The Egyptian Journal of Hospital Medicine (January 2019) Vol. 74 (8), Page 1791-1798

Comparative Study between Metformin and Insulin in Controlling Gestational Diabetes Mellitus

Ehab Hassanin Mohamad[1], Abdel Monsef Abdel Hamed Sedek[1], Ahmed Fathy Abdel Aziz[2], Hisham Adel Abo Elez[1]*

[1]Departments of Obstetrics & Gynecology and [2]Clinical Pathology, Faculty of Medicine, Al-Azhar University

***Corresponding author:** Hisham Adel Abo Elez, **Mobile:** 01026596980, **Email:** drhishamez@gmail.com

ABSTRACT

Background: the use of antidiabetic drugs to control gestational diabetes was controversial. Some studies suggest a possible link between the use of oral antidiadetics and fetal anomalies, fetal macrosomia and neonatal hypoglycemia whereas others have demonstrated no such relationship.

Objective: This study aims to assess the efficacy of metformin in controlling maternal blood glucose level compared to insulin in women with GDM.

Patients and Methods: The present study included 116 pregnant women who have been diagnosed as gestational diabetics before 34 weeks gestation with singleton pregnancy. They had FBG level ranging from 90-169 mg/ dl or 2-hour postprandial blood glucose level ranging from 110-176 mg/dl. The exclusion criteria include pregnant women with preexisting DM and underlying diseases known to affect fetal growth, preeclampsia, unbalanced chronic disease, twin pregnancy, or refused to participate.

Results: Comparison of the baseline characteristics was performed between 2 groups and there were no significant differences between the two groups regarding maternal age, gravidity, parity, GA at time of diagnosis, GA at beginning of treatment, and BMI at time of diagnosis. Analysis of the results revealed that metformin was an effective medication for control of blood glucose in women with GDM who failed to achieve euglycemic with diet only.

Keywords: Gestational diabetes mellitus, metformin, metformin in gestational diabetes.

INTRODUCTION

Gestational diabetes (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy, is increasing worldwide and currently holds up to 10% of pregnancies. GDM is characterized by insulin resistance or low glucose tolerance, which increases throughout pregnancy. GDM is associated with lower pregnancy outcomes and may have long-term effects on both mother and child. Therefore, it must be understood that it is managed early and appropriately. GDM is the most common cause of diabetes during pregnancy, accounting for up to 90% of complex pregnancies due to diabetes. Women with diabetes (GDM) have a 40-60% chance of developing diabetes within 5-10 years after pregnancy. Although GDM is recognized as a disease of time, it is remains, a controversial entity with conflicting guidelines and treatment protocols [(1)].

Treatment of gestational diabetes mellitus can be classified into:

1. Glucose monitoring: Self-monitoring of blood glucose is the cornerstone for achieving the set targets of plasma glucose in order to reduce perinatal mortality. Recommendations from fourth international workshop conference on gestational diabetes mellitus suggest lowering the capillary whole blood glucose concentration to: pre-prandial< or = 95 mg/dl and either 1h postprandial < or = 140 mg/dl or 2h values < or ~ 120 mg/dl [(2)].

2. Medical nutrition therapy (MNT) and exercise: Diet is the cornerstone of the management of hyperglycemia in gestational diabetes mellitus irrespective of the pharmacological therapy. The targets to be achieved by medical nutrition therapy are to provide sufficient nutrition to the mother and fetus, provide adequate calories for maternal weight gain, to achieve normoglycemic state and lastly to prevent ketosis. Addition of 300 kcal /day is usually required in 2nd and 3rd trimester in normal weight women. A minimum of 175g carbohydrate per day should be provided. A moderate exercise program might improve fasting and postprandial glucose level and insulin sensitivity [(3)].

3. Insulin therapy: Insulin therapy is the most validated treatment option when medical nutrition therapy fails to achieve the target glycemic control. Despite emerging evidence supporting the use of glyburide or metformin in the management of GDM, many guidelines continue to recommend insulin as the first-line therapy. This is primarily the result of two factors: pregnancy category B for all insulins except glulisine and glargine, and safety

Received:11/11/2018
Accepted:30/11/2018

data indicating clinically insignificant amounts of human insulin that cross the placenta. Two RCTs demonstrated that insulin compared with usual prenatal care in the management of GDM resulted in decreased numbers of births associated with shoulder dystocia, macrosomia, and preeclampsia [(4)].

Traditionally, insulin therapy has been a common practice for women with gestational diabetes who cannot be controlled by treatment with medical nutrition and physical activity. Insulin therapy can be difficult for pregnant women due to multiple injection requirements, risk of hypoglycemia, overweight requirements, risk of hypoglycemia, and weight gain [(5)].

4. Oral medication: Metformin is a biguanide oral hypoglycemic agent. Metformin decreases hepatic gluconeogenesis, improves peripheral and hepatic sensitivity to insulin and does not induce hypoglycemia or maternal weight gain. However, as Metformin crosses the placenta and the long-term effects in the offspring are unknown. There are more than 10 studies assessing Metformin safety and efficacy.

The largest study is known as Metformin in Gestational Diabetes (MiG) study and involved 751 pregnant women with GDM. Some smaller studies have been later performed. Globally, the results have been favorable to Metformin. Compared to women taking insulin, those under Metformin have no difference in maternal glycemic control, congenital abnormalities, macrosomia, rates of neonatal hypoglycemia or other maternal or neonatal adverse outcomes. Moreover, it has been reported less maternal hypoglycemia with the use of Metformin in comparison to insulin regimes [(6)].

Metformin is an alternative to insulin and is effective in treating women with gestational diabetes. The meta-analysis of pregnancy outcomes after exposure was not presented during the first three months of metformin. Showed an increased risk of major malformations and other systematic reviews did not find significant differences in maternal or neonatal outcomes with the use of oral diabetes factors compared to insulin in women - with gestational diabetes mellitus. Although it crosses the placenta, metformin appears to be safe in the second and third trimester of pregnancy [(6)].

AIM OF THE WORK

This study aims to assess the efficacy of metformin in controlling maternal blood glucose level compared to insulin in women with GDM.

PATIENTS AND METHODS

Materials:

Design: Randomized controlled trial.

Study population: 120 patients with GDM were recruited from the outpatient clinic of the El Sayed Galal Hospital, Cairo, Egypt from March 2016 to September 2018.

Ethical Issue: The study protocol was approved by the Hospital Ethics Committee. All patients gave their informed consent before entering into the study.

Study method:

All women attend to outpatient clinic were subjected to:

Careful History Taking: Full history taking especially previous history of macrosomic baby with weight 4 kg and above, previous history of GDM, family history of diabetes in first degree relatives, previous history of poor obstetric outcome (abortion, congenital anomalies, intrauterine fetal death, and neonatal death), pregnancy induced hypertension in present pregnancy, and hypersensivity to metformin.

Clinical examination: Careful general clinical examination including body weight, height, blood pressure and lower limb edema. Maternal body mass index (BMI) was calculated using the earliest available body weight (the weight in kilograms divided by the square of the height in meters. Abdominal examination for assessment of estimated fetal weight, fetal movement,

Ultrasonography: Ultrasonography to confirm gestational age, to exclude Intra uterine growth retardation, congenital fetal malformation and twin pregnancy.

Screening: Screening were done by using A; 50 g oral glucose challenge test (GCT) as an initial screening test irrespective of the fasting status and a blood sugar level >140 mg/dl (7.8 mmol/1) was considered a positive GCT. Then these women had a 3 h 100 g oral glucose tolerance test -after an overnight fast of 8-14 h. Diagnosis of GDM was made with at least two out of three elevated plasma glucose levels fasting glucose >95 mg/dl (5.3 mmol/1), 1 h >180 mg/dl (10 mmol/1), 2 h > 155 mg/dl (8.6 mmol/1), and 3 h > 140. These testes were done for pregnant women with high risk for GDM on booking visit and pregnant women with low risk for GDM were screened at 24-28 weeks.

Patient diagnosed to have GDM were subjected to the following inclusion criteria: Treatment initiated before 34 weeks of gestation. Agree to participate in the study.

Exclusion Criteria: Essential hypertension. Preeclampsia. Intra uterine growth retardation. Abnormal glucose tolerance before pregnancy. Unbalanced chronic disease. Twin pregnancy. Treatment initiated before 12 weeks or after 34 weeks of gestation.

Allocation and Concealment: Sealed envelope technique was suggested as a method for randomization of subjects in both groups 58 sealed envelopes was contained letter M and another 58 sealed envelopes was contained letter I every patient was asked to choose an envelope, and was allocated in the corresponding group. **Group M:** Including 58 women that received metformin **Group I:** Including 58 women that received insulin.

Randomization: Recruited cases were randomized based on computer system numbering.

Intervention: Before intervention patients were advised to take standard nutritional instruction for three meals and four snakes daily.

Group M: Metformin was started at dose of 500 rug and increased up to 1500 mg in 3 divided doses as tolerated until glycemic control was achieved. Target blood glucose levels for glycemic control were FBS < 100 mg/dl (5.5 mmol/1) and 2 hour post parandial < 126 mg/dl (7 mmol/1). If blood glucose levels were higher than the cut off values 1-2 weeks after treatment or at anytime during treatment with maximum dose of metformin, the patient was shifted to insulin group [7].

Group I: Insulin was prescribed as a combination of short acting and intermediate acting human insulin, twice daily before meals in the morning (before breakfast) and in the evening (before dinner). A 24 h total insulin dose was calculated using 1 units/kg body weight. Two thirds of total dose was given in morning before breakfast and one third at night before dinner. Two thirds of the morning insulin dose was given as intermediate acting human insulin and one third as short acting human insulin with both as single injection. Half of the night insulin is intermediate acting and half was short acting insulin in a single injection [7].

Follow up: Follow up visits were arranged in-the same antenatal clinic every 2 weeks till 36 weeks then weekly till delivery. All patients were taught self-blood sugar monitoring using home glucose monitors and were advised to maintain written record of blood sugar levels. Patients who could not monitor and record their blood glucose levels were tested using glucose monitors at each antenatal visit. Fasting and post prandial blood glucose levels 2 h after breakfast were done at each visit and HbAlc each trimester. At each antenatal visit blood pressure and weight were measured, abdominal examination was done, and Ultrasound was done at first visit at 16-19 weeks (anomaly scan) and then monthly. Follow up was continued till delivery to evaluate the pregnancy outcome (macrosomia, shoulder dystocyia, and rate of cesarean section).

Outcome Measures: Primary outcome measure was control of diabetes mellitus; monitored by fasting blood sugar level, two hour postprandial, and HbA1C. Secondary outcome measure was obstetric complications; macrosomia, shoulder dystocyia, and rate of cesarean section.

Data Analysis

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

Descriptive statistics were done for quantitative data as minimum & maximum of the range as well as mean± SD (standard deviation) for quantitative normally distributed data, while it was done for qualitative data as number and percentage.

Inferential analyses were done for quantitative variables using independent t-test in cases of two independent groups with normally distributed data and paired t-test in cases of two dependent groups with normally distributed data and. In qualitative data, inferential analyses for independent variables were done using Chi square test for differences between proportions. The level of significance was taken at P value < 0.050 is significant, otherwise is non-significant.

RESULTS

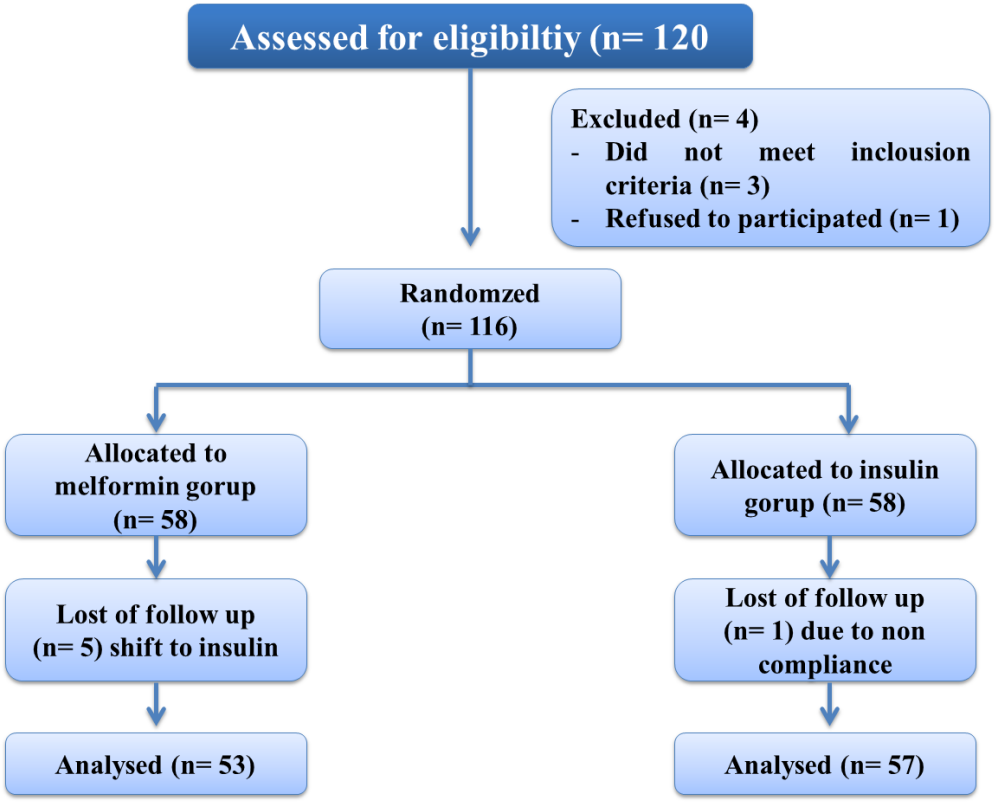

Figure (1): Study flow chart

Table (1): Age, parity, BMI and GA among the studied groups at beginning of the study

Variables		Metformin (N=58)	Insulin (N=58)	P
Age (years)	**Mean±SD**	30.4±12.8	30.6±12.5	^0.747
	Range	25.0-35.0	25.0-35.0	
BMI (kg/m^2)	**Mean±SD**	29.6±1.3	29.4±1.4	^0.483
	Range	26.9-33.4	26.4-32.5	
Parity (n, %)	**Primigravida**	39 (67.2%)	34 (58.6%)	#0.336
	Multigravida	19 (32.8%)	24 (41.4%)	
GA (weeks)	**Mean±SD**	28.9±1.1	29.0±1.1	^0.493
	Range	26.0-32.0	25.0-31.0	

^ independent t-test, #Chi square test

Table (2): Comparison between Metformin and insulin regarding FBG (mg/dL)

Time	Measures	Metformin (N=58)	Insulin (N=58)	^P
Weeks-2	**Mean±SD**	166.7±9.7	169.8±10.4	0.096
	Range	148.5-186.4	140.3-187.6	
Month-1	**Mean±SD**	89.8±6.1	87.3±8.1	.059
	Range	76.7-102.6	69.3-104.3	
Reduction increase	**Mean±SD**	87.8±6.1	87.3±8.1	0.666
	Range	74.7-100.6	69.3-104.3	
	#P	< 0.001*	< 0.001*	
Value of use of metformin				
Items		**Mean ± SE**	**95% CI**	
Reduction increase		0.6±1.4	-2.1-3.3	

^Independent t-test, Paired t-test, *Significant, CI: Confidence interval

Table (3): Comparison -between Metformin and insulin regarding 2 hr PPBG (mg/dL)

Time	Measures	Metformin (N=58)	Insulin (N=58)	^P
Weeks-2	**Mean±SD**	177.7±11.0	175.7±12.5	0.373
	Range	142.0-199.6	134.4-199.3	
Month-1	**Mean±SD**	111.5±10.0	109.7±10.8	0.353
	Range	90.1-131.1	85.3-132.2	
Reduction increase	**Mean±SD**	67.0±3.2	66.3±5.4	0.426
	Range	44.5-70.1	36.6-75.1	
	#P	< 0.001*	< 0.001*	
Value of use of metformin				
Items		**Mean ± SE**	**95% CI**	
Reduction increase		0.7±0.8	-1.0-2.4	

^Independent t-test, Paired t-test, *Significant, Cl: Confidence interval

Table (4): Comparison between Metformin and insulin regarding HbAlc

Time	Measures	Metformin (N=58)	Insulin (N=58)	^P
First trimester	**Mean±SD**	7.6±0.4	7.5±0.4	0.277
	Range	6.9-8.8	6.8-8.6	
Second trimester	**Mean±SD**	6.9±0.4	6.7±0.5	0.100
	Range	6.2-8.4	6.2-8.2	
Third trimester	**Mean±SD**	6.5±0.4	6.4±0.4	0.084
	Range	5.8-7.8	5.6-7.6	
Reduction (Second trimester)	**Mean±SD**	0.8±0.2	0.8±0.2	0.559
	Range	0.4-1.2	0.4-1.6	
	#P	**< 0.001***	**< 0.001***	
Reduction (Third trimester)	**Mean±SD**	1.1±0.1	1.2±0.1	0.164
	Range	0.8-1.3	0.7-1.3	
	#P	**< 0.001***	**< 0.001***	
Value of use of metformin				
Items		**Mean ± SE**	**95% CI**	
Reduction (Second trimester)		0.01±0.01	-0.1±0.1	
Reduction (Third trimester)		0.01±0.01	-0.1-0.0	

∧ Independent t-test, Paired t-test, *Significant, CI: Confidence interval

Table (5): Comparison between Metformin and insulin regarding CS

Time	Metformin (N=58)	Insulin (N=58)	^P
Present	24 (41.4%)	26(44.8)	0.798
Absent	34 (58.6%)	32 (55.2%)	
Value of use of metformin in avoiding CS			
Items	**Value**	**95% CI**	
Rate in metformin group	58.6%	49.5%-71.3%	
Rate in insulin group	55.2%	42.4%- 68.0%	
Relative rate	1.01	0.7-1.5	
Rate reduction	2.5%	-17.0%-21.8%	
Number needed to treat	40.3	4.6-100.0	
Efficacy	4.4%	25.8%-47.0%	

∧Chi square test, *Significant, CI: Confidence interval

Table (6): Comparison, between Metformin and insulin regarding shoulder dystocia

Time	Metformin (N=58)	Insulin (N=58)	^P
Present	1 (1.7%)	5 (8.6%)	0.094
Absent	57 (98.3%)	53 (91.4%)	
Value of use of metformin in avoiding CS			
Items	**Value**	**95% CI**	
Rate in metformin group	98.3%	94.9%-98.8%	
Rate in insulin group	91.4%	84.2%- 98.6%	
Relative rate	1.1	1.0-1.1	
Rate reduction	6.9%	-2.6%-10.2%	
Number needed to treat	14.5	9.8-100.0	
Efficacy	7.5%	2.7%-11.3%	

∧Chi -square test, *Significant, CI: Confidence interval

Table (7): Comparison between Metformin and insulin regarding birth weight (gm)

Time	Metformin (N=58)	Insulin (N=58)	^P
Mean±SD	3556.3±260.7	3685.0±272.5	**0.012***
Range	2866.0-4237.0	3160.0-4309	
Value of use of metformin in avoiding CS			
Items	**Mean±SE**	**95% CI**	
Weight lowering	129.1±50.4	29.2-229.1	

∧independent-test, *Significant, CI: Confidence interval

Table (8): Comparison between Metformin and insulin regarding Macrosomic baby

Time	Metformin (N=58)	Insulin (N=58)	^P
Present	2 (3.4%)	8 (13.8%)	0.047*
Absent	56 (96.6%)	50 (86.2%)	
Value of use of metformin in avoiding CS			
Items	**Value**	**95% CI**	
Rate in metformin group	96.6%	91.9%-98.8%	
Rate in insulin group	86.2%	77.3%- 95.1%	
Relative rate	1.1	1.0-1.2	
Rate reduction	10.3%	-1.6%-16.0%	
Number needed to treat	9.7	6.2-100.0	
Efficacy	12.0%	1.7%-19.2%	

∧Independent-test, *Significant, CI: Confidence interval

Table (9): Fetal condition at delivery

Time	Measures	Metformin (N=58)	Insulin (N=58)	^P
elivery GA (weeks)	**Mean±SD**	38.4±1.0	38.1±1.0	0.162
	Range	36.0-40.0	36.0-40.0	
APGAR 1	**Mean±SD**	6.9±0.8	6.6±0.6	0.068
	Range	5.0-9.0	5.0-9.0	
APGAR 2	**Mean±SD**	8.1±0.8	7.9±0.6	0.175
	Range	7.0-10.0	7.0-10.0	

∧Independent-test

DISCUSSION

The management of GDM is important because appropriate therapy can decrease many of its adverse pregnancy outcomes. Effective treatment regimens consist of dietary therapy, exercise, self blood glucose monitoring, and administration of insulin if target blood glucose values are not met with diet regulation alone **[8].**

Standard medical treatment to achieve adequate glucose levels is insulin therapy. However, this therapy requires multiple daily injections, which may reduce patient compliance; furthermore its high cost may preclude treatment for some patients. A safe and effective oral agent would offer advantages over insulin and may well prove more acceptable to patients **(9).**

Metformin is a biguanide hypoglycemic agent that reduces hepatic gluconeogenesis and increases peripheral insulin sensitivity is a rational option for women with GDM. Evidence from the Metformin in Gestational Diabetes (MiG) trial showed that, compared with insulin, metformin was not associated with increased prenatal complications although there was an increase in spontaneous preterm births. When asked to choose, metformin was preferred to insulin by GDM women

A recent metanalysis of six large studies, outside Egypt, has shown that the use of oral hypoglycemic agents (OHAs) in treating GDM was not associated with neonatal hypoglycemia, macrosomia or increased incidence of cesarean section **(10).**

The present study was conducted to evaluate the effectiveness and safety of metformin in treating patients with GDM in Egypt. The Egyptian woman is different in culture as regards commitment to medicine and examinations courses, partially also due to the high personal cost of treatment. This may make it easier to give her oral drug (and reduce the need to daily glucose monitoring) rather than injectable drugs. Also, the cost of metformin is cheaper than the cost of insulin.

Concerning patients' characteristics in both groups, there were no significant differences between the two groups regarding maternal age (in metformin treated group 30.4±2.8 versus 30.6±2.5 in the insulin treated group, p=0.747), primigravida, GA at time of diagnosis (in metformin treated group 39 (67.2%) versus 34 (58.6) in insulin treated group, p0.336), GA at the beginning of treatment (in metformin treated group 28.9±1.1 versus 29±1.1 weeks in insulin treated group, p^O.493), BMI at the time of diagnosis (in metformin treated group 29.6±1.3kg/m^2 versus 29.4±1.4kg/m^2, p-0.483, and HbAlc at time of diagnosis (in metformin treated group 7.6±0.4 versus 7.5±0.4 in insulin treated group %, p-0.277).

This was in agreement with the study of **Rowan *et al.*** **(12)** who reported that there were no significant differences between the two groups as regards patients' characteristics this agreement might be due to the similarity in inclusion criteria and study design between our study and the study of **Rowan *et al.*** **(12)**.

With respect to glycemic control, no significant difference in mean pre-treatment glucose levels was observed between the two groups (fasting glucose levels were 166.7 ±9.7 mg/dl in metformin treated group versus 169.8±10.4 mg/dl in insulin treated group, p^0.096 and 2-hours postprandial glucose levels were 177.7±11 in metformin treated group versus 175.7±12.5 mg/dl in insulin treated group, p=0.373),

However, after introduction of the drugs, the average postprandial glycemic levels during the first month after randomization were significantly lower in both metformin and insulin treated groups (111.5±10.0 mg/dl versus 109.7±10.8 mg/dl, p=0.353).

Concerning the gestational age at time of delivery, the insulin versus metformin groups did not show significant difference. GA, at time of delivery, in the metformin treated group was 38.4±LO weeks and in the insulin treated group was 38.1±1.0 weeks, p=0.162. Also there was no difference in the rate of cesarean section between the two groups. In the metformin treated group, the ratio of C.S were (41.4%), while in insulin treated group were (44.8%), p=0.798. This was in agreement with studies of **Tertti *et al.*** **(11)**, but not in agreement with the study *of* **Rowan *et al.*** **(12)** who reported that the average gestational ages at delivery were significantly lower in the metformin group (p-0.001) and preterm birth rate was significantly more common in the metformin group. This inconsistency may be due to chance or unrecognized effect of metformin on the labor. On the contrary, **Balani *et al.*** **(13)** showed that preterm delivery was more common in the insulin treated group, but the study of **Balani *et al.*** **(13)** was merely a case-control study.

Concerning 1-min Apgar score there was no significant difference between the 2 groups with p=0.068, 5-min Apgar score also there was no significant difference between the 2 groups with p-0.175).

In the present study, five (8.62%) of the 58 women, in the metformin group, required supplemental insulin for adequate glycemic control. This, percentage is similar to that reported by **Rowan *et al.*** **(12)**.

CONCLUSION

Metformin has efficacy as that of insulin in glycemic control of GDM and has the following

beneficial effect: reduction the rate of shoulder dystocia, reduction the rate of cesarean section, and reduction the rate of macrosomia more than insulin.

REFERENCES

1. **Mpondo C and Alex E (2015):** Gestational diabetes mellitus: challenges in diagnosis and management. Journal of Diabetes & Metabolic Disorders, 12:15-37.
2. **Catherine A, Elie S and Julie M (2014):** Gestational Diabetes Mellitus Identification Based on Self-Monitoring of Blood Glucose. Canadian Diabetes Association, 5:1-9.
3. **Franz MJ, BantSe JP, Beebe CA, Brunzell JD, Chiasson JL and Garg A (2002):** Evidence-based nutrition principles and recommendations for the treatment and prevention of Diabetes and related complications (Technical Review). Diabetes Care, 25:148-98.
4. **Kristi WK, Dana GC and Allison M (2015):** A review of current, treatment strategies for gestational diabetes mellitus. Drugs Context, 4:212-222.
5. **Nicholson W and Baptiste-Roberts K (2011):** Oral hypoglycaemic agents during pregnancy: the evidence for effectiveness and safety. Best Pract Res Clin Obstet Gynaecol., 25: 51-63.
6. **Pedro M (2014):** Metformin in the Gestational Diabetes. Journal of Diabetes, Metabolic Disorders & Control, DOI: 10.15406/ jdmdc. 2014. 01.00001.
7. **Jahanara A, Nasam K and Sanower AH (2014):** Metformin versus insulin treatment in gestational diabetes in pregnancy in a developing country. A randomized control trial. Diabetes Res Clin Pract., 107(2):290-9.
8. **Kim C (2010):** Gestational diabetes: risks, management, and treatment options. Int. J Women's Health, 2: 339-351.
9. **Hayer L and Shehata HA (2005):** Gestational diabetes mellitus. Curr Obstet Gynecol., 15: 368-374.
10. **DhuSkotia JS, OSa B, Fraser R and Farrell T (2010):** Oral hypoglycemic agents vs insulin in management of gestational diabetes: a systematic review and meta-analysis. Am J Obstet Gynecol., 203: e451-459.
11. **Tertti K, Ekblad U, Koskinen P, Vahlberg T and Ronnemaa T (2012):** Metformin vs. insulin in gestational diabetes. A randomized study characterizing metformin patients needing additional insulin. Diabetes Obstet Metab., 15: 246-251.
12. **Rowan JA, Haque WJVI and Gao W (2008):** Metformin vs insulin for the treatment of gestational diabetes. The New England Journal of Medicine, 358: 2003-2015.
13. **Balani J, Hayer SL, Rodin DA and Shehata H (2009):** Pregnancy outcomes in women with gestational diabetes treated with metformin or insulin: a case-control study. Diabet Med., 26: 798-802.