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Insulin versus Metformin in Treatment of Gestational Diabetes Mellitus (Randomized Controlled Clinical Trial)

Hatem El Gamal [1], Mohamed Abd Elaleem [1], Sherif Sadek [2], Marwa R. Elhadary
[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Ain-Shams University
[2]Department of Internal Medicine, Faculty of Medicine, Ain-Shams University
Corresponding author: Marwa R. Elhadary; Mobile: +201119975534; Email: dr_marwa2050@yahoo.com

ABSTRACT

Background: the use of anti-diabetic drugs to control gestational diabetes (GDM) was controversial. Some studies suggested a possible link between the use of oral anti-diabetics and fetal anomalies, fetal macrosomia and neonatal hypoglycemia whereas others have demonstrated no such relationship. Metformin is a biguanide hypoglycemic agent that reduces hepatic gluconeogenesis and increases peripheral insulin sensitivity. Although it crosses placenta, metformin appears to be safe in pregnancy.

Aim of the Work: this study aimed to assess the efficacy of metformin in controlling maternal blood glucose level compared to insulin in women with GDM.

Patients and Methods: this randomized controlled trial was conducted on 116 patients with GDM recruited from the outpatient clinic of Ain Shams University Maternity Hospital (ASMH), Cairo, Egypt from February, 2016 to January, 2017.

Results: macrosomic baby was significantly less frequent among metformin group than among insulin group (p= 0.047).

Conclusion: metformin has efficacy as that of insulin in glycemic control of GDM and has the following beneficial effects: reduction the rate of shoulder dystocia, reduction the rate of cesarean section and reduction the rate of macrosomia more than insulin.

Recommendations: metformin is recommended as an alternative to insulin therapy in control of blood glucose in patient with GDM when diet therapy and exercise fail to reduce blood glucose values sufficiently. The time for metformin as an alternative treatment to insulin has come; however, it should be prescribed after careful consideration of these patient characteristics to minimize the need for supplemental insulin.

Keywords: insulin, metformin, gestational diabetes.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy, is increasing worldwide and currently complicates up to 10% of the pregnancies. GDM is characterized by insulin resistance or decreased glucose tolerance, which increases throughout pregnancy.

GDM is associated with poorer pregnancy outcomes and might have long-term implications for both mother and child. Therefore, it must be recognized precociously and appropriately managed.

GDM is the most common cause of diabetes during pregnancy, accounting for up to 90 % of pregnancies complicated by diabetes. Women with GDM have a 40–60 % chance of developing diabetes mellitus over 5–10 years after pregnancy. Although GDM has been recognized as a disease for time, it remains a controversial entity with conflicting guidelines and treatment protocols [(1)]. Gestational diabetes mellitus is generally asymptomatic, usually being detected through systematic screening after the 24th week of pregnancy. Evidence to support screening for gestational diabetes mellitus is indirect and strongly based on the potential adverse effects of hyperglycemia on pregnancy outcomes, and on the effectiveness of gestational diabetes mellitus treatment in preventing these outcomes [(2)]. Treatment of gestational diabetes mellitus using lifestyle advice ± supplementary insulin has shown to be effective and to significantly improve pregnancy outcomes. Lifestyle advice (including dietary advice and exercise) is the primary intervention offered to women diagnosed with gestational diabetes mellitus. However, lifestyle advice alone does not achieve adequate glycemic control in up to 20% of women and needs to be supplemented with either oral hypoglycemic or subcutaneous insulin [(3)].

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 suggested 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 [(4)].

Diet is the cornerstone of the management of hyperglycemia in gestational diabetes mellitus

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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 the 2nd and 3rd trimesters 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 [(5)].

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 insulin except glulisine and glargine and safety 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 [(6)].Traditionally, insulin therapy had been considered standard practice for women with gestational diabetes mellitus who could not have been controlled by medical nutrition therapy and physical activity. Insulin therapy can be difficult for pregnant women due to multiple injection requirements, risk of hypoglycemia, and weight gain [(7)].

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 was 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 had 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 [(8)].

Metformin is an alternative to insulin and is effective in the treatment of women with gestational diabetes mellitus. A meta-analysis of pregnancy outcomes after first trimester exposure to metformin didn't show an increased risk of major malformations and other systematic reviews didn't find substantial maternal or neonatal outcome differences with use of oral diabetes agents compared with 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 [(8)].

AIM OF THE WORK

This study aimed 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.
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- **Study Population:**

116 patients with GDM were recruited from the outpatient clinic in Ain Shams University Maternity Hospital , Cairo, Egypt from February, 2016 to January, 2017.

- **Ethical Issue:**

The hospital ethics committee was approved in this study. All patients gave their informed consent before entering into this study.

- **Study Method**

  - **Recruitment**

All women attend to outpatient clinic were subjected to:

1) 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.

2) 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.

3) Ultrasonography:

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

4) 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/l) 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/l), 1 h ≥180 mg/dl (10 mmol/l), 2 h ≥ 155 mg/dl (8.6 mmol/l), 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.

➢ **Inclusion Criteria:**

1. Treatment initiated before 34 weeks of gestation.
2. Agree to participate in the study.

➢ **Exclusion Criteria:**

1. Essential hypertension.
2. Preeclampsia.
3. Intra uterine growth retardation.
4. Abnormal glucose tolerance before pregnancy.
5. Unbalanced chronic disease.
6. Twin pregnancy.
7. 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 further randomized based on computer system numbering.

Table 1: randomization of group M and group I

SN									
1	Group M	25	Group M	49	Group M	73	Group I	97	Group M
2	Group I	26	Group I	50	Group I	74	Group I	98	Group M
3	Group M	27	Group M	51	Group M	75	Group I	99	Group M
4	Group I	28	Group I	52	Group I	76	Group M	100	Group M
5	Group M	29	Group M	53	Group M	77	Group M	101	Group I
6	Group I	30	Group I	54	Group I	78	Group M	102	Group M
7	Group M	31	Group I	55	Group I	79	Group M	103	Group I
8	Group I	32	Group M	56	Group I	80	Group I	104	Group I
9	Group M	33	Group M	57	Group M	81	Group M	105	Group M
10	Group I	34	Group I	58	Group M	82	Group I	106	Group M
11	Group M	35	Group I	59	Group I	83	Group M	107	Group M
12	Group I	36	Group I	60	Group M	84	Group I	108	Group I
13	Group M	37	Group M	61	Group I	85	Group M	109	Group M
14	Group I	38	Group M	62	Group M	86	Group I	110	Group I
15	Group M	39	Group I	63	Group M	87	Group M	111	Group I
16	Group I	40	Group I	64	Group M	88	Group I	112	Group M
17	Group M	41	Group M	65	Group I	89	Group M	113	Group I
18	Group I	42	Group I	66	Group I	90	Group I	114	Group M
19	Group M	43	Group M	67	Group I	91	Group I	115	Group I
20	Group I	44	Group I	68	Group M	92	Group M	116	Group M
21	Group I	45	Group M	69	Group I	93	Group I		
22	Group M	46	Group I	70	Group M	94	Group I		
23	Group M	47	Group I	71	Group I	95	Group M		
24	Group I	48	Group M	72	Group M	96	Group I		

➢ **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 mg and increased up to 2500 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/l) and 2 hour post parandial ≤ 126 mg/dl (7 mmol/l). 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 [(9)].

- **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 was intermediate acting and half was short acting insulin in a single injection [(9)].

➢ **Follow up**

1. Follow up visits were arranged in the same antenatal clinic every 2 weeks till 36 weeks then weekly till delivery
2. All patients were taught self-blood sugar monitoring using home glucose monitors and were advised to maintain written record of blood sugar levels.
3. Patients who could not monitor and record their blood glucose levels were tested using glucose monitors at each antenatal visit.
4. Fasting and post prandial blood glucose levels 2 h after breakfast were done at each visit and HbA1c each trimester.
5. 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.
6. Follow up was continued till delivery to evaluate the pregnancy outcome (macrosomia, shoulder dystocyia, and rate of cesarean section).

➢ **Outcome Measures:**

A- Primary outcome measure will be control of diabetes mellitus monitored by fasting blood sugar level, two hour postprandial, and HbA_1C.

B- Secondary outcome measure (obstetric complication).

- Macrosomia.
- Shoulder dystocyia.
- Rate of cesarean section.

➢ **Sample Size Justification**

The required sample size has been calculated using the IBM© Sample Power© Software (IBM© Corp., Armonk, NY, USA).

The primary outcome measure is the adequacy of glycemic control and weight gain after study entry. The secondary outcome measures are the CS rate, proportion of babies with a birth weight > 90^{th} percentile, and occurrence of obstetric complication such as shoulder dystocyia and postpartum hemorrhage.

A previous study reported that the weight gain after study entry was 3.3±1.4 kg or 4.5±1.7 kg in patients receiving metformin or insulin for GDM, respectively [(10)].

So, it is estimated that a total sample size of 104 patients equally randomized into either study group (n=52 patients per group) would achieve a power of 90% (type II error, 0.1) to detect a statistically significant difference between the two groups as regards the weight gain after study entry using a two-side unpaired Student *t* test with a confidence level of 99% (type I error, 0.01).

The mean ± SD weight gain in both groups after treatment is assumed to be identical and to equal 4.5±1.7 kg under the null hypothesis. Under the alternative hypothesis, the mean±SD weight gain is assumed to equal 3.3±1.4 kg or 4.5±1.7 kg in patients receiving metformin or insulin, respectively.

This sample size of 52 patients in each study group were achieved a power of 85% (type II error, 0.15) to detect a statistically significant difference between the two groups as regards the qualitative outcome measures (i.e., adequacy of glycemic control, proportion of babies with a birth weight >90^{th} percentile, and incidence of shoulder dystocyia and postpartum hemorrhage) for a medium effect size *(w)* of 0.35 using a two-sided chi-squared test with a confidence level of 99% (type I error, 0.01). The effect size *(w)* is calculated as follows:

$$w = \sqrt{\chi^2/N},$$

where χ^2 is the chi-squared statistic and N is the total sample size [(11)].

Assuming a drop-out rate of 10%, a total sample size of 116 patients will be recruited (58 patients per group).

- **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

This study included 116 pregnant women who had GDM, 58 of them were treated with metformin and the remaining number (58) was treated with insulin.

Table 2: 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±2.8	30.6±2.5	^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 showed no significant difference between metformin and insulin groups regarding age, BMI, parity and GA at beginning of this study.

Table 3: comparison between metformin and insulin regarding FBG (mg/dL)

Time	Measures	Metformin (N=58)	Insulin (N=58)	^P
Week-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	0.059
	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 showed no significant difference between metformin and insulin groups regarding FBG at week-2 and change of FBG from week-2 to month-1. FBG significantly decreased from week-2 to month-1in both Metformin and insulin groups.

Table 4: comparison between metformin and insulin regarding 2 hr PPBG (mg/dL)

Time	Measures	Metformin (N=58)	Insulin (N=58)	^P
Week-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, **CI:** Confidence interval

Table 4 showed no significant difference between metformin and insulin groups regarding 2h-PPBG at week-2 and change of 2h-PPBG from week-2 to month-1. 2h-PPBG significantly decreased from week-2 to month-1 in both Metformin and insulin groups.

Table 5: comparison between metformin and insulin regarding HbA1c

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 increase (Second trimester)			0.01±0.01	-0.1–0.1
Reduction increase (Third trimester)			0.01±0.01	-0.1–0.0

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

Table 5 showed no significant difference between Metformin and insulin groups regarding HbA1c at first, second and third trimesters and change of HbA1c from first trimester to second and third trimesters. HbA1c significantly decreased from first trimester to second and third trimesters in both Metformin and insulin groups.

Table 6: comparison between metformin and insulin regarding CS

Findings	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 showed that **CS** was non-significantly less frequent among metformin group than among insulin group.

Table 7: comparison between metformin and insulin regarding shoulder dystocia

Findings	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 shoulder dystocia			
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 elevation	6.9%	-2.6%–10.2%	
Number needed to prevent	14.5	9.8–100.0	
Efficacy	7.5%	2.7%2.7%11.3%	

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

Table 7 showed that shoulder dystocia was non-significantly less frequent among Metformin group than among insulin group.

Table 8: comparison between metformin and insulin regarding birth weight (gm)

	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			
Items	**Mean±SE**	**95% CI**	
Weight lowering	129.1±50.4	29.2–229.1	

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

Table 8 showed that birth weight was significantly lower in metformin group than insulin group.

Table 9: comparison between metformin and insulin regarding macrosomic baby

Findings	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 Macrosomic baby			
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 elevation	10.3%	-1.6%–16.0%	
Number needed to prevent	9.7	6.2–100.0	
Efficiacy	12.0%	1.7%–19.2%	

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

Table 9 showed that macrosomic baby was significantly less frequent among metformin group than among insulin group.

Table 10: fetal condition at delivery

Variables		Metformin (N=58)	Insulin (N=58)	P
Delivery 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 5	Mean±SD	8.1±0.8	7.9±0.6	0.175
	Range	7.0–10.0	7.0–10.0	

^Independent t-test

Table 10 showed no congenital malformations conditions recorded in both groups**.** Delivery GA, APGAR1 and APGAR5 were non-significantly lower in insulin group than in metformin group.

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 [(12)]. 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 [(13)].

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 [(14)].

A metanalysis of six large studies, outside Egypt, had 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 [(2)].

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 patient's 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, p=0.336), GA at the beginning of treatment (in metformin treated group 28.9±1.1 versus 29±1.1 weeks in insulin treated group, p=0.493), BMI at the time of diagnosis (in metformin treated group 29.6±1.3kg/m² versus 29.4±1.4kg/m², p=0.483, and HbA1c 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*.** [(14)] who reported that there were no significant differences between the two groups as regards patient's 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***. [(14)].

With respect to glycemic control in this study, 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±1.0 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 is in agreement with study of **Tertti *et al.*** [(15)], but not in agreement with the study of **Rowan *et al***. [(14)] 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.*** [(16)] showed that preterm delivery was more common in the insulin treated group, but it was merely a case-control study.

In the present study, there was a significant difference between both groups as regards fetal birth weight. Average birth weights were slightly lower in the metformin treated group (metformin 3556.3±260.7 gms versus 3685.0 ±272.5 gms in insulin group, p=0.012). There were 2 fetuses (3.4%) with macrosomia in the metformin treated group, and 8 fetuses (13.8%) in insulin group. The pooled results showed significant difference between the two groups as regards the rate of large for gestational age (LGA). This is in agreement with the study of

Ainuddin *el al.* [9]; there were 10 (23.3%) with macrosomia in the metformin treated group and 28 fetuses (37.3%) p= 0.209, but was not in agreement with the study of **Moore *et al.*** [17] p=0.039.

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 58 women in metformin group required supplemental insulin for adequate glycemic control. This percentage is similar to that reported by **Ainuddin *el al.*** [9] (14.6%), but differs to rates reported by **Rowan *et al.*** [14] (46.3%).

The findings of our study suggested that metformin is an effective and safe treatment option for women with GDM. Metformin is comparable with insulin in glycemic control, providing additional evidence for the use of metformin in GDM. The results of this study showed no significant difference in the risk of maternal or perinatal adverse outcomes with the use of metformin compared to insulin in treating GDM. This study shows the potential advantages of metformin over insulin in cost, similar glucose level after control, faster reaching ideal glucose levels, patient compliance, easier use, and neonatal birth weight adjusted for gestational age.

CONCLUSION AND RECOMMENDATIONS

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

1. Reduction of rate of shoulder dystocia
2. Reduction of rate of cesarean section
3. Reduction of rate of macrosomia more than insulin

Thus,

- Metformin is recommended as an alternative to insulin therapy in control of blood glucose in patient with GDM when diet therapy and exercise fail to reduce blood glucose values sufficiently.
- Further larger studies are needed to prove our results and to study the optimum dose of metformin and its side effects in treatment of GDM.

The time for metformin as an alternative treatment to insulin has come; however, it should be prescribed after careful consideration of these patient characteristics to minimize the need for supplemental insulin.

REFERENCES

1) **Mpondo BC, Ernest A and Dee HE (2015):** Gestational diabetes mellitus: challenges in diagnosis and management. Journal of Diabetes and Metabolic Disorders, 14(1):42-49.
2) **Dhulkotia JS, Ola 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: 457 -463.
3) **Landon MB, Spong CY and Thom E (2009):** A multicenter, randomized trial of treatment for mild gestational diabetes. N. Engl. J. Med., 361:1339–1348.
4) **Allard C, Sahyouni E and Menard H (2015):** Gestational diabetes mellitus identification based on self-monitoring of blood glucose. Canadian Journal of Diabetes, 39(2):162-168.
5) **Franz MJ, Bantle 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 . Diabetes Care, 25:148-98.
6) **Kelley K, Carroll D and Meyer A (2015):** A review of current treatment strategies for gestational diabetes mellitus. Drugs in Context , 4: 212282. DOI: 10.7573/dic.212282.
7) **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.
8) **Marques P (2014):** Metformin in the gestational diabetes. Journal of Diabetes, Metabolic Disorders and Control: DOI: 10.15406/jdmdc.2014.01.00001.
9) **Ainuddin J, Karim N and Ali S (2014):** Metformin versus insulin treatment in gestational diabetes in pregnancy in a developing country. A randomized control trial, diabetes research and clinical practice, Elsevier, DOI: 10.1016/j.diabres.2014.10.001.
10) **Niromanesh S, Alavi A, Sharbaf FR, Amjadi N, Moosavi S and Akbari S (2012):** Metformin compared with insulin in the management of gestational diabetes mellitus: a randomized clinical trial. Diabetes Res. Clin. Pract., 98(3):422-431.
11) **Chow S-C, Shao J and Wang H (2003):** Sample Size Calculations in Clinical Research. First Edition. Marcel Dekker Inc. New York.
12) **Kim C (2010):** Gestational diabetes: risks, management, and treatment options. Int. J. Women's Health, 2: 339-351.
13) **Thomas A. and Anny H (2005):** Gestational diabetes mellitus. The journal of clinical investigation, J Clin Invest. ,115(3): 485–491.
14) **Rowan JA, Haque WM and Gao W (2008):** Metformin vs insulin for the treatment of gestational diabetes. The New England Journal of Medicine, 358: 2003-2015.
15) **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.
16) **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.
17) **Moore LE, Briery CM, Clokey D, Martin RW, and Williford NJ (2007):** Metformin and insulin in the management of gestational diabetes mellitus: preliminary results of a comparison. J. Reprod. Med., 52: 1011-1015.