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A COMPARATIVE CROSS-SECTIONAL STUDY OF ENDOTHELIAL PROLIFERATION, VILLOUS CONGESTION, AND INTERVILLOUS HEMORRHAGE IN NORMAL, DIABETIC, AND HYPERTENSIVE PREGNANCIES: INSIGHTS INTO PLACENTAL ANATOMY AND HISTOPATHOLOGY

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Abstract:
The placenta plays a critical role in fetal development, serving as the primary interface for nutrient exchange, hormonal regulation, and waste removal between mother and fetus. Its examination is pivotal in understanding pregnancy complications and guiding postnatal care, particularly in conditions such as diabetes mellitus, hypertension, intrauterine growth restriction (IUGR), and stillbirth. Previous studies indicate that up to 92% of placentas examined exhibit relevant pathological findings, emphasizing the value of histopathological analysis in predicting maternal and fetal outcomes.

This study focused on full-term placentas (37–40 weeks of gestation) from pregnancies affected by diabetes and hypertension, excluding cases with additional clinical complications. A total of 150 placentas were analyzed and divided into three groups: control (A), diabetic (B), and hypertensive (C), with 50 samples in each. Non-probability purposive sampling was used, and the sample size was calculated using OpenEpi software, based on hospital delivery records.

Significant histological findings included a strong association between maternal disease and endothelial proliferation in cord vessels. At 10x magnification, endothelial proliferation was observed in 22% of the control group, 60% of the diabetic group, and 52% of the hypertensive group ($p < 0.005$). In contrast, villous congestion showed no significant association with maternal conditions, occurring in 38% of both control and diabetic groups and 26% of the hypertensive group ($p > 0.005$). Similarly, intervillous hemorrhage occurred in 36% of controls, 50% of diabetics, and 42% of hypertensive cases, also without statistical significance ($p > 0.005$).

These findings underscore the significance of endothelial proliferation as a placental marker linked to maternal pathology, while also suggesting that villous congestion and intervillous hemorrhage may be less predictive of underlying maternal disease.

Key words: Reproductive & developmental health, placenta, gestational diabetes, preeclampsia, endothelial proliferation, villous congestion, intervillous hemorrhage

INTRODUCTION

The placenta is a vital, multifunctional organ essential for fetal development, arising from fetal membranes and maternal endometrium. While its primary function is to facilitate the exchange of nutrients between maternal and fetal circulations, it also plays critical roles in gaseous exchange, waste excretion, hormonal regulation, hemopoiesis, and hepatic-like metabolic processes. Ultimately, its central purpose is to maintain an optimal intrauterine environment for fetal growth and development.

Maternal circulation introduces various substances—including nutrients, xenobiotics, and endogenous compounds—into the placenta. Although there was once debate regarding its diagnostic value, it is now widely acknowledged that placental examination is crucial in understanding pregnancy management, identifying pathological contributors to adverse outcomes, and informing care in subsequent pregnancies [1].

Comprehensive gross and microscopic examination of the placenta and umbilical cord—including assessments of weight, completeness, and structural abnormalities—is particularly recommended in cases involving systemic maternal disorders such as diabetes and hypertension [2]. The diagnostic utility is further emphasized in placentas from pregnancies complicated by fetal conditions such as intrauterine growth restriction (IUGR) and stillbirth, where underlying placental pathology can provide critical etiological insight. Notably, one study found that 92% of placentas sent for pathological assessment had relevant findings, underscoring the placenta's diagnostic value [3].

It has therefore been proposed that placental examination should be an integral component of neonatal-perinatal care, especially when maternal or fetal illness is present [4]. In such cases, the histopathological insights gained can inform both immediate clinical decisions and long-term maternal-infant health strategies. This is particularly relevant in pregnancies affected by gestational diabetes and hypertensive disorders, which may influence future obstetric outcomes.

Interestingly, the placenta expresses high levels of insulin receptors—more than many other tissues in the body. These receptors undergo localization changes during gestation, initially present at the syn-cytio-trophoblast microvillus membrane and later shift to the endothelium near term [5]. By term, insulin has a more pronounced effect on the placental endothelium, a fact with relevance for diabetic pregnancies. Fetal hyperinsulinemia in such cases may significantly impact placental endothelial function [6].

In pregnancies complicated by hypertensive disorders, especially pre-eclampsia, the failure of the second phase of trophoblast invasion into spiral arteries is widely considered a contributing factor. The resultant shallow invasion limits uteroplacental perfusion, often leading to extensive fibrin deposition around terminal villi. These changes reduce the surface area available for nutrient and oxygen exchange, compromising fetal development [7]. Morphological changes in the placenta frequently mirror maternal pathophysiology and are often indicative of underlying fetal compromise, especially in cases involving hypertensive pregnancy syndromes [8].

This study aims to analyze and compare placental morphological changes in diabetic and hypertensive pregnancies, with specific focus on endothelial proliferation, villous congestion, and intervillous hemorrhage, to better understand their correlation with maternal systemic conditions

METHOD:

Inclusion And Exclusion Criterion: This study conducted in 2 tertiary care hospital in Karachi, Pakistan public and private sector with consent, included full-term placentas from deliveries between 37 and 40 weeks of gestation. Placentas from preterm (<37 weeks) and post-term (>40 weeks) pregnancies were excluded. The diabetic group comprised placentas from mothers diagnosed with diabetes mellitus without any coexisting clinical conditions such as hypertension, infections, or other systemic disorders. Similarly, the hypertensive group included only those cases free from any other medical complications. Placentas from mothers at extremes of maternal age—specifically below 17 or above 42 years—were also excluded to reduce age-related bias. Only placentas preserved in 10% buffered formalin within 40 minutes of delivery were considered for histopathological examination to ensure tissue integrity.

Study Duration: The primary study spanned one year.

Sample Size Estimation: Sample size was calculated with the assistance of a statistician and epidemiologist using the OpenEpi software toolkit, based on the annual delivery turnover of the selected hospitals. A total of 150 placentas were included in the study and divided equally into three groups of 50 samples each:

- Group A: Control (normal pregnancies)
- Group B: Diabetic pregnancies
- Group C: Hypertensive pregnancies

Sampling Technique: A non-probability purposive sampling method was employed. Eligible participants were identified and recruited through the outpatient departments (OPDs) of two hospitals, one in the public sector and the other in the private sector. This approach ensured diversity in the patient population while maintaining study relevance and feasibility.

RESULT:

Table 1 presents the statistical associations between various placental variables and the disease groups (control, diabetic, and hypertensive). Although the insertion site of the umbilical cord shows an overall significant association with the disease groups (P = 0.007), this variation is not uniformly significant across all three groups. Notably, central cord insertion was approximately five times more frequent in the diabetic group (22%) compared to the hypertensive group (4%), reflecting an 18% higher occurrence. In contrast, eccentric insertion was more commonly associated with hypertensive cases.

A statistically significant difference was observed in the frequency of endothelial proliferation in cord vessels among the groups (P < 0.005). This feature was most prevalent in the diabetic group (60%), followed by the hypertensive group (52%), and the control group (22%). These differences were statistically significant in all pairwise group comparisons (A vs. B, A vs. C, and B vs. C).

With respect to pregnancy outcomes, the diabetic group had a higher frequency of live births with healthy outcomes. However, fetal distress was more common in the hypertensive group compared to the diabetic group (P < 0.005), further underscoring differences in perinatal health linked to maternal condition.

Endothelial Proliferation in Cord vessels: At 10x magnification, the presence of endothelial proliferation was significantly associated with maternal disease (P < 0.005). It was observed in 60% of diabetic cases (Group B), 52% of hypertensive cases (Group C), and only 22% of the control group (Group A). The control group exhibited a 30–34% higher absence rate of endothelial proliferation compared to the diseased groups. The hypertensive group demonstrated a near-equal distribution between presence and absence of this feature, while the diabetic group showed a markedly higher frequency. (Refer to Table 1, Photograph 1)

Villous Congestion: No statistically significant association was observed between villous congestion and maternal disease (P > 0.05). The frequency of villous congestion was identical in the control (38%) and diabetic (38%) groups, and slightly lower in the hypertensive group (26%). These differences were not statistically significant in any of the group comparisons (A vs. B, A vs. C, B vs. C). The number of patients without villous congestion was 12% higher in the hypertensive group compared to the other two groups. Similarly, the number of cases with villous congestion was equal in the control and diabetic groups but 12% lower in the hypertensive group.
(Refer to Table 1, Photograph 2)

Intervillous Hemorrhage: Intervillous hemorrhage did not demonstrate any statistically significant association with disease group (P > 0.05). It was observed in 36% of control (Group A), 50% of diabetic (Group B), and 42% of hypertensive (Group C) placentas. Comparisons between all groups (A vs. B, A vs. C, B vs. C) yielded non-significant p-values.

In the diabetic group, the frequency of hemorrhagic and non-hemorrhagic cases was equal. In contrast, the hypertensive and control groups had a higher number of non-hemorrhagic placentas -by 16% and 28%, respectively. (Refer to Table 1, Photograph 2)

Table 1: Association within the study groups

Endothelial proliferation of cord vessels f (%)	**Study group**			
	Diabetic	**Hypertensive**	**Normal**	**P-value**
Negative	20 (40)	24 (48)	39 (78)	<0.005
Positive	30 (60)	26 (52)	11 (22)	
insertion site of cord				
central	11 (22)	02 (4)	06 (12)	0.007
eccentric	22 (44)	30 (60)	36 (72)	
marginal	17 (34)	18 (36)	8 (16)	
Villous congestion f (%)				
No	31 (62)	37 (74)	31 (62)	0.343
Yes	19 (38)	13 (26)	19 (38)	
Hemorrhage f (%)				

No	25 (50)	29 (58)	32 (64)	0.365
Yes	25 (50)	21 (42)	18 (36)	

Table 1. illustrate the association between different variables and disease groups.

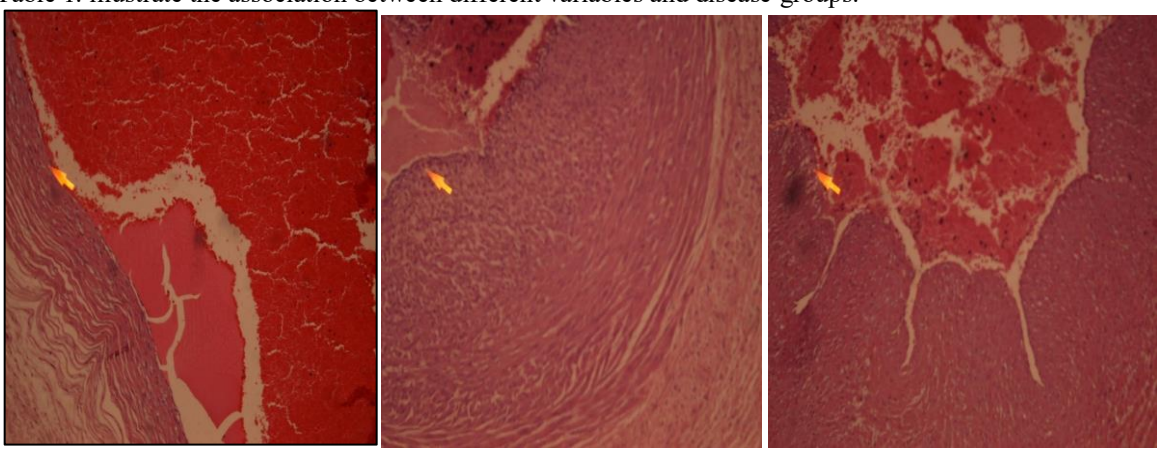

Fig No1. Photomicrograph shows endothelial lining of placental vessels in normal, diabetic & hypertensive placental tissue at 40x magnification /hpf with H&E stain.

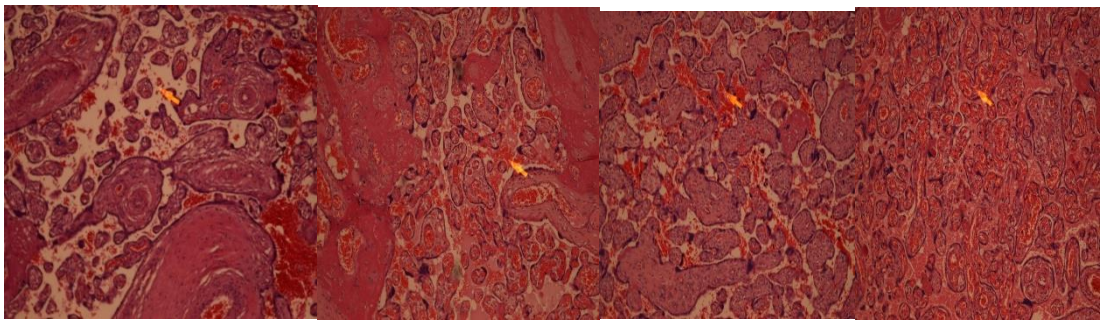

Fig No. 2. Photomicrograph showing intervillous hemorrhage and villous congestion in normal diabetic & hypertensive (separately) placental tissue at 10 magnification /lpf with H&E stain

DISCUSSION:

The anatomical and pathological evaluation of the placenta has emerged as a highly informative, objective, and noninvasive method to assess the intrauterine environment and predict perinatal outcomes. [8] a study showed the placental pathology like intervillous hemorrhage are seen more in preeclampsia and villous endothelial layer thickening is demonstrated more in diabetic placentas [9] In this study, the placenta was selected as a key organ for investigating the pathophysiological changes associated with maternal diabetes and hypertension, both of which are well-documented contributors to adverse pregnancy outcomes.

Our findings reaffirm the hypothesis that pregnancies complicated by diabetes and hypertension exhibit significant morphological and histological alterations in the placenta compared to normal pregnancies. These results are in line with previous literature emphasizing the detrimental impact of maternal systemic conditions on placental architecture. Timely and detailed placental examination in such cases provides critical information that can guide obstetric and neonatal management, helping to mitigate complications and enhance maternal-fetal outcomes.[10]

Endothelial Proliferation

A notable finding in this study was the significantly increased endothelial proliferation in the diabetic group, followed by the hypertensive group, with the control group showing the lowest frequency. These results are consistent with earlier reports that describe diabetes-induced vascular changes in the placenta. Diabetes leads to reduced maternal blood flow within the intervillous space, often due to inflammatory processes like endarteritis, which injures endothelial cells and prompts reactive proliferation. [11] This hyperplasia can result in luminal narrowing of maternal vessels and impaired uteroplacental perfusion. Prior studies have also reported features such as syncytial knot formation and endothelial thickening in diabetic placentas. [12]

Similarly, in pre-eclampsia, deficient remodeling of uterine spiral arteries compromises placental and fetal perfusion, contributing to systemic endothelial dysfunction. [13–14] the endothelial changes observed in our hypertensive group align with these findings and highlight a shared vascular pathology between hypertensive and diabetic pregnancies, though differing in underlying mechanisms.

Villous Congestion

In our cohort, villous congestion showed no significant difference between the diabetic and control groups, although it appeared less frequently in the hypertensive group. This observation suggests that villous congestion may not serve as a reliable marker for distinguishing placental pathology in diabetic versus hypertensive pregnancies.

Endothelial proliferation and vascular abnormalities are key features to reduced placental perfusion and in turn poor fetal outcome has resulted [15].Interestingly, prior research on diabetic placentas—particularly in type 1 diabetes—has shown increased placental angiogenesis, potentially linked to elevated fetal fibroblast growth factor-2 levels. [16] This results in hyper capillarization, which may contribute to congestion; however, the evidence in gestational diabetes mellitus (GDM) remains inconsistent. [17–18]

In contrast, hypertensive disorders, due to inadequate spiral artery remodeling, are associated with decreased placental perfusion. This leads to hypoxic conditions and subsequent trophoblast differentiation changes, contributing to an increase in villous capillaries and syncytial knot formation. [19]

Additional Insights

Our findings are further substantiated by recent animal studies, such as one investigating the impact of prenatal nicotine exposure on placental development. This research demonstrated reduced placental size, increased apoptosis, and lower fetal weight in nicotine-exposed rat models, underscoring the placenta's vulnerability to vascular insults. [20]

A prospective human study analyzing 84 term placentas from GDM pregnancies also reported significant histopathological findings, including increased syncytial knots, calcifications, villous agglutination, decidual vasculopathy, retroplacental hemorrhage, and villous edema. These results highlight the profound effects of GDM on both maternal and fetal vascular components of the placenta. [21]

A systematic review by Huynh J et al. provided a comprehensive overview of placental pathology in various forms of maternal diabetes (type 1, type 2, and GDM). The authors observed both common and distinct placental changes among these groups, reflecting differences in underlying pathophysiology. They also emphasized the need for consistent terminology in reporting placental lesions and called for future research to explore how clinical factors and glycemic control influence placental structure and function. [22] M. Rani, et al during their research focused on highlighting specific histopathological changes, such as endothelial proliferation, villous congestion, and intervillous hemorrhage, which are often seen in cases of compromised placental function.[23] Placental morphology and histopathology are affected in hypertensive pregnancies, which might be the reason for placental insufficiency in these cases.[24]

In conclusion, our study reinforces the clinical value of histopathological placental evaluation in pregnancies with gestational diabetes and preeclampsia. Recognizing and documenting these changes not only enhances understanding of the maternal-fetal interface but also supports informed clinical decisions aimed at improving perinatal outcomes.

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