ORIGINAL ARTICLE

Morphological and Histopathological Features of Placenta in Women with Gestational Diabetes Mellitus and Its Association with Perinatal Outcome

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Abstract

Background: Placenta, a unique vascular organ, acts as a barrier between maternal and fetal circulation, protecting the fetus from adverse effects of maternal diseases. Gestational diabetes mellitus (GDM) alters the placental function leading to histological and morphological changes in placenta. Hyperglycemia affects placental development leading to adverse maternal and perinatal outcomes.

Aim: To understand the morphological and histopathological variations of the placenta in GDM pregnancies and its association with the perinatal outcome.

Materials and methods: A hospital-based cross-sectional study was conducted in women with singleton pregnancy between 37 and 40 weeks of gestation with GDM (Cases) and compared with women without GDM (Control). The morphological and histopathological features of the placenta were studied, and the associated perinatal outcome was analyzed.

Results: In cases, most of the women had babies with birth weight of 3.51–4 kg (57.1%) and was statistically significant ($p = 0.001$). The mean placental weight among cases and controls was 719.57 ± 110. 8 gm and 380.71 ± 50.59 gm, respectively. Placental histopathological changes (calcification of the placenta, fibrinoid necrosis of villi and immature villous) were noted in cases and were statistically significant ($p = 0.001$). Abnormal perinatal outcomes were observed in cases with an oval-shaped placenta (64.7%), increased cord thickness (68.4%), fibrinoid necrosis of villi (50%), syncytial knots (61.9%), and immature villous (54.5%).

Conclusion: Gestational diabetes mellitus causes an alteration in morphological and histological features of the placenta resulting in adverse perinatal outcomes. Early diagnosis, treatment, and glycemic control aid in reducing perinatal morbidity and mortality.

Keywords: Calcification, Gestational diabetes mellitus, Infarction, Placental weight, Placental shape, Villous edema.

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Introduction

The placenta is an important indicator for fetal and maternal disorders. Many maternal disorders are responsible for placental dysfunction resulting in morphological and histological alterations.[1]

Pregnancy is a state which induces insulin resistance under various physiological changes.[2] Gestational diabetes mellitus (GDM) complicates 2–4% of all pregnancies and is responsible for macrosomia, perinatal morbidity and mortality[3–7] and placenta is pale due to villous edema, significantly enlarged, thick and plethoric.[8,9] Neonates of GDM mothers are prone for respiratory distress, growth abnormalities, neonate hypoglycemia and congenital malformations.[10–12] Gestational diabetes mellitus results in histopathological abnormalities like syncytial knot formation, fibrinoid necrosis of villi, villous immaturity, and excessive cytotrophoblastic proliferation.[13]

The objective was to study the morphological and histopathological variations of the placenta in women with GDM and the effect of these changes on the perinatal outcome.

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Patient consent statement: The author(s) have obtained written informed consent from the patient for publication of the case report details and related.

Materials and Methods

Study Population

The hospital-based cross-sectional study was conducted in Lady Goshen Hospital and KMC Hospital Attavar, Mangaluru, from September 2019 to August 2021. Women with singleton pregnancy at 37–40 weeks of gestation with GDM were selected for the case group and women without GDM were controls. The study population in each group was sampled through convenient sampling. The study was begun after approval from the Institutional ethical committee of Kasturba Medical College, Mangaluru. Informed Consent from the study participants were taken.

Exclusion Criteria

Women with overt diabetes mellitus, Rh-isoimmunization, hypertension complicating pregnancies, thyroid disorders, anemia, and fetus with congenital anomalies.

Determination of GDM

The study population was evaluated for GDM at 24–28 weeks period of gestation with the two-step method. They were screened by the glucose challenge test (GCT) with 50 gm glucose and a diagnostic test, glucose tolerance test (GTT) with 100 gm glucose was done to confirm GDM (ACOG).

Placental and Perinatal Parameters

Demographic details and relevant history were taken, and general and abdominal examination were done. Following delivery, the umbilical cord was cut, placenta was collected, washed under tap water and morphological features were examined. Placenta was preserved in formalin (10%) and sent for histopathological examination. During histopathological investigation, parallel slices at 2 cm intervals were taken using bacon slicer/long sharp knife and fixed in formalin (10%) for a minimum of 7 days and examined.

Perinatal outcome was compared based on morphological and histopathological features of the placenta. The morphological features like placental weight, cord insertion, attachment, vessels, and knots of the placenta and the shape of the placenta were evaluated. Placental histopathological features like calcification, infarction, syncytial knots, excessive cytotrophoblastic proliferation, fibrinoid necrosis of villi, basement membrane thickening, stromal fibrosis, villous immaturity, villous edema, presence of nucleated red blood cells, and chorangiosis were recorded. Perinatal outcomes like baby weight, NICU admission, neonatal hypoglycemia, Apgar score, respiratory distress, and perinatal deaths were assessed. The data were collected using predesigned proforma and placental dictation template.

Statistical Analysis

Data were analyzed with SPSS version 25.0. Descriptive statistics such as standard deviation for quantitative variables, frequency, and proportions for qualitative variables of the explanatory and outcome variables were calculated. Comparison between two groups was done using Chi-square test and unpaired *t*-test. The *p*-value < 0.05 was considered significant.

Results

The study included 70 women with 35 in each group. Majority of the women were in the age-group of 31–35 years (45.7%) in the case group, followed by 26–30 years (37.1%). Among controls, majority was seen in the age-group of 21–25 years (34.3%), followed by 26–30 years (31.4%) and 31–35 years (31.4%). The mean age in the case and control group was 31.46 + 3.713 years and 28.06 + 4.36 years, respectively.

Among the parity, 60 and 40% were primigravida and multigravida in both the groups. Majority of the study population were in the gestational age of 37–38 weeks in cases (57.1%), whereas in controls, there were 18 (51.4%) and 17 (48.6%) study subjects who belonged to 39–40 weeks and 37–38 weeks, respectively. The mean gestational age of study subjects in the case and control group was 38.68 + 0.63 weeks and 38.69 + 0.58 weeks, respectively.

Among the cases, the majority of the study subjects had babies with a birth weight of 3.51–4 kg (57.1%), followed by 3.1–3.5 kg (31.4%) (Fig. 1). In controls, the majority of the study subjects had babies with a birth weight of 2.5–3 kg (60%), followed by 3.1–3.5 kg (37.1%). The mean birth weight among cases and controls was 3.64 + 0.29 kg and 3.00 + 0.28 kg, respectively. Unpaired *t*-test shows the significant mean difference of birth weight between the groups ($p = 0.001$).

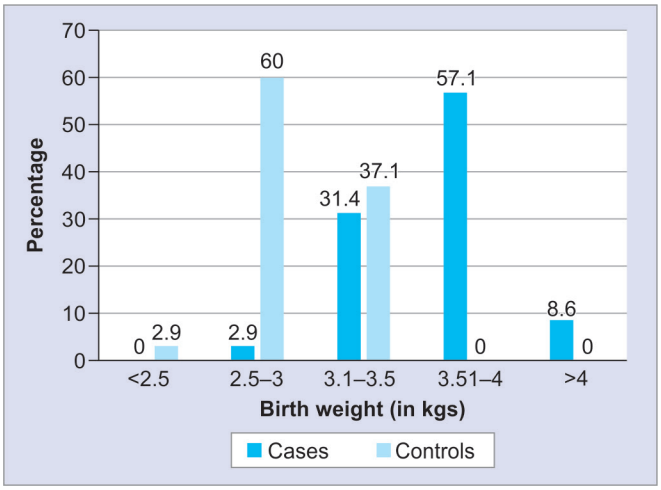

Fig. 1: Birth weight of babies in study population

Table 1: Fetoplacental ratio in study population

Fetoplacental ratio	*Case*	*Control*	*Total*
<1:4.1	2	0	2
	5.7%	0.0%	2.9%
1:4.1–6	30	2	32
	85.7%	5.7%	45.7%
1:6.1–8	3	17	20
	8.6%	48.6%	28.6%
1:>8	0	16	16
	0.0%	45.7%	22.9%
Total	35	35	70

The placental weight was between 501–700 gm and 701–900 gm in 19 (54.3%) and 14 (40%) of the study subjects, respectively, in cases. Among controls, the majority had a placental weight of 300–500 gm (94.3%). The mean placental weight among cases and controls was 719.57 ± 110.8 gm and 380.71 ± 50.59 gm, respectively. Unpaired *t*-test shows the significant mean difference of placental weight between the groups ($p = 0.001$).

The fetoplacental ratio was between 1:4.1 and 6 in the majority of the cases (85.7%) (Table 1). The mean fetoplacental ratio among cases and controls was 5.11 + 0.74 and 7.94 + 1.13, respectively. Unpaired *t*-test shows the significant mean difference of fetoplacental ratio between the groups ($p = 0.001$).

Among cases and controls, most of the study subjects had caesarean (65.7%) and normal (60%) modes of delivery, respectively (Table 2), which was found to be statistically significant ($p = 0.031$). All the study subjects had an APGAR score of more than 7 at 1 and 5 minutes (Table 3). The most common adverse perinatal outcome complications observed were neonatal hypoglycemia (48.6%) and respiratory distress (11.4%) among cases. The NICU admission was found in 13 (37.1%) and 2 (5.7%) study subjects in the case

and control group, respectively, and was statistically significant ($p = 0.003$). There was one perinatal death (2.9%) in both the groups.

Morphological Features of the Placenta

Oval (48.6%) and circular (42.9%) shape of the placenta were most commonly seen in the study group whereas the most common shape in controls were circular (68.6%) and oval (20%) (Table 4).

True and false cord knot were seen in 4 (11.4%) and 2 (5.7%) study subjects in cases, respectively. Cord thickness was increased in cases (54.3%) as compared to controls (2.9%). Hypercoiled cord was observed in 3 (8.6%) and 4 (11.4%) subjects of cases and controls, respectively. Insertion of the cord was marginal (68.6%) and central (28.6%) among cases. In controls, the central type of cord insertion was seen in the majority (77.1%), followed by the marginal type of cord insertion (20%) and was found to be statistically significant ($p = 0.003$).

Table 2: Mode of delivery in study population

Mode of delivery	*Case*	*Control*	*Total*
Caesarean delivery	23	14	37
	65.7%	40.0%	52.9%
Normal vaginal delivery	12	21	33
	34.3a%	60.0%	47.1%
Total	35	35	70

Table 3: APGAR score in study population

Apgar score at 1st minute			
Apgar score at 1st minute	*Case*	*Control*	*Total*
<7	0	0	0
>7	35	35	70
Total	35	35	70
Apgar score at 5th minute			
Apgar score at 5th minute	*Case*	*Control*	*Total*
<7	0	0	0
>7	35	35	70
Total	35	35	70

Histological Features of the Placenta

In the study group, calcification of the placenta, infarction, syncytial knots, and focal extra cytotrophoblastic proliferation and fibrinoid necrosis of villi, stromal fibrosis, immature villous, villous edema, and chorangiosis were observed. In control group, calcification of the placenta, infarction, syncytial knots, fibrinoid necrosis of villi, BMT, stromal fibrosis, immature villous, villous edema, presence of NRBCs, and chorangiosis was observed (Table 5). There was a significant difference found with calcification, fibrinoid necrosis of villi, villous immaturity, and groups ($p < 0.001$).

Abnormal Perinatal Outcome in Relation to Morphological and Histological Changes in Placenta

Perinatal outcome in relation to shape of the placenta in cases showed most study subjects with the oval shape of the placenta had abnormal perinatal outcome 11 (64.7%) whereas, among controls, the abnormal perinatal outcome was observed in study subjects with the circular type of placenta (83.3%).

In cases, most of the study subjects with abnormal perinatal outcomes did not have a true knot (81%). Among controls, none had any cord knot. Among cases, most of the study subjects with abnormal perinatal outcomes had the marginal type of cord insertion 13 (54.2%), followed by central (33.3%) and velamentous type of cord insertion (4.8%). Among controls, most of the study subjects with abnormal perinatal outcomes had the central type of cord insertion (83.3%). However, there was no significant difference found between the type of cord insertion and perinatal outcome both in cases ($p = 0.866$) and controls ($p = 0.65$). A total of 13 (68.4%) study subjects with increased cord thickness had abnormal perinatal outcomes. However, there was no statistically significant difference between perinatal outcome and cord thickness in both cases ($p = 0.26$) and controls ($p = 0.65$) (Table 6).

Study subjects with hypercoiled cord and abnormal perinatal outcome observed were noted in 2 (9.5%) and 1 (16.7%) in cases and

Table 4: Morphological features of placenta in study population

Morphological features of placenta	*Shape*	*Case*	*Control*	*Total*	*Chi-square*	*p-value*
Shape	Circular	15 (42.9%)	24 (68.6%)	39 (55.7%)	5.016	0.08
	Irregular	3 (8.6%)	4 (11.4%)	7 (10%)		
	Oval	17 (48.6%)	7 (20%)	24 (34.3%)		
Cord knot	True	4 (11.40%)	0	4 (5.70%)		
	Absent	29 (82.9%)	35 (100%)	64 (91.4%)		
	False	2 (5.7%)	0	2 (2.9%)		
Cord thickness	Decreased	0	2 (5.7%)	2 (2.9%)		
	Increased	19 (54.3%)	1 (2.9%)	20 (28.6%)		
	Normal	16 (45.7%)	32 (91.4%)	48 (68.6%)		
Coiling of cord	Hypercoiled	3 (8.6%)	4 (11.4%)	7 (10%)	0	1
	Normal	32 (91.4%)	31 (88.6%)	63 (90%)		
Cord insertion	Central	10 (28.6%)	27 (77.1%)	37 (52.9%)	15.677	0.003*
	Marginal	24 (68.6%)	7 (20%)	31 (44.3%)		
	Velamantous	1 (2.9%)	1 (2.9%)	2 (2.9%)		

*$p < 0.05$ considered as significant

Table 5: Histopathological features of placenta in study population

Histological features of placenta	*Case*	*Control*	*Total*	*Chi-square*	*p-value*
Calcification					
Absent	13	26	39	9.785	0.002
	37.1%	74.3%	55.7%		
Present	22	9	31		
	62.9%	25.7%	44.3%		
Infarction					
Absent	25	31	56	3.214	0.073
	71.4%	88.6%	80%		
Present	10	4	14		
	28.6%	11.4%	20%		
Syncytial knots					
Absent	14	14	28	0	1
	40%	40%	40%		
Present	21	21	42		
	60%	60%	60%		
Extra cytotrophoblastic proliferation					
Absent	34	35	69	–	–
	97.1%	100%	98.6%		
Focal	1	0	1		
	2.9%	0	1.4%		
Fibrinoid necrosis of villi					
Absent	13	26	39	9.785	0.002
	37.1%	74.3%	55.7%		
Present	22	9	31		
	62.9%	25.7%	44.3%		
Present	0	4	4		
	0	11.4%	5.7%		
Stromal fibrosis					
Absent	30	23	53	3.807	0.051
	85.7%	65.7%	75.7%		
Present	5	12	17		
	14.3%	34.3%	24.3%		
Villous immaturity					
Immature	22	32	54	6.563	0.01
	62.9%	91.4%	77.1%		
Mature	13	3	16		
	37.1%	8.6%	22.9%		

*($p < 0.05$ considered as significant)

controls, respectively. Study subjects 14 (63.6%) had calcification of placenta with abnormal perinatal outcome.

Among cases and controls, 7 (33.3%) and 1 (16.7%) had infarction of the placenta and abnormal perinatal outcomes. Focal extra cytotrophoblastic proliferation was observed in 1 (7.1%) of cases with the normal perinatal outcome, and it was not statistically significant ($p = 0.83$).

Fibrinoid necrosis of villi with abnormal perinatal outcome was observed in 11 (50%) cases. The Chi-square test showed no statistical significance between fibrinoid necrosis of villi and perinatal outcome in both groups ($p > 0.05$). Subjects had 1 (20%) and 1 (16.7%) stromal fibrosis with abnormal perinatal outcomes in case and control groups, respectively.

Immature villous with abnormal perinatal outcomes was observed in 12 (54.5%) of cases. Whereas, among controls, 6 (100%) study subjects had immature villous with abnormal perinatal outcomes. There was no statistical significance between villous immaturity and perinatal outcome in both groups ($p > 0.05$).

Villous edema with abnormal perinatal outcome was present in 1 (50%) of the study subject among cases. In the case group, 2 (40%) study subjects had chorangiosis had neonatal hypoglycemia whereas in the control group, 2 (40%) and 1 (3.4%) had chorangiosis with respiratory distress and normal perinatal outcome, respectively.

Discussion

The fetus, placenta, and mother form a three-way balance.[14–16]

In the present study, the majority of women were in the age-group of 31–35 years (45.7%) and 21–25 years (34.3%) in the case and control group, respectively. These observations were comparable with the results of the study conducted by Bhanu et al.[17]

In the study, 60 and 40% of study subjects were primigravida and multigravida, respectively. In a study conducted by Sheela et al., 72% were multiparous and 28% were primiparas.[18]

In the study, the mean placental weight among cases and controls was 719.57 and 380.71 gm, respectively. The mean birth weight of infants among cases and controls was 3.64 and 3.00 g, respectively. The mean fetoplacental ratio among cases and controls was 5.11 and 7.94, respectively. Placental weight, birth weight of the neonates and fetoplacental ratio were found to be statistically significant ($p = 0.001$) between the groups.[19,20] In a study conducted by Hertig and Woodling et al., normal placental weight ranged between 450 and 550 gm.[21,22] Teasdale observed that the placental weights in diabetic mothers are more than the nondiabetic mothers.[23] Boyd et al. noted that increased placental growth was the result of a concomitant metabolic or endocrine effect of hyperinsulinemia in diabetes.[24] The placental weight, volume, diameter, central thickness, and number of cotyledons were significantly more in GDM compared to control group in a study conducted by Bhanu et al.[17]

The present study showed that majority of the babies born to diabetic mothers had birth weight more than 4000 g and similar observations were noted in other studies.[25,26] In a study conducted by Bhanu et al., mean birth weight of the newborn babies was 2527 ± 516 gm in the control group and 3040 ± 464 gm in the GDM group which was highly significant ($p < 0.0001$).[17]

In the current study, fetoplacental ratio was increased in the study group and similar observations were found in a study conducted by Hayward et al. and Ahmed study.[17,27,28]

In the present study, histological and morphological features observed in GDM pregnancies were comparable to other studies. Insertion of the cord was marginal (68.6%) and central (28.6%) among cases. In controls, the central type of cord insertion was seen in the majority (77.1%), followed by the marginal type of cord insertion (20%) and was found to be statistically significant ($p = 0.003$). According to a study conducted by Pathak et al., the cord insertion did not show any marked importance between normal and pregnancies complicated by GDM.[29] A study conducted by Saha et al. found that cord insertion was eccentric in GDM.[30]

In the study group, histological features such as calcification of the placenta, infarction, syncytial knots, focal extra cytotrophoblastic proliferation, fibrinoid necrosis of villi, stromal fibrosis, immature

Table 6: Adverse perinatal outcome in association with morphological and histological features of placenta in study population

	Adverse perinatal outcome		
Morphological and histological features of placenta	*Hypoglycemia*	*Respiratory distress*	*Total*
Oval shape placenta	5 (45.5%)	6 (54.5%)	11 (64%)
True cord knot	1 (50%)	1 (50%)	2 (50%)
Marginal insertion of placenta	5 (38.4%)	8 (61.5%)	13 (54.2%)
Increased cord thickness	7 (53.8%)	6 (46.2%)	13 (68.4%)
Hypercoiling of cord	1 (50%)	1 (50%)	2 (66.7%)
Calcification	8 (57.1%)	6 (42.8%)	14 (63.6%)
Infarction	3 (42.8%)	4 (57.1%)	7 (70%)
Syncytial knots	8 (61.5%)	5 (38.5%)	13 (61.9%)
Fibrinoid necrosis of villi	7 (63.6%)	4 (36.3%)	11 (50%)
Stromal fibrosis	0	1 (100%)	1 (20%)
Immature villi	5 (41.6%)	7 (58.3%)	12 (54.5%)
Villous edema	1 (100%)	0	1 (50%)
Chorangiosis	0	2 (100%)	2 (40%)

villous, villous edema, and chorangiosis were found. Which was statistically significant ($p < 0.001$). Similar histological abnormalities were noted in the placenta of GDM mothers in other studies.[30] Memon et al. found that chorangiosis is common in placenta of GDM women.[31] Similar findings were observed in other studies.[32–35]

In the present study, the most common adverse perinatal outcome observed was neonatal hypoglycemia (48.6%) and respiratory distress (11.4%). Furthermore, NICU admission was found in 13 (37.1%) of study subjects in neonates born to GDM mothers, which was statistically significant ($p = 0.003$). There is evidence to suggest that untreated GDM has higher perinatal morbidity. According to Potter, infants born to GDM mothers with glucose intolerance are at an increased risk of morbidity and mortality associated with respiratory distress, large for gestational age, and hypoglycemia.[36]

In the present study, most study subjects with the oval shape of the placenta, marginal type of insertion, increased cord thickness, hypercoiled cord, calcification of placenta, infarction of placenta, focal extra cytotrophoblastic proliferation had abnormal perinatal outcome in 11 (64.7%), 13 (54.2%), 13 (68.4%), 2 (9.5%), 14 (63.6%), 7 (33.3%), 1 (7.1%), respectively. This suggested that morphological changes in placenta in GDM mothers results in perinatal morbidity. Abnormal perinatal outcomes such as NICU admission, hypoglycemia, and respiratory syndrome were observed in abnormal histological changes in placenta in GDM mothers. A total of 11 (50%) with fibrinoid necrosis of villi, 1 (20%) with stromal fibrosis, 12 (54.5%) with immature villi, 1 (50%) with villous edema, and 2 (40%) with chorangiosis had adverse perinatal outcome. Saha et al. observed that the placentae of diabetic mothers were significantly bigger in size, weight, volume, area, thickness, diameter, and circumference. Also, there was significant increase in villous edema, fibrin deposition, calcification, and congestion of blood vessels and they concluded that these placental changes were associated with birth weights of babies and adverse perinatal outcomes.[30]

Khaskhelli et al. studied the morphological changes of placentae in diabetic mothers and found that placentae are larger and heavier as compared to controls. Microscopic examination revealed dilated blood vessels, necrotic and degenerative foci in placentae. They suggested that a good glycemic control is necessary to prevent the perinatal morbidity associated with diabetes.[37]

Limitations of the Study

Sample size included was small. Intrauterine fetal demise as outcome, is not included. Impaired placental function due to GDM in terms of abnormal placental morphology and histopathology may implicate for unexplained fetal demise.

Conclusion

Gestational diabetes mellitus causes an alteration in morphological and histological features of placenta. Placental histomorphological abnormalities result in adverse perinatal outcome. Early diagnosis and treatment of GDM and glycemic control are necessary to reduce the perinatal morbidity and mortality.

Ethical Approval

This study was begun after approval from the Institutional ethical committee of Kasturba Medical College, Mangaluru.

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