Section: Pathology

Original Research Article

ANALYSIS OF VILLOUS CAPILLARY LESIONS IN THE PLACENTA DURING COMPLICATED PREGNANCIES: A STUDY AT A TERTIARY CARE CENTER

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Abstract

Background: Complicated pregnancies often lead to various histopathological changes in the placenta, which can impact fetal and maternal outcomes. This study aims to analyze these changes, particularly focusing on villous capillary lesions and microvascular density, in a tertiary care setting. **Material & Methods:** This observational study was conducted over two years (October 2019 – September 2021) at King George Hospital, Andhra Medical College, Visakhapatnam. The sample comprised 50 term pregnancies, including 25 complicated pregnancies (Group 1) and 25 normal pregnancies (Group 2) as controls. Inclusion criteria were primi gravida women aged 18 to 40 years with term pregnancies, while multiparous women, infections including Covid-19, and abortions before 37 weeks were excluded. Histopathological examination was performed using Hematoxylin and Eosin (H&E) staining and immunohistochemistry with CD31 markers. Statistical analysis was conducted using SPSS 17, with an unpaired t-test for significance testing. **Results:** Significant differences were observed between complicated and normal pregnancies in terms of maternal age, fetal birth weight, placental weight, and fetoplacental weight ratio. Histopathological analysis revealed increased incidences of syncytial knots, fibrinoid necrosis, and other abnormalities in complicated pregnancies. Microvascular density, assessed using CD31, showed significant variation in cases of diabetes mellitus, intrauterine fetal demise, and anemia compared to controls. **Conclusion:** The study highlights the crucial role of placental histopathology in understanding the implications of complicated pregnancies. The observed changes in placental structure and microvascular density could serve as important indicators for fetal and maternal health in high-risk pregnancies.

INTRODUCTION

Pregnancy, a transformative phase in a woman's life, brings about profound physiological changes, most notably within the placenta.[1] This essential organ not only facilitates a crucial bridge between the mother and the fetus but also performs indispensable functions such as nutrient and gas exchange, hormone production, and waste disposal.[2] Despite its resilience, the placenta is susceptible to a range of pathological changes induced by complications like anemia, hypertension, diabetes mellitus, preeclampsia, eclampsia, and heart disease.[3] These alterations can significantly influence both maternal and fetal health outcomes, warranting a deeper understanding of their nature and implications.[4]

Histopathological examination of the placenta acts as a gateway to unravel these intricate changes. It provides invaluable insights into the structural and functional deviations occurring within the placenta in

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the face of various pregnancy complications.[5,6] This study is particularly focused on exploring two crucial aspects of placental histopathology: the incidence and implications of villous capillary lesions and the dynamics of microvascular density. These components are pivotal in understanding the adaptive or pathological transformations the placenta undergoes, shedding light on the complex interplay of factors affecting pregnancy outcomes.

In recent years, the advent of CD31 immunohistochemistry has significantly enhanced our ability to scrutinize microvascular alterations in the placental tissue.[7] This technique allows for a nuanced assessment of the microvascular architecture, enabling researchers to dissect the changes in placental blood flow dynamics associated with complicated pregnancies more precisely.[8]

Conducted at the tertiary care hub of King George Hospital, Andhra Medical College, Visakhapatnam, this study embarks on a detailed examination of placental histopathology in the context of complicated pregnancies. Our aims are threefold:

To dissect the role of placental histopathology in a spectrum of complicated pregnancies, thereby uncovering patterns and anomalies specific to different conditions.

To investigate the occurrence and impact of villous capillary lesions within the placenta, understanding their significance in the broader context of pregnancy health.

To quantitatively evaluate the intraplacental villous microvascular density and the vascular surface area, particularly using CD31 immunohistochemistry, to discern the subtleties of vascular changes in complicated pregnancies.

MATERIALS AND METHODS

Study Population and Setting: This hospital-based observational study was carried out over a two-year period, from October 2019 to September 2021. It was conducted at the Obstetrics and Gynecology department of King George Hospital, Andhra Medical College in Visakhapatnam, a renowned tertiary care center. This setting was chosen for its diverse patient population and comprehensive medical facilities, which are conducive to conducting a study of this nature.

Sample Size: The study comprised a total of 50 term pregnancies. This sample size was determined to be statistically significant for identifying differences in placental histopathology between complicated and normal pregnancies.

Inclusion Criteria

The study focused on primi gravida women aged between 18 to 40 years. It included term pregnancies, defined as gestational periods of 37 weeks or more, which were complicated by conditions like anemia, hypertension, diabetes mellitus, preeclampsia, eclampsia, heart disease, and stillbirths (Intrauterine fetal demise).

Exclusion Criteria

To ensure specificity in the study outcomes, the exclusion criteria were:

Multiparous women, to eliminate the potential influence of previous pregnancies on placental pathology.

Cases of infections, including Covid-19, as these might confound the results related to placental changes.

Abortions or pregnancies less than 37 weeks of gestation, as the focus was on term pregnancies.

Study Groups: The study was divided into two distinct groups for a comparative analysis:

Group 1 included placentae from 25 complicated pregnancies, ensuring a broad spectrum of complications was represented.

Group 2 comprised placentae from 25 control cases without any history of complications, serving as a baseline for comparison.

Procedures

Detailed obstetric history and mode of delivery were meticulously recorded for each participant.

Upon delivery, placentae were immediately fixed in 10% neutral buffered formalin for 12-24 hours to preserve tissue integrity.

A standardized protocol was followed for grossing of the placenta and section preparation, ensuring consistency across all samples.

Tissues underwent paraffin embedding and were stained with Hematoxylin and Eosin (H&E) for histological examination.

Histopathological analysis was conducted in accordance with Altschuler's criteria to maintain rigor and precision.

Immunohistochemistry was performed using the CD31 marker, a reliable endothelial marker, to quantitatively assess microvascular density and the vascular surface area.

Image analysis was systematically executed using Image J 1.49 software, which allowed for accurate measurement and quantification of the histological parameters.

Statistical Analysis

The data were meticulously tabulated in Microsoft Excel. Descriptive statistics such as mean values and percentages were computed. For inferential statistics, the study employed SPSS 17 to perform tests of significance. An unpaired t-test was used to compare the data between the test and control groups. A P-value of ≤ 0.05 was established as the threshold for statistical significance.

Ethical Considerations

Prior to commencement, the study received approval from the Institutional Ethics Committee of Andhra Medical College, Visakhapatnam, ensuring adherence to ethical standards. Written and informed consent was obtained from all participants, guaranteeing their autonomy and understanding of the study's purpose and procedures.

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RESULTS

General Characteristics and Comparative Analysis

Our study's findings, presented in Table 1, demonstrated significant differences between complicated pregnancies and the control group. The average age of mothers in complicated pregnancies was significantly lower (22.71 years) compared to the control group (24 years), with a P-value of 0.00001. Fetal birth weight was also lower in complicated pregnancies (2780 grams) compared to the control group (2950 grams), with a statistically significant difference (P = 0.01). Placental weight was found to be lower in complicated pregnancies (532 grams) than in controls (577.1 grams), with a P-value of 0.032. The fetoplacental weight ratio showed a significant decrease in complicated pregnancies (4.81) compared to controls (5.54), with a P-value of 0.0001.

Histopathological Characteristics in Pregnancy Induced Hypertension (PIH)

Table 2 outlines the histopathological differences observed in cases of PIH. Our study found a significant increase in syncytial knots (68 ± 10 per 100 villi) in PIH compared to controls (25.3 ± 5 per 100 villi), with a P-value of 0.0001. Fibrinoid necrosis, hyalinised villi, cytotrophoblastic proliferation, and calcified area per 10Lpf were all significantly higher in PIH cases compared to controls, with P-values of 0.0001, 0.0002, 0.000183, and 0.0001, respectively.

Villous Vascularity in PIH

As demonstrated in Table 3, the study revealed a decrease in normal vascularity in PIH cases (72%) compared to controls (92%). Decreased vascularity was observed in 28.57% of PIH cases, significantly higher than the control group's 5%. Chorangiosis and chorangioma were also more prevalent in PIH cases at 57.14% and 14.28%, respectively, compared to the control group (8% and 2%).

Comparative Analysis of Various Complications

Table 4 presents the microvessel density findings across different complications. Oligohydramnios cases showed a significantly lower microvessel density (38 ± 2 pixels) compared to controls (60 ± 5 pixels, P = 0.005). In Diabetes Mellitus, the microvessel density was higher (71 ± 6 pixels) than in controls (61 ± 5.5 pixels, P = 0.001). The most marked difference was observed in cases of Intrauterine Fetal Demise (IUFD) and Anemia, with P-values of 0.0001 for both, indicating significantly altered microvessel densities in these complications.

Histopathology in Cases of Oligohydramnios, **Diabetes Mellitus, IUFD, and Anemia**

Table 5 details histopathological changes in various complications. Oligohydramnios was characterized by increased syncytial knots, intervillous fibrinous deposition, and calcification. Diabetes Mellitus presented with high incidences of villous immaturity and fibrinoid necrosis. Accelerated villous immaturity and villous agglutination were prominent in IUFD. Anemia cases showed a mixed pattern of decreased and increased villous vascularity.

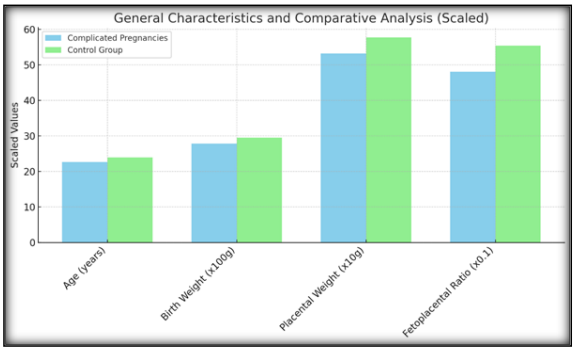

Figure 1: General Characteristics and Comparative Analysis

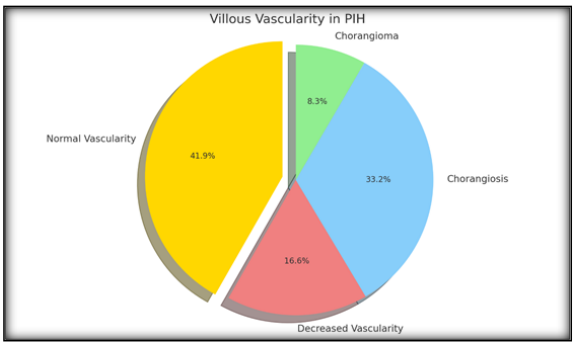

Figure 2: Villous Vascularity in PIH

PREGNANCY INDUCED HYPERTENSION (PIH) PLACENTAL AND VILLOUS CAPILLARY CHANGES

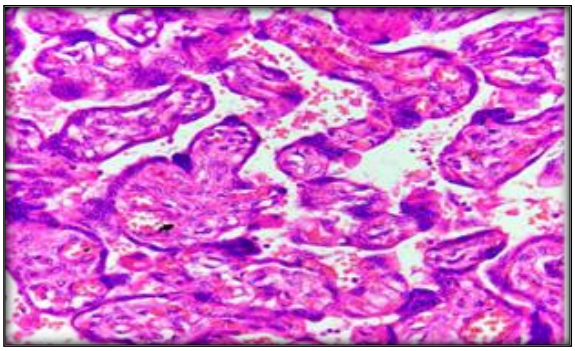

Figure 3: Increased Syncytial knots (H&E,400X)

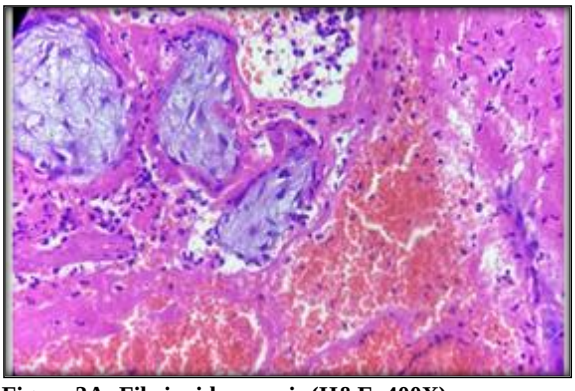

Figure 3A: Fibrinoid necrosis (H&E, 400X)

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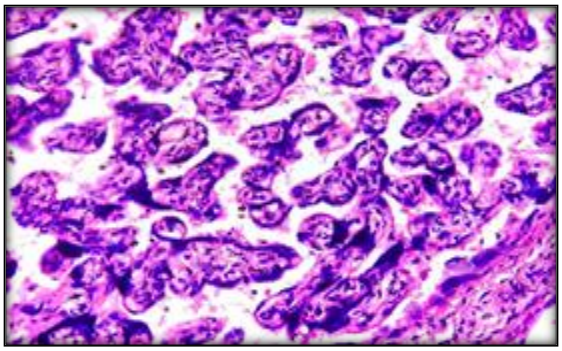

Figure 3B: Hypovascular Villi (H&E, 400X)

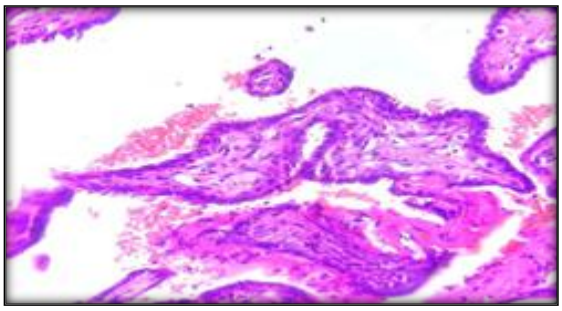

Figure 3C: Hyalinised Villi (H&E,400X)

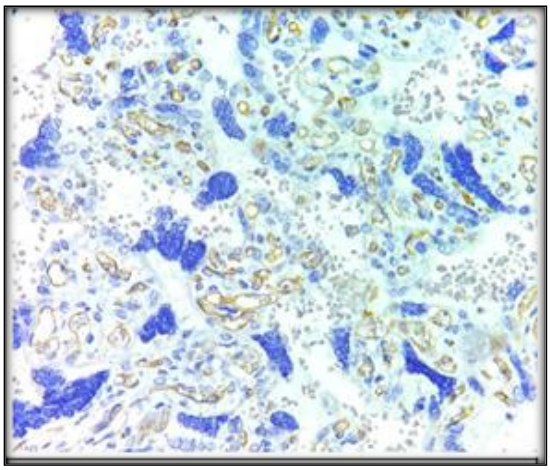

Figure 3D: PIH - Vascular density by CD31 (IHC, 400X)

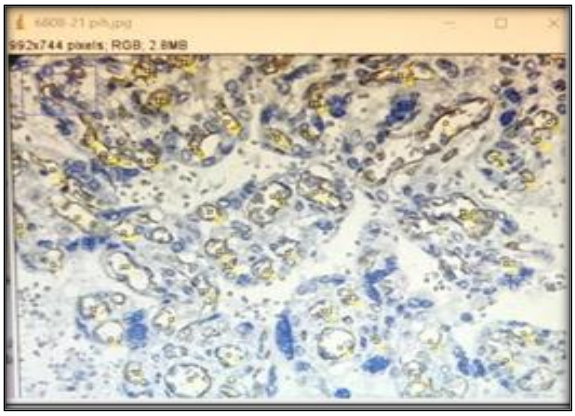

Figure 3E: PIH- Micro Vascular density 54±5 compared to controls 61±5.5 (Image analysis)

DIABETES MELLITUS (DM) PLACENTAL AND VILLOUS CAPILLARY CHANGES

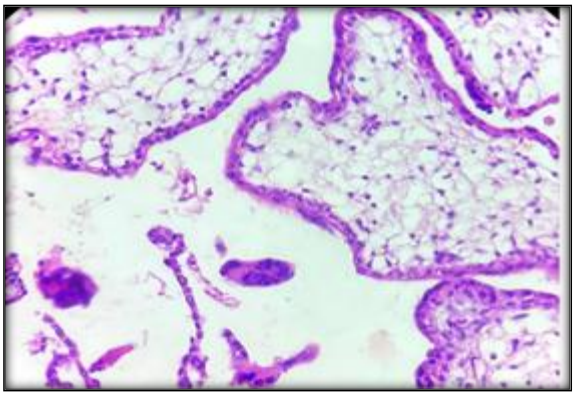

Figure 4: Villous Dysmaturity (H&E,400X)

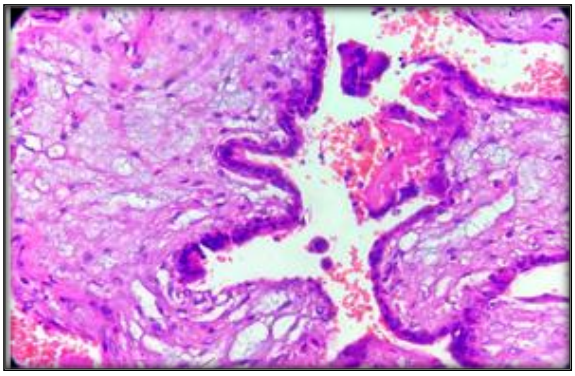

Figure 4A: Villous edema (H & E,400X)

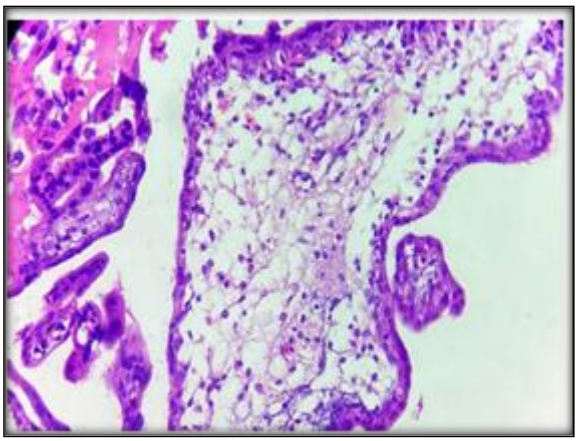

Figure 4B: Focal thickening of basement membrane

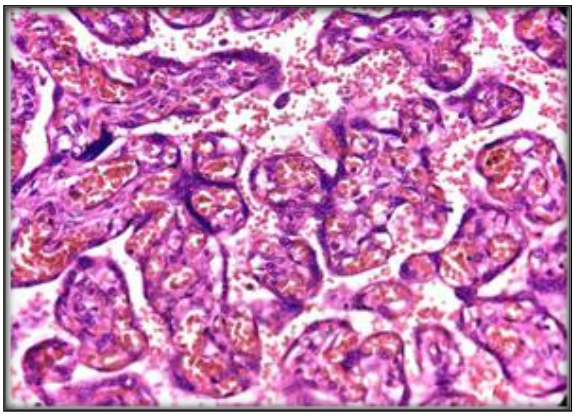

Figure 4C: Chorangiosis (H&E,400X) of Villi (H & E,400X)

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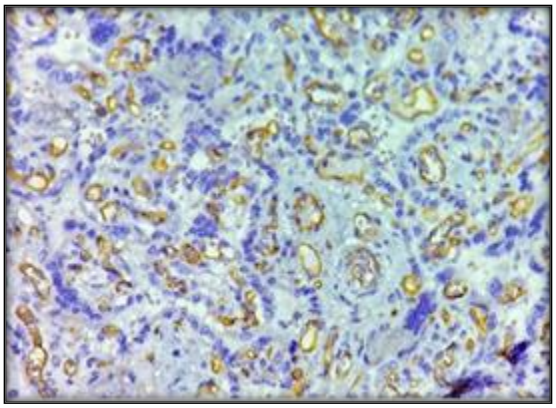

Figure 4D: DM-VasculardensitydensitybyCD31 byCD3 (IHC, 400X)

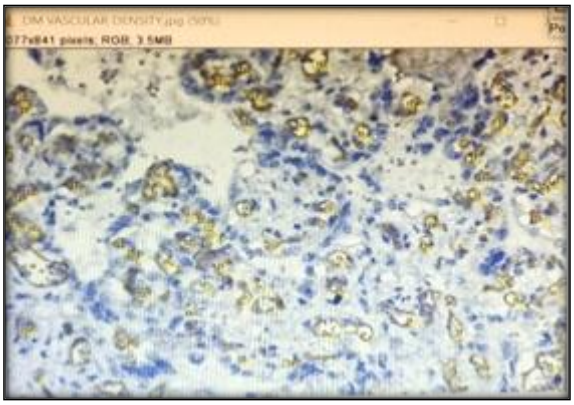

Figure 4E: DM-Micro Vascular density71±6 compared to controls 61±5.5 (Image analysis)

Table 1: General Characteristics and Comparative Analysis

Parameter	Complicated Pregnancies (Mean ± SD)	Control Group (Mean ± SD)	P-value
Age of Mother (years)	22.71	24.00	0.00001
Fetal Birth Weight (grams)	2780	2950	0.01
Placental Weight (grams)	532	577.1	0.032
Fetoplacental Weight Ratio	4.81	5.54	0.0001

Table 2: Histopathological Characteristics in Pregnancy Induced Hypertension (PIH)

Feature	PIH (per 100 villi)	Control Group (per 100 villi)	P-value
Syncytial Knots	68 ± 10	25.3 ± 5	0.0001
Fibrinoid Necrosis	10 ± 4	4 ± 1	0.0001
Hyalinised Villi (per 10Lpf)	12 ± 4	1 ± 1	0.0002
Cytotrophoblastic Proliferation	15 ± 3	2 ± 1	0.000183
Calcified Area (per 10Lpf)	4 ± 1	1 ± 1	0.0001

Table 3: Villous Vascularity in PIH

Vascular Change	PIH (Percentage)	Control Group (Percentage)
Normal Vascularity	72% (Hypothetical)	92%
Decreased Vascularity	28.57%	5%
Chorangiosis	57.14%	8%
Chorangioma	14.28%	2%

Table 4: Comparative Analysis of Various Complications

Complication	Parameter	Complicated Pregnancies (Mean ± SD)	Control Group (Mean ± SD)	P-value
Oligohydramnios	Microvessel Density (CD 31; pixels)	38 ± 2	60 ± 5	0.005
Diabetes Mellitus	Microvessel Density (CD 31; pixels)	71 ± 6	61 ± 5.5	0.001
Intrauterine Fetal Demise (IUFD)	Microvessel Density (CD 31; pixels)	6 ± 7.7	61 ± 5.5	0.0001
Anemia	Microvessel Density (CD 31; pixels)	43 ± 21	61 ± 5.5	0.0001

Table 5: Histopathology in Cases of Oligohydramnios, Diabetes Mellitus, IUFD, and Anemia

Complication	Histopathological Feature	Incidence (%)
Oligohydramnios	Increased Syncytial Knots	6.66
	Intervillous Fibrinous Deposition	66.66
	Calcification	33.33
Diabetes Mellitus	Villous Immaturity	80
	Villous Fibrinoid Necrosis	80
IUFD	Acclerated Villous Immaturity	57.14
	Villous Agglutination	57.14
Anemia	Decreased Villous Vascularity	33.33
	Increased Villous Vascularity	66.66

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DISCUSSION

The complex interplay of pathological changes in the placenta during various pregnancy complications has been extensively studied. In this context, we focus on conditions like Pregnancy-Induced Hypertension (PIH), oligohydramnios, Diabetes Mellitus, Intrauterine Fetal Demise (IUFD), anemia, and others.

Pregnancy-Induced Hypertension (PIH): In PIH, the placenta manifests significant alterations, often leading to maternal and fetal health complications. Histological features like syncytial knots and fibrinoid necrosis, highlighted in studies by Van Horn et al,[9] and Gore et al,[16] point to the placenta's response to hypertensive stresses. These features are reflective of placental dysfunction and can lead to compromised fetal development. Redline et al,[10] and Zhang et al,[13] further detail the maternal vascular underperfusion associated with PIH. This underperfusion contributes to a spectrum of complications, underscoring the complex nature of PIH and its impact on placental morphology and function.

Oligohydramnios: In the context of oligohydramnios, the placenta undergoes adaptations in response to reduced amniotic fluid volume. Increased syncytial knots and intervillous fibrinous deposition, as noted in the research by Aparna et al,[15] are indicative of the placenta's efforts to compensate for this altered environment. These histopathological changes can have significant implications for fetal development and maternal health, necessitating careful monitoring and management.

Diabetes Mellitus: Diabetes mellitus during pregnancy is associated with distinct placental changes. Mathew et al,[14] have demonstrated an increased prevalence of villous immaturity and chorangiosis in diabetic pregnancies. These changes reflect the placenta's response to the altered metabolic environment and have crucial implications for both maternal and fetal health, particularly in the context of gestational diabetes management.

Intrauterine Fetal Demise (IUFD): In cases of IUFD, the placental response is characterized by accelerated villous maturity and increased syncytial knots. The findings of Sundari et al,[18] support this observation, suggesting these changes as markers of the placenta's adaptation to compromised fetal circulation and oxygenation. Understanding these changes can aid in better diagnosing and potentially preventing IUFD.

Anemia: Anemia in pregnancy leads to varied vascularity and an increased incidence of syncytial knots. The studies by Burton et al,[11,12] discuss the oxidative stress and physiological adaptations of the placenta in response to anemic conditions. These changes are significant as they can affect the oxygen and nutrient transport to the fetus, impacting fetal growth and development.

Additional Considerations: The impact of maternal conditions such as antiphospholipid syndromes on placental histology, as explored by Van Horn et al,[9] and the implications of SARS-CoV-2 infection on placental pathology, as investigated by Zaigham et al,[17] highlight the diverse nature of placental responses. These conditions illustrate the critical role of the placenta in maternal and fetal health and the need for ongoing research in this area.

Limitations of the Study

Small Sample Size: A primary limitation of this study was the relatively small sample size, primarily due to the Covid-19 pandemic. The unprecedented challenges and restrictions imposed by the pandemic significantly impacted our ability to recruit a larger cohort of participants.

Impact of Covid-19 Pandemic: The study commenced in October 2019, coinciding with the Covid-19 pandemic. A considerable number of pregnant women with complicated pregnancies also had associated Covid-19 infections. Due to our exclusion criteria, which specifically omitted cases with infections, these women could not be included in the study. This exclusion potentially limits the generalizability of our findings to the broader population of pregnant women with complications.

Inclusion Criteria: The study focused exclusively on cases with term pregnancies complicated by conditions other than Covid-19 infection. While this approach allowed for a more controlled study environment, it also restricted the diversity and scope of the study population, potentially affecting the breadth of the findings.

CONCLUSION

Our study emphasizes the crucial role of villi maturity and capillary loop development in placental functionality, especially under hypoxic conditions. Disruptions in this balance, favoring anti-angiogenic factors, were evident across various pregnancy complications. Histopathological examination revealed chorangiosis as a frequent finding in oligohydramnios, intrauterine fetal demise, diabetes mellitus, and anemia, but it was less prevalent in pregnancy-induced hypertension. Increased syncytial knots were mainly seen in pregnancy-induced hypertension, anemia, and oligohydramnios. Distinct histopathological features included fibrinoid necrosis and hyalinized villi in pregnancy-induced hypertension, and villous immaturity in diabetes mellitus. The study also noted a general reduction in mean fetal birth weight in pregnancy-induced hypertension, oligohydramnios, intrauterine fetal demise, and anemia, in contrast to an increase in diabetes mellitus cases. Microvessel density, determined using CD31 immunohistochemistry, decreased significantly in pregnancy-induced hypertension, oligohydramnios, and anemia, and markedly in intrauterine fetal demise, while it increased in diabetes mellitus. This comprehensive

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examination of placental villous capillary lesions provides essential insights into pregnancy complications, enhancing our understanding and potentially improving clinical management and outcomes in these cases.

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