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Placental Changes in Women with Gestational Diabetes Mellitus and its association with Perinatal Outcome

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Abstract

Background: Gestational diabetes mellitus (GDM) is defined as diabetes with onset or first recognition during gestation. It is a common complication of pregnancy that has become more prevalent over the past few decades. Abnormalities in fetal growth, including increased incidence of both large and small for gestational-age babies, suggest placental dysfunction. The diabetic metabolic situation causes hyperglycemia, hypoglycemia, hyperinsulinemia, and oxidative stress in the mother and the fetus. These alterations trigger a sequence of changes in the development of the vessels in the placenta. Consequently, the fetus is affected by this lack of supply of necessary substances or overstimulated by pathological factors with a significant risk for abnormal development. **Aim and objective:** To observe & study the various gross morphological changes in the placentas of diabetic mothers and their comparison with normal-term placentas. **Method and material:** The total number of specimens studied in the present study was 80, 40 placentas were from the mothers with uncomplicated/normal pregnancy which were taken as a control group, and 40 placentas from the mother with either gestational or overt diabetes which were taken as a study group. The specimens were collected from the NCMCH, Panipat for 1 year and the study was conducted in the Department Of Obstetrics and Gynecology. **Result:** The presence of degenerative lesions such as fibrinoid necrosis and vascular lesions like cholangitis was apparent, mainly in the diabetes group. Villous immaturity and the presence of NFRBC as an indication of chronic fetal hypoxia were significantly increased in the placentas of women with diabetes compared with the control group. The fetal/placental weight ratio was significantly lower in the diabetic group. **Conclusion:** Histological abnormalities were observed more frequently in the diabetic placentas compared to the controls. These findings support the hypothesis that impaired placental function is one of the main reasons for the increased frequency of fetal complications in diabetic pregnancies.

Keywords: Gestational diabetes mellitus, Pregnancy, Placental

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Introduction

Gestational diabetes mellitus (GDM) is a common complication of pregnancy, and its prevalence is increasing worldwide [1]. GDM is defined as glucose intolerance with onset or first recognition in pregnancy, although as discussed below, the procedures and criteria for diagnosing GDM have changed over time and differ amongst institutions. Pregnancies complicated by GDM are more likely to result in adverse obstetric outcomes including preterm labor, cesarean-section, macrosomia, and shoulder dystocia [2]. Even for infants born at normal weight, exposure to GDM has lifelong consequences for growth patterns, obesity risk, and the development of diabetes [3, 4]. Additionally, although fetal overgrowth is a widely recognized consequence of GDM, there are also more babies born small for gestational age (SGA) in GDM than in normoglycemic pregnancies, and pregnancies with SGA babies are at higher risk of poor fetal outcomes [5]. Collectively, these abnormalities in fetal growth point to placental dysfunction. As will be discussed, multiple histological abnormalities have been described in GDM placentas examined after delivery. However, it is not clear when in pregnancy these abnormalities arise, or even whether they precede or follow the onset of glucose intolerance. Improvements in imaging technologies have allowed the visualization of placental features progressively earlier in gestation.

The Centres for Disease Control and Prevention (CDC) has shown that the crude incidence of the cases diagnosed with diabetes mellitus has increased, from 3.3 per 1000 to 7.4 per 1000, i.e. 124%, from the year 1980 to 2005 and hence, diabetes mellitus is now considered to be one of the major health problems in our society. Various studies suggested that the increased prevalence of diabetes mellitus (DM) amongst women of childbearing age is due to an increase in sedentary lifestyles, changes in dietary habits, and the virtual epidemic of childhood and adolescent obesity.[6]GDM or Gestational Diabetes Mellitus is defined as a variable degree of intolerance to glucose with either onset or first recognition during pregnancy. Maternal glucose intolerance occurs in 3-10% of pregnancies.[7]Pregnancy complications like gestational diabetes are reflected grossly and microscopically in the placenta. A placental examination can yield information about the existence and effects of maternal, placental, or fetal disease, the cause of stillbirth, and potential risks in future pregnancies.

The various pathological changes occurring in the placenta of diabetic mothers are considered to be the important risk factors contributing to fetal anoxia and fetal compromise in pregnancy [8]. Previous studies on the functional morphology of placentas from diabetic mothers have produced inconsistent results and conclusions

Material and Method

The study was conducted for the period of 1 year from September 2022 to August 2023, after clearance from the Institutional Ethical Committee.

Forty singleton pregnancies complicated by gestational diabetes were recruited at the time of diagnosis between 28 and 35 weeks of gestation and compared to 40 consecutive normal pregnancies (control group). The placentas from women with gestational diabetes and the control group were obtained over 1 year, between 2022 and 2023 in our institutional hospital, from uncomplicated deliveries and 5-min Apgar scores 8. In both groups, deliveries occurred in term pregnancies (between 37 and 41 weeks of gestation). Routine ultrasonographic examination was performed at 23- 24

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and 33- 36 weeks gestation, which confirmed a normal pattern of fetal growth. Gestational age was assessed by the last menstrual period or by a first-trimester ultrasound scan if there was a discrepancy of more than 1 week. GDM was diagnosed in the presence of a 100-g oral glucose tolerance test (OGTT) at 24-32 weeks.

For GDM diagnosis, the American Diabetes Association (ADA) criteria-2000 was used. GDM women were treated with diet (GDM-D), and when ADA glucose targets were not fulfilled insulin was additionally administered (GDM-I). Following diagnosis, all patients began home blood glucose monitoring while undertaking an appropriate diet. The level of glycemic control achieved by the patient was assessed by maternal glycosylated hemoglobin (HbA1c) during the first, second, and third trimesters of pregnancy (Nycocard Reader; normal reference value: 4.0 6.0%). Mean glycemic control during pregnancy was calculated. Excellent glycemic control during pregnancy was defined as a mean HbA1c level of 56.0%, good glycemic control as a mean HbA1c level of 6.1 7.0%, and a mean HbA1c of 7.0% as non-optimal glycemic control. The inclusion criterion was optimal glycemic control throughout pregnancy (HbA1c level 57.0%).

Exclusion criteria were the presence of hypertension, pre-eclampsia, intra-uterine growth retardation (birth weight B10th percentile), or major congenital fetal malformations. Inclusion criteria for normal pregnancies were non-smoking women with a negative 50g oral glucose challenge test (OGCT) and no obstetrical complications. OGCT was performed between 24 and 28 weeks gestation and was considered negative with plasma glucose after 1 h B140 g/dl. The BMI was calculated as weight (kg)/height2 (m2). Birth weight was expressed as a birth weight percentile corrected for gestational age, according to standard birth weight charts. Information about maternal characteristics (age, race, pre-pregnancy weight, BMI, parity, education level, and social occupation) and neonatal data (gestational age, Apgar score, sex, weight, Ponderal Index (PI)) were collected. PI was calculated as fetal weight/(fetal length)3 100. A pathologist blinded to all clinical data except gestational age (to assess the villous maturation) reviewed all histological samples. The placentas were rinsed in water and left to drain blood for at least 2 h, then weighed without the umbilical cord and membranes. In all cases, the placenta was sliced into 2 cm thick coronal sections. The samples were controlled macroscopically for umbilical vessel abnormalities. Representative specimens (2 samples) were taken from the cord, the cord insertion, and the placental membranes, and at least 3 full thickness samples were obtained from microscopically normal placenta and abnormal areas. All samples were embedded in paraffin and stained with hematoxylin and eosin. We calculated the ratio (placental ratio) between infant birth weight and placental weight, corrected for gestational age.

The histological assessment was carried out about the following aspects: fetal vessel thrombosis, villous immaturity, cholangitis, presence of nucleated fetal red blood cells (NFRBC), mural thrombosis, ischemia, ischemic villitis, infarction, presence of hydropic or avascular villi, massive perivillous fibrin deposition and villous fibrinoid necrosis.

Data are presented as means with standard deviations or as percentages. The significance of the difference between groups was calculated with two-tailed Student's t-tests for independent samples. All scalar variables for comparison were tested with

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the Kholmogorov-Smirnof test and were found normally distributed. This allows the use of parametric tests. Categorical data were compared using the x2 -test (or Fischer's exact test). For differences and correlations, a two-tailed p-value of B5% was considered statistically significant.

Observation & Results

In this present study, we included a total of 80 placentas out of which 40 placentas were of diabetic mothers and 40 placentas were of normal mothers.

Table no. 1 – Age distribution in both groups

		GROUP		Total
		DIABETES	NORMAL	
AGE GROUP	< = 19 YEARS Count	1	4	5
	% within GROUP	2.5%	10.0%	6.3%
	20 - 30 YEARS Count	34	34	68
	% within GROUP	85.0%	85.0%	85.0%
	> 30 YEARS Count	5	2	7
	% within GROUP	12.5%	5.0%	8.8%
Total Count		40	40	80
% within GROUP		100.0%	100.0%	100.0%

The above pie chart [table no. 1] shows the age distribution of cases in a normal group with the majority of the cases i.e. 85% between the age of 20-30 years, 10% of cases were > 30 years of age while only 5% of cases were <=19 years of age.

Table no.2 – Placental shape distribution in both groups

		GROUP		Total
		DIABETES	NORMAL	
SHAPE	ROUND Count	20	24	44
	% within GROUP	50.0%	60.0%	55.0%
	OVAL Count	16	16	32
	% within GROUP	40.0%	40.0%	40.0%
	IRREGULAR Count	4	0	4
	% within GROUP	10.0%	.0%	5.0%
Total Count		40	40	80
% within GROUP		100.0%	100.0%	100.0%

The above graph [table no.2] shows, in the normal group 60% of cases had round placentas, 40% of cases had oval-shaped placentas and none of the cases showed irregular shapes of the placenta. In comparison, the diabetic group showed 50% of cases with a round shape, 40% of cases with an oval shape, and 10% of cases with an irregular shape of the placenta.

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Table no. 3 – Site of cord insertion

			GROUP		Total
			DIABETES	NORMAL	
CORD INSERTION	CENTRAL	Count	17	11	28
		% within GROUP	42.5%	27.5%	35.0%
	MODERATELY ECCENTRIC	Count	11	14	25
		% within GROUP	27.5%	35.0%	31.3%
	HIGHLY ECCENTRIC	Count	12	11	23
		% within GROUP	30.0%	27.5%	28.8%
	MARGINAL	Count	0	4	4
		% within GROUP	.0%	10.0%	5.0%
Total		Count	40	40	80
		% within GROUP	100.0%	100.0%	100.0%

As shown in the above table[Table no.3] shows that overall the most common site of insertion of the umbilical cord was central. accounting for about 28 cases out of a total of 80 cases, and the least common was marginal shown only in 4 cases out of 80.

TABLE NO. 4 – Comparison of gross morphological parameters of diabetic placenta with reference to normal placenta

Parameters	Normal Mean±SD	Diabetic Mean±SD	P- value
Placental weight(gms)	469.63±88.39	563.75±96.78	0.000
Diameter(cm)	17.62±1.61	18.15±1.59	0.145
Circumference(cm)	55.39±5.05	56.98±5.02	0.161
Area(sq.cm)	243.43±45.93	258.87±44.76	0.132
Central thickness(cm)	1.79±0.37	2.51±0.57	0.000
Baby weight(Kg)	2.82±0.36	3.14±0.35	0.000
Fetal/placental ratio	6.10±0.60	5.68±0.75	0.008

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The above table shows that there was a significant difference between the weight of the placenta amongst the normal and diabetic groups. The mean weight of the placenta in the normal group was 469.63 gms while in a diabetic group, the mean weight was 563.75 gms and the difference between the 2 groups was statistically significant. (<0.05) [Table no.4].

there was no significant difference between the diameter of the placenta between the two groups. The mean diameter of the placenta in the normal patient was 17.62cm while in the case of diabetic patients, it was 18.15cm, and the p-value is .145(>0.05) hence the difference between the 2 groups was not statistically significant in our study[Table no.4].

There was no significant difference between the circumference of the placenta between the 2 groups. The mean circumference of the placenta in normal patients was 55.39cm while it was 56.98cm in the case of a diabetic patient, and the p-value is 0.161 (> 0.05) hence the difference between the 2 groups was not statistically significant[Table no.4].

There was no significant difference between the areas of the placenta between the two groups. The mean area of the placenta in normal patients was 243.43sq.cm while in the case of diabetic patients it was 258.87sq.cm, and the p-value is 0.132 (> 0.05) and hence the difference between the 2 groups was not statistically significant [Table no.4].

There was a significant difference between the central thickness of the placenta between the two study groups. The mean placental thickness in a normal patient was 1.79cm while it was 2.51cm in the case of a diabetic patient , and the p-value is 0.000 (< 0.05) hence the difference between the 2 groups was statistically significant [Table no.4].

There was a significant difference in the birth weight of the baby between the two study groups. The mean birth weight of the baby in the normal patient was 2.82Kg while in the case of diabetic patients, it was 3.14Kg, and the p-value is 0.000 (< 0.05) hence the difference between the 2 groups was statistically significant

There was a significant difference between the fetal/placental ratio between the two study groups. The mean fetal/placental ratio in normal patients was 6.10 while it was 5.68 in the case of diabetic patients, and the p-value is 0.008(<0.05) hence the difference between the 2 groups was statistically significant

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Table no.5 – Pearson's r correlation between the weight of the baby and various gross parameters of the placenta in both groups

		Placental weight	Diameter	Circumference	Area	Central thickness	Fetal/placental ratio
Normal	Baby birth weight	0.682	0.154	0.195	0.141	0.371	0.048
Diabetic	Baby birth weight	0.839	0.451	0.448	0.428	0.515	0.25

As shown in the above table [Table no.5], in the normal group there was a strong correlation between the weight of the baby and placental weight. The correlation between the birth weight of the baby and the diameter, circumference, area, and central thickness of the placenta was fair, while the fetal/placental ratio shows a negative correlation.

On the other hand in the diabetic group, there was a fair correlation between the birth weight of the baby and the placental weight as well as central thickness. There was a poor correlation between the birth weight of the baby and the diameter, circumference and area of the placenta in diabetic group.

Table no. 6 – Comparison of Histopathological parameters of Diabetic Placenta about normal Placenta

Parameters	Normal Mean of rank	Diabetic Mean of rank	p- value
Villous edema (figure 12)	25.44	55.56	0.000
Villous fibrosis (figure 13)	28.58	52.43	0.000
Synctial knots (figure 14)	24.15	56.85	0.000
Fibrinoid necrosis (figure 15)	22.53	58.48	0.000

Table no. 6 shows that the p-value for all 4 parameters i.e. villous edema, villous fibrosis, syncytial knots, and fibrinoid necrosis seen on histopathological examination, was <0.05, and hence there was a significant difference between these findings in both the groups.

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Discussion

Obstetrical and fetal or neonatal complications are common in diabetic pregnancies. Maternal hyperglycemia results in fetal hyperglycemia, producing macrosomic or LGA fetuses due to fetal insulin overproduction. The placenta acts as a barrier to maternal insulin and is placed between the two circulations. It is believed that impaired placental function, in terms of abnormal placental weight or histology, may to some extent account for the emerging pathology. We defined several histological abnormalities of clinical significance in the placentas of diabetic and occasionally of control women [9]. Histological abnormalities, such as the presence of villous fibrinoid necrosis, villous immaturity, cholangitis, and the presence of NFRBCs, were observed more frequently in the diabetic placentas compared to the controls. This is in agreement with other studies and confirms the association of DM with significant placental pathology (10,11,12].

Chronic fetal hypoxemia is suggested by the presence of NFRBCs. Fibrinoid necrosis may also affect oxygen exchange, and villous immaturity can lead to the same result because of the increased diffusion distance between the intervillous space and fetal capillaries [11]. Diabetic infants may compensate for such immaturity by the high relative placental weight and by increasing the exchange surface [7,13]. Placentas from diabetic pregnancies show an increased incidence of vascular pathological changes. Such changes can affect the arteries and veins and are most frequently observed in stem villi of different sizes, corresponding to peripheral vessels. These lesions affect the fetoplacental circulation [14]. This is further supported by the findings in cholangitis. Ischemic villitis represents a lesion with focal syncytial necrosis and perivillous fibrin deposition, which together with placental infarction seem to be morphological markers of placental vascular disease in association with impaired umbilical blood flow and chronic fetal hypoxia [15,16]. It has long been known that both maternal prepregnancy weight and weight gain independently influence newborn weight [12,17]. Similarly, in this study fetal weight was positively correlated with maternal pre-pregnancy weight in both normal and GDM pregnancies. We assessed the relative placental weight, which is increased in gestational diabetes [18,17]. As suggested before, increased placental size, especially enlargement of the surface for maternal-fetal exchange, could be part of a mechanism to compensate for any impaired effectiveness of blood oxygen release capacity. The etiology of this is attributed to the increased maternal hemoglobin oxygen affinity in diabetic women or to placental abnormalities [19,11,13,20,21).

In this study population, optimal maternal glycemic control throughout pregnancy was accomplished. The strict control of maternal glucose values is associated with average fetal weights within normal ranges, although significantly higher than in a non-diabetic population after correction for gestational age. However, the increased placental weight was proportionally greater than the increased fetal weight in the diabetic group. This leads to a decreased fetal/ placental weight ratio probably because much placental growth occurs in the first half of gestation, well before GDM diagnosis and the start of treatment, but surely after the onset of maternal disease [17].

Age of the mother: Our study was supported by In the year 2004, Emmanuel Odar et al. observed in his study that the age group at risk of getting gestational diabetes was between 20-39 years in 96.8% of cases.[22]

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Parity: In the year 2003, A. Ben-Haroush, observed that high parity was one of the risk factors for GDM 92. In the year 2004, a study done by Ma‟asoumah A. Makhseed et al also revealed that the percentage of multiparity was higher, with 60% of cases in the impaired gestational glucose tolerance group.[23] In our study 65% of cases in the study group were multigravida.

The shape of the placenta: In 1951, Hamilton showed that the term placenta is circular to oval in outline and is determined by the form of villi left on the chorionic sac.[24] According to the study conducted by Muhammad Ashfaq in the year 2005, the shape of the placentas in the diabetic and non-diabetic group was roughly oval or round except for one bilobed placenta.[25] In our study, 50% of cases in the diabetic group had a round shape of the placenta, and 40% had an oval shape which was almost similar to the result we got for the normal group. In the diabetic group, we got 4 placentas i.e. 10% with an irregular shape, out of which 3 were having succenturiate lobes. Placenta extrachorialis, which is a morphological abnormality of the placenta, is defined as "a condition in which the transition from a membranous to villous chorion occurs at some variable distance within the circumference of the placenta and not at the placental edge" and hence the basal plate is larger than the chorionic plate.[26]

Site of cord insertion: In our study, there was not much difference in the distribution of the site of insertion of the umbilical cord between the two groups which was similar to a study done by Pathak et al in the year 2010 and by Soma Saha et al in the year 2014. [27,28] But in the study conducted by Soma Saha et al, the most common site of insertion of the umbilical cord was marginally observed in 33.8% of cases, while in our study it was central, observed in 35% of cases. Weight of the placenta: In our study, the minimum placental weight in the diabetic group was 340gms, the maximum was 800gms and the mean placental weight was 563.75±96.78gms, which showed a statistically significant difference from the mean weight of the normal group which was 469.63±88.93gms.A significant increase in the fetal and placental weights was found in the diabetic group compared to the normal group in a study conducted by Jauniauxa, and Burton in the year 2006.[29]The increased placental weight in diabetes may be because of reactionary hyperglycemia in fetuses of diabetic mothers which leads to compensatory hyperplasia of the villous structure and fetal macrosomia. Another factor that leads to villous hyperplasia could be because of vascular compromise in diabetes mellitus which causes low oxygen tension in chorionic villous blood.[30]Teasdale stated that the cause of heavier placenta in gestational diabetes is mainly because of a significant accumulation of non-parenchymal tissue and a moderate increase in parenchymal tissue. Birth weight of baby: The weight of the newborn baby depends directly on the environment it experienced during the intrauterine life. In the case of gestational diabetes mellitus, glucose crosses the placental barrier and causes fetal hyperglycemia which in turn stimulates the pancreatic islet cells and leads to fetal hyperinsulinemia, as insulin itself is an anabolic hormone. In our study, the minimum birth weight of the newborn in the diabetic group was 2.500 kg, while the maximum birth weight was 3.700 Kg with a mean birth weight of 3.143±0.35kg. In the control group, the minimum birth weight of the newborn was 2.090 Kg, the maximum was 3.493 Kg with a mean birth weight of 2.824±0.36Kg. The difference in the birth weight of 2 groups was statistically significant in our study.

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Villous edema: Villous edema is defined as accumulation of fluid in the interstitium of the villi with disruption and replacement of intravillous cellular architecture. As hyaluronic acid molecules have the property to retain water, it was concluded that, the presence of abnormal deposits of mucopolysaccharides in the villous stroma can lead to the appearance of the true villous edema in placentas of diabetic mothers.[31] In the year 1994, Majid S. Al-Okail et al mentioned in their study that villus oedema was slightly observed in well-controlled diabetic placentas but it was very clearly observed in gestational diabetic placentas.[32] In the present study, we found an increased incidence of villous edema in the placentas of diabetic patients as compared to normal group and it was statistically significant.

In the year 2010, Verma R et al noticed increased villous fibrosis in GDM controlled by insulin, but such observation was not observed in GDM controlled by diet and in control patients.[33] In the present study, we find an increased incidence of villous fibrosis in the placentas of diabetic patients as compared to the normal group and it was statistically significant.

Fibrinoid necrosis: In the year 2011, Vineeta Tewari et al noticed an increase in intravillous fibrinoid necrosis in 80% of diabetic cases.[34] In the present study, we find an increased incidence of both intervillous and perivillous fibrinoid necrosis in the placentas of diabetic patients as compared to the normal group and it was statistically significant.

Our results demonstrate that treatment of gestational diabetes using achieving the optimal glycemic state of the mother can modulate fetal weight proportionally more than placental weight, correlating to a better perinatal outcome. Further studies are needed to better evaluate maternal insulin sensitivity as a determinant of fetal and placental growth.

Conclusion

Infants of diabetic women may be protected against chronic hypoxemia because of a relatively high placental weight corresponding to an increased exchange surface. The question of whether an interaction exists between placental pathological changes and fetal vascular function early during life in the uterus seems to be of substantial base (6,17). Changes due to diabetes in physiological development during an early critical period of pregnancy may permanently modify organ functions or maternal-fetal metabolic profiles, which cannot be restored by a normalization of the environment later in pregnancy. Thus, histological lesions associated with impaired glucose metabolism may persist despite tight metabolic control and explain the steady occurrence of fetal and neonatal complications.

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