ORIGINAL ARTICLE

Metformin versus Insulin Treatment in Gestational Diabetes Mellitus: their effects on neonates and women in 24 months' follow-up

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ABSTRACT

Aim: To compare the metformin versus insulin treatment in gestational diabetes mellitus (GDM) in pregnant women and their effect on neonates and treatment effect on women up to 24-month post-partum follow-up.
Methods: This was a randomized controlled study conducted study done in Private Hospital. The study conducted from 10-June-2016 to 10-June-2019. The study inclusioncriteria was; age above 18 years and the singleton pregnancy women who presented with GDM. We assigned 44 individuals to metformin treatment (group A) and another 44 individuals to insulin treatment (group B) by randomized method. The primary study outcomes were birth weight, pre-term birth, mother's and baby's weight at follow-up period.
Results: The average gestational age in group A was 39.13±1.02 weeks and 38.52±1.69 weeks in group B (p-value=0.003). Preterm births were less in group A 10(22.7%) than group B 14(31.8%), the birth weight was 3.1±0.29 kg versus 3.6±0.29 kg (p-value <0.001), group A versus group B, respectively. Babies weight was 9.55±0.33 kg, 14.03±0.82 kg in group A, versus 9.36±0.21 kg, 13.16±0.21 kg at 12, and 24 months in group B. The women BMI was26.16±0.33 kg/m^2 and 23.82±5.62 in group A and B at 12 months follow-up.
Conclusion: We concluded that metformin exposed neonates had low birth weight and at follow-up period weight gain was more in these neonates. Those women treated with insulin therapy had a high incidence of pre-term births. Women taking metformin gain more weight after child birth.
Keywords: Gestational diabetic mellitus (GDM), metformin, insulin, birth weight, pre-term births.

INTRODUCTION

Gestational diabetes mellitus (GDM), the most effective risk factor in women during pregnancy. GDM prevalence rate is 3% to 25% around the world.[1] GDM can define as intolerance of glucose with the onset of early recognition during pregnancy.[2]In the long-term, GDM is associated with adverse outcome risk to pregnant women and fetus. According to our observations, the occurrence of GDM is growing rapidly in many countries' populations including Pakistan. According to the international diabetic federation 2017 census, 1 in 7 of all neonates being given birth by GDM-affected mothers[3]. From pregnant women's point of view, there may be chances to increase the risk of the caesarian section, post-labor type-2 diabetes mellitus and obesity[4,5]. From the fetus point of view, there is a chance of pre-term birth, congenital defects, neonatal hypoglycemia & death. Apart from that, there are higher chances of admission to neonatal care and macrosomia .[6, 7]Normally in GDM affected women, medical intervention to control glycaemiaand to maintain normal parameters of fetal development is done[8].

At present best of the two treatments available to treat GDM; insulin and metformin. Insulin is a hormone produced in pancreatic beta cells to regulate glucose homeostasis, insulin does not pass through the placental barrier. Insulin injection therapy is one of the treatments for GDM[9,10]. This has the drawback of daily injection pricks, excess weight gain, and maternal hypoglycemia[11]. Oral therapy, is another method of treating GDM. Metformin (N, N-dimethyl biguanide) is a first-line selected oral therapy drug to treat type-2 diabetic mellitus. Metformin is recognized as an essential medicinal list by the WHO[12]. There is a lot of controversy about neonatal birth weight when using the metformin.[13, 14] The drawback of metformin is that it crosses the placental barrier via organic cation transporters (metformin traces of concentration found in fetal placental tissues). This exposure may affect the fetus development by direct or indirect pathways[15,16]. As mentioned, the controversy still presents the effect of metformin on neonates and pregnant women's weight. The present study concentrated on metformin versus insulin treatment effects on the neonate and pregnant women outcomes in GDM patients. To know the frequency of preterm birth, oro-facial clefts, congenital heart defects, and periodical changes of neonate BMI for up to two years. Our study also conducted on the post-partum two-year follow-up of mother's BMI changes who were treated with metformin, and insulin.

METHODS AND MATERIAL

This is a randomized control study conducted in a private hospital. The study inclusioncriteria was age above 18 years and the singleton pregnancy women who presented GDM. The exclusion criteria were age below 18 years, known DM taking treatment with hypoglycemic agents, in-vitro fertilization acquired women and surrogacy mothers. There were 88 pregnant women diagnosed with GDM, they were treated with either insulin therapy or metformin oral therapy during the study period. We assigned 44 individuals to insulin treatment and another 44 individuals to metformin treatment by randomized method.

The identification of GDM was based on the oral glucose tolerance test (OGTT), normally done after 20 weeks of gestational period, a two-hour, 75 g of OGTT used for test. All pregnant patients arrived at the hospital within 8 hours fasting in the early morning. For OGTT test they were advised to avoid going to the bathroom just before the procedure, a healthcare provider obtain a fasting blood sample as per hospital policy, then we ask the patient to drink 75g glucose contained 250 ml of water. After two hours, the healthcare provider again collected blood sample in the first and second hour. The OGTT test values for diagnosis of GDM are shown in table-1. We categorized the patients randomly into equal two groups, Group –A: patients were given metformin therapy (500mg twice a day) to manage GDM. Group-B: patients were given NPH insulin subcutaneously to manage GDM.

The dose of metformin was depending upon the glycemic levels of the pregnant women, the women were informed to note their blood sugar levels daily in a dairy and after one week, their doses of insulin and metformin were adjusted according to past week mean glucose level.

The primary study outcomes were birth weight, pre-term birth, mothers and baby weight at follow-up period. The birth weight of neonates was measured immediately after birth in kilograms (kg), pre-term birth was consideredif labor delivery occurs before 37 weeks. Oro-facial cleft was recorded post-delivery, congenital heart defects finding was done by 2-dimensional (2D) echocardiography, neonate weight (kilogram) and pregnant women BMI ($kg/m^{2)}$ were recorded at post-partum, 12 months and 24 months of post-partum.

The current study approved by the institutional ethical committee and research body. before the data collection, written and informed consent obtained from all pregnant women. We ensured the patient, that her data and identity never disclosed at any circumstances.

Data analysis was carried out by SPSS v23.0 (IBM corp., USA), quantitative variables were calculated as Mean ± Standard deviation, and Categorical variables calculated as frequency and percentage. Independent sample t-test was used for comparison of quantitative variables, and for comparison of qualitative variables chi-square test was used. P-value ≤0.05 was taken significant.

RESULTS

The baseline parameters of the pregnant women with GDM were as follows; the mean age of women 31.47±5.43 in group A, 29.45±5.3 in group B. The BMI was measured & calculated at the time of inclusion in study was 24.06±5.68 Kg/m^2 in group A and 25.29±4.78 Kg/m^2 in group B (p-value 0.27), Baseline glucose in was 96.86±8.12 mg/dL in group A, and in group B it was 95.90±8.24 mg/dL (p-value 0.58) (Table-2).

The mean gestational age at the time of delivery in group A was 39.13±1.02 weeks and in group B was 38.52±1.69 weeks, p-value 0.003. Preterm birth rate was lower in group A 10 (22.7%) than group B 14(31.8%). Mean birth weight was a statistical different between two groups [3.1±0.29 kg versus 3.6±0.29 kg (p-value <0.001)]. The babies weight at 12 month's follow-up, in group A was, 9.55±0.33 kg, in group B it was 9.36±0.21 kg (p-value 0.02). The babies' weight after 24 months was, 14.03±0.82 kg in group A, and 13.16±0.21 kg in group B (p-value <0.001).

The women early post-partum BMI was 28.33±5.36 kg/m^2 in group A, versus 26.94± 6.36 in group B (p-value 0.27). At 12 months of post-partum, the women BMI was 26.16±0.33 kg/m^2 versus 23.82±5.62 in group A and B respectively (p-value 0.04). At 24 months of delivery, BMI was 25.76±4.90 in group A, 23.29±5.50 in group B (p-value 0.02). [Table 3]

Table-1: Blood glucose levels for the OGTT test.

Blood drawn time	GDM(mg/dL)
Fasting	>92
After 1 hour	>180
After 2 hours	≥153
*Any one abnormal value is labelled as GDM	

Table 2: Baseline characteristics of pregnant women

Parameters	Group A (n=44)	Group B (n=44)	p-value
Age ± SD (years)	31.47±5.43	29.45±5.3	0.080
BMI (1^{st} trimester) kg/m^2	24.06±5.68	25.29±4.78	0.27
Baseline glucose (1^{st} trimester) mg/dL	96.86±8.12	95.90±8.24	0.58

Table 3: babies and women's post-partum 24 months' follow-up parameters

Parameters	Group A (n=44)	Group B (n=44)	p-value
Gestational age(weeks)	39.13±1.02	38.52±1.69	0.003
Preterm births (%)	10(22.7%)	14(31.8%)	0.47
Birthweight (kg)	3.1±0.29	3.6±0.29	<0.001
babies weight at 12 months (kg)	9.55±0.33	9.36±0.21	0.02
babies weight 24 months (kg)	14.03±0.82	13.16±0.21	<0.001
women BMI (post-partum) kg/m2	28.33±5.36	26.94± 6.36	0.27
women BMI (12 months post-partum) kg/m^2	26.16±0.33	23.82±5.62	0.04
Women BMI (24 months post-partum) kg/m^2	25.76±4.90	23.29±5.50	0.02
Orofacial cleft n(%)	2 (100%)	0	0.49
Congenital heart disease n(%)	1(50%)	1(50%)	1.0

DISCUSSION

Occurrence of gestational diabetes mellitus (GDM) is an absolute insulin deficiency that causes maternal hyperglycemia. The prevalence rate of GDM is increasing at a rapid pace. The change in dietary habits, physical training, and healthy food intake may reduce the occurrence of GDM. The treatment for GDM is insulin therapy or metformin oral therapy, the drawback of metformin is that it can easily cross the placenta through organic cation transporters and reaches the fetus. [16] The organic cat-ion transports are developing in the fetus placenta at 25 to 32 weeks of gestation.[17] The metformin inhibits the mitochondrial respiration and resiststo enter the

nutrients of glucose and amino acids into the fetus through the mTOR pathway.[18]Insulin (NPH) action is beta-subunit of insulin binding to glycoprotein receptor (alpha-subunit) of the cell's surface, which stimulated and generate a signal that causes insulin to act on glucose[19]. There is a lot of controversy regarding the subcutaneous insulin therapy and oral metformin outcomes in pregnant women.

It has been concluded in different studies that the fetus's growth in the uterus and early post-partum periods may be related to metabolic functions[20]. A meta-analysis conducted by Terry-Adkins et al. found that children exposed to metformin have a lower birth weight and significantly increased their weight by mid-childhood.[1,21] In our present study, there is significantly low birth weight in metformin-exposed group (3.1±0.29 kg) compare to insulin-exposed group (3.6±0.29 kg). One more study conducted by Slagjana Simeonova-Krstevskaet al.[22]concluded that preterm birth rate is higher in the insulin-treated group than the metformin-treated group. In our study, we found similar results; mean gestational age 39.13±1.02 weeks in insulin-exposed versus 38.52±1.69 weeks in metformin group. In present study,at 24-month follow-up, we found a significant difference in maternal BMI outcomes in Metformin versus insulin exposed mothers; average BMI was 26.16±0.33 kg/m^2 versus 23.82±5.62 kg/m^2 (12 months), 25.76±4.90 kg/m^2 versus 23.29±5.50 kg/m^2 (24 months) respectively.

The present 24 months' follow-up values mimic the Ainuddinet al study,[13] in their study significant difference in weight gain of mothers in insulin versus metformin found. A follow-up study of offspring born to women exposed Metformin in GDM found that children who had been prenatally exposed to metformin did not differ from children exposed to insulin concerning weight, height, or abdominal fat at age 2 years.[23]

The risk of preterm birth is more in the insulin-treated group than the metformin-treated group, whilethe incidence of LBW is higher in the metformin-exposed group. The women who were treated with metformin during pregnancy gained weight significantly at the 12 and 24 months of post-partum compared with the insulin-treated group. The metformin exposed babies were gained weight at 12 and 24 months of age compared to the insulin exposed group.

Boundaries of the present study:the duration of the study was short (24 months' follow-up) and the sample size was small. Further research has to be done in large sample hospitals to look into the outcomes with long-term results.

CONCLUSION

Based on our study results, metformin and insulin both drugs are a safe and effective treatment for gestational diabetes mellitus (GDM), we observed metformin exposed neonates have low birth weight and 12 and 24-month age children have heavy-weight gain compared to insulin exposed neonates. we observed, an increased BMI in metformin treated women at 12 and 24 months of post-partum compared to insulin therapy group. Those women treated with insulin therapy had a high incidence of pre-term births compare to metformin treated. This outcome provides clear guidance to the clinician to make treatment decision.

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