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ORIGINAL ARTICLE

Impact of metformin versus dietary interventions on placental morphology in women with gestational diabetes mellitus.

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ABSTRACT… Objective: To evaluate the effects of dietary control and Metformin on placental morphology in women with Gestational Diabetes Mellitus (GDM). **Study Design:** Clinical study. **Setting:** Services Hospital Lahore and Shaikh Zayed Hospital Lahore. **Period:** June 2023 till June 24. **Methods:** A total of 56 women with GDM were enrolled after providing informed consent. Of these, 28 women with blood sugar levels of 140 mg/dl or less were assigned to Group B (2500-3000 kcal/day diet and 30-minute walks three times a week) and were placed on dietary control. The remaining 28 women with blood sugar levels greater than 140 mg/dl were assigned to Group C, where they were managed with a diet and Metformin (500 mg TDS). A control group (Group A) consisted of 25 healthy pregnant women. Placental tissue samples were collected and analyzed for morphology after delivery. **Results:** Group B exhibited heavier placentas with more extensive villous immaturity, charangoids, and syncytial knots. In contrast, Group C showed signs of fibrinoid necrosis and calcification. Significant differences in placental and cord widths were observed in Group B compared to Group A, while only cord width differed significantly in Group C compared to Group A in gross morphology. Light microscopy revealed the presence of charangoids, infarction, and syncytial loops in Group B, along with increased villous maturity. Charangoids and syncytial knots were observed in Group B compared to Group C, with minimal differences noted between Group C and Group A in placental width. **Conclusion:** Metformin demonstrated more favorable effects on placental morphology compared to dietary control, with results comparable to those observed in normal pregnancies.

Key words: Gestational Diabetes Mellitus, Metformin, Placental Morphology.

INTRODUCTION

Gestational diabetes mellitus (GDM) is a disorder characterized by glucose intolerance identified usually during the second trimester of pregnancy, primarily caused by the diabetogenic effects of placental hormones that induce insulin resistance.[1,2] GDM offers significant risks for both mother and fetus, including complications during pregnancy and delivery.[3] Globally, the prevalence of GDM is around 10%[4], whereas in Asian community it is even higher 11.7%.[5] Poor outcomes are further exacerbated by limited healthcare access and inadequate awareness, emphasizing the need for timely diagnosis and effective management.[6]

The placenta is a vital organ in pregnancy, necessary for provision of nutrient and oxygen to the fetus.[7] Structurally, it is a discoid-shaped organ housing villi containing blood vessels and mesenchymal tissues.[8] Maternal metabolic environment has profound influenced on its development and function. In diabetes, including GDM, placental morphology undergoes significant gross and microscopic changes, such as increased stromal density, trophoblastic proliferation and enhanced villous capillary formation, driven primarily by elevated fetal insulin levels.[9]

Hypoxia is a crucial factor contributing to these alterations.[10] As fetal demands increase, oxygen delivery to the placenta becomes inadequate, leading to structural adaptations such as increased placental size, thickness, and glucose deposition. Microscopic examination of GDM

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placentas reveals increase in hypoxic markers and vascular changes, which are associated with adverse outcomes like preterm delivery, macrosomia and stillbirth.[11,12]

The management of GDM involves not only lifestyle modifications but pharmacological interventions too to control the blood glucose level.[13] Insulin has long been the standard therapy that can effectively lower the blood glucose levels. However, it is associated with complications such as maternal weight gain, placental hypoxic alterations, which exacerbate pregnancy risks.[14]

In contrast to the past, when oral anti-diabetic drugs were generally considered teratogenic, Metformin, a category B drug, has recently gained acceptance as a safe and effective alternative. It improves insulin sensitivity, reduces hepatic glucose production, and enhances glucose uptake, thereby achieving euglycemia.[15] Additionally, it improves the endothelial function and reduces the frequency of diabetes related micro and macrovascular complications.

The placental morphology is significantly affected by the diabetes, with hyperglycemia driving profound structural and functional changes. Therefore, this study was designed to see the role of Metformin counteracting these effects and offering a protective influence on placental morphology and its potential as a therapeutic agent in managing GDM, improving both maternal and fetal health.

METHODS

This clinical study was conducted from June 2023 till June 24 at Services Hospital Lahore and Shaikh Zayed Hospital Lahore after ethical approval (Letter No. F-38/NHRC/AQMIN/FRB/205). Fasting blood sugar (FBS) and random blood sugar (RBS) levels of pregnant women enrolled in this clinical trial were monitored during their prenatal visits. Gestational Diabetes Mellitus (GDM) was initially diagnosed using a glucometer and later on confirmed through laboratory testing, with FBS > 110 mg/dl and RBS > 130 mg/dl serving as diagnostic criteria. In high risk patients, like those with prior history of GDM or poor obstetric history, a 55 gm oral glucose challenge test (value RBS 150mg/dl) was used to make the diagnosis, which was later verified by oral glucose tolerance test (OGTT).

Nonprobability sampling method was used to include the participant. A total of 25 pregnant females with no concomitant disorders were selected for control (Group A). Furthermore, 56 GDM females were registered for the research after their fully informed and signed consent. These GDM females were equally divided into two groups, with 28 participants in each: Group B (managed through dietary control) and Group C (administered Metformin in doses ranging from 500 to 1600 mg). The pregnant females of group A and B were motivated to follow the provided diet chart that included 2800 calories intake per day and to walk three times per week for almost 30 minutes. The participant of Group C were administered 500mg Metformin tablets in parallel with stringent food management comprising of 2600 calories intake per day besides 30 minutes of walk for three times in a week. Initially 500 mg of Metformin was administered orally and depending on the glycemic as well as tolerance levels of patient, the dose of drug was gradually increased up to 1600 mg. invariably, these participants were kept under surveillance at the prenatal hospitals until their term. On every visit, all the participant s were examined for their general health (weight gain, temperature, blood pressure and RBS). The pregnant females of Group B & C were especially looked for their blood sugar level and any adverse effects like weight gain, body swelling and infections. Additionally, the Metformin dose of Group C was carefully monitored, all necessary and desirable management was reiterated. 2 participants of group B and 3 from group C were excluded from this clinical trial as these individuals either received insulin as part of their treatment or gave birth somewhere else. Placentas of these females were collected within an hour after birth and were kept in 10% formalin in labeled containers.

Placentas were grossly observed for morphological features (Table-I, II A, II B). To prepare slides for histopathology, samples of

the tissue were taken from center, at 7 o'clock position and at 12 o'clock. Then these samples were treated well with alcohol along with xylene and get embedded in paraffin wax. By using a manual microtome, 4μm thin sections of the embedded tissue were cut. The slides stained with hematoxylin and eosin stain were observed under a light microscope to look for hypoxic changes (Table-III).

For analysis of data SPSS version 22 was used. The results were considered statistically significant with the P value of less than 0.05. The Dependent t test was used to evaluate mean of quantitative variables, however chi square tests was applied to categorical variables for evaluating percentages. The Fisher exact test was applied where cell counts was low in lieu of chi square test.

RESULTS

Groups A showed significant differences in umbilical cord width with Group B (p=0.001) and Groups C (p=0.01) whereas this difference was insignificant between Group B and C. Similarly, statistically significant difference was observed in placental width of Groups B with A and C (p=0.001) whereas this difference was insignificant between Group A and C. All the other parameters differed insignificantly among the three Groups A, B and C (normal control, diet-controlled GDM, and metformin-treated GDM (Table-I, II A & B).

Histologically, villous immaturity, chorangiosis, infarction, and syncytial knots, were observed significantly different among Groups A and B, p= 0.05, 0.04, 0.04, and 0.003, respectively (Table-III). This difference remained statistically insignificant between Groups A and C (Table-III). Statically notable differences were noted in chorangiosis (p= 0.01) and syncytial knot (p= 0.04) when Groups B was compared with C but remained insignificant between all other groups.

Among GDM and non GDM groups significant differences in FBS, RBS, and HbA1c levels were observed (Table-IV). In Group C (metformin-treated), significantly low levels of HbA1c were found at 36 weeks of pregnancy while these levels were significantly high in Group B (diet-controlled GDM) in comparison to the control group (Table-IV).

Sr #	Groups	Characteristics						
		Placental size1(cm)	Placental size2 (cm)	Placental width (cm)	Placental weight (gm)	Cord length (cm)	Cord width (cm)	Cord vessels (n)
1	A	16.34±2.37	13.78±1.95	2.14±0.57	577.6±128.9	41.97±7.87	1.44±0.46	3±0
2	B	15.77±3.31	12.78±2.82	2.74±0.72	598±157.9	42.86±7.5	1.74±0.35	3±0
3	C	15.62±2.38	14.92±2.82	2.26±0.53	656.4±142.6	45.44±7.47	1.69±0.46	3±0
P value								
1	B v/s A	0	0.14	0.001*	0.53	0.61	0.001*	N/A
2	C v/s A	1	0.9	0.61	0.12	0.1	0.01*	N/A
3	B v/s C	0	0.13	0.001*	0.37	0.21	0.17	N/A

Table-I. Comparison of parameters of Placentas within and between groups (N=75; n=25 per group)

Sr #	Groups	Characteristics							
		Placental Consistancy		Placental Shape		Color of Membrane		Cord Insertion	
		Soft	Hard	Discoid	Other	Blue	pale	central	Peripheral
1	A	18(72%)	7(28%)	19 (76%)	6 (24%)	9(36%)	16 (64%)	8 (32%)	17 (68%)
2	B	17(68%)	8(32%)	18 (72%)	7 (28%)	11 (44%)	14 (56%)	9 (36%)	16 (64%)
3	C	16 (64%)	9 (36%)	16(64%)	9(36%)	11 (44%)	14 (56%)	11 (44%)	14 (56%)
	p Value								
4	B v/s A	0.76		>0.99		0.38		0.76	
5	C v/s A	0.77		0.53		0.39		0.38	
6	B v/s C	>0.99		0.52		>0.99		0.6	

Table-II (A). Comparison of gross parameters of placentas within and between groups (N=75; n=25 per group)

Sr #	Groups	Characteristics					
		Cord Knots		Cord Stricture		Cord Hematoma	
		P	A	P	A	P	A
1	A	2 (8%)	23 (92%)	1(4%)	24 (96%)	9 (36%)	16 (64%)
2	B	7 (28%)	18 (72%)	7 (28%)	18 (72%)	5 (20%)	20(80%)
3	C	4 (16%)	21 (84%)	6 (24%)	19 (76%)	10(40%)	15 (60%)
	p Value						
4	B v/s A	0.26		0.08		0.4	
5	C v/s A	>0.99		0.09		0.75	
6	B v/s C	0.48		>0.99		0.15	

Table-II (B). Comparison of gross parameters of Placentas within and between groups (N=75; n=25 per group)

Sr #	Groups	Characteristics											
		Villous Immaturity		Chorangiosis		Infarction		Villous fibrinoid necrosis		Calcification		Syncitial Knot	
		P	A	P	A	P	A	P	A	P	A	P	A
1	A	5 (20%)	20 (80%)	7 (28%)	18 (72%)	8 (32%)	16 (64%)	19 (76%)	6 (24%)	10 (40%)	15 (60%)	4 (16%)	21 (84%)
2	B	11 (44%)	14 (56%)	14 (56%)	11 (44%)	15 (60%)	10 (40%)	20 (80%)	5 (20%)	12 (36%)	13 (62%)	14 (56%)	11 (44%)
3	C	6 (24%)	19 (76%)	5 (20%)	20 (80%)	9 (36%)	16 (64%)	22 (88%)	3 (12%)	16 (64%)	9 (36%)	7 (28%)	18 (72%)
	p Value												
4	B v/s A	0.05*		0.04*		0.04*		0.73		0.74		0.003*	
5	C v/s A	>0.9		0.73		0.52		0.16		0.26		0.3	
6	B v/s C	0.12		0.01*		0.16		0.25		0.15		0.04*	

Table-III. Comparison of microscopic parameters of placentas within and between groups (N=75; n=25 per group)

		Maternal Characteristics					
		Age (years)	Weight (kg)	FBS (mg/dl)	RBS (mg/dl)	HbAIC 1	HbAIC 2
Sr #	Groups	Mean ± S.D	Mean ± S.D	Mean ± S.D	Mean ± S.D	%	%
1	A	29.1±4.47	73.74±9.87	73.24±9.35	128.8±36.8	4.74	4.98
2	B	30.07±3.18	78.64±6.94	90.9±16.7	149.72±37.9	5.43	5.84
3	C	29.86±3.51	78.9±7.6	105.4±13.12	172±38.44	5.29	5.44
	p-value						
1	B v/s A	0.32	0.058	<0.001*	0.02*	<0.001*	<0.001*
2	C v/s A	0.48	0.11	<0.001*	0.00*	0.001*	0.00*
3	B v/s C	0.74	0.76	<0.001*	0.04*	0.683	0.01*

Table-IV. Comparison of maternal parameters within and between groups (N=75; n=25 per group

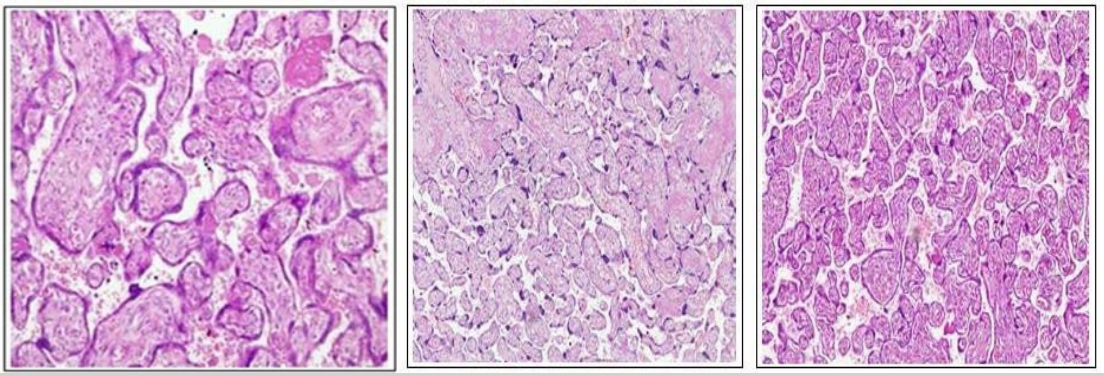

Figure-1. Histology of placenta; A; normal control B; Diet control, C; Metformin-treated

DISCUSSION

Gestational diabetes mellitus (GDM) is linked with structural and functional alterations in the placenta, the key tissue facilitating communication between the mother and the developing fetus.[3,9] These changes in the placental morphology can be seen at both macroscopic and microscopic levels which can lead to fetal hypoxia, illness and even stillbirth. Hypoxia-induced placental changes in GDM include ischemia, villous immaturity and areas of villous fibrosis and necrosis. Other observed abnormalities include chorangiosis, the formation of syncytial knots and calcification.[9] Variations from normal placental morphology in GDM cases are marked by villous immaturity, infarction, chorangiosis, and an increase in syncytial knots. Our findings of edema, fibrosis, ischemic alterations, increased syncytial knots and fibrinoid necrosis observed in placentae from GDM cases managed with diet alone are consistent with the study conducted by Verma et al. (2010).[16] In contrast, placentae treated with metformin exhibited no significant differences in gross morphology compared to normal controls, except for cord width. Other gross and microscopic markers of hypoxia remained insignificantly different across groups, suggesting near to normal control cases.[17]

However, light microscopic analysis of metformin-treated placentae exhibited significantly reduced thickness, chorangiosis, and syncytial knot formation compared to diet-managed cases. Additionally, the remaining microscopic indicators of hypoxia were statistically significantly lower in the metformin group than in the diet control group.[17] These finding differ from a case report presented by Campbell (2009) who observed villous dysmaturity, chorangiosis, and villous fibrosis in GDM patient with preeclampsia treated with Metformin.[18] However, it remains unclear whether these placental changes were solely attributable to GDM or the combined effects of GDM and hypertension.[18] This could be due to the fact reported by numerous in-vivo and in-vitro studies that Metformin primarily reduces gluconeogenesis by inhibiting lactate uptake in adipocytes. Another key mechanism observed is a decrease in actin polymerization in hepatocytes, leading to reduced glucose production from glycogen in liver cells. Additionally, Metformin interferes with the mitochondrial respiratory chain in hepatocytes, affecting cellular oxidation processes. Metformin significantly lowers HbA1c levels. As illustrated in Figure-1, Metformin-treated placentae may play a role in its beneficial effects for cases with GDM.[19] The multifaceted actions of Metformin on diabetic cells likely explain its positive impact on placental function compared to diet management alone.

CONCLUSION

In conclusion, this study demonstrates that Metformin positively influenced placental morphology and outcomes in Gestational Diabetes Mellitus (GDM). It reduces gluconeogenesis, lowers HbA1c and improves placental structure by reducing hypoxia markers, offering favorable benefits over diet management alone. These findings highlight Metformin's potential as an effective treatment for GDM, though further research is needed to explore its long-term effects on maternal and fetal outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Amber Salman:** Conceived the idea, designed the study, sample collection, all experimental work, recorded all observation, compiled results and wrote first draft of manuscript
2	**Momna Riaz:** Interpret the data and helped in compilation of results, revised and finalized the manuscript.
3	**Shireen Hamid:** Helped in sample collection and experimental work.
4	**Sadia Alam:** Helped in sample collection and experimental work.
5	**Faiza Hanif:** Helped in experimental work and in observation.
6	**Sana Fatima:** Helped in sample collection and experimental work.