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Impact of Metformin Versus Insulin on Diabetic Pregnancy Outcome, Aljalaa Maternity Hospital

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ABSTRACT

In recent years, metformin has gained acceptance as a safe, effective and rational option for reducing insulin resistance in pregnant women with type 2 diabetes, gestational diabetes (GDM). The study aimed to compare the efficacy and safety of Metformin versus insulin in the treatment of gestational diabetes mellitus (GDM) by evaluating the influence of medication on maternal and fetal outcomes. A retrospective study included 550 diabetic women who were under antenatal follow up in diabetic pregnancy outpatient department and who gave birth in the period from 1st Jan. 2012 up to 31st Dec. 2014 in Aljalaa Maternity Hospital, Tripoli-Libya.

The percentage of patients who had normal vaginal delivery was higher in Metformin group (35.6%) compared with insulin group (17.5%) the relationship was significant ($P < 0.05$), HbA1c% level was < 7% in 35.1% of insulin patients and 66.5% in metformin patients group. About 45% of patients on metformin need supplemental insulin in different stages of pregnancy to fulfill perfect blood sugar control. In this study there was no difference in neonatal outcomes between insulin and metformin patients groups, and there were no statistically significant differences in birth weight between insulin treated patients and metformin treated patient (P =0.5).

Metformin was efficacious in controlling diabetes in pregnancy, associated with decreased chance of caesarean delivery and not associated with increased perinatal complications.

Keywords- *Gestational diabetes mellitus; Metformin; Outcome.*

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[1]Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance occurring first time during pregnancy. GDM commonly develops, when maternal glucose metabolism is unable to compensate for the progressive development of insulin resistance, arising primarily from the consistently rising diabetogenic placental hormones.[2]

Maternal hyperglycaemia is associated with an increased risk of perinatal complications, especially fetal macrosomia, that is large for gestational age (LGA), which increases the risk of labour complications, such as shoulder dystocia, the need for caesarean sections, and perinatal morbidity as birth asphyxia. Maternal hyperglycaemia is also associated with an increased rate of gestational hypertension and pre-eclampsia.[3]

Active management of GDM has been found to reduce the incidence of macrosomy and perinatal morbidity. Diet and lifestyle counseling are the corner stones in the treatment of gestational diabetes. If normoglycaemia is not attained with diet, insulin is traditionally considered to be the first-line medical treatment. Women who begin insulin therapy require education to ensure the safe administration of insulin. Use of insulin is also associated with hypoglycemia and weight gain. Safe and effective oral therapy would be more acceptable and simpler for women with GDM.[3,4]

Metformin is a compound used for its anti-hyperglycemic effect; it alleviates hyperglycemia by three different primary mechanisms. Its main effect is to decrease liver glucose production by inhibiting hepatic gluconeogenesis and glycogenolysis.[5] Secondly, metformin functions as an insulin sensitizer in skeletal muscles.[2,5] Thirdly, metformin delays intestinal absorption of glucose (decreased postprandial hyperglycemia), and also decreases appetite and may result in weight reduction.[6]

It improves lipid metabolism by inhibiting lipolysis, and it lowers the concentration of free fatty acids and triglycerides in

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the plasma. Metformin does not increase insulin production, so it does not induce hypoglycemia.[6,7]

The most common adverse effect of metformin is gastrointestinal upset, including diarrhea, cramps, nausea, vomiting and increased flatulence.[26]The serious potential side effect of metformin is lactic acidosis. The incidence of lactic acidosis is 5-9 per 100 000 person[8], but the risk is much lower if metformin is not used in patients with kidney or liver failure, alcohol overdose, conditions associated with hypoxia (cardiac and pulmonary disease), septic infection or febrile gastroenteritis. Long-term (4 years) use of metformin may cause vitamin B12 and folate deficiency. Results from studies on the effects of short-term (6-28 weeks) metformin use on vitamin levels are inconsistent.[9]

Although it crosses the placenta, there is no evidence of adverse fetal effects or increased risk of major malformations when metformin is used in pregnant women.[10]

The metformin treatment, alone or in association with insulin, was not linked to increased perinatal complications or serious adverse effects.[6]

The results of previous studies for differences in glycemic control, pregnancy, and neonatal outcomes between insulin and metformin are contradictory; hence, the present study was conducted to compare the efficacy and safety of Glucophage (Metformin) versus insulin in the treatment of gestational diabetes mellitus (GDM) by evaluating the influence of medication on maternal and fetal outcomes.

MATERIALS AND METHODS

A retrospective study included 550 diabetic women who were under antenatal follow up in diabetic pregnancy outpatient department and who gave birth in the period from 1st of January 2012 up to 31st Dec. 2014 in Aljalaa maternity hospital, Tripoli -Libya.

The number of deliveries of diabetic mothers in 2012 year was 319 from the total 7609 deliveries, 121 from the total 3293 deliveries in 2013, and 306 from the total 6166 deliveries in 2014. A detailed information was collected from medical records including the types of diabetes, types of treatment, age of the patients, gravidity, parity and abortions number, mode of delivery, type of caesarian section and HbA1c level, in addition the neonatal complications including prematurity, macrosomia, Neonatal hypoglycemia, respiratory distress and birth injury were studied.

After the medical records were analyzed, the participants were grouped into 3 treatment groups: (1) insulin, (2) metformin,(3) metformin + insulin.

Statistical analyses were performed using SPSS software for Windows, version 16.

The data were summarized as frequencies or percentages for categorical variables and as means and standard deviations or medians for continuous variables, depending on the distribution. Differences between the treatment groups were compared by the chi-square or Fisher's exact test for categorical variables and a two-sample t-test for continuous variables; and $P < 0.05$ was regarded as statistically significant.

RESULTS

Of the 550 women enrolled, 223 (40.5%) were type 2 DM and 327(59.5%) had GDM**.**

The mean age of the patients was 35.69 ± 4.83 years, the minimum age was 20 years and the maximum age was 46 years. The mode of delivery was 25.3% normal vaginal delivery, 44% elective C/S and 30.7% emergency C/S.

Insulin was received by 17.6% of patients, 51.6% on Metformin and 30.7% on both Insulin and Metformin (Table 1).

Table 1: Clinic-demographic characteristics of the patients

Character	No.	%
Type of delivery		
NVD	139	25.3
ELcs	242	44
EMcs	169	30.7
type of DM:		
Type 2 DM	223	40.5
GDM	327	59.5
Type of treatment		
Insulin	97	17.6
Metformin	284	51.6
Insulin and metformin	169	30.7

Regarding the treatment, 37.2% of the women with Type 2 diabetes mellitus (DM) were treated with insulin alone, 20.6% with metformin, and the remainder with a metformin and insulin association (42.2%). About 4.3% of GDM patients were on insulin, 72.8% on metformin, and 22.9% on metformin with supplemental insulin. There was a significant difference between the groups (P =0.0001).

The frequency of normal vaginal delivery was higher in Metformin group (35.6%) than the other two groups (insulin group 17.5%, insulin and metformin group 12.4%). Caesarean deliveries were more likely in women treated with insulin and metformin (87.6%) than in the other groups (P=0.0001).

The percent of the glycemic control (HbA1c<7%) was statistically significantly higher in metformin-treated group versus other groups (Table 2).

The percent of prematurity was statistically significantly higher in the insulin group than in the metformin groups and metformin + insulin group.Low birth weight was reported in 5.5% of patients, > 4000 g in 18.5% of patients, there was non-significant difference between the groups. The respiratory distress was recorded in 4.9% of neonates (Table 3).

Neonatal hypoglycemia was higher among insulin treatment group, and neonatal birth injury was 0.9% of all deliveries, more with metformin treatment (Figure 1).

Table 2: Maternal characteristics according to type of treatment

	Insulin	Metformin	Insulin + metformin	*P*-value
Type of DM: Type 2DM GDM	 83(85.6%) 14(14.4%)	 46(16.2%) 238(83.8%)	 94(55.6%) 75(44.4%)	0.0001
Mode of delivery NVD El CS Em CS	 17(17.5%) 42(43.3%) 38(39.2%)	 101(35.6%) 104(36.6%) 79(27.8%)	 21(12.4%) 96(56.8%) 52(30.6%)	0.0001
HbA1c level: ≥7% <7%	 63(64.9%) 34(35.1%)	 95(33.5%) 189(66.5%)	 109(64.5%) 60(35.5%)	0.0001

El CS: Elective Caesarean section, EmCS: emergency Caesarean section

Table 3: Neonatal outcome according to type of treatment

Baby outcome	Insulin	Metformin	Insulin + metformin	p-value
Gestational age Preterm Term	 21(21.6%) 76(78.4%)	 34(12%) 250(88%)	 21(12.4%) 148(87.6%)	0.04
Baby status: Alive Stillbirth	 96(99%) 1(1%)	 281(98.9%) 3(1.1%)	 167(98.8%) 2(1.2%)	0.9
Birth weight **<2500g** **2500-4000 g** **>4000 g**	 2(2.1%) 77(79.4%) 18(18.6%)	 19(6.7%) 214(75.4%) 51(18%)	 9(5.3%) 127(75.1%) 33(19.5%)	0.5

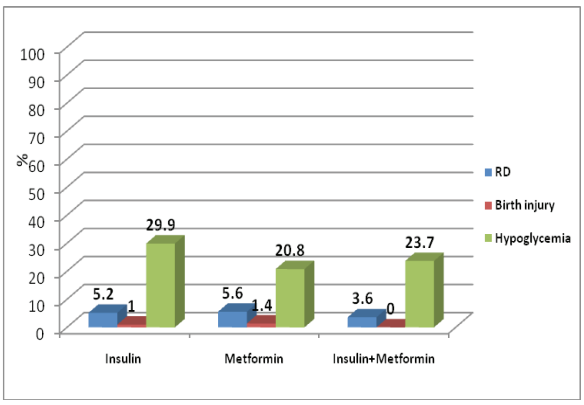

Figure 1: Neonatal complication according to therapeutic modalities

DISCUSSION

The incidence of diabetes among reproductive-aged women is rising worldwide. Diabetes in pregnancy is associated with an increased incidence of adverse outcomes, for both mother and infant, if the glycemic control during pregnancy is not adequate. Optimal glycemic control can be achieved with medications. Standard treatment for achieving adequate glucose levels is insulin therapy. However, this therapy requires multiple daily injections of insulin, which may reduce patient adherence. Furthermore, its high cost may preclude treatment for some patients, needle phobia, potential for hypoglycemia, weight gain and psycho-social stigma, perhaps, makes injectable therapy, somehow cumbersome for many pregnant patients.[2,11]

However, recent studies have suggested that certain oral hypoglycemic agents (metformin and glyburide) may be safe and be acceptable alternatives. There are no serious safety concerns with metformin, despite it crossing the placenta. Neonatal outcomes are also comparable, with benefit of reductions in neonatal hypoglycemia, maternal hypoglycemia and weight gain, and improved treatment satisfaction.[11]

In this study about 37.2% of type 2 DM patients were on insulin, 20.6% on metformin and 42.2% on Metformin with supplemental insulin, while about 4.3% of GDM patients were on insulin, 72.8% on Metformin and 22.9% on Metformin with supplemental insulin; and about 45% of patients on Metformin need supplemental insulin. The same result obtained in the study by Rowan et al[4] (MiG trial), which revealed that approximately 46% of women using Metformin at the maximum dose used in the trial required supplemental insulin.

The caesarean section (CS) rate was lower in metformin group (64.4%) compared with other groups, insulin alone (82.5%), and those who received the combination of metformin and insulin (87.7%) (*P*=0.0001). This

finding in accordance with Goh et al (2011)[12] study, which revealed that women treated with insulin had higher rates of caesarean delivery (45.6% with insulin, 37% with metformin, and 34% with diet, ($P = 0.02$). Disagreement with Ijas et al study, there were more caesarean deliveries (38%) and vacuum extraction deliveries (15%) in the metformin group than in the insulin group (20 and 8%, respectively).[3]

In present study, there was a significant difference between insulin treated patients group and Metformin treated group regarding HbA1c % value, where glycemic control was more frequent in metformin patients group. A study by Mesdaghinia et al (2013)[13], reported that HbA1c at the time of delivery was lower in those taking metformin, Significant statistical difference was observed between groups, P =0.021.

In another randomized control trial (RCT)carried out at Maternal and Child Health center (MCH), Pakistan institute of medical sciences, Islamabad, 2011, revealed that comparison of post-treatment HbA1c showed normal levels in 79.4% of women on insulin and 82.3% of women on Metformin, but it revealed no statistical differences between groups.[14]

Preterm delivery in current study, was 21.6% in Insulin patients group, 12% in Metformin patients group and 12.4% in Metformin + Insulin patients group, which is statistically significant P value = 0.04.These results were much closed to those in a study by Goh et al[12], which showed that women treated with insulin had more preterm births (19.2% with insulin, 12.5% with metformin, 12.1% with diet, $P = 0.005$).

There were no significant differences in incidence of still birth, 1% in patients on Insulin, 1.1% in patients on Metformin and 1.2% in patients on Metformin + Insulin ($P = 0.9$). Respiratory distress was reported in 5.2% of Insulin patients group, 5.6% of Metformin patients group and 3.6% in Metformin + insulin patients group, this was statistically insignificant ($P = 0.6$).Birth injury was reported in 1% of Insulin patients group, 1.4% inMetformin patients group, and 0% in Metformin + insulin patients group,there was no significant difference ($P = 0.3$).

In addition, there were no significant differences in neonatal hypoglycemia between insulin patients group (29.9%), Metformin patients group (20.8%) and in Metformin + Insulin patients group (23.7%) ($P = 0.19$). Similar finding reported by Ijäs et al, the frequency of neonatal hypoglycaemia, was slightly but not significantly higher in the insulin group.[3]

MiG trial revealed that neonatal hypoglycemia was similar in both groups, but severe hypoglycemia (< 28.8 mg/dL) occurred significantly less often among infants of women taking metformin.[4]

In present study, the birth weight of the newborns did not differ significantly between the metformin and insulin groups; this result is in line with other studies.[3,4]

The preliminary study by Moore et al[15] the neonatal outcomes of birth weight, hypoglycemia, and respiratory distress syndrome, did not differ between both groups.

In 2016, Butalia et al. systematically reviewed all public trials involving the impact of metformin on pregnancy outcomes. Amongst 41 relevant studies, the authors concluded that there was no increased risk of preterm labour, small for gestational age/large for gestational age babies, neonatal ICU admission, perinatal morbidity, or mortality in RCTs with a short-term follow-up period.[16]

Similarly, Najafian et al reported, neonatal outcomes including intrauterine growth restriction, intrauterine fetal death, fetal anomaly, polyhydramnios, macrosomia, oligohydramnios, and NICU hospitalization did not differ significantly between two groups.[17]

CONCLUSIONS

The study concluded that metformin efficacious in controlling diabetes in pregnancy either alone (in about 55% of cases) or in combination with insulin (in 45% of cases). Also associated with increased incidence of normal vaginal delivery and decreased chance of caesarean delivery and not associated with increased perinatal complications, also it is not associated with an increased occurrence of an adverse outcome for the fetus or neonate when compared with insulin. In addition to its oral intake (which improves the patient`s compliance) and its cheapness (which make it cost effective), all these advantages make Metformin a good and accepted substitute in controlling diabetes in pregnancy.

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