RESEARCH PAPER

Comparative Histopathological Study of Placentae in Normal Pregnancy and Gestational Diabetes Mellitus

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ABSTRACT

Introduction:

The placenta serves as a mirror of intrauterine health, reflecting both maternal and fetal metabolic status. Gestational Diabetes Mellitus (GDM) induces hyperglycemia-driven structural and vascular alterations in the placenta, influencing fetal outcomes. Evaluating the microscopic changes provides critical insight into placental adaptation and efficiency in diabetic pregnancies.

Aim:

To observe the microscopic changes of placentae complicated by GDM and comparing the features with normal placenta.

Materials and methods:

A hospital-based comparative cross-sectional study was conducted on 150 placentae—75 from GDM and 75 from healthy controls were collected immediately after delivery with prior informed consent. Detailed microscopic examinations were done on placentas from both the groups and the results were documented. Statistical analysis was performed using SPSS version 25.0

Results: On microscopic examination villous edema (p-value < 0.0001), villous immaturity (p-value <0.0001), nucleated RBCs inside the capillaries (p-value < 0.0001) were noted to be significantly higher in the GDM group.

Conclusion:

This study shows significant microscopic changes in the GDM placentas, the most significant histological changes noted were the villous immaturity, thickened Basement Membrane (BM) and villous fibrinoid necrosis. These findings, consistent with published literature, underscore the need for careful metabolic control and placental monitoring in diabetic pregnancies to improve perinatal outcomes.

Keywords: Gestational Diabetes Mellitus, Placenta (GDM) , Villous immaturity, Villous fibrinoid necrosis, crowding of villi, syncytial knots, Hofbauer cells, villous stromal fibrosis.

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INTRODUCTION

The placenta is a critical organ that supports fetal development during pregnancy by facilitating the exchange of gases, nutrients, and waste products between the mother and fetus.(1) Maternal metabolic disorders, particularly Gestational Diabetes Mellitus (GDM), can disrupt the uteroplacental environment and significantly influence placental growth, morphology, and function.(2) GDM, defined as glucose intolerance first recognized during pregnancy, is among the most common complications of gestation and has been shown to impact both maternal and fetal health outcomes.(3) GDM-associated hyperglycemia and hyperinsulinemia lead to various structural and vascular alterations in the placenta. Histopathological studies reveal features such as villous immaturity, increased syncytial knots,

fibrinoid necrosis, and vascular congestion, reflecting both adaptive and pathological responses to the diabetic intrauterine milieu. (4,5) These placental changes may impair its efficiency, contributing to adverse outcomes such as fetal overgrowth, hypoxia, or preterm birth. Consequently, analyzing placental histopathology provides key insights into the pathophysiology of GDM and may help predict complications and inform clinical management strategies.(6,7) The present study focuses on a comparative evaluation of placental histopathological characteristics between gestational diabetes mellitus (GDM) and normal pregnancies, aiming to identify deviations that signify altered placental efficiency, vascular remodeling, and adaptive responses associated with maternal hyperglycemia.

MATERIALS AND METHODS

A total of 150 placentae were collected immediately after delivery 75 from mothers with GDM and 75 from healthy normoglycemic mothers from Geetanjali Medical College & hospital.

The study aimed to compare placental microscopic changes between Gestational Diabetes Mellitus (GDM) and those with normal pregnancies.

Study design: A comparative cross-sectional study

Inclusion Criteria:

- Pregnant women diagnosed with GDM based on the **Oral Glucose Tolerance Test (OGTT)** following standard International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. (8)
- Age between 20–35 years.

Exclusion Criteria:

- Pregnancies complicated by pre-existing diabetes, hypertension, pre-eclampsia, eclampsia, or chronic systemic illness.
- Intrauterine growth restriction, or congenital fetal anomalies.
- Placentae showing gross post-delivery damage or incomplete membranes.

Preparation for Examination of Placenta

Fresh placentas were collected immediately after delivery. The membranes were trimmed up to the margins of the placentas; umbilical cords were cut at about 2 cm from their insertions. Clots were removed. The specimens were kept for 48 hours in 10% formal saline for fixation and hardening to make it suitable for further routine histology processing. Three samples of at least 1 cm in diameter were taken from constant areas of each placenta. Sections were fixed in formalin, dehydrated in a graded ethanol series, and embedded in paraffin according to a standard protocol sections were cut at a thickness of 4 μm and mounted on glass slides for Haematoxylin-Eosin (H&E) staining. All the histopathological parameters were evaluated on the placentae from both the groups.

STATISTICAL ANALYSIS

Both the groups were compared for the histological features. Statistical analysis of data was done by using the SPSS version 25. Comparisons of categorical variables between the two groups were assessed using chi-square test. In the statistical test, a p-value <0.05 was considered statistically significant.

RESULTS

Histological Examination

Sections stained with haematoxylin-eosin and light microscopy was done under different magnifications for following parameters of both the groups; villous immaturity, crowding of the villi, villous oedema, villous fibrinoid necrosis, thickened BM, syncytial sprouts or knots, villous stromal fibrosis, stromal cells and Hofbauer's cell, Hyalinized villi, chorangiosis, Calcification

nucleated foetal RBCs, thickening of blood vessels, proliferation of endothelial lining of capillaries, decreased villous vascularity and infarction.

Histology of normal group placenta showed normal appearing widely isolated villi with maintained intervillous spaces and foetal capillaries (FC) [fig -1]

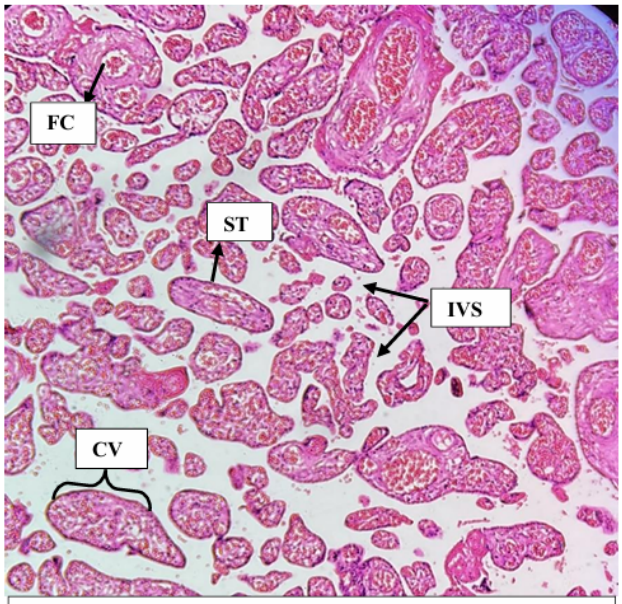

Fig-1 Photomicrograph of placenta from normal group showing Chorionic villi (CV), Intervillous space (IVS), Syncytiotrophoblast (ST) and Foetal Capillaries (FC) (H&E 40x)

Significant structural microscopic differences were observed between normal and GDM groups. Overcrowding of villi with reduced inter-villous space was noted in the GDM placentas in comparison to normal. Plenty of syncytial knots and fibrinoid necrosis were also observed in the GDM group.[Fig-2] Chorangiosis was another remarkable feature note in GDM group which is increased number of feotal capillaries in villous stroma. Some of the feotal capillaries showed Nucleated foetal red blood cells (NFRBCs) [Fig-3] In intra-villous fibrinoid degeneration, villi were completely occupied by fibrinoid material (resembling ghost villi) and also in some areas showed villous stromal fibrosis. Numerous Hofbauer cells and other stromal cells were seen in this connective tissue stroma of terminal villi[Fig-4]

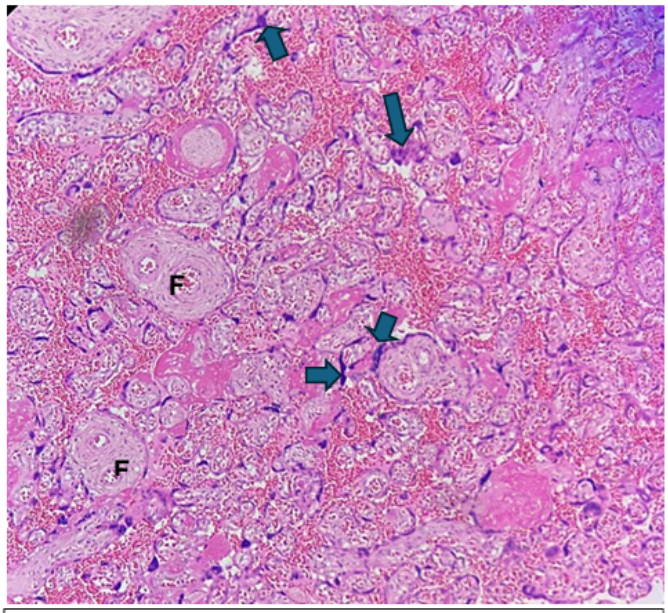

Fig- 2 Photomicrograph of placenta from GDM group showing crowding of villi with reduced inter-villous space. Plenty of syncytial knots (arrow heads), fibrinoid necrosis(F) (H&E 10x)

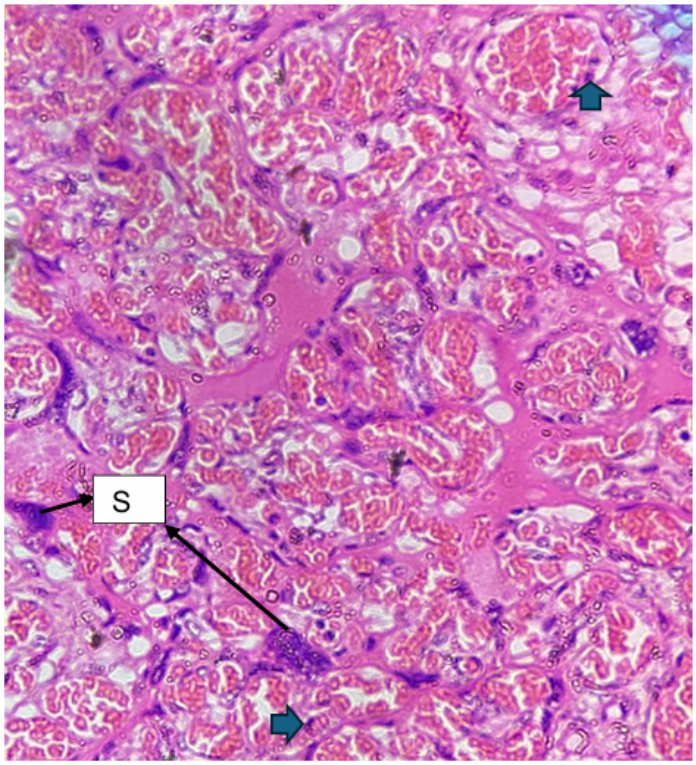

Fig- 3 Photomicrograph of placenta from GDM group showing chorangiosis , syncytial knots (H&E 40x), nucleated foetal RBCs inside the foetal capillaries (arrow head) (H&E 40x)

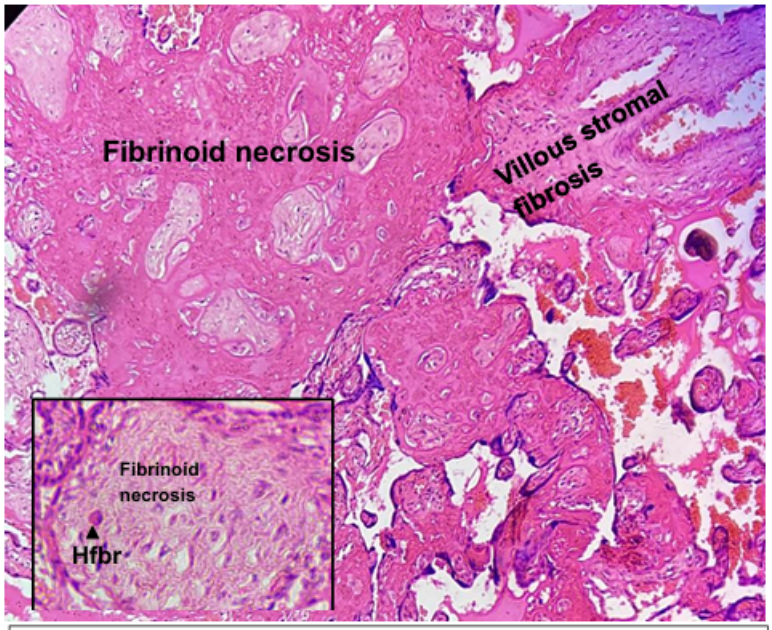

Fig- 4 Photomicrograph of placenta from GDM group showing large intravillous fibrinoid necrosis(F), villous stromal fibrosis, and Hofbauer cells(Hfbr) (H&E 40x)

Table -1: Comparison of histological features pf placenta in normal and GDM group.

Histological features	Normal group (n=75)	GDM group (n=75)	Chi-square value	p-value
Villous edema	14 (18.7%)	58 (77.3%)	49.386	<0.0001
Crowding of villi	22 (29.3%)	47 (62.7%)	15.459	<0.0001
Villous immaturity	14 (18.7%)	62 (82.7%)	58.917	<0.0001
Nucleated RBCs	8 (10.7%)	36 (48%)	23.446	<0.0001
Villous fibrinoid necrosis	30 (40%)	63 (84%)	28.976	<0.0001
Syncytial knots	29 (38.7%)	75 (100%)	63.493	<0.0001
Calcification	33 (44%)	28 (37.3%)	0.442	0.506
Hofbauer cells	16 (21.3%)	41 (54.7%)	16.299	<0.0001
Hyalinized villi	24 (32%)	12 (16%)	4.423	0.036

Histological features	Normal group (n=75)	GDM group (n=75)	Chi-square value	p-value
Infarction	6 (8%)	8 (10.7%)	0.079	0.779
Villous stromal fibrosis	28 (37.3%)	64 (85.3%)	34.436	<0.0001
Trophoblast basement membrane thickening	13 (17.3%)	60 (80%)	56.467	<0.0001
Chorangiosis	13 (17.3%)	59 (78.7%)	54.087	<0.0001
Thickening of blood vessels	2 (2.7%)	54 (72%)	74.117	<0.0001
Proliferation of endothelial lining of capillaries	0 (0%)	1 (1.3%)	0.000	1.000
Decreased villous vascularity	0 (0%)	0 (0%)	0.000	1.000

DISCUSSION

The present study was undertaken to evaluate microscopic changes in normotensive pregnancies and those complicated gestational diabetes mellitus. By systematically comparing histopathology between the groups, the study provides a comprehensive assessment of how metabolic disorders influence placental structure and function.

Villous Structural Histopathological Changes

Study demonstrates statistically significant differences in villous structural histopathological changes among the groups, with higher frequencies of villous edema, immaturity, nucleated RBCs, and fibrinoid necrosis in complicated pregnancies. Fox and Langley (1968) described villous edema as an early manifestation of placental injury resulting from altered osmotic balance and impaired intervillous circulation. Villous edema is commonly associated with diabetic pregnancies. (9) Daskalakis et al. (2008) emphasized that villous edema represents a reversible but clinically significant placental response to metabolic stress, indicating early placental compromise. (10)

Kingdom et al. (2000) highlighted crowding of villi as a structural hallmark of placental hypoperfusion and reduced intervillous space. This alteration reflects adaptive villous branching in response to chronic hypoxia, frequently seen in metabolically complicated pregnancies. (11) Villous crowding is often accompanied by impaired maternal–fetal exchange due to reduced intervillous blood flow. Mayhew et al. (2003) further noted that excessive villous density may paradoxically reduce placental efficiency despite increased surface complexity, signifying maladaptive remodeling. (12) Al-Adnani et al. (2015) described villous immaturity as a feature of delayed placental maturation commonly observed in diabetic pregnancies. Immature villi are characterized by enlarged stromal cores and reduced vasculosyncytial membranes, leading to inefficient gas exchange. (13) Kovo et al. (2021) reported that persistent villous immaturity is strongly associated with adverse perinatal outcomes, emphasizing its clinical significance in complicated pregnancies. (14)

Redline (2004) identified the presence of nucleated red blood cells as an indicator of chronic fetal hypoxia and increased erythropoietic activity. Their accumulation within placental villi reflects prolonged intrauterine stress rather than acute events. (15) Such findings are frequently observed in pregnancies complicated by diabetes. Baschat (2011) further explained that nucleated red blood cells serve as histological markers of fetal adaptation to chronic oxygen deprivation, correlating with placental insufficiency. (16) Villous edema, crowding of villi, villous immaturity, nucleated RBCs, and villous fibrinoid necrosis showed significant variation across groups.

Villous Vascular Histopathological Changes

Study result demonstrates statistically significant differences in syncytial knots and Hofbauer cells among the groups, with increased villous vascular stress and inflammatory activity. Tenney and Parker (1940) were among the first to describe syncytial knots as

morphological indicators of placental aging and altered villous perfusion. Increased formation of syncytial knots is commonly associated with reduced uteroplacental blood flow and chronic hypoxic stress. (17) In diabetic pregnancies, excessive syncytial knot formation reflects accelerated villous turnover and trophoblastic stress. Burton et al. (2009) further emphasized that exaggerated syncytial knotting represents maladaptive placental remodeling in response to prolonged maternal vascular compromise. These changes indicate disturbed villous vascular dynamics in complicated pregnancies. (18)

Wallingford et al. (2018) described placental calcification as a feature of chronic placental injury associated with oxidative stress and impaired nutrient exchange. Although calcification may occur as part of normal placental maturation, increased or premature deposition is often linked to pathological pregnancies. (19) In diabetic conditions, placental calcification reflects vascular injury and degenerative changes within the villous tree. Grannum et al. (1979) reported that excessive calcification is associated with reduced placental functional reserve, suggesting compromised placental efficiency in high-risk pregnancies. (20) Castellucci et al. (1980) identified Hofbauer cells as placental macrophages involved in villous angiogenesis, immune regulation, and tissue repair. Increased Hofbauer cell activity has been observed in diabetic pregnancy states, reflecting heightened placental immune activation. (21) Originally proposed that these cells play a central role in placental defense and remodeling, underscoring their importance as markers of chronic placental stress. Syncytial knots were markedly increased GDM group, indicating accelerated villous aging and vascular stress. Hofbauer cells were most frequent in GDM group, reflecting heightened inflammatory and reparative activity, while calcification did not differ significantly among the groups.

Ischemic, Degenerative, and Chronic Placental Injury Changes

Result demonstrates statistically significant differences in ischemic, degenerative, and chronic placental injury changes, with hyalinized villi, placental infarction, stromal fibrosis, and basement membrane thickening most prominent in GDM group.

K Mayhew (2009) described villous stromal fibrosis as a feature of chronic placental injury resulting from repeated ischemic insults and prolonged oxidative stress. Fibrotic villi exhibit reduced elasticity and impaired exchange capacity, reflecting irreversible placental remodeling. (22) Such degenerative changes are particularly prominent in diabetic pregnancies, where metabolic stress accelerates collagen deposition within the villous stroma. **Jauniaux et al. (2018)** emphasized that stromal fibrosis represents the cumulative effect of long-standing placental injury rather than a single pathological event. (23) Huppertz (2008) explained that trophoblast basement membrane thickening reflects chronic trophoblastic stress and impaired cellular turnover. Thickening of the basement membrane disrupts normal maternofetal exchange by increasing diffusion distance and reducing nutrient transfer efficiency. (24) This lesion is frequently observed in pregnancies complicated by diabetes where oxidative stress and inflammation persist throughout gestation. Aplin et al. (2018) reported that such chronic degenerative changes indicate reduced placental adaptability and are associated with unfavorable pregnancy outcomes. (25) Villous stromal fibrosis and trophoblast basement membrane thickening were most frequent in GDM, indicating pronounced chronic and degenerative placental injury in diabetic pregnancies.

CONCLUSION

The present study significantly supports the relationship between placental histopathology and GDM. Despite having a good glycemic control in the GDM group, significant microscopic changes were observed in the placenta. The most significant histological changes noted were villous immaturity, thickened BM, and villous fibrinoid necrosis. This may cause injury to both mother and foetus. Hence, careful monitoring of blood glucose levels during gestation is of profound importance. Thus, we conclude that histopathological examination of placenta is indispensable and has to be carried out as a routine protocol.

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