Effect of metformin on maternal and neonatal outcomes in pregnant obese diabetic patients: New potentials for an old drug

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Abstract

Background: Pregnancy complicated by diabetes whether gestational or pregestational diabetes, could be associated with adverse maternal and neonatal outcomes; if optimum glycemic control was not achieved. Metformin is an insulin sensitizing drug that has been approved for treatment of gestational diabetes and type II pregestational diabetes. In this study, we have studied the role and effectiveness of metformin in improving glycemic control and the prevention of maternal and neonatal adverse outcomes in obese pregnant diabetic women.

Patient and Methods: This was a prospective cohort study that included 189 obese pregnant diabetic women recruited to Kasr Al Aini Obstetrics and Gynecology department over the period from September 2022 till March 2023. The study population included three groups according to the treatment modality; metformin only group, metformin and insulin group and insulin only group.

Results: The use of metformin was associated with significant reduction in the incidence of preeclampsia and neonatal lactic acidosis with a p value 0.033 and 0.002 respectively. However, use of metformin whether alone or in addition to insulin, compared to insulin alone was not shown to be superior in improving glycemic control, or reduce adverse neonatal outcomes..

Conclusion: Metformin use in obese diabetic pregnant women improves maternal and neonatal outcomes.

Keywords: Metformin, Diabetes mellitus, pregnancy, Obesity.

Introduction

Obesity is defined as a BMI > 30 kg/m, over the past decades obesity has become a growing global epidemic (1). With the increasing number of obese population, the prevalence of maternal obesity has accordingly been increasing, with rising concerns regarding obesity related health issues. Obese pregnant women are at increased risk of gestational diabetes, pregnancy induced hypertension, preterm labor and miscarriages (2).

Diabetes mellitus is an endocrine disorder characterized by hyperglycemic state, which may develop for the first time during pregnancy secondary to glucose intolerance induced by the pregnancy hormones; known as gestational diabetes (3). Diabetes mellitus type II is a state of hyperglycemia secondary to insulin resistance that may predate pregnancy known as pregestational diabetes. PGD affects 1-2 % of the pregnant population, with observed rising rates. The diabetic pregnant population are at increased risk of adverse maternal and neonatal outcomes (4).

Pharmacological therapy of diabetes during pregnancy includes metformin, glyburide and insulin (5). Metformin is a synthetic analogue of guanidine that is commonly prescribed in the treatment of type II diabetes. It can be used alone or combined with other antidiabetic drugs. Metformin exerts its effect through suppression of hepatic gluconeogenesis without inducing hypoglycemia (6). Metformin has been widely used during pregnancy both for gestational diabetic mothers and obese no diabetic mothers with established safety and successful outcomes (7).

Several studies have addressed the use of metformin during pregnancy and how it could affect maternal and neonatal outcomes. The safety of metformin use during pregnancy regarding the long term neonatal effects was established by a recent study (8). Some studies showed that metformin use was associated with lower maternal weight gain and decreased incidence of pregnancy induced hypertension (9,10) in addition it was more cost-effective and associated with lower rates of maternal and neonatal hypoglycemia and NICU admission (9,).

In this study, the effect of metformin on different maternal outcomes as glycemic control and the development of PIH; and neonatal outcomes will be assessed and compared to that of insulin either alone or combined with metformin.

Patients and Methods

This was a prospective study that was conducted at the OBGYN department, high risk pregnancy unit at Kasr Al Aini in period between October 2020 and October 2021.

Patients included in our study were diabetic pregnant women aged 25-40 years, either having gestational diabetes or type II pregestational diabetes. Obese pregnant women (BMI>30), pregnant 28-39 weeks, with a singleton viable fetus, eligible for elective lower segment cesarean section were candidates for our study. All patients with the following criteria were excluded from the study, those with established fetal or maternal compromise necessitating urgent delivery, associated fetal anomalies, associated hypertensive disease, kidney disease, systemic lupus erythematosus and type I diabetes. Also patients not compliant to drug therapy and those who were intolerant to metformin were excluded from our study.

The recruited patients were equally divided in to 3 groups according to their drug therapy as advised by the endocrinologist, Group 1: pregnant women using metformin in a dose of 500-2000 mg per day, Group 2: pregnant women receiving both metformin and insulin and Group 3: pregnant women receiving insulin only.

All patients were subjected to full history taking and clinical examination. The body weight was recorded at every visit in addition to the blood pressure as part of their routine ANC . All pregnant women had their routine investigations (CBC, fundus examination, complete urine analysis) and ultrasound scans done as per the local unit schedule. The blood glucose levels sheet was checked at each visit, and drug compliance was checked by the attending obstetrician and endocrinologist at the joint clinic. Also fasting and 2 hour postprandial blood sugar and HbA1C were measured at recruitment and before elective delivery. The glycemic control among the three groups was the main

outcome of our study.

Neonatal outcomes were also assessed, mainly NICU admission and clinical and biochemical outcomes. All neonates were assessed following delivery for the APGAR score at 1, 5 and 10 minutes. The cord blood was assessed for ph., lactic acid and oxygen saturation; in addition a blood sample was obtained from the neonate and assessed for the following: blood sugar and hemoglobin levels.

Statistical methods: The statistical program for the social sciences (SPSS) version 28 (IBM Corp., Armonk, New York, United States) was utilized in order to code the data and enter it. For quantitative variables, the data were summarized by using the mean & standard deviation, as well as for categorical variables, the information were summarized by using frequencies (number of cases) as well as relative frequencies (%). Quantitative parameters having a normal distribution were compared using analysis of variance (ANOVA) followed by a multiple comparisons post hoc test, whereas those with an irregular distribution were compared using the non-parametric Kruskal-Wallis test or the Mann-Whitney U test. Paired t test was employed for normally distributed quantitative parameters & non-parametric Wilcoxon signed rank test for non-normally distributed quantitative data for assessing data collected in series within each group (11). The two categorical data sets were compared using Chi-square. When the expected rate was under five (12), an exact test was performed. Significant findings have p-values under 0.05.

Discussion

Our study was a prospective study that included 189 obese pregnant women having either type II pregestational diabetes or gestational diabetes. The study had three groups according to the pharmacological treatment which was decided by the endocrinologist. They were all comparable regarding the BMI and gestational age at delivery. Thus excluding differences among groups that could be related to prematurity rather than the drug used. The significant difference in the glycemic control among the three groups could be related to the diabetes state and not to the pharmacological treatment. However the three groups showed no significant improvement in the glycemic control between presentation and delivery.

Regarding maternal outcomes and development of preeclampsia, the metformin group had a significantly lower incidence of preeclampsia compared to the metformin and insulin, and insulin only groupv14.3%, 30.2 %, 33.3% respectively, with a P value 0.0033. Several studies addressed this issue and supported the role of metformin in reducing the incidence of severe pregnancy induced hypertension (10).

Regarding neonatal outcomes, the metformin group had significantly lower incidence of neonatal acidosis compared to the insulin and metformin group and insulin only group respectively, 1.2, 2.2, 2.3. The incidence of neonatal hypoglycemia, APGAR score, O2 saturation and NICU admission was not different among the three studied groups.

In a recent meta-analysis that included 24 randomized controlled trials that addressed the use of metformin, whether alone or together with insulin in pregnant women having type II GDM; regarding its effects on short term neonatal outcomes, birthweight, and neonatal hypoglycemia and NICU admission. The use of metformin was associated with lower incidence of macrosomia, NICU admission and neonatal hypoglycemia, when compared to insulin, risk ratio [RR] 0.68; 95% CI 0.54, 0.86; p = 0.001), (RR 0.73; 95% CI 0.61, 0.88;p = 0.0009), (RR 0.65; 95% CI 0.52, 0.81; p = 0.0001). The authors concluded that metformin is a safe drug for both the mother and the neonate and helps in limiting maternal and fetal weight gain especially in women who could not use insulin safely or

have financial obstacles in using it (13).

A large double blind multi center RCT by Benham J et Al in 2021, studied the role of adjunctive use of metformin to insulin to that of insulin alone in pregnant women having type II GDM. The study was in favor of the metformin group in reducing the gestational weight gain, insulin doses, cesarean section rate, macrosomia compared to insulin alone. However, number of small for gestational age neonates was higher in the metformin group which was not clear whether it was a direct effect of metformin or secondary to improved glycemic control, they concluded that metformin could be safely used in type II GDM as long as there are no risks for SGA (14).

The Italian study group of diabetes in pregnancy stated that metformin can be used in obese and very obese pregnant women having type II GDM, as this may decrease the weight gain during pregnancy, as well as the insulin dose (15).

The Italian study group concluded their statement based on the results obtained from a former

Study in 2008. In this study, 700 women with GDM were enrolled and randomized in to

Metformin group and insulin group. Regarding the maternal effects, neither glycemic control was not different between both groups, and the development of hypertension. The gestational weight gain was less in the metformin group. Regarding the neonatal outcomes, the metformin group had significant decrease in the incidence of neonatal hypoglycemia (16).

In another meta-analysis that compared insulin, metformin and gylpuride on glycemic control and neonatal outcomes from 23 trials, the Authors found that the metformin group had lower birth weight gain (SMD − 0.17; 95%CI − 0.25, − 0.08 and maternal weight gain 0.61; 95%CI − 0.86, − 0.35 compared to the insulin group. The met analysis concluded that metformin could be as effective as insulin for maternal glucose control and effective in the prevention of maternal and neonatal complications (17).

To the best of our knowledge, this was the first study to compare metformin only, to metformin and insulin, and insulin only treatment in type II pregestational and gestational DM. It measured different maternal and fetal parameters as PIH, macrosomia, PTL and neonatal acidosis, hypoglycemia and NICU admission. The sample size was representative, however a larger sample size would be more representative.

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Results

Table 1 shows that three groups were comparable regarding the age, parity, gestational age at delivery and type of diabetes.

Table 1

	Group 1 (metformin only)		Group 2 (metformin and insulin)		Group 3 (insulin only)		P value
	Mean	±SD	Mean	±SD	Mean	±SD	
Age	32.29	5.22	31.17	5.76	31.24	5.52	Age
gravidity	3.46	1.98	2.78	1.44	2.97	2.05	0.109
parity	2.57	1.13	2.14	1.19	2.19	1.53	0.056
BMI	32.13	1.77	32.19	1.96	32.35	2.13	0.807
G.A	37.67	0.84	37.11	0.95	37.05	1.10	0.001

		Group 1 (metformin only)		Group 2 (metformin and insulin)		Group 3 (insulin only)		P value
		Count	%	Count	%	Count	%	
Type of D.M	GDM	44	69.8%	39	61.9%	29	46.0%	0.022
	PGDM II	19	30.2%	24	38.1%	34	54.0%	

Table 2 Glycemic control

The groups 2 and 3 showed significant glycemic control between presentation and delivery, compared to group 1 (metformin group).

	Group 1 (metformin only)		Group 2 (metformin and insulin)		Group 3 (insulin only)		P value
	Mean	±SD	Mean	±SD	Mean	±SD	
FBS at presentation	119.48	30.31	121.48	37.36	133.25	43.46	0.085
2hPP at presentation	166.25	36.28	183.95	55.14	204.24	65.96	0.001**
HbA1C at presentation	6.95	0.76	7.14	0.77	7.30	1.12	0.097
Mean FBS	113.14	17.28	119.21	23.60	117.92	20.15	0.219
FBS at delivery	112.52	20.69	108.06	30.49	119.57	24.01	0.039*
Mean 2hPP	151.40	27.09	160.90	43.21	167.81	41.81	0.055
2hPP at delivery	157.25	33.24	151.51	41.16	169.22	41.86	0.036*
HbA1C at delivery	6.91	0.80	6.89	0.79	7.28	1.14	0.038*
Group 1 (metformin only)	at presentation			at delivery			P value
	Mean		±SD	Mean		±SD	
FBS (mg/dl)	119.48		30.31	112.52		20.69	0.110
2hPP (mg/dl)	166.25		36.28	157.65		33.91	0.071
HbA1C (%)	6.95		0.76	6.91		0.80	0.424
Group 2 (metformin and insulin)	at presentation			at delivery			P value
	Mean		±SD	Mean		±SD	
FBS (mg/dl)	121.48		37.36	108.06		30.49	0.013*
2hPP (mg/dl)	183.95		55.14	151.51		41.16	< 0.001**
HbA1C (%)	7.14		0.77	6.89		0.79	< 0.001**
Group 3 (insulin only)	at presentation			at delivery			P value
	Mean		±SD	Mean		±SD	
FBS (mg/dl)	133.25		43.46	119.57		24.01	0.019
2hPP (mg/dl)	204.24		65.96	169.22		41.86	< 0.001
HbA1C (%)	7.30		1.12	7.28		1.14	0.736

Table 3: Comparison of the Glycemic control among the 3 groups, and development of preeclampsia

The 2hpp blood sugar was significantly higher in the insulin group thus explaining the need for insulin treatment in this group.

The use of metformin was associated with significantly less number of cases that developed preeclampsia.

Post-HOC pairwise comparison (P value between each 2 groups) in significant items								
			Group 1 vs Group 2		Group 1 vs Group 3		Group 2 vs Group 3	
2hPP at presentation			0.200		<0.001**		0.108	
FBS at delivery			0.325		0.121		0.012*	
2hPP at delivery			0.409		0.086		0.011*	
HbA1C at delivery			0.892		0.059		0.027*	
		Group 1 (metformin only)		Group 2 (metformin and insulin)		Group 3 (insulin only)		P value
		Count	%	Count	%	Count	%	
developed P.E	yes	9	14.3%	19	30.2%	21	33.3%	0.033
	no	54	85.7%	44	69.8%	42	66.7%	

Table 4: Neonatal outcomes

There was no significant difference regarding neonatal birth weight, APGAR scores and random blood sugar levels.

	Group 1 (metformin only)		Group 2 (metformin and insulin)		Group 3 (insulin only)		P value
	Mean	±SD	Mean	±SD	Mean	±SD	
Birth weight (gm)	3086.67	575.08	3105.56	626.76	3186.19	543.43	0.596
Neonatal RBS (mg/dl)	78.27	20.16	76.75	20.14	72.27	17.71	0.198
Apgar score 1 min	4.11	0.72	4.00	0.76	3.86	0.93	0.213
Apgar score 5 min	6.95	0.91	6.90	0.91	6.73	1.02	0.384
Apgar score 10 min	8.56	0.59	8.54	0.59	8.44	0.64	0.542

Table 5: NICU admission and biochemical parameters

The insulin group had significantly higher blood cord lactic acid and consequently significant lower ph. However no difference regarding NICU admission and other biochemical parameters.

		Group 1 (metformin only)		Group 2 (metformin and insulin)		Group 3 (insulin only)		P value
		Count	%	Count	%	Count	%	
Need for M.V	Yes	2	3.2%	2	3.2%	2	3.2%	1
	NO	61	96.8%	61	96.8%	61	96.8%	
NICU admission	Yes	8	12.7%	9	14.3%	14	22.2%	0.302
	NO	55	87.3%	54	85.7%	49	77.8%	
		Group 1 (metformin only)		Group 2 (metformin and insulin)		Group 3 (insulin only)		P value
		Mean	±SD	Mean	±SD	Mean	±SD	
PH of cord		7.28	0.06	7.25	0.07	7.23	0.11	0.002
lactic acid		1.90	0.47	2.22	0.69	2.36	0.97	0.002
O2 saturation		32.57	6.54	32.29	6.77	32.29	6.77	0.965
Hb (g/l)		149.37	11.78	148.35	12.15	147.71	12.76	0.747
O2 contents (mmol/l)		29.11	6.55	28.64	6.62	28.49	6.54	0.857