INTRODUCTION

“Gestational Diabetes is defined as any degree of glucose intolerance with onset or first recognition during the pregnancy”. In pregnancy insulin sensitivity decreases, thereby pregnant females are at greater risk to have deranged blood glucose levels and subsequently some of them develop gestational diabetes mellitus (GDM). This occurs in 3-9% of pregnancies and is growing in prevalence1,2 WHO criteria is the most preferred criteria for GDM diagnosis, followed by Oral Glucose Tolerance Test for confirmation.3 If left untreated, GDM has effects on placenta, fetus and mother. According to modified Pedersen hypothesis, when hyperglycemic blood is carried to the fetus thru placenta, fetal pancreas releases large amounts of insulin leading to fetal hyper-insulinemia. This increased endogenous insulin acts as growth factors for fetus leading to storage of excessive amounts of glucose as glycogen and fat in the fetal body making these babies larger than the normal. Due to large sized fetus oxygen demand increases causing hypoxic condition in utero. This has direct and indirect effects on placenta leading to structural and functional alterations.4,5 Human placenta has a complex vascular system that allows exchange of different materials between fetal and maternal blood without actual mixing of

ABSTRACT

Objective: To observe the effects of exogenous insulin on placental, fetal and maternal outcomes in Gestational Diabetes Mellitus (GDM).

Methods: After screening and diagnoses(WHO criteria) 30 GDM patients(Group A) were kept on diet control and 39 GDM (Group B) who did not achieve glycemic targets were added subcutaneous insulin. Term placental weight, size, shape, consistency, fibrinoid necrosis, hemorrhages, cord color, length of the cord, completeness of membranes, weight and condition of baby and mode of delivery were assessed in 25 patients in each group.

Result: Placental weight, cord width and baby weight were found to be more in Group B, than Group A and were statistically significant with p value 0.005, 0.02 and 0.003 respectively. Ten patients in group A and 17 patients in group B had cesarean deliveries.

Conclusion: Exogenous insulin produces significant effects on the placental, fetal and maternal outcomes in patients with GDM

KEY WORDS: Gestational diabetes, Insulin, Placenta, Gross morphology, Fetal outcome, Maternal outcome.

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the two. The successful development, growth and maturity of feto-placental vessels are important for normal fetal growth and survival.\textsuperscript{6,7} Complications of GDM encountered in fetus are increased birth weight, birth trauma, respiratory distress syndrome (RDS), hypoglycemia, hyperbilirubinemia, polycythemia, hypocalcemia, major congenital anomalies, intrauterine deaths at term and even still births where as in mother there are more chances of excessive weight gain, pre-eclampsia, cesarean sections and development of Type 2 diabetes in subsequent years.\textsuperscript{8}

Blood glucose levels in the mother can be controlled by nutritional therapy (diet control) and exercise but in uncontrolled cases, where target glycemic levels could not be achieved medication are also required. Subcutaneous insulin is the traditional therapy and gold standard under such circumstances.\textsuperscript{9} Even with this pharmacotherapy, fetal and maternal morbidity and mortality are well documented in the literature.\textsuperscript{10} Morphological study of placenta which occupies central position between the mother and fetus might be helpful in elucidating these adverse fetal and maternal outcomes in gestational diabetes. With this background present study was designed to observe the effect of exogenous insulin on the gross morphology of placenta, fetal and maternal outcomes in gestational diabetics in our setting.

**METHODS**

This non-randomized clinical trial was conducted at Lyari General Hospital and Mamji Hospital Karachi in a period of 9 months. The study was approved by Ethical Review Board (ERB) and Institutional Review Board (IRB) of Dow University of Health Sciences. Screening of high risk patients (High risks for GDM include patients with the history of GDM in previous pregnancies, females having babies large for gestational ages in previous pregnancies, history of still births, preterm delivery, recurrent abortions in previous pregnancies and females with strong family history of diabetes)\textsuperscript{11} was done in antenatal diabetic clinics and diagnosis was established according to WHO criteria. A written informed consent was taken from all the participants before enrollment in the trial. Initial screening was done with 50 gm oral glucose challenge test (OGCT, positive if ≥140mg/dl) in antenatal clinics, followed by 75 grams, 2 hours oral glucose tolerance test (OGTT) for confirmation. At least two abnormal readings, FBS > 95, 1 hr ≥ 180, 2 hr 155 mg/dl is diagnostic for GDM.\textsuperscript{12} Women between 18-45 years of age, diagnosed as GDM, having singleton pregnancy with no other co morbid were enrolled. Maternal demographic details (weight and age), FBS and RBS were noted in the start of the study on predesigned data form. These patients were kept on diet control for a week then their RBS was checked. Thirty patients with RBS between 126-129mg/dl were kept in Group A with the nutritional (diet control) and exercise therapy. They were advised and taught to take 2000-2500 kcal/day and special diet charts were provided. They were also advised to do 30 minutes of mild exercise (walk) thrice weekly. In Group B, thirty nine diagnosed GDMs with RBS more than 200 mg/dl were enrolled. They were given s/c insulin therapy (2/3 NPH + 1/3regular) according to the weight of the patient (0.8 units/kg/day in 2\textsuperscript{nd} trimester and 0.9units/kg/day in 3\textsuperscript{rd} trimester).\textsuperscript{13} The total dose of the drug was divided so as to take 2/3 of the drug in the morning and 1/3 drug in the evening. They were taught regular glucose monitoring and later the dose of the drug was adjusted accordingly with the targeted glucose level of FBS <100mg/dl and post prandial glucose ≤ 126mg/dl. The patients were followed in the antenatal clinics twice a month up till 36 weeks of pregnancy and then weekly till term. After childbirth the placentae were collected from twenty five patients in each group (A & B) who completed the study and delivered babies in the above mentioned hospitals. Within 30-40 minutes of delivery placentae were preserved in 10% formalin in labeled containers of adequate sizes, and then transferred to Dow Diagnostic Reference and Research Lab (DDRL). Gross morphological evaluation of placenta including placental weight, size, shape, consistency, membranes, any obvious deformity color and length, width and insertion of the umbilical cord was done. Feto-maternal outcomes including condition of the baby, weight of the baby and mode of delivery were noted down at the time of delivery. Data was analyzed by SPSS version 16. P value of 0.05 or less was considered statistically significant for the results. For the numerical variables mean with Independent t test and for categorical variables percentages with chi square tests were applied for evaluation. Fisher exact test was used where chi square test was not applicable due to decreased cell counts.

**RESULTS**

Results are documented for 50 patients, 25 in each group who completed the study. Mean age of the patients was 30.08± 3.16 and 31.60 ± 4.27 years, mean weight was 78.54± 6.93 and 77.9±9.03kgs
in GROUP A and Group B respectively, all being statistically non-significant. However FBS and RBS showed statistically significant results after one week of enrollment (Table-I).

Placental weight and cord width were more in Group B with significant p value of p=0.005 and p=0.02 respectively. Placental length, placental breadth, placental width, cord length, placental shapes, consistency, membranes completeness, cord insertion, cord color was statistically non-significant between the groups. More gross pathologies were found in Group B placentae (16/25) when compared with placentae in Group A (12/25). (Table IIa and IIb)

On comparison of fetal outcome, mean neonatal birth weight was more in Group B with p=0.003 and p=0.00 respectively. Placental length, placental breadth, placental width, cord length, placental shapes, consistency, membranes completeness, cord insertion, cord color was statistically non-significant between the groups. More gross pathologies were found in Group B placenta (16/25) when compared with placenta in Group A (12/25). (Table Ia and Ib)

In maternal outcomes, 15 (60%) mothers delivered normally, and 10 (40%) had cesarean sections in Group A. In Group B 8(32%) females delivered normally and remaining 17(68%) delivered by cesarean section due to big babies (Table-III).

### DISCUSSION

In our results statistically non-significant differences were present in between the two groups, in mean maternal age and mean maternal weight and same is documented by Dabella D in her study. FBS and RBS after 1 week indicate the WHO criteria for allocation and grouping of the patients.

Gestational diabetes produces changes in placenta secondary to change in the milieu of the mother and the fetus. To compensate the hyperglycemic blood from the mother, there is islets cell hypertrophy and beta cell hyperplasia of fetal pancreas with the release of excessive amounts of insulin in the

| Variables          | Group A (n=25) | Group B (n=25) | Significance |
|--------------------|----------------|----------------|--------------|
| Patient age (years)| 30.08±3.16     | 31.60±4.27     | 0.159        |
| Patient weight (kg)| 78.54±6.93     | 77.9±9.03      | 0.78         |
| FBS                | 90.96±16.84    | 117±29.0       | 0.00*        |
| RBS                | 123±38.9       | 239±99.7       | 0.00*        |

Group A: GDM on Diet and exercise control, Group B: GDM on insulin treatment

Student’s t test applied, *statistically significant.

| Categorical Variables | Group A (n=25) | Group B (n=25) | Significance |
|-----------------------|----------------|----------------|--------------|
| Disc like             | 19             | 18             | 0.74         |
| Non-disc like         | 6              | 7              |              |
| Placental consistency: |
| Soft                  | 16             | 17             | 0.76         |
| Hard                  | 9              | 8              |              |
| Cord insertion:       |
| Central               | 8              | 9              | 0.76         |
| peripheral            | 17             | 16             |              |
| Cord Colour:          |
| Pale                  | 17             | 10             | 0.55         |
| Blue                  | 8              | 15             |              |
| Membranes:            |
| Complete              | 22             | 19             | 0.43^        |
| incomplete            | 3              | 6              |              |

Obvious gross pathology in placental parenchyma:

- Hemorrhages: 2(8%) vs 2(8%) (NA)
- Fibrinoid-necrosis: 2(8%) vs 3(12%) (NA)
- Both necrosis and hemorrhages: 5(20%) vs 4(16%) (NA)
- No gross lesion: 13(52%) vs 9(36%) (NA)
- Other pathology: 3(12%) vs 7(28%) (NA)

Group A: GDM on Diet and exercise control, Group B: GDM on insulin treatment.

Fisher exacts test applied as Chi square test not applicable due to less cell counts

Chi square test applied, *Statistically significant
^Fisher exacts test applied as Chi square test not applicable due to less cell counts

NA Chi square and Fisher exact test not applicable.
Effects of insulin on placental, fetal & maternal outcomes

Table-III: Fetal and maternal outcomes.
(Group A V/S Group B (n=50)).

| Variables            | Group A   | Group B   | Significance |
|----------------------|-----------|-----------|--------------|
|                      | (n=25)    | (n=25)    |              |
| Weight of the baby (kg) | 3.09±0.3  | 3.44±0.46 | 0.003*       |
| **Condition of the baby** |           |           |              |
| Alive baby           | 24(96%)   | 23(92%)   |              |
| IUD                  | 1(4%)     | 2(8%)     |              |
| Still births         | 0         | 0         |              |
| **Mode of delivery** |           |           |              |
| Normal vaginal       | 15(68%)   | 8(32%)    |              |
| Cesarean section     | 10(40%)   | 17(68%)   |              |

Group A: GDM on Diet and exercise control.
Group B: GDM on insulin treatment
Chi square test and students T test applied accordingly.
* Statistically significant.

is the result of increased delivery of amino acids to the fetus in gestational diabetes (GDM), even when metabolic control is strict. So might be for this reason even when truly normal maternal substrate levels are achieved in diabetic pregnancies, the defect lies in altered placental nutrient transport and metabolism.22

Persson stated that babies of GDM mothers on insulin treatment and on diet control are similar in the weight.23 But a recent study by Wong has proven the fact that the babies of insulin treated GDM were heavier than diet control GDM mothers, so more GDM mothers on insulin treatment delivered through cesarean section due to fetal overgrowth and heavy term babies24 and is coinciding with our findings. We observed more intrauterine deaths in insulin treated group and the probable reason is the excessive growth of fetus which increases the oxygen demands. Placenta tries to compensate this to an extent but when the baby is grown enough and is near term, it cannot fulfill the requirements
of fetus resulting in unexplained term intrauterine death in these patients. Our findings suggest that exogenous insulin probably improves the glycemic values but is unable to control the related problems completely as is evident from statistics. This point towards the presence of unknown areas in GDM pathology and need of alternative pharmacotherapy for GDM patients.

CONCLUSION
Insulin has produced significant effects on the placental, fetal and maternal outcomes in patients having gestational diabetes mellitus in comparison to GDMs controlled on diet and exercise.

Limitations of the study: Following the patients throughout the pregnancy in the diabetic antenatal clinic and then collecting the placentae resulted in a long individual study period. Small sample size in the groups due to long individual study period. Lost to follow up 19 patients’ in our study in-spite of vigorous counseling at each antenatal visit.

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Conflict Of Interest Notification Page: This study was done as part of requirement of M Phil in Basic Medical Sciences in pharmacology at Dow University of Health Sciences. Financial burden was taken by RA, Dow University, Administration of Lyari General Hospital and Patients themselves at private obstetric clinics. Informed written consent was taken from all the patients. This study was approved by funding committee and institutional ethics review board of Dow University of Health Sciences (IRB, DUHS).

REFERENCES
1. Serlin DC, Lash RW. Diagnosis and management of gestational diabetes. Am Fam Physician. 2009;80(1):57-62.
2. Colomiere M, Permezel M, Riley C, Desoye G, Lappas M. Defective insulin signaling in placenta from pregnancy complicated by gestational diabetes mellitus. Euro J Endocrinol. 2009;160:567-578. doi: 10.1530/EJE-09-0031
3. World Health Organization. 1999. Definition, diagnosis and classification of diabetes Mellitus and its complications Part 1. Provisional report of a WHO Consultant. Diabetes Medicines. 1999;15(7):539-553.
4. Madazal R, Tuten A, Calary Z, Uzun H, Uludag S, Ocal 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. doi: 10.1159/0001 3045.
5. Akhter F, AnjumanBano ML, Ferdaus R. Effects of gestational diabetes mellitus on gross morphological structure of preterm placenta. Bangladesh J Anat. 2010;8(1):34-38.
6. Fowden L, Forhead J, Coan PM, Burton GJ. The placenta and intrauterine programming. J Neuroendocrinol. 2008;20(4):439-450.
7. Leach L, Taylor A, Sciota F. Vascular dysfunction in the diabetic placenta: cause and consequences. J Anat. 2009;215:69-76. doi: 10.1111/j.1469-7580.2009.01998.x
8. Mento.G, Bo S, Signorile A, Gallio ML, Cotrino I, Poala C et al. Current management of gestational diabetes mellitus. Expert Rev Obstet Gynecol. 2008;3(1):73-79.
9. Nolte MS, Karam JH. Pancreatic hormones and anti diabetic drugs, “Basic and Clinical Pharmacology (10th edition)”. Katzung(ed), MacgrawHill. USA: 2007:684-686.
10. Nicholcon W, Bolen S, Witkop CT, Neale D, Wilson L, Bass E. Benefits and risks of oral diabetic agents compared with insulin in women with Gestational Diabetes Mellitus: A systemic review. Obstet Gynecol. 2009;113(1):206-17.
11. Mumtaz M. Gestational diabetes mellitus. Malaysian J Med Sci. 2000;7(1):4-9.
12. Samad NJ, Hassan JA, Shera AS, Mqsood A. Gestational Diabetes Mellitus: Screening in a developing country. J Pak Med Assoc. 1996;46(11):249-252.
13. Veciana MD, Major CA, Morgan MA, Asart T, Tookey JS, Lien JM, et al. Post prandial versus pre- prandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. N Eng J Med. 1995;333(19):1237-1241.
14. Debella D, Snell-Bergeon JK, Hartsfield CL, Bischoff JK, Hamman RF, McDuffie RS. Increasing prevalence of gestational diabetes mellitus over time and by birth cohort. Diabetes Care. 2005;28:579-584.
15. Boyd PA, Scott AK, Keeling JW. Quantitative structural studies, on placentas from pregnancies complicated by diabetes mellitus. Br J Obstet Gynaecol. 1986;93:31-35.
16. Mayhew TM, Sorensen FB, Klege JG, Jackson MR. The effects of mode of delivery and sex of new born on placentar morphology in control and diabetic pregnancies. J Anat. 1993;183:545-552.
17. Chowdhury AM, Anwer S, Begum M, Eva KN, Shahnaz F. Effects of insulin treated Established Diabetes Mellitus on the volume of placental parenchyma and weight of the neonate. Bangladesh J Anat. 2009;7(1):45-48.
18. Verma R, Mishra S, Kaul M. Cellular changes in placenta in pregnancies complicating with diabetes. Int J Morphol. 2010;28(1):259-264.
19. Evers IM, de Valk HW, Mol BW, terBraak EW, Visser GH. Macrosomia despite good glycaemic control in Type I diabetic pregnancy; results of a nationwide study in The Netherlands. Diabetologia. 2002;45:1484-1489. doi: 10.1007/s00125-002-0958-7
20. Bane AL, Gillan JE. Massive pervillosfibrinoid causing recurrent placental failure. BJOG. 2003;110:292-5.
21. Odar E, Wandabwa J, Kiondo P. Maternal and fetal outcome of gestational diabetes mellitus in Mulago Hospital, Uganda. Afr Health Sci. 2004;4(1):9-14.
22. 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(A):109-113.
23. Persson B, Stangenberg M, Hanson U, Norlander E. Gestational Diabetes Mellitus (GDM): Comparative evaluation of two treatment regimens; Diet versus insulin and diet. Diabetes. 1985;34(2):101-105.
24. Wong VW, Jalaluddin B. Gestational diabetes mellitus: Who requires insulin therapy? Aust NZ J Obstet Gyneco. 2011;51(5):432-436. doi: 10.1111/j.1479-828x2011.01329.x
25. Farooq MU, Ayaz A, Ali Bahool A, Ahmed I. Maternal and neonatal outcomes in gestational diabetes mellitus. Int J Endocrinol Metab. 2007;5:109-115.