# Research Journal of Obstetrics & Gynecology

ISSN 1994-7925

science alert

ANSInet
an open access publisher
http://ansinet.com

OPEN ACCESS Research Journal of Obstetrics and Gynecology

ISSN 1994-7925
DOI: 10.3923/rjog.2019.23.27

# Research Article
# Metformin Versus Insulin in Treatment of Gestational Diabetes Mellitus: A Randomized Controlled Trial

[1]Mohammad Galal, [1]Walaa Mohammad El Bassioune and [2]Lobna Sherif

[1]Department of Obstetrics and Gynaecology, Faculty of Medicine, Al-Azhar University, New Damietta, Egypt
[2]Resident of Obstetrics and Gynaecology, Damietta General Hospital, Egypt

## Abstract

**Background and Objective:** Metformin as an oral anti-diabetic drug is an attractive option for control of gestational diabetes. However, its safety during pregnancy needs further evaluation. This study aimed to evaluate the safety and efficacy of oral medication (metformin) in comparison to insulin as regard maternal and neonatal outcome. **Materials and Methods:** Comparative prospective randomized controlled study was carried out in Obstetrics and Gynaecology Department, Al-Azhar University hospital (New Damietta) during the period from January, 2017-October, 2018. Pregnant women diagnosed with gestational diabetes mellitus were included. The first group received insulin while second group received metformin. Both groups were compared as regard maternal and neonatal outcome. **Results:** About 106 patients were included. About 50 patients received insulin and 56 patients received metformin. There were statistically significant differences as regard mean fasting and post prandial blood glucose level (92.42±4.93, 129.82±7.88 vs. 86.88±5.02, 117.30±8.84) and mean birth weight ( 3.52±0.14 vs. 2.99±0.12) in insulin and metformin group, respectively. Also, increased CS rate (81.5% vs. 57.7%) between insulin and metformin group, respectively. **Conclusion:** It was concluded that Metformin is more effective in controlling mild GDM with comparable maternal and neonatal outcomes to insulin therapy.

Key words: Gestational diabetes, insulin therapy, metformin, glycemic control, anti-diabetic drug, neonatal hypoglycemia

Citation: Mohammad Galal, Walaa Mohammad El Bassioune and Lobna Sherif, 2019. Metformin versus insulin in treatment of gestational diabetes mellitus: A randomized controlled trial. Res. J. Obstet. Gynecol., 12: 23-27.

Corresponding Author: Walaa Mohammad El Bassioune, Department of Obstetrics and Gynaecology, Faculty of Medicine, Al-Azhar University, New Damietta, Egypt Tel: 00201002223131



Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

## INTRODUCTION

Gestational Diabetes Mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy[1]. The definition applies whether insulin or only diet modification were used for treatment and whether or not the condition persists after pregnancy. Both type 1 diabetes and type 2 diabetes in pregnancy confer significantly greater maternal and fetal risk than GDM[2].

In general, specific risks of uncontrolled diabetes in pregnancy include spontaneous abortion, fetal anomalies, preeclampsia, fetal demise, macrosomia, neonatal hypoglycemia and neonatal hyperbilirubinemia. In addition, diabetes in pregnancy may increase the risk of obesity and type 2 diabetes in offspring later in life[3]. Traditionally, insulin has been the drug of choice for GDM management however, the use of oral agents has been increasing and the American College of Obstetrics and Gynaecology supports the use of either oral or injectable medications as acceptable therapies for women with GDM[2]. Oral medication is attractive options for GDM patients given their ease of administration, lower cost, comparable efficacy and improved adherence[4].

Metformin, an oral biguanide may be more logical alternative to insulin for women with GDM who are unable to cope with the increasing insulin resistance of pregnancy, metformin works primarily by decreasing hepatic glucose output, improving peripheral glucose uptake and decreasing free fatty acid levels, thus reducing insulin resistance without as much risk of resulting hypoglycemia[5]. The diabetes in pregnancy has been increasing day by day and the increase in GDM and type 2 diabetes in corresponding with obesity[6]. So, the aim of the present study was to evaluate the safety and efficacy of metformin as an oral anti-diabetic drug in comparison to insulin as an oral hypoglycemic drug for control of gestational diabetes mellitus.

## MATERIALS AND METHODS

**Type of study:** This comparative prospective randomized controlled study was carried out in Obstetrics and Gynaecology Department, Al-Azhar University Hospital (New Damietta) during the period from January, 2017 to October, 2018. The study was granted ethics approval by Al-Azhar, Faculty of Medicine Ethics Committee (ADIM-IRB23032019). Also, written informed consent was provided from all participants.

**Patients selection:** About 106 pregnant women with gestational diabetes mellitus enrolled in the study (using 75 g oral glucose tolerance test (OGTT), patient is considered diabetic if the plasma glucose fasting more than or equal 92 mg $dL^{-1}$, 1 h more than or equal 180 mg $dL^{-1}$, 2 h more than or equal[6] 153 mg $dL^{-1}$ and not controlled by diet, gestational age 28th-34th weeks, BMI[2]: 25-35 kg $m^{-1}$ and Singleton pregnancy.

In this study exclusion criteria included women with pregestational diabetes mellitus, renal or hepatic dysfunction, fetal congenital anomalies before enrolling in the study and previous adverse reaction to metformin.

**Interventions:** Patients were randomized (electronic randomization) into 2 groups. Group A (insulin group) 50 patients, received human insulin (combination of intermediate acting and short acting) given in divided doses with starting dose was 0.8 unit $kg^{-1}$/day, with 2/3 of the dose being administered in the morning (before breakfast) and 1/3 of the dose in the evening (before dinner). The doses were adjusted to achieve adequate glycemic control. If 1 h post prandial glucose levels were high, regular insulin (1 unit/30 mg $dL^{-1}$) over target value was added.

**Group B (metformin group):** About 56 patients, received metformin tablet with initial dose of 500 mg once daily and increased by 500 mg every one week and up to 2000 mg/day in divided doses if blood sugar not controlled. The study outcome measures were maternal and neonatal outcome.

**Maternal outcome:** The assessment of maternal outcome was made by glycemic control (Good glycemic control is considered if the fasting capillary blood glucose <95 mg $dL^{-1}$ and 1 h post prandial <140 mg $dL^{-1}$, 2 h post prandial[2] <120 mg $dL^{-1}$), mode of delivery, development of complications (as pre-term delivery and hypertension) and maternal weight gain).

**Neonatal outcome:** The assessment of neonatal outcome made by birth weight, APGAR score 1 and 5 min and neonatal hypoglycemia (defined as plasma glucose level (serum) <30 mg $dL^{-1}$ in the first 24 h of life and <45 mg $dL^{-1}$ thereafter[7]).

**Statistical analysis:** Data analysis was done using SPSS 21.0 computer based statistical software[8]. The results were statistically analyzed using independent sample student's t-test to compare numerical value and chi-square test or Fisher exact test to compare categorical data. The $p<0.05$ was considered statistically significant.

## RESULTS

The study included 106 pregnant women with gestational diabetes mellitus. About 50 patients received insulin and 56 patients received metformin. During follow up of metformin group, 19 patients were controlled by 500 mg metformin, 13 patients were controlled by 1000 mg metformin, 12 patients were controlled on 1500 mg metformin, 8 patients were controlled on 2000 mg metformin and 4 patients were uncontrolled and shifted to insulin (Fig. 1).

Both groups were comparable as regardage, gravidity, parity, gestational age, BMI, liver function, kidney function and urine analysis and both groups are not significantly different as shown in Table 1.

**As regard fasting and post-prandial blood glucose level:** There were statistically significant differences (92.42±4.93, 129.82±7.88) versus (86.88±5.02, 117.30±8.84) in insulin and metformin group, respectively (Table 2).

**As regard maternal outcome**

**Mode of delivery:** There were statistically significant differences; 81.5% vs. 57.7% and 18.5% vs. 42.3% for CS and VD rates between insulin and metformin group, respectively (Table 3).

**Maternal weight gain:** There were statistically significant differences (5.40±0.5 vs. 4.00±0.5) between insulin and metformin group, respectively (Table 3).

**Hypertension:** There were no statistically significant differences between 2 groups (Table 3).

Table 1: Characteristics of patients in both groups

| Parameters | Insulin group (N = 50) | Metformin group (N = 56) | p-value |
|---|---|---|---|
| **Age (years)** | | | |
| Range | 28-39 | 25-38 | 0.202# |
| Mean±SD | 32.82±3.02 | 31.98±3.49 | |
| **Gravidity** | | | |
| Range | 1-7 | 1-7 | 0.180♀ |
| Median (IQR) | 3 (2) | 3 (3) | |
| **Parity** | | | |
| Range | 0-6 | 0-6 | 0.907♀ |
| Median (IQR) | 2 (2) | 2 (3) | |
| **G.A (weeks)** | | | |
| Range | 28-34 | 28-34 | 0.710# |
| Mean±SD | 30.8±2.22 | 30.64±2.06 | |
| BMI (kg $m^{-2}$) | | | |
| Range | 26-34 | 28-33 | 0.654# |
| Mean±SD | 30.52±2.49 | 30.74±2.41 | |
| **Liver function tests** | | | |
| Normal | 50 (100%) | 56 (100%) | 1.00♀ |
| Abnormal | 0 (0%) | 0 (0%) | |
| **Kidney function tests** | | | |
| Normal | 50 (100%) | 56 (100%) | 1.00♀ |
| Abnormal | 0 (0%) | 0 (0%) | |
| **Urine analysis** | | | |
| Normal | 48 (96%) | 50 (92%) | 0.352♀ |
| Proteinuria | 2 (4%) | 6 (8%) | |

*Statistically significant (p<0.05), #Independent t-test used, ♀Fisher exact test used

Table 2: Comparison of mean glucose level between both groups after 1 week of treatment

| Mean glucose level | Insulin group (N = 50) | Metformin group (N = 56) | p-value |
|---|---|---|---|
| **Fasting** | | | |
| Range | 85-100 | 80-97 | 0.0001#* |
| Mean±SD | 92.42±4.93 | 86.88±5.02 | |
| **Post-prandial** | | | |
| Range | 110-140 | 105-135 | 0.0001#* |
| Mean±SD | 129.82±7.88 | 117.30±8.84 | |

*Statistically significant (p<0.05), #Independent t-test used

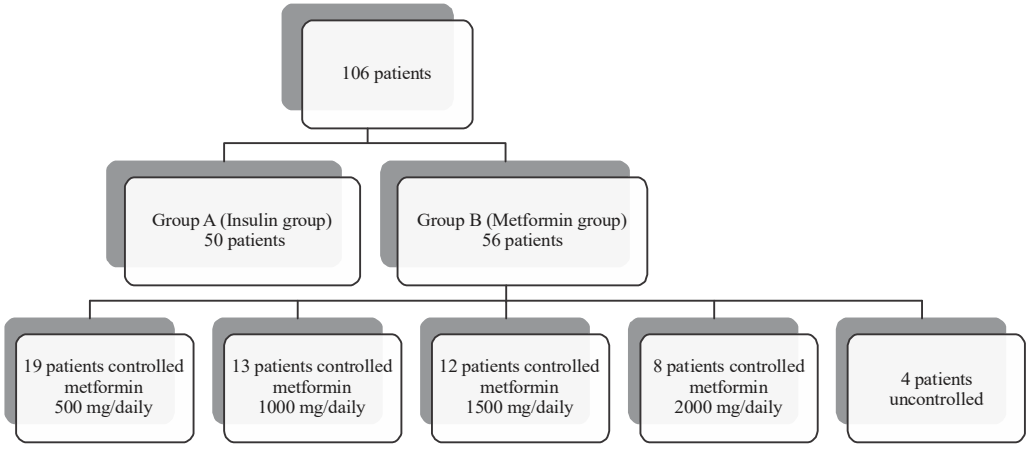


Fig. 1: Algorism for all cases in the study

Table 3: Comparison of maternal outcomes between both groups

| Maternal complications | Insulin group (N = 54) | Metformin group (N = 52) | p-value |
|---|---|---|---|
| Hypertension | 0(0%) | 0(0%) | 1.00[1] |
| Pre-term labor | 4(7.4%) | 7(13.5%) | 0.056[1] |
| **Mode of delivery** | | | |
| CS | 44(81.5%) | 30(57.7%) | 0.031[♀]* |
| VD | 10(18.5%) | 22(42.3%) | |
| Maternal weight gain (Mean±SD) | 5.4±0.5 | 4±0.5 | 0.024[♀]* |

*Statistically significant (p<0.05), [#]Fisher-exact test used, [♀]Chi-square test used

Table 4: Comparison of neonatal outcomes between both groups

| | | Metformin groups (N = 52) | | | | |
|---|---|---|---|---|---|---|
| Neonatal outcomes | Insulin group (N = 54) | 500 mg (N = 19) | 1000 mg (N = 13) | 1500 mg (N = 12) | 2000 mg (N = 8) | p-value |
| Birth weight (Mean±SD) | 3.52±0.14 | 3.21±0.11 | 3.14±0.12 | 3.36±0.12 | 2.99±0.12 | 0.046[#]* |
| Apgar 1 min (Mean±SD) | 7.28±0.6 | 7.76±0.4 | 7.48±0.6 | 7.38±0.7 | 7.45±0.6 | 0.035[#]* |
| Apgar 5 min (Mean±SD) | 8.90±1.0 | 9.80±0.3 | 9.60±0.4 | 9.70±0.6 | 9.60±0.6 | 0.052[#]* |
| **Serum glucose level (mg dL$^{-}$1)** | | | | | | |
| 1 h (Mean±SD) | 22.34±2.3 | 25.56±2.4 | 26.31±1.9 | 27.38±2.7 | 28.12±1.7 | 0.035[#]* |
| 2 h (Mean±SD) | 40.54±0.9 | 43.23±1.1 | 43.21±1.6 | 42.38±2.7 | 43.65±0.9 | 0.041[#]* |

*Statistically significant (p<0.05), [#]ANOVA test used

**Pre-term delivery:** There were statistically significant differences (7.4% versus 13.5%) between insulin and metformin group, respectively (Table 3).

**As regard neonatal outcome**

**Birth weight:** There were statistically significant differences (3.52±0.14 versus 2.99±0.12) between insulin and metformin group, respectively (Table 4).

**APGAR score (1 min):** There were statistically significant differences (7.28±0.6 versus 7.45±0.6) between insulin and metformin group, respectively (Table 4).

**APGAR score (5 min):** There were statistically significant differences (8.90±1.0 versus 9.60±0.6) between insulin and metformin group, respectively (Table 4).

**Serum glucose level (1 h):** There were statistically significant differences (22.34±2.3 vs. 28.12±1.7) between insulin and metformin group, respectively (Table 4).

**Serum glucose level (2 h):** There were statistically significant differences (40.54±0.9 vs. 43.65±0.9) between insulin and metformin group respectively (Table 4).

## DISCUSSION

There is an increased recommendation for the usage of metformin as an oral anti-diabetic drug for control of GDM. It is also recommended as a combination therapy for patients with type 2 diabetes[9]. These recommendations are based primarily on the glucose-lowering effects, relatively low cost and generally low level of side effects than insulin therapy[10].

In the present study, the glycemic control between both groups was higher in insulin group than metformin group and this agreed with Gui *et al.*[11]. It is also agreed with previous study that glycemic control was better with metformin after 1 week of therapy and also throughout gestation compared to insulin[12]. It was also reported that there is no major complications or perinatal deaths related to metformin uptake[13]. This proved that metformin considered clinically efficient, inexpensive and a harmless alternative to insulin therapy in pregnant diabetic women. The present study also investigated that, metformin intake during pregnancy was not associated with increasing rate of preeclampsia or neonatal complications and this agreed with Glueck *et al.*[14].

In the present study there was insignificant statistical difference as regard of pre-term delivery between 2 groups. However, the incidence of preterm labor was higher in metformin group than insulin group with insignificant statistical difference which is consistent with study done by Gui *et al.*[11] and Rowan *et al.*[15] and this may denote that metformin might have unrecognized effect on labor process. In the present study, the rate of caesarean section was also higher in insulin group versus metformin group with significant statistical differences. As regard maternal weight gain, it was higher in insulin group versus metformin group with significant statistical differences. The mean birth weight was also higher in insulin group than metformin group with significant statistical differences and these findings are agreed with another study[16].

Mean neonatal serum glucose level was lower in insulin group than metformin group significant statistical differences which is also consistent with a previous study[15] which found that the rates of neonatal hypoglycemia were similar in the two groups but sever hypoglycemia less than 28.8 mg $dL^{-1}$ occurred less often in infants of women taking metformin and this also agreed with Janet *et al.*[15] which showed that infants of metformin group had a lower rate of hypoglycemia compared with infants of insulin group. However, this study showed that metformin seems to be promising drug on the neonates but larger studies is recommended to establish the long-term outcomes in exposed offspring.

## CONCLUSION AND RECOMMENDATIONS

Metformin as an oral anti-diabetic drug was found to be safe and effective in controlling mild GDM with comparable maternal and neonatal outcomes to insulin therapy. Metformin was also, associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin. So the metformin was recommended over insulin in controlling gestational diabetes. These recommendations are based primarily on the glucose-lowering effects, relatively low cost and generally low level of side effects and more acceptable, with comparable maternal and neonatal outcome. However, the rate of pre-term delivery is slightly increased with metformin therapy.

## SIGNIFICANCE STATEMENT

This study showed that the use of metformin as oral hypoglycemic drug is safe and effective in controlling mild gestational diabetes mellitus in comparable with insulin and the benefit of avoiding the drawback of insulin. This study will help the researchers and clinician to carefully balance the risk-benefit profile of different treatments according to various situations.

## REFERENCES


1. American Diabetes Association, 2003. Gestational diabetes mellitus. Diabetes Care, 26: S103-S105.
2. Song, C., Y. Lyu, C. Li, P. Liu, J. Li, R.C. Ma and X. Yang, 2018. Long-term risk of diabetes in women at varying durations after gestational diabetes: A systematic review and meta-analysis with more than 2 million women. Obesity Rev., 19: 421-429.
3. Farrar, D., D.J. Tuffnell, J. West and H.M. West, 2016. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. Cochrane Database Syst. Rev., Vol. 6. 10.1002/14651858.CD005542.pub3.
4. Ryu, R.J., K.E. Hays and M.F. Hebert, 2014. Gestational diabetes mellitus management with oral hypoglycemic agents. Seminars Perinatol., 38: 508-515.
5. Cosson, E., L. Carbillon and P. Valensi, 2017. High fasting plasma glucose during early pregnancy: A review about early gestational diabetes mellitus. J. Diabetes Res., Vol. 2017. 10.1155/2017/8921712.
6. American Diabetes Association, 2016. Management of diabetes in pregnancy. Diabetes Care, 39: S94-S98.
7. Cranmer, H., 2018. Neonatal hypoglycemia: Practice essentials, background, etiology. https://emedicine.medscape.com/article/802334-overview
8. IBM Corp, 2012. IBM SPSS statistics for windows, version 21.0. IBM Corp, Armonk, New York.
9. American Diabetes Association, 2016. Older adults. Diabetes Care, 39: S81-S85.
10. American Diabetes Association, 2011. Summary of revisions to the 2011 clinical practice recommendations. Diabetes Care, 34: S3-S3.
11. Gui, J., Q. Liu and L. Feng, 2013. Metformin vs insulin in the management of gestational diabetes: A meta-analysis. PLoS One, Vol. 8, No. 5. 10.1371/journal.pone.0064585.
12. Rai, L., D. Meenakshi and A. Kamath, 2009. Metformin-a convenient alternative to insulin for indian women with diabetes in pregnancy. Indian J. Med. Sci, 63: 491-497.
13. Priya, G. and S. Kalra, 2018. Metformin in the management of diabetes during pregnancy and lactation. Drugs Context, Vol. 7. 10.7573/dic.212523.
14. Glueck, C.J., S. Bornovali, J. Pranikoff, N. Goldenberg, S. Dharashivkar and P. Wang, 2004. Metformin, pre-eclampsia and pregnancy outcomes in women with polycystic ovary syndrome. Diabet. Med., 21: 829-836.
15. Rowan, J.A., W.M. Hague, W. Gao, M.R. Battin and M.P. Moore, 2008. Metformin versus insulin for the treatment of gestational diabetes. N. Engl. J. Med., 358: 2003-2015.
16. Ainuddin, J., N. Karim, A.A. Hasan and S.A. Naqvi, 2015. Metformin versus insulin treatment in gestational diabetes in pregnancy in a developing country: A randomized control trial. Diabetes Res. Clin. Pract., 107: 290-299.