Al-Azhar University Journal
for Virus Research and Studies

# Metformin versus Insulin in the Management of Pregnant Women with Gestational Diabetes Mellitus

**Marwa Mohammed Fathi[1], Iman Bayoumi Abd Rabou[1], and Iman Ibrahim Al-Noor[1]**

**[1]Department of Obstetrics and Gynecology, Faculty of Medicine for Girls, Al-Azhar University**

***E-mail: dr_marwa_fathi91@yahoo.com**

## Abstract

Gestational diabetes mellitus is a major and prevalent pregnancy-related complication. Its identification and treatment improve perinatal outcomes. Aim is to assess the efficacy and short-term safety of Metformin versus Insulin in relation to maternal, fetal and neonatal outcomes in gestational diabetes mellitus after 20 weeks gestation. This is a prospective randomized study, carried out at the Diabetic Clinic of Nasser central hospital, from July 2020 to May 2021. The study included 85 pregnant women with gestational diabetes mellitus, were classified into 2 groups: *Group (A)* included 43 women received insulin and group (B) included 42 women received metformin. Fasting, random, postprandial blood glucose (PPBG), HbA1c, were determined. Primary outcome (diabetic control) and secondary outcome (maternal and neonatal outcome) were assessed. Regarding demographic characteristics, no significant difference was found. Regarding diabetic control, both Insulin and metformin achieved good comparable diabetic control. Similar results were found in HbA1C after 1, 2 and 3 months of treatment in both groups. The birth weight was significantly lower in Metformin group. While, the 5 minutes APGAR score was significantly higher in Metformin group. No significant differences were noticed regarding almost all neonatal outcome in terms of macrosomic baby, prematurity, shoulder dystocia, respiratory distress, neonatal jaundice, neonatal hypoglycemia and NICU admission. There was non-significant decrease in the percentage of macrosomic baby, neonatal hypoglycemia and NICU admission in the Metformin group. Metformin has efficacy as that of insulin in glycemic control of GDM and it may reduce the risk of some adverse neonatal outcomes.

**Keywords:** Metformin, Insulin, Management, Gestational diabetes mellitus.

## 1. Introduction

Gestational diabetes mellitus (GDM) has been agreed upon as any degree of glucose intolerance that develops or is first recognized during pregnancy. It is one of the most prevalent medical problems of pregnancy, and it is characterized by relative insulin deficiency that leads to maternal hyperglycemia [1]. The global incidence rate of GDM was estimated to be between 1 to 28% [2].

Approximately 204 million women had GDM around the world in 2017, with the number expected to rise to 308 million by 2045, primarily in developing countries [3]. GDM has been linked to an increased risk of pregnancy-induced hypertension and

preeclampsia, as well as a significantly higher risk of developing type 2 diabetes and comorbidities such as cardiovascular diseases latterly in mothers [4].

In terms of pregnancy outcomes, offspring have greater potentials to be macrosomic, and have birth trauma at delivery, and they are more likely to have juvenile obesity, poor glucose tolerance, and vascular problems after birth. In addition, new evidence suggests that these youngsters are at a higher risk for autism and have a lower IQ. (Intelligence Quotient) [5].

For a long time, insulin has been considered the pharmacological medication of choice in the management of GDM during pregnancy. Nonetheless, the requirement for regular subcutaneous injections has caused many individuals a great deal of discomfort. Furthermore, it has been linked to an increased risk of hypoglycemia as well as weight gain in mothers [6]. Other disadvantages of Intensive Insulin Therapy include higher costs, the necessity for numerous daily injections and more frequent SMBG (Self-Monitoring Blood Glucose), as well as more time investment by health-care providers and more frequent clinic visits [4]. Oral anti-diabetic medicines, mainly Metformin, have been studied for their efficacy and safety. Metformin is a biguanide treatment that regulates serum glucose levels by modifying hepatic metabolism, reducing gluconeogenesis, and lowering peripheral insulin resistance [7].

Metformin has a number of characteristics that make it an appealing option for the treatment of GDM, including an oral method of administration, low cost, less intense monitoring, easy dose titration, and a reduced risk of hypoglycemia {5} Clinical evidence of better outcomes, such as decreased maternal weight gain, lower risk of pregnancy-induced hypertension (PIH), lower risk of neonatal hypoglycemia, neonatal intensive care unit (NICU) admission, and macrosomia [8], backs this notion. The medication's most common side effects include gastrointestinal symptoms like nausea, vomiting, a metallic taste, and diarrhea, which can be mitigated by being involved meals. [9].

Vitamin B12 malabsorption with long-term dose, moderate erythema in hypersensitive individuals, and, in rare cases, lactic acidosis [1] are less prevalent side effects. Metformin is more convenient to take than insulin, which has led to an increase in its popularity among physicians and patients. Despite the fact that extensive study into the efficacy and safety of this drug has filled the pages of numerous scientific journals, the data have not been sufficiently convincing, and hence further research is being conducted with persistence [10].

The aim of this work is to assess the efficacy and short-term safety of Metformin versus Insulin in relation to maternal, fetal and neonatal outcomes in gestational diabetes mellitus (GDM) after 20 weeks gestation.

## 2. Patients and Methods

This is a prospective randomized study that was carried out at the Diabetic Clinic of Nasser central hospital during the period from July 2020 for May 2021. The study included a total of 85 pregnant women with gestational diabetes mellitus who were randomly classified into two groups: Group (A) Insulin group which included 43 women received insulin and group (B) Metformin group which included 42 women received metformin.

### 2.1 Ethical approval

Approval of ethical committee was obtained from quality education assurance unit, Al-Azhar university, faculty of medicine, Egypt. The data used in this work were confidential and was used only for a scientific purpose.

## 2.2 Methods

Group (A) Insulin group (n=43) which included women received insulin (the starting dose was 0.7 units/kg/day, with 2/3 of the dose being administered in the morning "before breakfast", and 1/3 in the evening at 8 PM "before dinner" and group (B) Metformin group (n=42) which included women received an initial metformin dose of 500 mg/once daily with food and increased 500 mg every one or two weeks (according to patient's blood glucose investigations) toward targets (FBG below 95 mg/dl and 2-hr postprandial blood glucose below 120 mg/dl) or up to a maximum daily dose of 1500 mg divided doses with each meal.

The Inclusion criteria were Pregnant women with single fetus at second trimester (after 20 weeks gestation) and have been diagnosed with GDM, failed to achieve glycemic control with exercise and diet during one week (When fasting blood glucose (FBG) levels exceed 105 mg/dl,or 1 hr PG exceeds 155 mg/dl and 2 hrs PG exceeds 130 mg/dl) then diet and exercise regimens was not be sufficient and starting a medication would be necessary, Absence of pre-gestational diabetes mellitus and absence of lactic acidosis risk factor (as having kidney problems or congestive heart failure).

While the exclusion criteria were Pregnant women with preexisting diabetes mellitus, Chronic heart diseases, Presence of congenital fetal anomalies, Hypersensitivity to metformin, Underlying diseases known to affect fetal growth or drug clearance such as severe chronic hypertension, thyroid disease, chronic renal insufficiency, hepatic disease, thrombophilia, systemic lupus erythromatosis and history of intrauterine growth retardation and BMI >30.

All included women were subjected to full history taking, general and abdominal examinations and sonographic evaluation. Fasting, random and postprandial blood glucose (PPBG), HbA1c, CBC, liver function tests, RH, were determined. All infants examined immediately after birth to be assessed for any congenital malformations and birth weight. laboratory investigations performed by the pediatrician on the newborn, such as heel stick glucose, bilirubin levels for neonatal jaundice.

Comparison was done between the two groups regarding the effect of each drug on Primary outcome (diabetic control) including FBG and PPBG and HbA1c, Secondary outcome including amniotic fluid index (AFI) (poly hydramnios), macrosomic baby, mode of delivery, Gestational age at delivery, birth weight (gm) and fetal condition at delivery (APGAR score) And neonatal complications including Prematurity, Shoulder dystocia, Respiratory distress, Neonatal jaundice, Neonatal hypoglycemia, and NICU admission.

## 2.3 Statistical analysis

The collected data statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences software version 22.0, IBM Corp., Chicago, USA, 2013.

Descriptive statistics was done for quantitative data as range, mean and SD "standard deviation", and for qualitative data as number and percentage.

In qualitative data, inferential analyses for independent variables were done using Chi square test for differences between proportions and Fisher's exact test for variables with small, expected numbers. The level of significance was below 0.050 (P value < 0.050).

## 3 .Results

The study initially included 94 pregnant women with regular antenatal care having GDM and met all our inclusion criteria. These cases were divided into two groups; Group (A) Insulin group, that initially included 45 women received insulin than 2

cases in this group lost for follow up, and the finally analyzed cases in insulin group were 43 cases. Group (B) Metformin group, that initially included 49 women received metformin, then 2 cases in this group lost for follow up and 6 cases needed supplementary insulin therapy, so the finally analyzed cases in metformin group were 42 cases **(Figure 1).**

No significant statistical differences were noticed between the two studied groups regarding baseline and demographic characteristics. (**Table 1&2**) Regarding diabetic control, both Insulin and metformin achieved good comparable diabetic control, there were no significant differences between insulin and metformin groups regarding both basal (values at joining the study) fasting blood sugar and their values after 2 months. The reduction in FBG after 2 months of treatment was highly significant in both insulin and metformin groups ($p<0.01$**).** Table. 1 show that there was no statistically significant difference between the two studied groups regarding the demographic data (Age and BMI). Table. 2 shows that (46.5 %) of patients in Group A were multi para, and (47.6 %) of patients in Group B were also multi para. So that there was no statistically significant difference between the two studied groups regarding gestational age ($p = 0.95$) and parity ($p = 0.49$). Table. 3 shows that there were no statistically significant differences between the two studied groups regarding positive family history of some chronic diseases. Table.4 showed that the reduction in both basal FBG and after 2 months of treatment was highly significant in both groups ($p <0.01$). Table. 5 showed that the change (reduction) in both basal 2h PPBG and after 2 months of treatment was highly significant in both groups ($p<0.01$)**.** Also, similar results were found in 2-hour PPBG, its decrease after 2 months of treatment was highly significant ($p<0.01$) in both groups Table. 5. Similar results were found in HbA1C after 1, 2 and 3 months of treatment in both groups Table. 6.

.

**Table (1):** Comparison between the two study groups regarding demographic data.

| Variable | Groups | | P. value (Sig.) |
|---|---|---|---|
| | Group (A) Insulin (n=43) | Group (B) Metformin (n=42) | |
| **Age (years)** | 25.3 ± 3.9 (19.0-34.0) | 25.5 ± 4.6 (19.0-33.0) | $0.81^{NS}$ |
| **Body mass index (BMI) ($kg/m^2$)** | 26.5 ± 1.4 (24.0-29.0) | 26.6 ± 1.7 (22.0-29.0) | $0.91^{NS}$ |

**Table (2):** Comparison between the two study groups regarding obstetric data.

| Variable | | Groups | | P. value (Sig.) |
|---|---|---|---|---|
| | | Group (A) Insulin(n=43) | Group (B) Metformin(n=42) | |
| Gestational age (wks.) | | 26.0 ± 1.8 (21.0-29.0) | 25.9 ± 1.7 (23.0-29.0) | 0.95$^{NS}$ |
| Parity | G1 P0 | 19 (44.2%) | 18 (42.9%) | 0.49$^{NS}$ |
| | G2 P0 A1 | 4 (9.3%) | 4 (9.5%) | |
| | G2 P1 | 2 (4.7%) | 1 (2.4%) | |
| | G3 P1 A1 | 1 (2.3%) | 0 | |
| | G3 P2 | 5 (11.6%) | 7 (16.7%) | |
| | G4 P2 A1 | 3 (7.0%) | 3 (7.1%) | |
| | G4 P3 | 7 (16.3%) | 6 (14.3%) | |
| | G5 P1 A3 | 0 | 1 (2.4%) | |
| | G5 P2 A2 | 0 | 2 (4.8%) | |
| | G5 P4 | 2 (4.7%) | 0 | |

**Table (3):** Comparison between the two study groups regarding positive family history of some chronic diseases.

| Variable | Groups | | P. value (Sig.) |
|---|---|---|---|
| | Group (A) Insulin (n=43) | Group (B) Metformin (n=42) | |
| **Type I DM** | **4** | **3** | 0.97$^{NS}$ |
| **Type II DM** | **1** | **2** | 0.99$^{NS}$ |
| **Hypertension (HTN)** | **3** | **4** | 0.97$^{NS}$ |
| **Thyroid Dysfunction** | **0** | **0** | 1.0$^{NS}$ |
| **Chronic kidney disease (CKD)** | **0** | **1** | 0.99$^{NS}$ |
| **Ischemic heart disease (IHD)** | **1** | **0** | 0.99$^{NS}$ |

**Table (4):** Comparison between the two study groups regarding the levels of FBG.

| Variable | | Groups | | P. value (Sig.) |
|---|---|---|---|---|
| | | Group (A) Insulin (n=43) | Group (B) Metformin (n=42) | |
| FBG (mg/dl) | Basal | 115.1 ± 5.7 (105-125) | 116.4 ± 6.8 (105-127) | 0.33$^{NS}$ |
| | After 2 months | 77.9 ± 2.5 (74-83) | 78.5 ± 3.4 (75-87) | 0.35$^{NS}$ |
| P. value (Sig.) | | <0.01** | <0.01** | |

**T-test was used, NS Not significant, * Significant (p<0.05) , ** highly Significant (p<0.01), FBG (Fasting Blood Glucose)**

**Table (5):** Comparison between the two study groups regarding the level of 2hrs post prandial blood glucose (2h PPBG).

| Variable | | Groups | | P. value (Sig.) |
|---|---|---|---|---|
| | | Group (A) Insulin (n=43) | Group (B) Metformin (n=42) | |
| 2hrs. PPBG (mg/dl) | Basal | 174.8 ± 10.4 (161-194) | 175.5 ± 9.4 (161-193) | $0.75^{NS}$ |
| | After 2 months | 109.4 ± 4.6 (105-120) | 110.9 ± 4.4 (104-118) | $0.13^{NS}$ |
| P. value (Sig.) | | <0.01** | <0.01** | |

T-test was used, NS Not significant, * Significant (p<0.05), ** highly Significant (p<0.01) 2h PPBG ( 2hrs post prandial blood glucose).

**Table (6):** Comparison between the two study groups regarding HbA1C.

| HbA1C | Groups | | P. value (Sig.) |
|---|---|---|---|
| | Group (A) Insulin (n=43) | Group (B) Metformin (n=42) | |
| Basal | 5.77 ± 0.52 (4.90-6.70) | 5.91 ± 0.50 (4.80-6.80) | $0.21^{NS}$ |
| 1 Month after treatment | $5.32^{\#}$ ± 0.48 (4.50-6.20) | $5.44^{\#}$ ± 0.46 (4.40-6.30) | $0.25^{NS}$ |
| 2 Months after treatment | $4.89^{\#}$ ± 0.41 (4.0-5.60) | $4.95^{\#}$ ± 0.45 (4.0-5.60) | $0.49^{NS}$ |
| 3 Months after treatment | $4.63^{\#}$ ± 0.44 (4.0-5.80) | $4.70^{\#}$ ± 0.41 (3.90-5.80) | $0.47^{NS}$ |
| P. value (sig) | <0.01 | <0.01 | |

**T-test was used, NS Not significant, # Significant difference compared to basal (p<0.01).**

Table. 6 shows that no statistically significant differences were noticed between insulin and Metformin groups in basal HbA1C, and its values after 1, 2 and 3 months of treatment, almost both groups were similar with slightly more reduction in insulin group. HbA1C was decreased after 1, 2 and 3 months of treatment as compared to basal values in both groups. In addition, a significant reduction in HbA1C was achieved at 3 months after treatment as compared to the 1- and 2-months values in both groups**.** The maternal weight gain was significantly higher in insulin group compared to Metformin group (p<0.01). and the birth weight was also significantly higher in insulin group (p<0.01). There were not statistically significant differences between the two study groups in AFI (p=0.74), and gestational age at delivery (p=0.35) Table. 7. Table. 7 shows that the maternal weight gain was significantly higher in insulin group compared to Metformin group (5.02 ± 0.76 vs. 4.51 ± 0.56, p<0.01)**.** And also, the birth weight was significantly lower in Metformin group compared to insulin group (3.44 ± 0.31 vs. 3.62 ± .34, p<0.01)**.** While there were no statistically significant differences between the two study groups in AFI (p=0.74), gestational age at delivery (p=0.35) **,**while, the 5 minutes APGAR score was significantly higher in Metformin group compared to Insulin group (p<0.01) Table 8. No statistically significant differences were noticed between insulin and Metformin groups regarding almost all neonatal outcome in terms of macrosomic baby, prematurity, shoulder dystocia,

respiratory distress, neonatal jaundice, neonatal hypoglycemia and NICU admission. But there was a non-significant decrease in the percentage of macrosomic baby, neonatal hypoglycemia and NICU admission in the Metformin group Table. 9. Table. 9 revealed that the APGAR score at delivery was almost similar in both groups with no statistically significant differences (p=0.19) while, the after 5 minutes APGAR score was significantly higher in Metformin group compared to Insulin group (9.11 ± 0.94 vs. 8.23 ± 1.17, p<0.01). -This table revealed that there were no statistically significant differences between insulin and Metformin groups regarding almost all neonatal outcome. But there was a non-significant decrease in the percentage of (macrosomic baby, neonatal hypoglycemia and NICU admission) in the Metformin group. While there was also a non-significant decrease in the percentage of (prematurity, respiratory distress and neonatal jaundice) in the Insulin group.

**Table (7):** Comparison between the two study groups regarding secondary outcomes including maternal weight gain and birth weight.

| Variable | | Groups | | P. value (Sig.) |
|---|---|---|---|---|
| | | Group (A) Insulin (n=43) | Group (B) Metformin (n=42) | |
| Weight gained (Kg) | | 5.02 ± 0.76 (3.70-6.30) | 4.51 ± 0.56 (3.40-5.30) | <0.01** |
| Amniotic fluid index | | 12.6 ± 3.1 (8.0-18.0) | 12.8 ± 3.1 (8.0-18.0) | 0.74$^{NS}$ |
| Mode of delivery | Vaginal | 21 (48.8%) | 25 (59.5%) | 0.32$^{NS}$ |
| | Cesarean section | 22 (51.2%) | 17 (40.5%) | |
| Gestational age at delivery (wks.) | | 38.2 ± 1.3 (36.0-40.0) | 38.0 ± 1.4 (36.0-40.0) | 0.53$^{NS}$ |
| Birth weight (kg) | | 3.62 ± 0.34 (3.15-4.27) | 3.44 ± 0.31 (3.0-4.15) | 0.01* |

**T-test and Chi square tests were used, NS Not significant, * Significant (p<0.05)**

**Table (8):** Comparison between the two study groups regarding APGAR score.

| APGAR score | Groups | | P. value (Sig.) |
|---|---|---|---|
| | Group (A)Insulin (n=43) | Group (B)Metformin (n=42) | |
| At delivery | 7.26 ± 1.60 (6.0-10.0) | 7.64 ± 1.0 (5.00-9.0) | 0.19$^{NS}$ |
| After 5 minutes | 8.23 ± 1.17 (6.0-10.0) | 9.11 ± 0.94 (6.0-10.0) | <0.01** |

**Table (9):** Comparison between the two study groups regarding neonatal outcome.

| Variable | Groups | | P. value (Sig.) |
|---|---|---|---|
| | Group (A) Insulin (n=43) | Group (B) Metformin (n=42) | |
| Macrosomic baby | 4 (9.3%) | 1 (2.4%) | 0.18$^{NS}$ |
| Prematurity | 5 (11.6%) | 8 (19.0%) | 0.34$^{NS}$ |
| Shoulder dystocia | 1 (2.3%) | 1 (2.4%) | 0.99$^{NS}$ |
| Respiratory distress | 2 (4.7%) | 3 (7.1%) | 0.62$^{NS}$ |
| Neonatal Jaundice | 7 (16.3%) | 9 (21.4%) | 0.54$^{NS}$ |
| Neonatal Hypoglycemia | 3 (7.0%) | 2 (4.8%) | 0.66$^{NS}$ |
| NICU Admission | 4 (9.3%) | 1 (2.4%) | 0.18$^{NS}$ |

## 4. Discussion

Gestational diabetes mellitus (GDM) is a medical disorder in which a woman develops or recognizes -for the first time- carbohydrate intolerance throughout pregnancy. It is estimated that one out of every six pregnancies in the world is accompanied with hyperglycemia, and around 1–14 percent of women have GDM [5]. Regardless, the pathogenesis of GDM is unknown, but it has been linked to hormonal abnormalities that alter insulin sensitivity and pancreatic Beta cell dysfunction1 [11]. Our study results showed that there was no significant difference between the two studied groups regarding baseline data in terms of age, BMI, gestational age, parity and positive family history of chronic diseases (Table 1&2&3). This non-significant difference is important to ensure the homogenization of the studied groups to get accurate results from the comparison between groups. Our results agreed with a recent study [12] who conducted a prospective randomized clinical comparison study on 240 pregnant women complicated by GDM. They evaluated the efficacy and safety between insulin and metformin in the management of GDM. They found that the demographic and baseline characteristics of insulin or metformin groups in terms of age, parity, family history of DM, BMI, gestational age, blood pressure, blood sugar and HbA1C were similar with no significant differences. The current study results revealed that there were no significant differences between insulin and Metformin groups regarding both basal FBG (values when patients joined the study) and their values after 2 months of treatment. But the change (reduction) in FBG after 2 months of treatment was highly significant in both groups ($p<0.01$) (Table 4). Also, similar results were found in 2-hour PPBG, its decrease after 2 months of treatment was highly significant ($p<0.01$) in both groups (Table 5). Our results also showed non-significant differences between insulin and Metformin groups in basal HbA1C (its values at joining the study) and its values after 1, 2 and 3 months of treatment, almost both groups were comparable with slight reduction in insulin group. While HbA1C decreased significantly ($p<0.01$) after 1, 2 and 3 months of treatment as compared to basal values in both groups. In addition, a significant reduction in HbA1C was achieved at 3 months after treatment as compared to the 1- and 2-months values in both groups (Table 6).

Similar to our results, a study [13] who carried out a randomized clinical trial on 286 pregnant women with GDM who were between the ages of 24 and 28 weeks pregnant. They examined metformin and insulin's efficacy in managing blood glucose levels and prenatal outcomes in GDM patients. They detected no statistically significant variations in FPG levels or 2hr PG between the two groups (insulin vs. metformin) at the start of treatment or during the trial period. Furthermore, no statistically significant variations in HbA1c were found between the two groups during the therapy period until delivery.

The results of our study demonstrated that the maternal weight gain was significantly higher in insulin group compared to Metformin group ($5.02 \pm 0.76$ vs. $4.51 \pm 0.56$, $p<0.01$) (Table 7).

In line with our findings, a study [13], conducted a randomized clinical trial on 286 pregnant patients with GDM and gestational age between 24 and 28 weeks. They found that there was also no significant difference between the two groups regarding the mode of delivery.

Our study doesn't agree with a recent Meta-Analysis [14], that compared the efficacy and safety of Metformin and Insulin in the treatment of GDM. 16 studies with 2853 GDM patients included birth weight as an endpoint when comparing metformin and insulin. Three trials including 526 GDM patients indicated that elective cesarean

section was included as an endpoint when metformin and insulin were compared. When compared to insulin, metformin had a lower rate of elective cesarean section (RR, 0.73; 95 percent CI, 0.54 to 1.00; P = 0:05).

In our study the fetal birth weight was significantly higher in insulin group compared to Metformin group (3.62 ±.34 vs. 3.44 ± 0.31, p<0.01) (Table 7). There was 1 fetus (2.4%) with macrosomia in the metformin treated group, and 4 fetuses (9.3%) in insulin group, p = 0.18. The pooled results showed no significant difference between the two groups as regards the rate of large for gestational age (LGA) and small for gestational age (SGA) newborns.

In a recent Meta-Analysis [14] metformin and Insulin were compared for their efficacy and safety in treating GDM. 16 studies with 2853 GDM patients included birth weight as an endpoint when comparing metformin and insulin. Metformin was observed to have a lower birth weight than insulin (MD, 114.48; 95 percent CI, 37.32 to 191.64; P 0:01).

In our current study, there was no significant difference between the insulin and metformin groups in terms of gestational age at birth. GA was 38.0 1.4 weeks in the metformin-treated group and 38.2 1.3 weeks in the insulin-treated group at the time of delivery, p=0.53NS.

Our findings don't agree with a study [15], who conducted a randomized controlled trial on 88 pregnant women with GDM. They compared metformin versus insulin in the treatment of GDM in pregnant women and their effect on neonates and treatment effect on women up to 24-month post-partum follow-up. They found that the mean gestational age was higher in metformin group (metformin treated group was 39.13±1.02 weeks and insulin treated group was 38.52±1.69 weeks, p-value 0.003).

Our results revealed that the APGAR score at delivery was almost similar in both groups with no significant differences (p=0.19) while, the after 5 minutes APGAR score was significantly higher in Metformin group compared to Insulin group (9.11 ± 0.94 vs. 8.23 ± 1.17, p<0.01) (Table 8).

A study [16] found that APGAR score at delivery and the after 5 minutes APGAR were non-significantly lower in insulin treated group than in metformin treated group.

Regarding neonatal outcome in our study, no significant differences were noticed between groups regarding almost all neonatal outcome in terms of macrosomic baby (p=0.18), prematurity (p=0.34), shoulder dystocia (p=0.99), respiratory distress (p=0.62), neonatal jaundice (p=0.54), neonatal hypoglycemia (p=0.66) and NICU admission (p=0.18). Also, there was non-significant decrease in the percentage of (macrosomic baby "1(2.4%) ", neonatal hypoglycemia"2(4.8%)" and NICU admission"1(2.4%)" in the Metformin treated group. While there was also non-significant decrease in the percentage of (prematurity" 5(11.6%)", Respiratory distress"2(4.7%)" and neonatal jaundice"7(16.3%)" in the Insulin treated group (Table 9).

Our present results are agreed a study [12], who found no significant differences between Insulin and metformin groups with regard to neonatal hypoglycemia (P = 0.11), fetal macrosomia (P = 0.71), 5-min Apgar score less than 7 (P = 0.6), respiratory distress syndrome (P = 1), phototherapy (P = 1), and NICU admission (P = 0.8) or mode of delivery (P = 0.76).

## 5. Conclusion

Metformin has efficacy as that of insulin in glycemic control of GDM. Also, metformin group had lower maternal weight gain and their neonates had low birth weight compared to insulin exposed neonates. Metformin may reduce the risk of some negative neonatal outcomes such as macrosomia, hypoglycemia and NICU admission. Metformin is administered

through the gastrointestinal tract, has no storage issues, and does not cause dependence. With all of these advantages, metformin is a better choice for women with GDM than insulin.

### 6. Recommendation

Based on our study results, Metformin has efficacy as that of insulin in glycemic control of GDM. Also, metformin group had lower maternal weight gain and their neonates had low birth weight compared to insulin exposed neonates.
Furthermore, studies are needed to study research questions about the efficacy and short-term safety of Metformin in treatment of GDM.

**Funding Sources:** There was no support for this study from any governmental, private, or non-profit organization.
**Conflicts of interest:** no competing interests.

## References

1. Burlina S, Dalfrà MG, Lapolla A. Clinical and biochemical approach to predicting post-pregnancy metabolic decompensation. Diabetes Res Clin Pract, 2018;145:178–183.
2. Hod M, Kapur A, Sacks A. The international Federation of Gynecology and Obstetrics (FIGO). Initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management, and care. J Gynecol Obstet 131(Suppl 3) 2015, S173–S211.
3. Yahaya, T.; Anyebe, D. Genes predisposing to neonatal diabetes mellitus and pathophysiology: Current findings. J. Neonatal-Perinatal Med. 2020, 1–11.
4. Egan, A. M., Dow, M. L., & Vella, A. A Review of the Pathophysiology and Management of Diabetes in Pregnancy. Mayo ClinicProceedings. doi:10.1016/ j. mayocp.2020.02.019.
5. Dickens, L.T., Thomas, C.C. Updates in Gestational Diabetes Prevalence, Treatment, and Health Policy. Curr Diab Rep 19, 33(2019). https://doi.org/ 10.1007/s11892-019-1147-0.
6. ADA; American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2018. Diabetes Care 2018, 41, S13–S27.
7. Saleh, H. S., Abdelsalam, W. A., Mowafy, H E., & Abd ElHameid, A. A. Could metformin manage gestational diabetes mellitus instead of insulin? International Journal of Reproductive Medicine, 2016, 3480629.
8. Landi SN, Radke S, Engel SM. Association of long-term child growth and developmental outcomes with metformin vs insulin treatment for gestational diabetes. JAMA Pediatr 2019;173: 160–8.
9. ACOG, Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. 2018; 131(2): e49-e64.
10. Spaight C, Gross J. Horsch A, Puder JJ. Gestational Diabetes Mellitus. Endocr Dev. 2016; 31:163-78. [PubMed].

11. Alejandro, E. U., Mamerto, T. P., Chung, G., Villavieja, A., Gaus, N. L., Morgan, E., & Pineda-Cortel, M. R. B. Gestational Diabetes Mellitus: A Harbinger of the Vicious Cycle of Diabetes. International Journal of Molecular Sciences (2020), 21(14), 5003.

12. Abdel Hamid A. N., Alaa M. Abd El-Gayeda, Ibarhim A. Saif-Elnasra, Mohamed H. Soliman. Comparison of the efficacy and safety between Insulin and Metformin in gestational diabetes mellitus management. Menoufia Medical Journal 2019, 32:1376–1381.

13. Ghomian N., Seyede Houra Mousavi Vahed. The efficacy of metformin compared with insulin in regulating blood glucose levels during gestational diabetes mellitus: A randomized clinical trial. J Cell Physiol. 2019 Apr;234(4):4695-4701.

14. Guo, L., Ma, J., Tang, J., Hu, D., Zhang, W., & Zhao, X. Comparative Efficacy and Safety of Metformin, Glyburide, and Insulin in Treating Gestational Diabetes Mellitus: A Meta-Analysis. Journal of diabetes research, 2019,9804708. https://doi.org/10.1155/2019/9804708.

15. Anwar Z, A. Anwar, S. Nighat. Metformin versus Insulin Treatment in Gestational Diabetes Mellitus: their effects on neonates and women in 24 months' follow-up. PJMHS, 2019, Vol. 13, No. 4, (10), 26-32.

16. El Gamal H., Mohamed Abd Elaleem 1, Sherif Sadek 2, Marwa R. Elhadary. Insulin versus Metformin in Treatment of Gestational Diabetes Mellitus (Randomized Controlled Clinical Trial). The Egyptian Journal of Hospital Medicine (July 2018) Vol. 72 (1), Page 3753-3761.