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MATERNAL AND PERINATAL OUTCOMES OF METFORMIN TREATMENT FOR GESTATIONAL DIABETES

[1]*Dr. Yusra Yousif Najm and [2]Dr. Ghadah Salah Abdulrazzaq

[1]Higher Diploma in Gynecology and Obstetrics/ Al-Salam Teaching Hospital.
[2]Higher Diploma in Gynecology and Obstetrics/ Al-Mosul Generaj Hospital.

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***Corresponding Author: Dr. Yusra Yousif Najm**

Higher Diploma in Gynecology and Obstetrics/ Al-Salam Teaching Hospital.

ABSTRACT

Background: GDM is an endocrine disorder affecting mothers and fetuses, causing insulin resistance, disrupting nutrient metabolism, and decreasing insulin sensitivity. It is often prescribed as a second-line medication after insulin. **Aim:** To assess the maternal and perinatal outcomes between the women managed for gestational diabetes by Metformin in relation to insulin. **Methodology:** A cohort study at Al-Khansaa Teaching Hospital involved 226 pregnant women with gestational diabetes, divided into two groups: 127 treated with metformin and 99 with insulin therapy. Patients were given individualized dietary advice and home blood glucose monitoring. Inadequate glycaemic control was identified in patients with three or more tests higher than target values within a two-week period. Treatment options were discussed, with metformin being contraindicated in certain cases. **Results:** The study compared baseline characteristics between Metformin and insulin groups, finding no significant differences. Metformin had lower HbA1c levels, higher BMI at early pregnancy, and no significant differences in family history. Induction of labor was performed in 11.0% and 26.3% of Metformin and insulin groups, respectively. Total cesarean section was lower in Metformin (23.6%) compared to insulin (36.4%). Postnatal OGTT glucose showed no significant difference at fasting, but abnormal postnatal glucose tests were found in 7.1% of Metformin and 21.2% of insulin groups. No significant differences were found in perinatal outcomes. **Conclusion:** Metformin treatment significantly improved labor induction, caesarean delivery, postnatal OGTT glucose, and reduced jaundice requiring phototherapy in women compared to insulin treatment.

KEYWORDS: Gestational Diabetes, Maternal outcomes, Metformin, Perinatal outcomes.

INTRODUCTION

A common prenatal endocrine condition, gestational diabetes mellitus (GDM) is demarcated as any grade of glucose intolerance that progresses or is initially identified throughout gestation. GDM can cause both mothers and their fetuses to have short- and long-term health issues.[1] Because of its rising prevalence and correlation with numerous adverse maternal-fetal outcomes, including pre-eclampsia as, well as, eclampsia, preterm birth, caesarean deliveries, neonatal hypoglycemia, macrosomia, and neonatal respiratory distress syndrome, along with an increased chance of type 2 diabetes (T2D) in those women and possibly even in their offspring, obesity, and cardiovascular disease after gestation, the WHO has designated GDM as a "global health research priority".[1,2] Depending on the research population, the global incidence is estimated to be between 1 and 14%.[3]

GDM occurred when a pregnant woman's β-cell developed resistance to insulin with the disruption of the mother's nutrient metabolism and decreased insulin sensitivity.[4] During early pregnancy, the maternal pancreas becomes further sensitive to insulin, storing more glycogen. As pregnancy progresses, counter-regulatory hormones reverse this sensitivity, causing insulin resistance. If these adaptations occur correctly, normoglycemia can be maintained, while if not, it rises.[4,5]

GDM is linked to decreased hepatic suppression of glucose production due to inadequate glucose sensing and increased hepatic delivery of substrates for gluconeogenesis.[6] The primary site of impact is skeletal muscle insulin resistance, which results in a 50–60% decrease in the body's ability to absorb insulin-stimulated glucose in pregnant women throughout the late gestational period. These changes involve the primary IR second messenger, IRS-1. Metabolic syndrome, T2D,

obesity, and gestational insulin resistance may all be influenced by proinflammatory variables and adipokines. The furthermost important modifiable element in the progression of GDM is elevated BMI prior to pregnancy.[7]

According to several international recommendations, metformin is a medication that is frequently prescribed for gestational diabetes mellitus. The Scottish Intercollegiate Guidelines Network (SIGN).[8] says that glibenclamide or metformin may be used to lower blood sugar in cases of gestational diabetes mellitus.[9] The American Diabetes Association (ADA).[10] determined metformin as a category B medication that should be used for GDM as a second-line option instead of insulin.[11] For gestational diabetes mellitus, the National Institute for Health and Care Excellence (NICE) advises a diet and exercise regime to achieve appropriate blood glucose levels, which, if not met within a fortnight, should be followed by the recommended administration of metformin.[12]

Although the incidence of lactic acidosis associated with metformin is extremely infrequent (6.3 cases /100,000 person-years), metformin is not recommended in conditions that carry a great risk of acidosis, as severe liver insufficiency, heart failure, or severe respiratory failure. Additionally, patients with chronic renal dysfunction with glomerular filtration rate of less than 30 mL/min or those who are liable for acute renal failure should not take metformin.[13,14] Patients typically tolerate metformin well. Although there is a little chance of gastrointestinal adverse effects, contemporary formulations that deliver the medication gradually over the course of 24 hours often have a better gastrointestinal tolerance than older formulations.[14] Neither hypoglycemia nor weight gain, which are common adverse effects of traditional antidiabetic drugs (insulin secretagogues/sulfonylureas, insulin), are linked to metformin.[15,16] Regarding the therapeutic advantages of metformin, the ground breaking United Kingdom Prospective Diabetic Study (UKPDS) demonstrated that this medication reduced the risk of coronary deaths by 50% and the risk of MI associated with T2D by 39%.[16] Additionally, observational studies showed a decreased risk of cancer in patients with T2D who took metformin as an anti-diabetic treatment.[17]

Purpose of the study

To assess the maternal and perinatal outcomes between the women managed for gestational diabetes by Metformin in relation to treatment by insulin.

Patients and Methods

A longitudinal cohort study design was conducted at Al-Khansaa Teaching Hospital from the 1st January to 1st June 2022 involving 226 pregnant women with singleton baby who developed gestational diabetes (GDM) and divided into two group: 127 women who treated by Metformin group and 99 women with insulin therapy. GDM was defined as one or more of the subsequent results after a 75 g glucose load: impaired fasting glycaemia,[18] 2 hours glucose more than 7.8 mmol/L in accordance with guidelines of WHO, and plasma glucose >6 mmol/L. Participants could also be women who had a history of GDM in prior pregnancies.

Each patient was initially given personalized food recommendations based on their weight, degree of activity, and desired weight increase. The diabetes specialist nurse instructed them on home blood glucose monitoring and suggested that they self-monitor four times a day. Within a period of 2 weeks, patients were deemed to have poor glycaemic control if ≥ 3tests exceeded the target values (fasting >5.6 mmol/L, 1 hour postprandial >8 mmol/L, and 2 hours >7 mmol/L). The patients were informed about the metformin and insulin treatment choices. Metformin should not be used in cases of hyperemesis gravidarum, when fetal growth is less than the tenth centile, estimated renal glomerular filtration rate impairment, or liver impairment. Every patient received a metformin information sheet. In accordance with the findings of home glucose monitoring, patients who gave their consent to use metformin were initiated with a tablet of 500 mg given twice daily with meals, the dose was progressively increased to a maximum of 3 g daily. In the joint antenatal diabetic clinic, every woman was treated in accordance with a well-established care pathway with the goal of achieving a vaginal delivery at term. This protocol states that metformin should be stopped if there is evidence of fetal growth restriction, which is defined as fetal weight less than the tenth centile, an oligohydramnios amniotic fluid index of less than two centimeters, or decreased end diastolic flow in the umbilical artery. The following outcomes were noted for each patient: 10 cases of neonatal jaundice requiring phototherapy, hypoglycemia (glucose <2.6 mmol/L), respiratory distress requiring respiratory support, congenital anomalies, shoulder dystocia, prematurity [<37 weeks gestation], birth weight, birth weight centile for gestational age, and so on.

Statistical analysis

The data analysis was done by using SPSS version 20. Chi square test with the fissure exact test was used instead of Chi square when any cell present with expected value less than 5. The t-rest for independent two mean was used for the numerical data. The p-value ≤ 0.05 considered as significant.

RESULTS

The baseline characteristics were showed in table (1) which revealed that the mean age among metformin group was 31.52±3.7 years while among the insulin group was 32.45±4.9; the difference was statistically not significant. The mean level of HbA1c among the Metformin group (5.1±0.7) was significantly lower (p=0.000) than that among the insulin group (5.9±0.4). Regarding the BMI at the early pregnancy, the women in

the Metformin group significantly higher BMI (p=0.021) in comparison to those in the insulin group. Family history found positive in 22.3% of the Metformin group and in 12.1% of the insulin group with a statistically significant difference (p=0.038) The previous gestational diabetes showed no statistically significant difference between the studied groups.

Table (1): Maternal characteristics at baseline.

Maternal characteristics at baseline.	Metformin group n=127	Insulin group n=99	p-value
Mean age in years /(mean± SD)	31.52±3.7	32.45±4.9	0.105*
HbA1c /(mean± SD)	5.1±0.7	5.9±0.4	**0.000***
Early pregnancy BMI/ (mean± SD)	31.8±6.7	29.4±8.8	**0.021***
Family history of DM /No.(%)	29(22.3%)	12(12.1)	**0.038****
Previous gestational diabetes	13(10.2%)	9(9.1%)	0.773**
*t-test for independent two means;**Chi square test			

The maternal pregnancy outcomes was demonstrated in table (2). It elicited that the induction of labour was done in 11.0% and 26.3% of the Metformin and insulin groups respectively with a statistically significant difference (p=0.003). The total cesarean section among the Metformin group (23.6%) was significantly lower (p=0.037) than that among the insulin group (36.4%); moreover, the elective cesarean section was found in 17.3% of the Metformin group and in 8.1% of the insulin group while the emergency cesarean section was done in 6.3% of Metformin group and in 32.3% of insulin group; the differences were statistically significant at (p=0.042) and (p=0.000). Postnatal OGTT glucose was performed for all the studied sample and showed no significant difference at fasting while after 2 hours, the Metformin group (4.9±1.2) showed significantly lower mean (p=0.000) than that of insulin group (5.6±1.7). Abnormal postnatal GTT among the Metformin group found in 7.1% while among the insulin group found in 21.2% with a statistically significant difference (p=0.002). Diabetes was found in 0.8% of Metformin group and in 7.1% of insulin groups; the difference was significant at (p=0.022). The impaired glucose tolerance found in 6.3% of the Metformin group and in15.2% of insulin group with a statistically significant difference (p=0.029). The impaired fasting glucose showed no significant difference.

Table (2): Maternal outcomes.

Maternal outcomes		Metformin group n=127	Insulin group n=99	p-value
Pre-eclampsia/ No.(%)		2(1.6%)	5(5.1%)	0.244*
Induction of labour/ No.(%)		14(11.0%)	26(26.3%)	**0.003****
Caesarean delivery/ No.(%)	Total	30(23.6%)	36(36.4%)	**0.037****
	Elective	22(17.3%)	8(8.1%)	**0.042****
	Emergency	8(6.3%)	32(32.3%)	**0.000****
Postnatal OGTT glucose	Fasting	4.7±1.1	4.9±1.4	0.230***
	2 hour	4.9±1.2	5.6±1.7	**0.000*****
Abnormal postnatal GTT/ No.(%)		9(7.1%)	21(21.2%)	**0.002****
Diabetes / No.(%)		1(0.8%)	7(7.1%)	**0.022***
Impaired fasting glucose no./total no.		6(4.7%)	11(11.1%)	0.071**
Impaired glucose tolerance no./total no.		8(6.3%)	15(15.2%)	**0.029****
*Fisher Exact test;**Chi square test;***t-test for independent two means				

The comparison of perinatal outcomes was demonstrated in table (3) between the Metformin and insulin groups and revealed that there were no statistically significant difference found concerning the congenital abnormalities, birth weight, preterm, hypoglycemia, neonatal nit admission, and shoulder dystocia. Jaundice requiring phototherapy was found in 4.7% of Metformin group and in 17.2% of insulin group; the difference was statistically significant (p=0.002).

Table (3): Perinatal outcomes.

Perinatal outcomes	Metformin group n=127	Insulin group n=99	p-value
Congenital abnormalities/ No. (%)	9(7.1%)	13(13.1%)	0.128*
Birth weight (BW) in g/ mean+ SD	3421.4±466	3565.8±989	0.148**
Preterm (<37 weeks)/No.(%)	15(11.8%)	21(21.2%)	0.055*
Jaundice requiring phototherapy/ No.(%)	6(4.7%)	17(17.2%)	**0.002***
Hypoglycaemia /No.(%)	10(7.9%)	11(11.1)	0.406
Neonatal unit admissions/No.(%)	14(11.0%)	18(18.2%)	0.126*
Shoulder dystocia/No.(%)	2(1.3%)	2(2.0%)	1.000***
*Chi square test; ** t-test for independent two means;*** Fisher Exact test			

DISCUSSION

Although some prior research combined metformin and insulin therapies alongside food interventions for both trial arms, to our knowledge no randomized trials (RCTs) directly evaluated the benefits of metformin to dietary/lifestyle interventions in pregnancy. An elevated risk of unfavorable consequences for the mother and the fetus is closely associated with uncontrolled gestational diabetes. The best pharmacologic treatment for GDM is debatable when women do not reach euglycemia by lifestyle changes.[19] Insulin has always been the go-to medication for GDM. Metformin may be a suitable substitute for insulin in the treatment of gestational diabetes.[20] This is supported by more recent evidence, such as the Metformin in Gestational Diabetes (MiG) experiment. Comparing the effectiveness of metformin and insulin in the management of gestational diabetes was a major goal of our research.

In the current study, the maternal age among both group showed no significant difference. Similarly, Awad *et al.*,[21] found that there was no significant differences between the two groups regarding maternal age. The women treated by Metformin in the present study had lower level of HbA1c than the women on insulin regimen. Prior research revealed that there was a statistically significant difference in the mean HbA1c among the metformin group when glycosylated hemoglobin was evaluated at the 37th week. According to the findings of Mesdaghinia *et al.*, study,[22] the metformin group's HbA1c levels were noticeably lower. This is consistent with the well-established theory that metformin primarily functions by inhibiting the synthesis of glucose by the liver, which lowers fasting plasma glucose levels and HbA1c, as documented by the George and McCrimmon study.[23] BMI of women receiving Metformin was higher than those on insulin only at early pregnancy, this result was identical to that reported by Simeonova-Krstevska *et al.*,[24] and by McGrath *et al.*,[25] Positive family history in the current study was found significantly much higher among the Metformin group in comparison to insulin group. While the family history was positive in insulin group higher than that among the Metformin group in Simeonova-Krstevska *et al.*, study.[24]

No difference was found in the current study regarding the preeclampsia between the studied groups. Simeonova-Krstevska *et al.*, study.[24] found that the preeclampsia was significantly higher among the Metformin group comparing to insulin group.

The induction of labour in the present study was significantly higher among the insulin group than the that among the Metformin group, which was corresponding to that of Picón-César *et al.*, study.[26] reported that labor inductions 45.7% of metformin group vs 62.5% of insulin group (p=0.029). Also, Huhtala *et al.*,[27] reported similar pattern. The mode of deliveries in the current study distributed as 23.0% and 36.4% respectively among the Metformin and diet groups as cesarean section (CS) with significant difference between the two studied groups. Most of women with Metformin treatment had elective CS while most of those received diet only underwent emergency CS. It was evident from the Awad *et al.*,[21] study that patients on insulin (30.8%) had substantially higher cesarean section (CS) deliveries owing to macrosomia than patients on metformin (16.7%), with a 2:1 ratio. However, the rate of CS was found to be negligible for both the insulin and metformin groups, at 78.0% and 76.6%, respectively. This was consistent with findings by Gui *et al.*,[28] and Tertti *et al.*,[29] indicating both groups' cesarean section rates were comparable. Ijäs *et al.*,[30] did discover, however, that the metformin group had a higher rate of Cesarean deliveries than the insulin group. In the current study, a statistically significant difference was observed between the groups as follows: abnormal postnatal GTT was detected in 7.1% of the Metformin group and 21.2% of the diet group. In parallel, Picón-César *et al.*, study.[26] found that the mean fasting and postprandial glycemia did not differ between groups, but postprandial glycemia was significantly better after lunch or dinner in the metformin-treated-group. We discovered that there was a negligible statistical difference between the two groups during the final week of delivery for the two-hour postprandial glucose levels. According to Ghomian *et al.*,[31] there was no statistically significant difference observed between 2 hours postprandial throughout the course of treatment until delivery. Furthermore, in terms of 2-hours plasma glucose (2hPG), a meta-analysis conducted by Guo *et al.*,[32] found no statistically significant difference between the insulin and metformin groups. Congenital anomaly showed no significant difference in the current study between the studied groups. Which was corresponding to the result of

Kjerpeseth *et al.*,[33] No significant difference was found between the studied groups in the current study concerning the birth weight. Picón-César *et al.*, study.[26] showed no significant difference between Metformin and insulin groups concerning the birth weight. While Ainuddin *et al.*,[34] showed that birth weight was significantly less in metformin treated groups (3.4 ± 0.4 kg vs. 3.3 ± 0.5 kg vs. 3.7 ± 0.5 kg $P < 0.01$). The prematurity in the current study showed no significant difference. Similarly, Bao *et al.*,[35] study reported that Metformin did not increase premature delivery ($p = 0.11$). Moreover, Balani *et al.*, study.[36] found that prematurity did not decrease as a result of metformin treatment. The current study found increase in neonatal jaundice requiring phototherapy in the insulin group in comparing to the metformin group. This was in contrast to the previously observed studies.[36,37] In correlation with the previous studies.[29,30] the incidence of neonatal hypoglycemia was reduced in the metformin group in comparison to the insulin group. Additionally, McGrath *et al.*,[25] discovered that the rate of neonatal hypoglycemia was the same for women treated with metformin alone as it was for the group that modified their diet and lifestyle (10.4% vs. 6.1%; $p = 0.497$). In the current study, the NICU was not differed between the studied groups. Similarly, Priya and Kalra study,[38] showed that there have been fewer admissions of neonates to the NICU than insulin use. While in studies conducted by Rai *et al.*,[39] and Balani *et al.*,[35] NICU admissions were significantly lower in metformin groups as compared to insulin group. Shoulder dystocia showed no significant difference between the studied groups which run in parallel to McGrath *et al.*,[25] and Spaulonci *et al.*,[40] which reported no difference in the incidence of shoulder dystocia with metformin compared to those managed with insulin.

CONCLUSION

Both, the women treated by metformin and insulin showed significant differences concerning induction of labour, caesarean delivery, postnatal OGTT glucose in favored of Metformin. Moreover, Jaundice requiring phototherapy was lower among the child of women among the Metformin group.

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