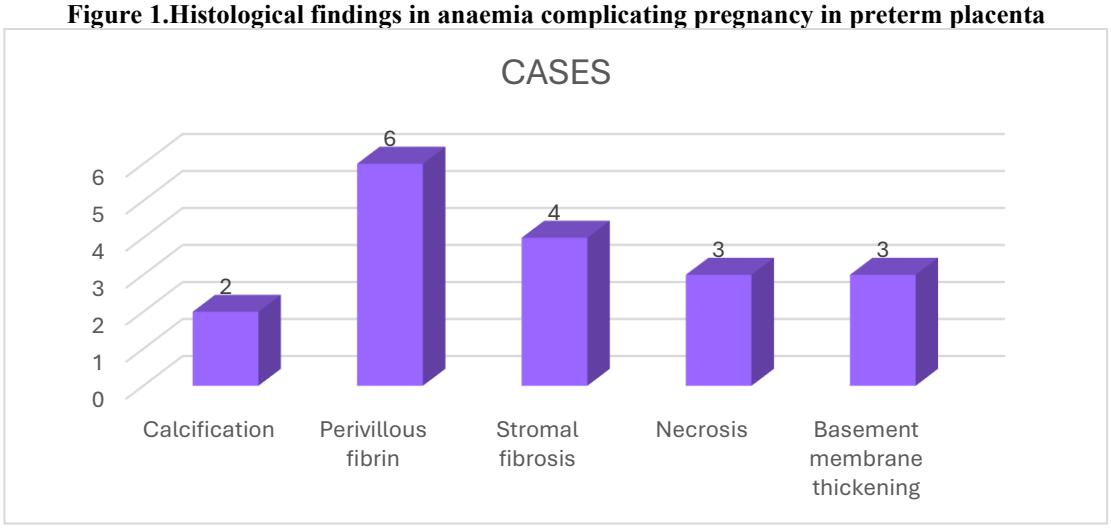


Figure 2.Histological findings in gestational hypertention complicating pregnancy in preterm placenta

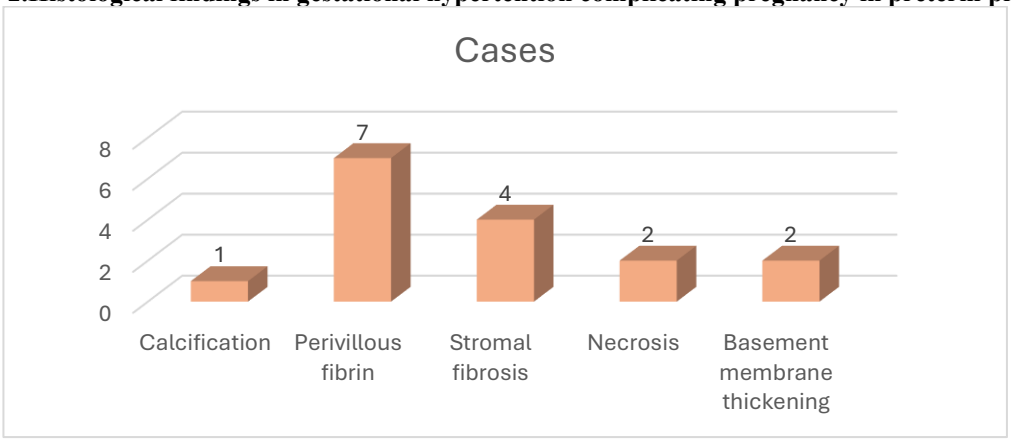
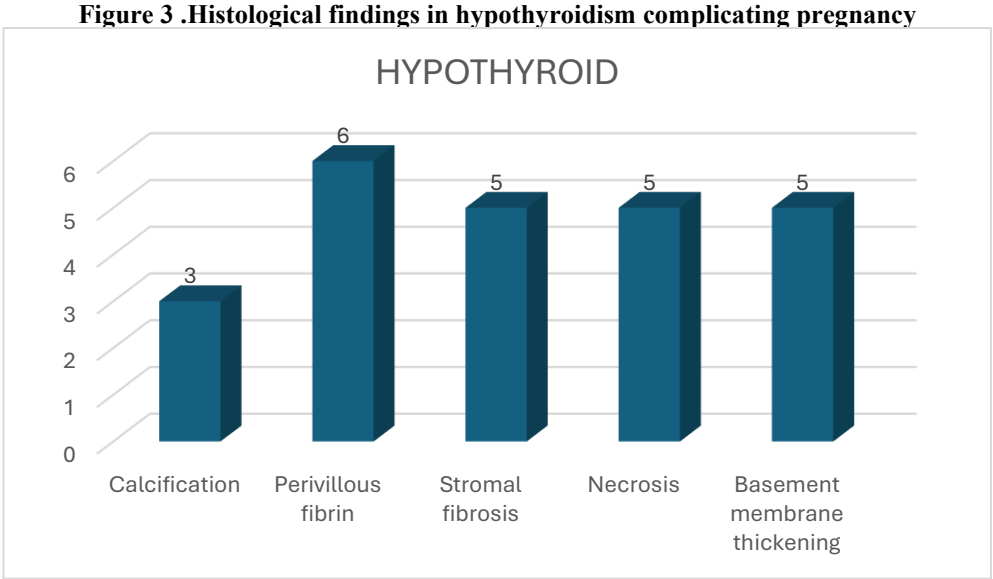


Figure 3 .Histological findings in hypothyroidism complicating pregnancy



The comparison of gross placental findings showed that central umbilical cord insertion was more common in term placentas (84.4%), whereas eccentric insertion was more frequent in preterm placentas (34.4%). Fetal surface hemorrhage and grey-white areas on the maternal surface were also relatively higher in preterm placentas (28.1% and 37.5%, respectively) compared to term placentas (12.5% and 21.9%, respectively). However, a normal fetal and maternal surface was more commonly observed in term placentas. Despite these observed differences, none were statistically significant ($p > 0.05$).These are summarized in Table 3

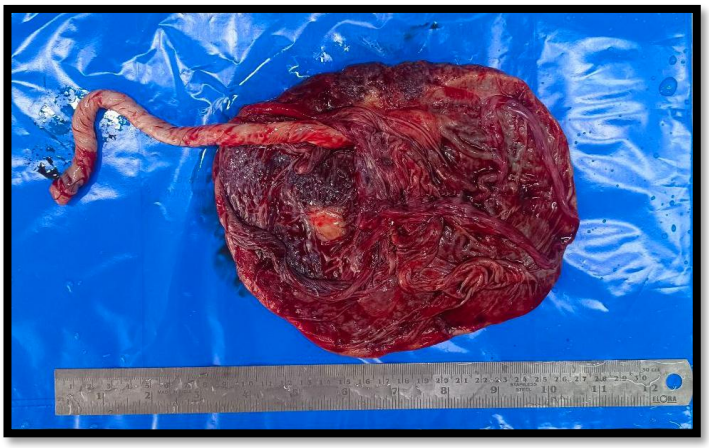


Figure 4.Fetal surface of preterm placenta with eccentrically placed umbilical cord and area of infarction.

TABLE :3 Comparison of gross features between the term and preterm placenta

Parameter	Finding	Preterm Placenta (n=32)	Term Placenta (n=32)	Total (n=64)	P value
Umbilical Cord Insertion	Central	21 (65.6%)	27 (84.4%)	48 (75.0%)	0.083
	Eccentric	11 (34.4%)	5 (15.6%)	16 (25.0%)	
Fetal Surface	Hemorrhage	9 (28.1%)	4 (12.5%)	13 (20.3%)	0.120
	Normal	23 (71.9%)	28 (87.5%)	51 (79.7%)	
Maternal Surface	Grey-white areas	12 (37.5%)	7 (21.9%)	19 (29.7%)	0.171
	Normal	20 (62.5%)	25 (78.1%)	45 (70.3%)	

Histopathological findings

Several histopathological alterations were observed in the placentas. Syncytial knot formation showed a strong association with preterm placentas, with more than 50% syncytial knots present in 59.4% of preterm placentas compared with only 6.3% of term placentas ($p < 0.001$). Perivillous fibrin deposition was also more frequently observed in preterm placentas (57.4%) compared with term placentas (42.6%), showing a statistically significant association ($p = 0.048$). Stromal fibrosis demonstrated a significant association with preterm placentas, being present in 68.8% of preterm placentas compared with 31.3% of term placentas ($p = 0.003$).

Villous necrosis was observed in 46.9% of preterm placentas and 25% of term placentas, showing a trend toward significance. Basement membrane thickening was also more frequent in preterm placentas (43.8%) than in term placentas (21.9%). Placental calcification was observed in both groups without a significant difference. Amyloid deposition was absent in all cases studied. The comparison of major histological findings between preterm and term placentas is shown in Table 4 .

TABLE :4 Comparison of histological finding of between the term and preterm placenta

Histological finding	Preterm n (%)	Term n (%)	P value
Syncytial knots >50%	19 (59.4%)	2 (6.3%)	<0.001
Calcification	10 (31.3%)	12 (37.5%)	>0.05
Perivillous fibrin deposition	27 (57.4%)	20 (42.6%)	0.048
Stromal fibrosis	22 (68.8%)	10 (31.3%)	0.003
Necrosis	15 (46.9%)	8 (25.0%)	0.068
Basement membrane thickening	14 (43.8%)	7 (21.9%)	0.062

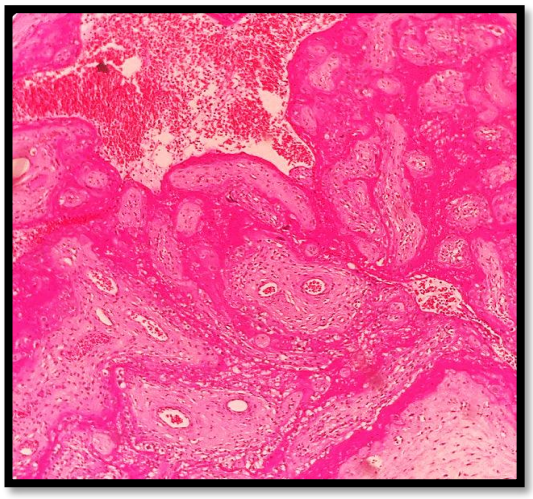


Figure 5.Placental parenchyma with perivillous and intervillous fibrin deposition and hemorrhage noted.(H&E-40X).Image from preterm placenta group.

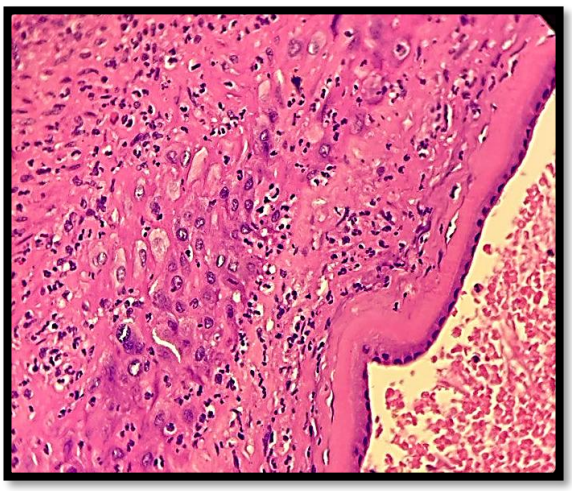


Figure 6.Membranes showing inflammatory infiltrates(H&E-40X). Image from the preterm placenta group..

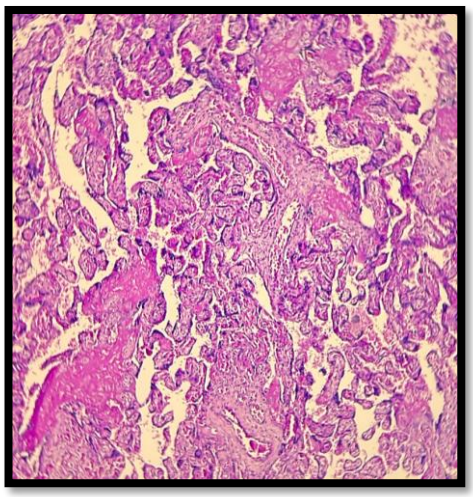


Figure 7.Section showing increased syncytial knots in chorionic villi(HPE-Periodic acid Schiff x10)Image from preterm placenta group.

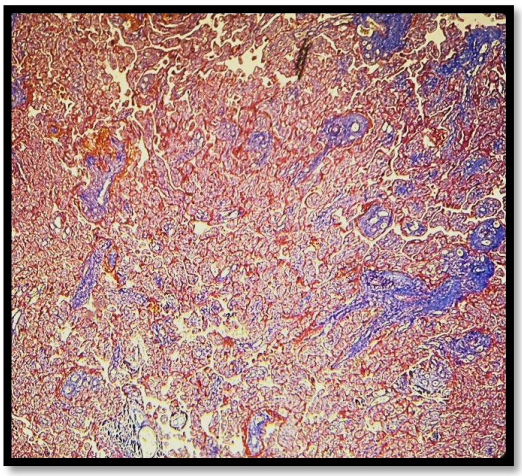


Figure 8.Placental parenchyma with perivillous and intervillous fibrin deposition noted. (HPE-masson's trichrome-10X).Image from the preterm placenta group.

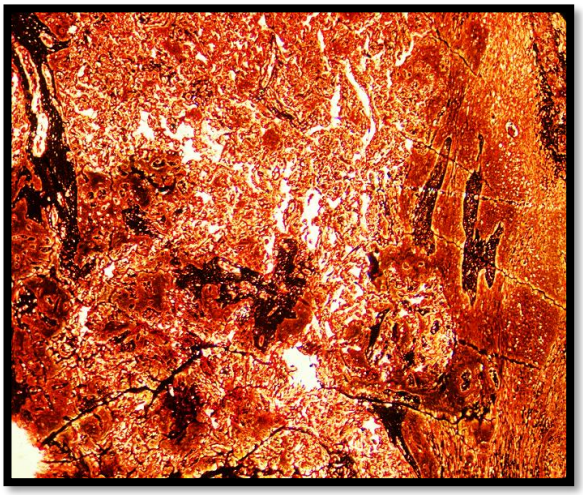


Figure 9.Intervillous fibrin deposition noted.(HPE-reticulin stain-10x). Image from the preterm placenta group.

Immunohistochemical findings

Immunohistochemical analysis demonstrated significantly higher VEGF expression in preterm placentas (4.12 ± 0.33) compared with term placentas (3.12 ± 0.22), with a statistically significant difference ($p = 0.030$). In contrast, CD34-based microvessel density was markedly lower in preterm placentas (82.93 ± 6.75) compared with term placentas (169.79 ± 12.18), showing a highly significant difference ($p < 0.001$). These findings indicate reduced vascular density and altered angiogenic activity in preterm placentas. The comparison of VEGF and CD34 expression between the groups is summarized in Table 5.

TABLE :5 Comparison of VEGF score and CD34 microvessel density between the term and preterm placenta

Marker	Preterm Mean ± SD	Term Mean ± SD	P value
VEGF score	4.12 ± 0.33	3.12 ± 0.22	0.030
CD34 microvessel density	82.93 ± 6.75	169.79 ± 12.18	<0.001

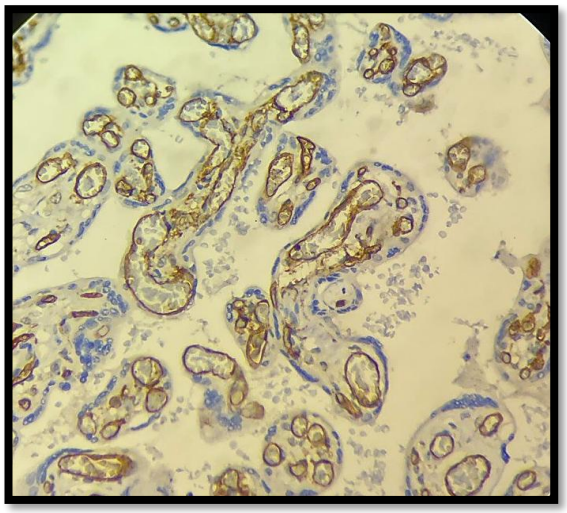


Figure 10.IHC 40x CD34 placental villi presenting intravillous capillaries with normal numerical density, immunolabeled at endothelial level using anti-CD34 antibody in term placenta

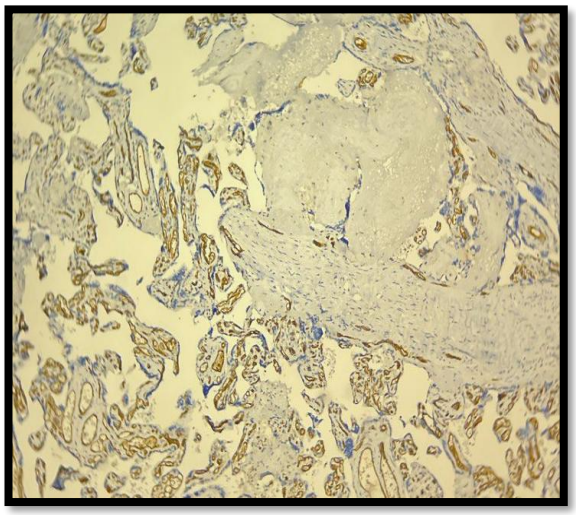


Figure 11.IHC 40x CD34 .Infarcted placental villi from preterm placenta, with the absence of endothelial immunolabeling at this level and its presence in the capillaries that have not yet undergone infarction processes.

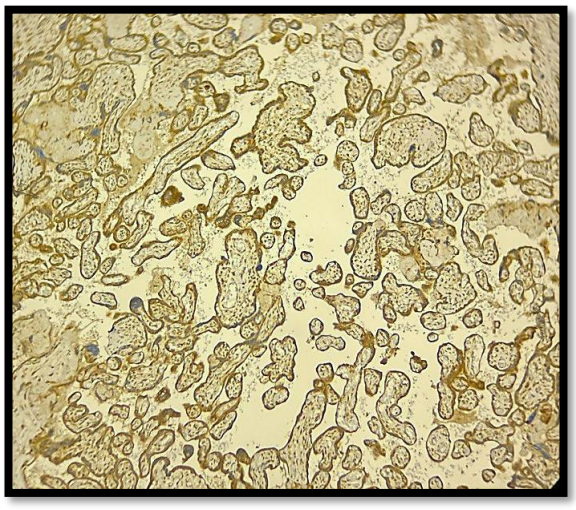


Figure 12.IHC 10X VEGF showing strong immunoreactivity in the cytoplasm of the syncitiotrophoblastic layer in preterm placenta .

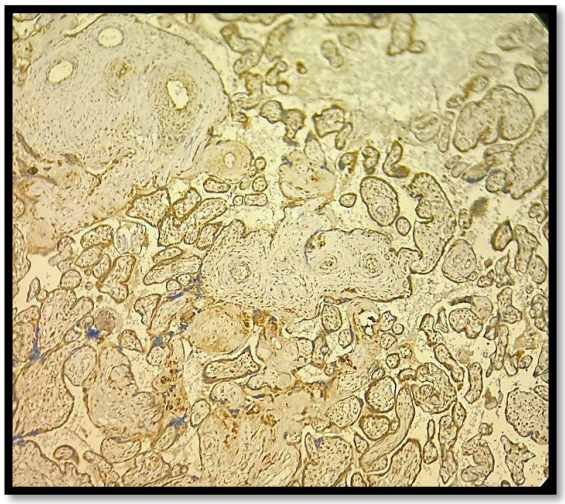


Figure 13.IHC 10X VEGF showing moderate immunoreactivity in the cytoplasm of the syncitiotrophoblastic layer in term placenta.

DISCUSSION

This study evaluated 64 placentas (32 preterm and 32 term) to correlate clinical parameters with histopathological findings and the immunohistochemical expression of CD34 and vascular endothelial growth factor (VEGF). Maternal age distribution was comparable between groups, consistent with the findings of Ananth et al.63. Preterm deliveries showed significantly lower gestational age and birth weight, similar to observations reported by Goldenberg et al.65 and Kramer et al.66. Placental weights were within the ranges described by Mifsud et al.67 while the fetal-to-placental weight relationship suggested relative placental adaptation in preterm deliveries, as described by Kingdom et al.68

Maternal risk factors such as gestational hypertension, hypothyroidism, anemia, and gestational diabetes were frequently observed. Hypertensive disorders are known contributors to preterm birth and are associated with features of maternal vascular malperfusion, as reported by Sibai et al.69 and Khong et al.70. Hypothyroidism and anaemia were also associated with placental abnormalities, including basement membrane thickening, stromal fibrosis, and increased syncytial knots, consistent with findings by Korevaar et al.71 and Scholl et al.72

Among gross features, eccentric cord insertion, grey-white areas, and fetal surface haemorrhage were more common in preterm placentas, similar to reports by Ebbing et al.,73 . Histologically, syncytial knot formation was the most significant finding and represents accelerated villous maturation related to placental hypoxia, as described by Khong et al.70 and Redline et al.78 Perivillous fibrin deposition and stromal fibrosis were also significantly increased in preterm placentas, reflecting chronic placental vascular injury as reported by Sebire et al.84 and Kraus et al.86 Villous necrosis and basement membrane thickening were more frequent in preterm cases, indicating ischemic placental injury, similar to observations by Naeye et al.88 .

Immunohistochemically, VEGF expression was significantly higher in preterm placentas, suggesting hypoxia-driven compensatory angiogenesis, as demonstrated by Zamudio et al.91 and Ahmed et al.92 In contrast, CD34-based microvessel density was markedly reduced in preterm placentas, indicating impaired placental vascular maturation, similar to findings by Arroyo et al.95 and Sultana et al.96 The coexistence of increased VEGF expression and reduced CD34 microvessel density may reflect chronic placental vascular insufficiency associated with preterm birth, as proposed by Levine et al.99 and Rajakumar et al.100 These findings highlight the importance of placental examination and suggest that VEGF and CD34 may serve as useful markers in evaluating placental vascular pathology.

LIMITATIONS

The sample size was small, with only 64 placentas, limiting statistical power, especially for variables that approached but did not reach significance, such as villous necrosis, basement membrane thickening, and cord insertion patterns. The preterm cohort was heterogeneous, spanning a wide gestational age range (<29 to 34–35 weeks), which may affect the uniform applicability of findings in the absence of subgroup analysis. As a single-institution study with a relatively uniform maternal population, the results may not be generalizable to other settings. Additionally, placental findings were not correlated with detailed neonatal outcomes such as NICU admission, respiratory distress syndrome, or neonatal sepsis, reducing clinical relevance. The inclusion of amyloid deposition as a variable was also a limitation, as its occurrence was unlikely in this young maternal population without systemic amyloidogenic disease.

CONCLUSIONS

Preterm placentas showed significantly increased syncytial knots ($p < 0.001$), perivillous fibrin deposition ($p = 0.048$), and stromal fibrosis ($p = 0.003$), along with higher VEGF expression ($p = 0.030$) and markedly reduced CD34 microvessel density ($p < 0.001$). These findings indicate chronic hypoxic placental stress with compensatory VEGF upregulation and structural vascular insufficiency.

The combined VEGF–CD34 pattern represents the key pathobiological signature of preterm placentas. Maternal comorbidities, particularly GHTN and hypothyroidism, further accentuated these changes. Larger multicentre studies are required for further validation.

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