CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1406304

Available online at: http://www.iajps.com Research Article

A CLINICAL TRIAL ON THE EFFECTIVENESS OF METFORMIN, EXERCISE & DIET ON GESTATIONAL DIABETES MELLITUS (GDM) PATIENT'S PLACENTAL MORPHOLOGY

[1]Dr.Muhammad Sibtain Iqbal, [1]Dr. Muhammad Zeeshan Nawaz, [2]Dr. Jaweria Nazir

[1]Allama Iqbal Medical College Lahore

[2]Punjab Medical College, Faisalabad

Abstract:

Objective: *Our research objective was to assess the Metformin and diet control effects in placental morphology during GDM (Gestational Diabetes Mellitus).*

Methods: *Our research was carried out on sixty patients at Mayo Hospital, Lahore (March 2016 to February 2017). We enrolled sixty GDM cases after taking their written approval for participation. As per the guidelines of WHO groups were made like that in A group thirty cases having level of blood sugar (< 130 mg/dl) and B group patients were included with an intake of (2000 – 2500) Kilo calorie per day with thrice thirty-minute walk were included having level of blood sugar (>130 mg/dl). Group C was given Metformin tablets during the diet period. Group A also held twenty-five normal cases who were pregnant as controls. We evaluated placental after delivery.*

Results: *Heavy placentae having ample chorangiosis, villous immaturity and syncytial knots in calcification and group Band fibrinoid necrosis were seen in C group. In "B Vs A" and "C Vs A" respectively we observed "cord and placental width" and "cord width" in the outcomes of gross morphology. "B Vs A" group was seen with chorangiosis, villous immaturity, syncytial knots and infarction in light microscopy; similarly, in group "B Vs C" chorangiosis, placental width and syncytial knots with significant outcomes; whereas, in group "C Vs A" non-significant outcomes were observed.*

Conclusion: *Beneficial outcomes were received with the use of Metformin on the placental morphology which can be compared with the outcomes of normal controls contrary to the cases on diet.*

Keywords: *Diet, Gestational Diabetes Mellitus (GDM), Exercise, Placenta, Metformin, Microscopic Morphology and Gross Morphology.*

*** Corresponding author:**

Dr.Muhammad Sibtain Iqbal,

Allama Iqbal Medical College,

Lahore

QR code

Please cite this article in press Muhammad Sibtain Iqbal et al., ***A Clinical Trial on the Effectiveness of Metformin, Exercise & Diet On Gestational Diabetes Mellitus (GDM) Patient's Placental Morphology.,*** *Indo Am. J. P. Sci, 2018; 05(08).*

INTRODUCTION:

GDM is an intolerance of glucose which can be seen in pregnant cases during 2nd trimester. Certain maternal and fetal consequences are associated with it with placental hormones diabetogenic effects [1]. GDM is prevalent all over the world and in Pakistan with the respective proportion of (3% – 9%) and (3% – 3.45%), worse outcomes can be linked with the scarcity of healthcare facilities and awareness [2].

Maturing fetus takes its nutritional intake from Placenta. Its structure is discoid shaped which has very minute vessels of blood, the membrane covering and mesenchymal supportive tissue. Central organ structure is disturbed by the influence of maternal atmosphere [3]. GDM alterations include an increase in trophoblasts proliferative rate, placental tissue's villous capillaries and stromal cells, which is caused because of the endogenous fetal insulin enhanced effects. Hypoxia is also considered as a major feature which results into weight gain, thickness and diameter of placenta [4]. Placenta tissue also accumulates excessive glucose [5]. Pathophysiology is also related to the alteration in the placental vascular endothelial factor of growth, insulin, IGF I, II and IGF. These factors also regulate the development of placenta [6]. Placenta weight and size ultimately increased. Moreover, with the help of microscopic assessment, there is a notable increase in the placentae of GDM cases [7].

Pharmaceutical management, exercise and diet are mandatory for the patient's management. Insulin intervention is gold standard but still, there are chances of stillbirth, term death, macrocosmic babies and maternal weight increase. Insulin also causes hypoxic alteration in placenta [8]. Previously oral anti-diabetic medicines were considered as teratogenic [8]. Presently, Metformin is considered as safe and effective as it improves insulin resistance, produces euglycemia, restricts intracellular production of glucose and enhances uptake of glucose. Moreover, capillary function is also improved and hyperglycemia is reduced [9]. Metformin has no side effects in the course of pregnancy [10]. Our research objective was to assesses the Metformin and diet control effects in placental morphology during GDM (Gestational Diabetes Mellitus).

METHODS:

Our research was carried out on sixty patients at Mayo Hospital, Lahore (March 2016 to February 2017). We enrolled sixty GDM cases after taking their written approval for participation. As per the guidelines of WHO groups were made like that in A group thirty cases having level of blood sugar (< 130 mg/dl) and B group patients were included with an intake of (2000 – 2500) Kilo calorie per day with thrice thirty-minute walk were included having level of blood sugar (>130 mg/dl). Group C was given Metformin tablets during diet period. Group A also held twenty-five normal cases who were pregnant as controls. We evaluated placental after delivery. Patients with higher risks having obstetrical history or GDM were diagnosed through oral glucose (50 G) test with RBS value (≥ 140) mg/dl, it was confirmed through OGTT [11]. Regular antenatal follow-up was carried out. We documented level of blood sugar, side effects and also assured proper treatment. We collected placenta from thirty to forty minutes during delivery and it was preserved in formalin (10%). Tissue sections were managed with xylene and alcohol after the paraffin wax was used to prepare blocks. Slides were four millimetres thin and stained with eosin and hematoxylin, after drying staining was carried out with trichome and PAS. Visualization was carry out through a light microscope and placental hypoxic features were also observed as shown in Table – III [12]. SPSS software was used for statistical data analysis.

RESULTS:

Detailed outcomes analysis of intergroup maternal features, gross and microscopic morphology have been carried out in the given tabular data with graphical representation about Placental and Cord weight, width and size.

Table – I: Gross Morphology within and between groups N=75 (n=25)

Group	Placental size1 (cm)		Placental size2 (cm)		Placental width (cm)		Placental weight (gm)		Cord length (cm)		Cord width (cm)		Cord vessels (n)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
A	16.32	2.34	14	1.91	2.12	0.58	567.6	139	41.98	7.88	1.34	0.45	3	0
B	15.06	2.41	12.88	2.92	2.84	0.62	590	148	42.96	7.4	1.84	0.34	3	0
C	15.88	2.58	13.92	2.72	2.2	0.5	626.4	123	45.54	7.37	1.68	0.45	3	0
P-value														
B Vs A	0.06		0.12		0		0.58		0.65		0		NA	
C Vs A	0.5		0.9		0.6		0.119		0.1		0.01		NA	
B Vs C	0.25		0.12		0.001		0.34		0.22		0.16		NA	

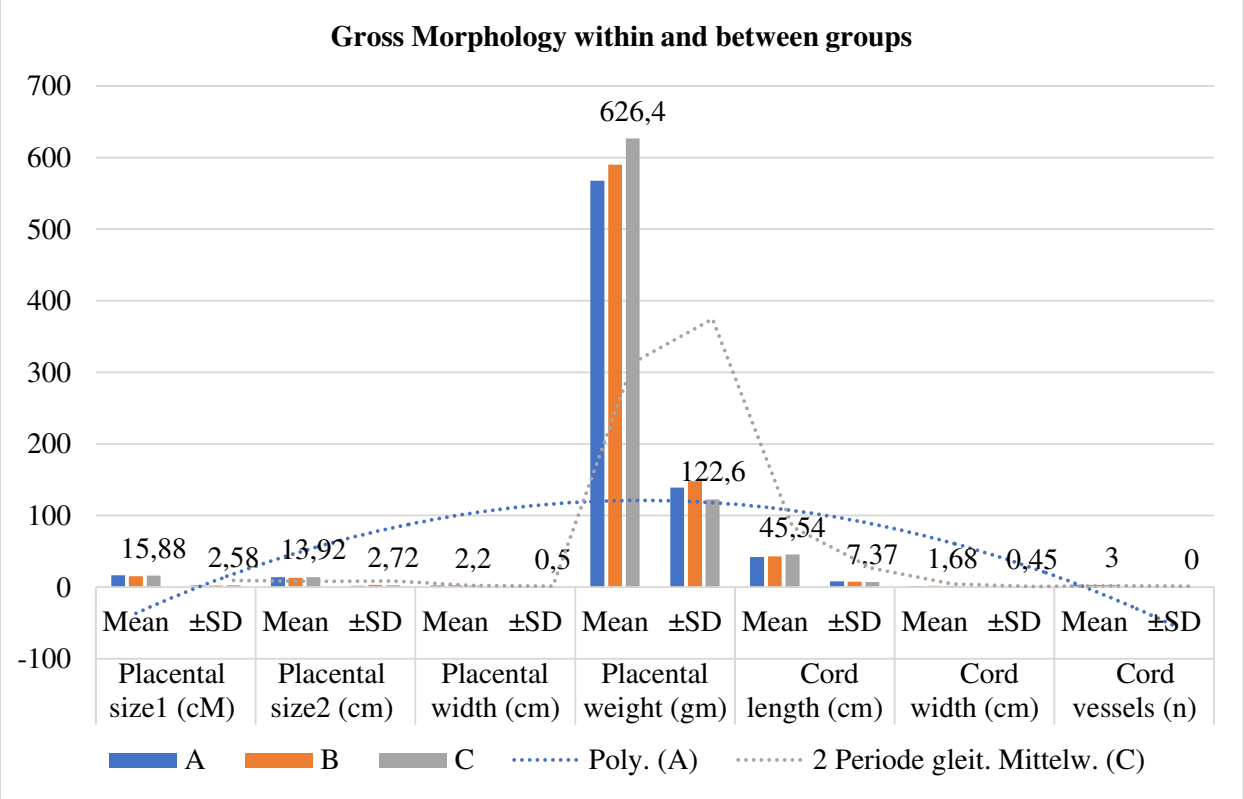


Table – II: Gross morphology within and between groups N=75(n=25)

Group			A	B	C	P-values	Group B Vs A	Group C Vs A	Group B Vs C
Placental consistency	Soft	No	17	16	16		0.76	0.76	> 0.99
		%	68	64	64				
	Hard	No	8	9	9				
		%	32	36	36				
Placental shape	Discoid	No	19	19	17		> 0.99	0.52	0.52
		%	76	76	68				
	Other	No	6	6	8				
		%	24	24	32				
Color of membrane	Blue	No	8	11	11		0.38	0.38	> 0.99
		%	32	44	44				
	Pale	No	17	14	14				
		%	68	56	56				
Cord insertion	Central	No	7	8	10		0.75	0.37	0.5
		%	28	32	40				
	Peripheral	No	18	17	15				
		%	72	68	60				
Cord knots	P	No	2	6	3		0.24	> 0.99	0.46
		%	8	24	12				
	A	No	23	19	22				
		%	92	76	88				
Cord strictures	P	No	1	6	6		0.09	0.09	> 0.99
		%	4	24	24				
	A	No	24	19	19				
		%	96	76	76				
Cord hematoma	P	No	9	5	10		0.2	0.77	0.12
		%	36	20	40				
	A	No	16	20	15				
		%	64	80	16				

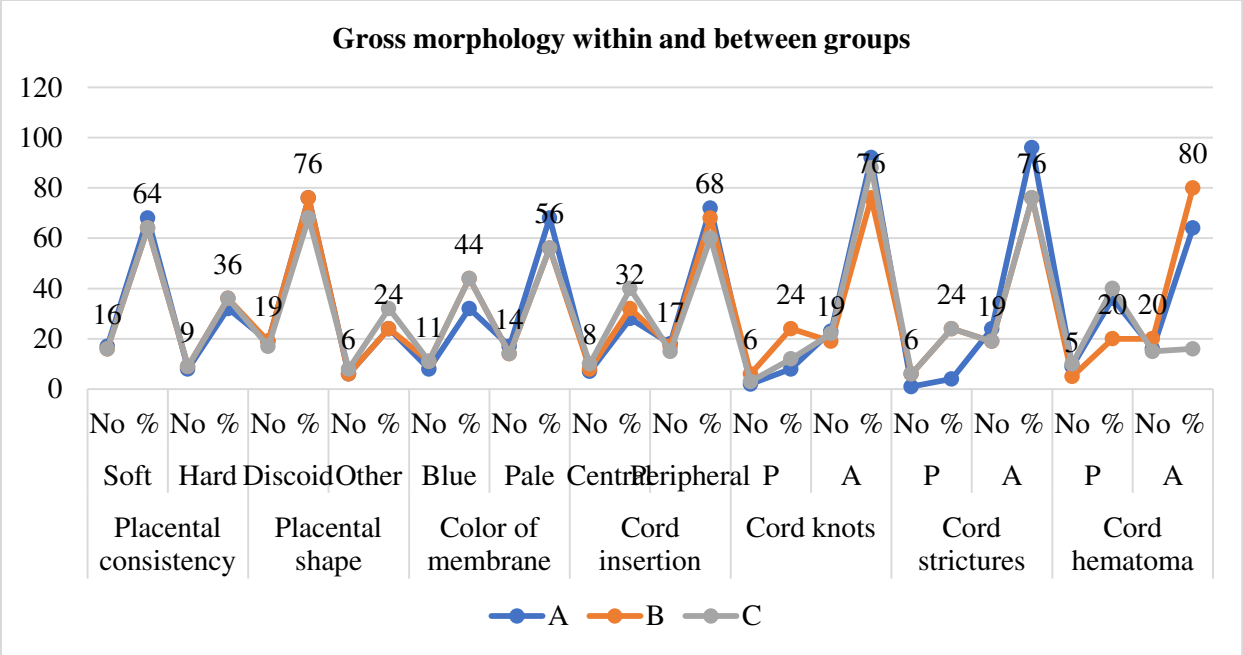


Table – III: Microscopic morphology within and between groups N=75 (n=25)

Group			A	B	C	P-value	B Vs A	C Vs A	B Vs C
Villous immaturity	**P**	No	4	10	5		0.05	> 0.9	0.12
		%	16	40	20				
	A	No	21	15	20				
		%	64	60	80				
Chorangiosis	**P**	No	6	13	5		0.04	0.73	0.01
		%	24	52	20				
	A	No	19	12	20				
		%	76	48	80				
Infarction	**P**	No	7	14	9		0.04	0.54	0.15
		%	28	56	36				
	A	No	18	11	16				
		%	72	44	64				
Villous fibroid necrosis	**P**	No	18	19	22		0.74	0.15	0.24
		%	72	76	88				
	A	No	7	6	3				
		%	28	24	12				
Calcification	**P**	No	11	10	15		0.77	0.25	0.15
		%	44	40	60				
	A	No	14	15	10				
		%	56	60	40				
Syncytial Knots	**P**	No	4	14	7		0.003	0.3	0.04
		%	16	56	28				
	A	No	21	11	18				
		%	84	44	72				

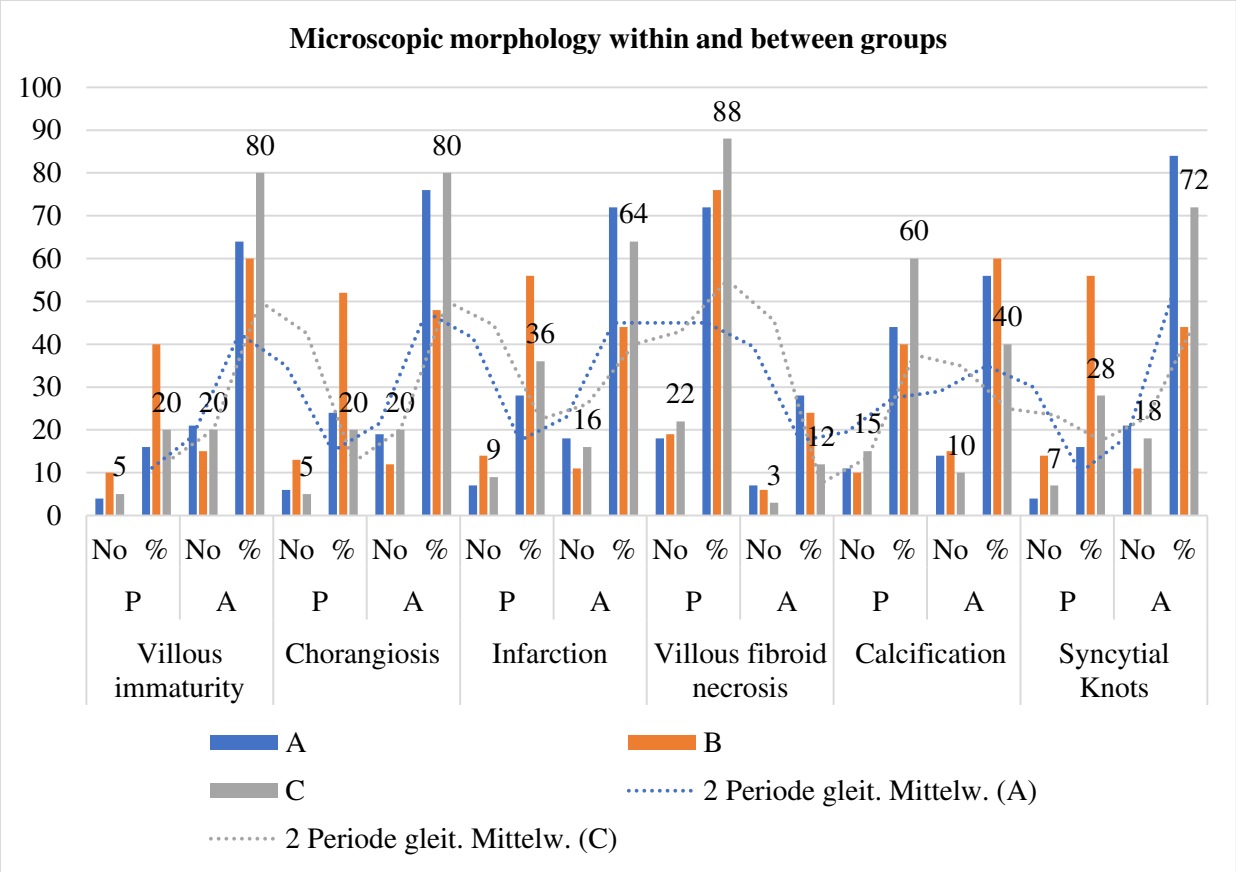
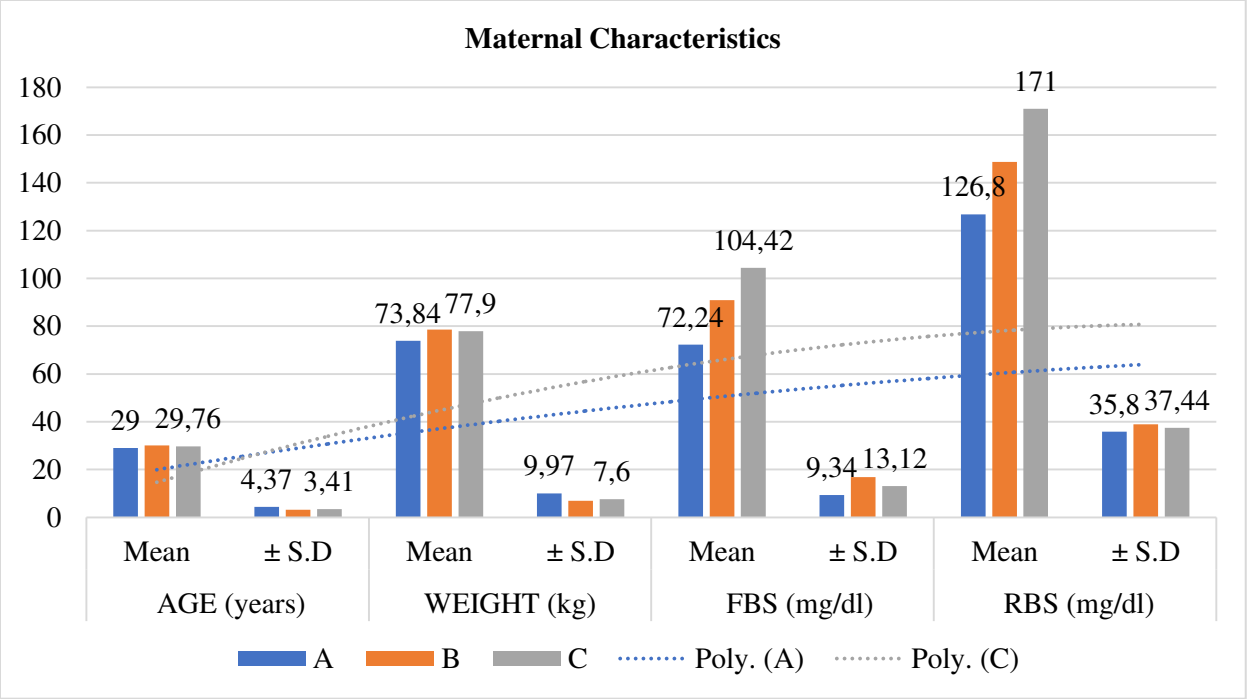
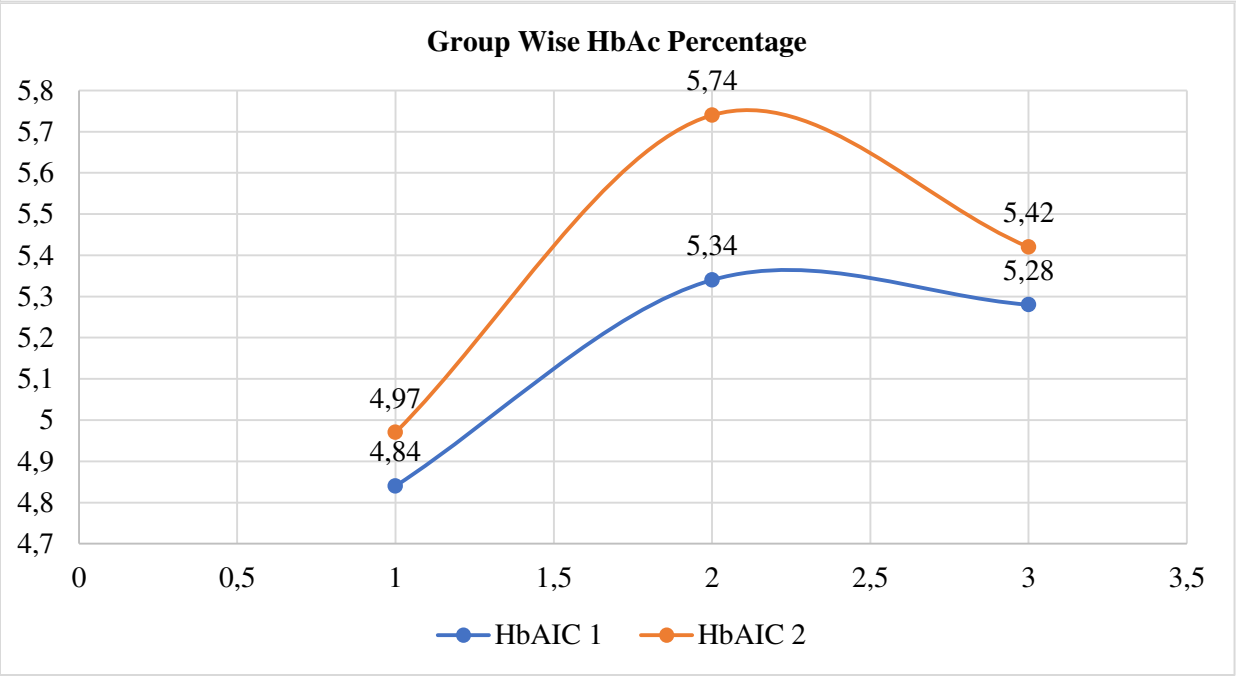


Table – IV: Maternal characteristics group (B v/s A) (C v/s A) & (B v/s C) N=75

Group	AGE (years)		WEIGHT (kg)		FBS (mg/dl)		RBS (mg/dl)		HbA_1C 1	HbA_1C 2
	Mean	± S.D	Mean	± S.D	Mean	± S.D	Mean	± S.D	Percentage	Percentage
A	29	4.37	73.84	9.97	72.24	9.34	126.8	35.8	4.84	4.97
B	30.08	3.16	78.54	6.93	90.9	16.8	148.7	38.9	5.34	5.74
C	29.76	3.41	77.9	7.6	104.4	13.12	171	37.44	5.28	5.42
P-value										
B Vs A	0.32		0.059		0.00		0.03		0.00	0.00
C Vs A	0.49		0.11		0.00		0.00		0.00	0.00
B Vs C	0.75		0.75		0.00		0.04		0.69	0.01





Heavy placentae having ample chorangiosis, villous immaturity and syncytial knots in calcification and group Band fibrinoid necrosis were seen in C group. In "B Vs A" and "C Vs A" respectively we observed "cord and placental width" and "cord width" in the outcomes of gross morphology. "B Vs A" group was seen with chorangiosis, villous immaturity, syncytial knots and infarction in light microscopy; similarly, in group "B Vs C" chorangiosis, placental width and syncytial knots with significant outcomes; whereas, in group "C Vs A" non-significant outcomes were observed.

DISCUSSION:

GDM is linked with still birth, term death, macrocosmic babies and maternal weight increase and hypoxic alteration in placenta [13]. Microscopic and gross placental morphological alterations, growing fetus and maternal communicating tissues can be observed. Major alterations during placental morphology because of hypoxia are ischemia,

immature villi, necrotic patches and villious fibrotic. Other signs of the altered placenta are Chorangiosis, syncytial knots, calcification and trophoblastic nuclear formation [14]. Maternal and fetal mortality also increases with the increase in placental tissues hypoxic features, and proper management can reduce these risks [15]. We compared controls with two groups of Metformin and diet. There was no visible variation in the placentae of normal morphology and diet groups due to strict control of level of glucose; whereas, Leo found minor heavier placental (590 ± 147.9 grams) change in diet group than normal controls (567.6 ± 138.9 grams) [16]. According to Kucuk increased placental was found in diet group than normal having respectively (694.8 ± 152.1) and (610.2 ± 116.6) grams [17].

There is an involvement of various factors in the placental weight such as diet, insulin, IGF I & II and IGF, which make cord and placenta thick [18]. Normal placenta was different from diet controlled with various outcomes as villous immaturity, chorangiosis, infarction and formation of syncytial knots. Verma observed diet-controlled GDM cases placental outcomes were observed with ischemic & fibrosis changes, increased syncytial knots, fibrinoid necrosis and mild oedema which can be compared to our outcomes [19]. Placenta treated with Metformin was observed with reduced thickness, formation of syncytial knot and chorangiosis than diet-controlled placenta as observed through light microscopic outcomes. All other hypoxic characteristics were also decreased in Metformin than diet group.

Campbell observed in GDM patients having preeclampsia on Metformin were observed with placental morphology and intrauterine death with changes like villous dysmaturity, villi fibrosis and chorioamnionitis [20]. Numerous other studies have also shown anti-diabetic effects of Metformin by decreasing gluconeogenesis by lactate uptake inhibition in adipocytes. ATP concentration reduction in hepatocytes is also among related factors which decrease the production of glucose. It also disturbs respiratory chain oxidation in liver cell mitochondria at cellular level [21]. HbAIC is also reduced through Metformin. Metformin is a multifunctional drug which is also a reason for its effectiveness on placenta than diet.

CONCLUSION:

It can be concluded that diet controlled placental morphology and Metformin managed placenta; morphology of Metformin was close to normal placenta; whereas, histological changes were observed in diet-controlled placenta. Larger populations managed with Metformin on the basis of immuno-histochemistry evaluation and electronic microscopy can be helpful for authors in many ways. Beneficial outcomes were received with the use of Metformin on the placental morphology which can be compared with the outcomes of normal controls contrary to the cases on diet and exercise.

REFERENCES:

1. Leo TT, Lee CP, Wong WM. Placental weight to birth weight ratio is increased in mild gestational glucose intolerance. Placenta.1997;18:227-230.
2. Kuck M, Doymaz F. Placental weight and placental weight to-birth weight ratio is increased in diet- and exercise treated gestational diabetes mellitus subjects but not in subjects with one abnormal value on 100-g oral glucose tolerance test, Journal of Diabetes and its Complications. J Diabetes Complications. 2009;23(1):25-31.
3. Hiden U, Glitzner E, Hartmann M, Desove G. Insulin and IGF system in human placenta of normal and diabetic pregnancies. J Anat. 2009;215(1):60-68.
4. Verma R, Mishra S, Kaul JM. Cellular changes in the placenta in pregnancies complicated with diabetes. Int J Morphol. 2010;28(1):259-264.
5. Cambell IW, Duncan C, Urquhart R, Evans M. Placental dysfunction and still birth in gestational diabetes mellitus. Br J Diabetes Vascular Dis. 2009;9(1):38-40.
6. Kirpichnikov D, Macferlarne SL, Sowers JR. Metformin: An update. Ann Intern Med. 2002; 137:25-33.
7. Akhter F, Anjuman Bano ML, Ferdaus R. Effects of gestational diabetes mellitus on gross morphological structure of preterm placenta. Bangladesh J Anat. 2010;8(1):34-38.
8. Tewari V, Tewari A, Bhardwaj N. Histological and histochemical changes in placenta of diabetic pregnant females and its comparison with normal placenta. Asian Pacific J Tropical Dis. 2011; 1:1-4.
9. Gutzin SJ, Kozer E, Magee LA, Feig DS, Koren G, The safety of oral hypoglycemic agents in first trimester of pregnancy: A meta-analysis. Can J Clini Pharm. 2003; 10(4):179-183.
10. Singh AK, Singh R, Metformin in gestational diabetes: An emerging contender, Indian. J Endocr Metab.2015;19(2):236-244.
11. Gandhi P, Bustani R, Madhuvrata P, Farrell T. Introduction of metformin for Gestational diabetes mellitus in clinical practice: Has it had an impact. Euro J Obstet Gynae Rep Bio.2012;160(2):147-150.

12. Perkins JM, Dunn JP, Jagasia SM. Perspectives in Gestational Diabetes Mellitus; A review of screening, Diagnosis and Treatment. Clin Diabetics. 2007;25(2):57-62.
13. Benirschke K, Lewis SH, Placenta in: Stacey E(ed), Histology of pathologists, Lippincott and Williams Inc, New York, pp.1096-1099.
14. Madazal R, Tuten A, Calary Z, Uzun H, Uludag S, Ocak V. Incidence of placental abnormalities, maternal and cord plasma malondialdehyde and vascular endothelial growth factors levels in women with gestational diabetes mellitus and non-diabetic controls. Gynecol Obstet Invest.2008;65(4):227-232.
15. Ghidin A, Salafia CM. Histological placental lesions in women with recurrent preterm delivery. Acta Obstet Gynacol Scand. 2005;84 (6):547-540.
16. Spaight C, Gross J, Horch A, Pudder JJ. Gestational Diabetes Mellitus. Endocr Dev. 2016;31: 163-178. doi:10.1159/000434913
17. Territi K, Ekbald U, Vehlberg T, Ronnemaa T. Comparison of metformin and insulin in the treatment of gestational diabetes: A retrospective; case control study. Rev Diabet Stud. 2008;5(2):95-101.
18. Ben Haroush A, Yogev V, Hod M. Epidemiology of gestational diabetes mellitus and its association with Type2 diabetes. Diabetic Med. 2003; 21:103-113.
19. Hiden U, Glitzner E, Hartmann M, Desove G. Insulin and IGF system in human placenta of normal and diabetic pregnancies. J Anat. 2009;215(1):60-68.
20. Cowet RM. The infant of diabetic mother. Neo Rev.2002;3(9):173-189.
21. Janson T, Certin I, Powell TL, Desoye G, Radaelli T, Ericsson A, et al. Placental transport and metabolism in fetal overgrowth, a workshop report. Placenta. 2006; 27: 109-113.doi: 10.1016/j.placenta.2006.10.017.