

*Research Article*

## Oral Hypoglycemic Drugs Versus Insulin for the Management of Gestational Diabetes

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### Abstract

**Introduction:** Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. **Aim of the work:** The aim of this study is to compare the efficacy of metformin with that of insulin in treatment of gestational diabetes mellitus. **Patients and Methods:** This two armed clinical trial was conducted prospectively on 100 pregnant women on regular antenatal care in the Diabetic Clinic of Minia Maternity Hospital during the period from January 2016 to September 2017. **Results:** This study included 95 pregnant women having GDM, 47 of them were treated with metformin, and the remaining number (48) were treated with insulin. **Conclusion:** Approximately 80% of women with GDM could be successfully and safely treated with metformin when diet therapy and exercise fail to reduce blood glucose values sufficiently. **Keywords:** Gestational diabetes, Insulin, treatment

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### Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy<sup>(1)</sup>.

GDM is characterized by insulin resistance or decreased glucose tolerance, which increases throughout pregnancy<sup>(2)</sup>.

The rise in insulin resistance is likely to be caused by increasing amounts of hormones related to pregnancy, such as (placental lactogen, cortisol, estrogen, progesterone and possibly tumor necrosis factor  $\alpha$ -from placenta) and changes in metabolism to meet the needs of the fetus. However, the entire causes are not clear<sup>(3)</sup>, whereas normal pregnant women are capable of mounting an increased output of insulin to maintain euglycemia in the face of insulin resistance.

Women destined to develop GDM appear to be unable to increase their insulin output to the same extent, and are particularly insulin resistant prior to pregnancy. The incidence of GDM depends on diagnostic criteria and varies widely between racial groups. The overall incidence of 3-6% has steadily increased over time, ranging from 2.2% in South America to 15% in the subcontinent of India<sup>(4)</sup>.

GDM affects approximately 7% of pregnancies in the United States (**American Diabetes Association, 2003**), and its incidence is increasing in parallel with the epidemic of obesity and type II diabetes mellitus. The prevalence of GDM is increasing as pregnant women become older and more obese<sup>(5)</sup>.

Control of blood glucose levels is of utmost importance during pregnancy. Uncontrolled glucose levels may result in complications for both mother and fetus. In patients with GDM, maternal complications such as hypertensive disorders are twice as likely; cesarean section delivery is needed in 13-32% of patients. There is a significant increase in the risk of type II DM later on in life<sup>(6)</sup>.

The fetus from pregnancies with GDM has a higher risk of macrosomia (associated with a higher rate of birth injuries), asphyxia, neonatal hypoglycemia and neonatal hyperinsulinemia. Uncontrolled GDM predisposes fetuses to accelerate and excessive fat accumulation, insulin resistance, pancreatic exhaustion secondary to prenatal hyperglycemia and possibly higher risk of child and adult obesity and type II DM later in adult life<sup>(7)</sup>.

**Aim of the work**

The aim of this study is to compare the efficacy of metformin with that of insulin in treatment of gestational diabetes mellitus.

**Patients and Methods**

This two armed clinical trial was conducted prospectively on 100 pregnant women on regular antenatal care in the Diabetic Clinic of Minia Maternity Hospital during the period from January 2016 to September 2017. A written informed consent to participate in the study was taken from all patients.

- **Inclusion Criteria:**

1. Patients have been diagnosed as gestational diabetics >16 weeks gestation with singleton pregnancy who failed to achieve adequate glucose control on diet therapy alone.
2. Patients with FBG level ranging from 95-120 mg/dl or 2h. Postprandial blood glucose level ranging from 120-180 mg/dl.

- **Exclusion Criteria:**

1. Pregnant women with preexisting diabetes mellitus.
2. Women who have contraindication to take metformin.
3. Chronic heart diseases.
4. Hypersensitivity to metformin.
5. 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.
6. Patients concurrently on anticoagulants.
7. Fetal anomalies identified on ultrasound prior to initiation of therapy.
8. Non-compliant patients.

**All patients were subjected to the following:****[1] Careful History Taking:**

At the initial visit, a detailed history was obtained including personal history and past history concerning:

- Previous history of GDM or family history of DM.

Any history suggestive of pregestational diabetes as abortion, repeated unexplained IUFD or fetal macrosomia.

- History of chronic heart diseases, chronic hypertension, thyroid disease, chronic renal

insufficiency, hepatic disease, thrombophilia and systemic lupus erythromatosis.

- History of hypersensitivity 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] Laboratory Investigations:****A. Initial Investigations:**

- Glycosylated hemoglobin (Hb A1c).
- Fasting and postprandial blood glucose level.
- Liver and renal function tests.

**B. Routine Pregnancy Care Investigations:**

- Complete blood picture.
- Urine analysis: Fresh urine sample was collected from each woman and analyzed for proteinuria.

**C. Specific Investigations:**

- Fasting and postprandial blood glucose levels: A drop of fresh capillary blood (e.g., from index finger or the thumb) was obtained from each woman and analyzed for fasting and two hours postprandial blood glucose level every 2 weeks until 28 weeks gestational age, then every week until delivery using blood glucose monitor device (ACCU-CHEK ACTIVE).
- Glycosylated hemoglobin (HbA1c): Will be assessed every 3 months to determine the efficacy of treatment.

**[4] Ultrasonography:**

- It was done before starting treatment especially at 18-20 weeks to rule out congenital fetal malformations and to confirm gestational age. Then, it was done during the follow up period for assessment of fetal well being.

- **Management Plan:**

A diagnosis of GDM at the time of study was established when the patient presented 2 or more altered results on the oral glucose tolerance test with 100g or 75 g glucose. After the diagnosis of GDM the women were referred

for follow-up to an outpatient clinic. For nutritional counseling, a calorie intake of 25 to 35 kcal/kg weight per day was recommended depending on the classification of the pregestational body mass index (BMI) of the patient. In addition, the calories were divided to comprise 55% carbohydrates, 15% proteins, and 30% lipids. A 30-minutes walk, 3 times a week, was recommended.

Unsatisfactory glycemic control was defined among patients who presented more than 30% of capillary glycemia results above the reference values 1 week after commencing diet therapy combined with physical activity. Medication based treatment was then initiated. At this time, patients who met all inclusion criteria were randomized to receive either metformin (study group) or insulin (control group) according to an electronic randomization list. Data were collected weekly during return visits.

The control group received human NPH insulin. The starting dose was 0.7 units per kg body weight per day, with 2/3 of the dose being administered in the morning (before breakfast), and 1/3 in the evening (before dinner).

This group was asked to monitor glucose 7 times per day (at fasting, 2 hours after breakfast, 1 hour before lunch, 2 hours after lunch, 1 hour before dinner, 2 hours after dinner and at 3 in the morning).

The doses were adjusted weekly to achieve adequate glycemic control. If preprandial glucose levels were normal and postprandial

glucose levels were high, regular insulin (1 unit for every 10 mg/dl over target value) was added half an hour before that meal in addition to NPH insulin.

The metformin group received an initial metformin dose of 500 mg/once or twice daily with food and increased 500mg every one or two weeks toward targets or up to a maximum daily dose of 2500 mg divided doses with each meal.

Metformin was continued until the time of delivery. Insulin was added if glycemic control was not achieved despite maximum doses of metformin..

The decision to allow a trial of labor or proceed directly to cesarean section without a trial of labor for the indication of macrosomia or any other indication was left to the attending obstetrician's discretion.

Women discontinued metformin in labor, or 12 hours before a scheduled induction to avoid neonatal hypoglycemia which may rarely occurs for unknown reason. Blood glucose was checked every hour in labor and insulin was administered as needed, either via subcutaneous injection or intravenously, for target intrapartum maternal serum glucose of 70 mg/dl to 100 mg/dl.

## Results

This study included 95 pregnant women having GDM, 47 of them were treated with metformin, and the remaining number (48) were treated with insulin.

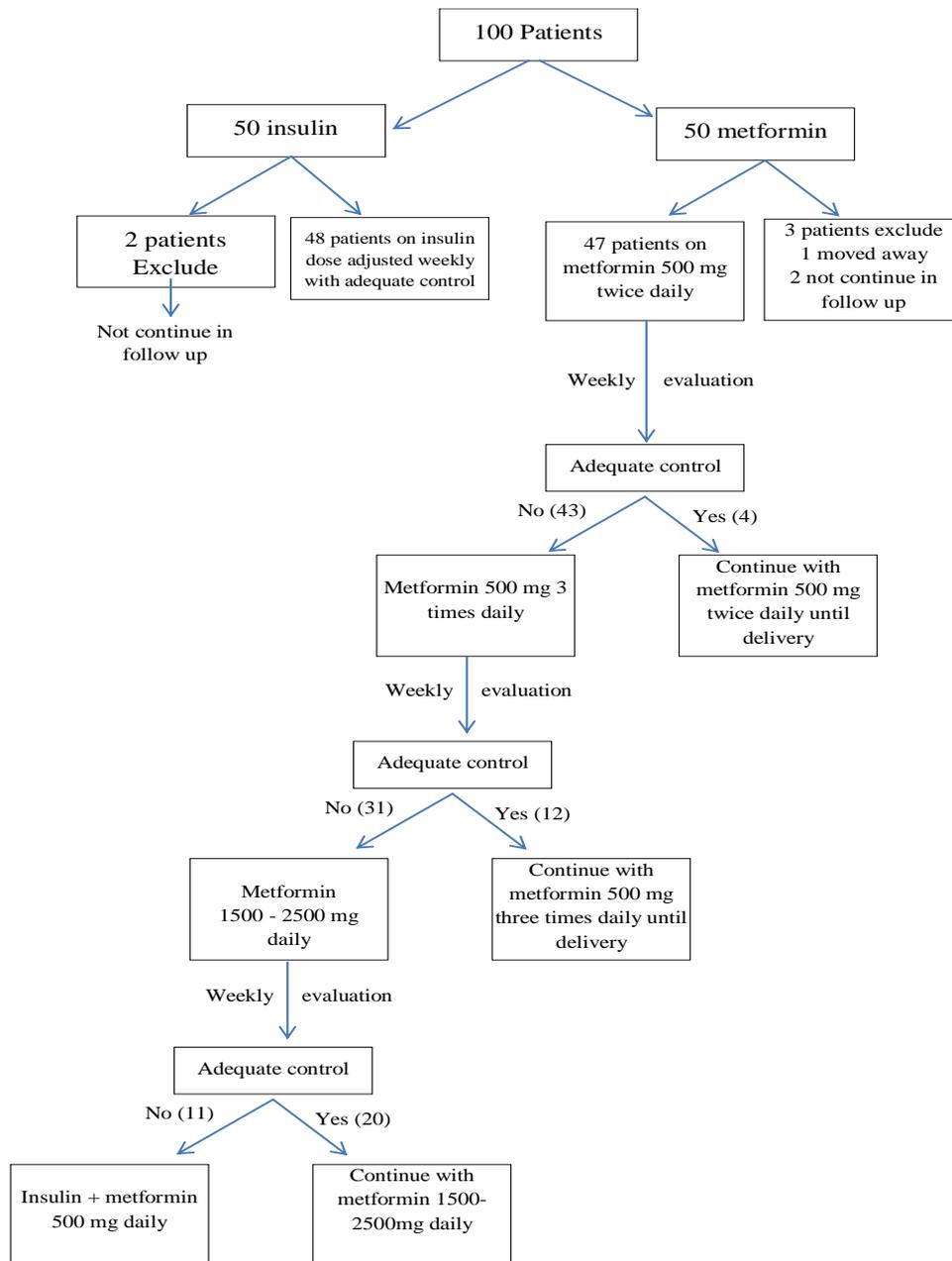


Figure (1): Flow chart.

**Table (1): Comparison between group treated with insulin and group treated with metformin as regards demographic data.**

	Treated with Insulin		Treated with Metformin		T <sup>(#)</sup> / Z <sup>(*)</sup>	p-value
<b>Age (yrs)</b>						
Range	27.0	39.0	28.0	38.0		
Mean±SD	32.1	3.2	31.6	2.8	0.830 <sup>#</sup>	0.409
<b>Gravidity</b>						
Range	1.0	7.0	1.0	6.0		
Median (IQR)	3.0	(1)	3.0	(2)	1.352*	0.180
<b>Parity</b>						
Range	0.0	5.0	0.0	5.0		
Median (IQR)	2.0	(1)	2.0	(2)	1.203*	0.232
<b>G.A at time of diagnosis (weeks)</b>						
Range	25.0	30.0	26.0	30.0		
Mean±SD	27.8	1.4	28.2	1.3	-1.445 <sup>#</sup>	0.152
<b>G.A at beginning of treatment</b>						
Range	27.0	32.0	28.0	32.0		
Mean±SD	29.7	1.9	30.0	1.4	-0.936 <sup>#</sup>	0.352
<b>BMI Kg/m<sup>2</sup> (At diagnosis)</b>						
Range	28.5	34.6	29.2	33.7		
Mean±SD	31.4	1.5	31.1	1.3	1.093 <sup>#</sup>	0.277
<b>HbA1c % At time of diagnosis</b>						
Range	4.9	7.1	5.0	6.7		
Mean±SD	5.8	0.6	5.7	0.4	0.990 <sup>#</sup>	0.325
<b>75 gm Oral Glucose tolerance curve (mg/dl)</b>						
<b>Fasting</b>						
Range	95.0	117.0	96.0	117.0		
Mean±SD	104.3	5.9	104.5	5.5	-0.171 <sup>#</sup>	0.865
<b>1 hr</b>						
Range	181.0	238.0	186.0	228.0		
Mean±SD	208.3	13.2	203.9	9.9	1.798 <sup>#</sup>	0.075
<b>2 hr</b>						
Range	161.0	194.0	154.0	192.0		
Mean±SD	177.6	8.8	175.5	10.3	1.088 <sup>#</sup>	0.280

- Data are expressed as mean ± SD for parametric data.
- Data are expressed as Median (IQR) for non-parametric data.
- t- Independent sample t<sup>#</sup>-test; \*z- Mann-Whitney test; IQR: Inter Quartile range
- p-value <0.05 S; p-value <0.001 HS; p-value >0.05 NS

## 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<sup>(8)</sup>. 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<sup>(9)</sup>.

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<sup>(10)</sup>.

A recent meta-analysis 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.<sup>(11)</sup>

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  $31.6 \pm 2.8$  versus

$32.1 \pm 2.8$  in the insulin treated group,  $p=0.409$ ), gravidity, parity, GA at time of diagnosis (in metformin treated group  $28.2 \pm 1.3$  weeks versus  $27.8 \pm 1.4$  weeks in insulin treated group,  $p=0.152$ ), GA at the beginning of treatment (in metformin treated group  $30 \pm 1.4$  weeks versus  $29.7 \pm 1.9$  weeks in insulin treated group,  $p=0.352$ ), BMI at the time of diagnosis (in metformin treated group  $31.1 \pm 1.3 \text{ kg/m}^2$  versus  $31.4 \pm 1.5 \text{ kg/m}^2$ ,  $p=0.277$  and HbA1c at time of diagnosis (in metformin treated group  $5.7 \pm 0.4\%$  versus  $5.8 \pm 0.6$  in insulin treated group %,  $p=0.325$ ).

This was in agreement with the study of Rowan et al., (2008) 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., On the other hand, the study of Spaulonci et al., (2013) reported that there was a significant difference in the number of pregnancies between groups with a median number of 2 pregnancies in metformin treated group versus 3 pregnancies in insulin treated group. This difference might result from the various ethnic groups and entry criteria as maternal age was slightly older.

With respect to glycemic control, no significant difference in mean pre-treatment glucose levels was observed between the two groups (fasting glucose levels were  $104.5 \pm 5.5$  mg/dl in metformin treated group versus  $104.3 \pm 5.9$  mg/dl in insulin treated group,  $p=0.865$  and 2-hours postprandial glucose levels were  $175.5 \pm 10.3$  in metformin treated group versus  $177.6 \pm 8.8$  mg/dl in insulin treated group,  $p=0.280$ ).

However, after introduction of the drugs, the average postprandial glycemic levels during the first week after randomization were just significantly lower in the metformin treated group ( $118.1 \pm 7.8$  mg/dl versus  $124.9 \pm 7.2$  mg/dl,  $p=0.042$ ).

These values did not differ significantly between 2 groups in the last 2 weeks before delivery ( $109.8 \pm 3.8$  mg/dl in metformin treated group versus  $111.3 \pm 4.2$  mg/dl in insulin treated group) a finding suggesting that glucose targets were reached sooner in the metformin group.

This was in agreement with the studies of Rowan et al., (2008) and Shirin et al., (2012) who reported that the postprandial glycemic levels at the first week after randomization were significantly lower in the metformin treated group ( $117.0 \pm 16.2$  mg/dl versus  $120.6 \pm 18$  mg/dl in insulin treated group). The likely explanation is that it takes time for the patients to master the usage and dose-calculation of insulin. Our

results were not in agreement with Moore et al., (2007) which revealed that the fasting and 2-hour postprandial glucose levels were not statistically different between insulin and metformin group. In both groups the fasting values were  $<100$  mg/dl ( $p=0.400$ ) and 2-hour postprandial glucose levels all averaged  $<120$  mg/dl in both groups ( $p=0.545$ ). In that study, Moore et al., considered any postprandial glucose level below 120 mg/dl to be normal irrespective of its exact value.

### Conclusion

Approximately 80% of women with GDM could be successfully and safely treated with metformin when diet therapy and exercise fail to reduce blood glucose values sufficiently. Moreover, it is observed that metformin is not associated with increased risk of adverse pregnancy outcomes.

The current study indicates that women clearly preferred metformin therapy over insulin where it offers a simpler, faster acting, cheaper and more convenient alternative to insulin in such individuals.

### Recommendation

Metformin is a relatively cheap, well-tolerated, safe and effective alternative to insulin therapy, for the control of blood glucose in patients with gestational diabetes mellitus. Metformin was found to provide adequate control with lower mean glucose levels throughout the day, less weight gain, less fetal body weight. Logistic regression analysis showed that gestational age at diagnosis, BMI at time of diagnosis and

pretreatment glucose level were predictors of the need of supplemental insulin therapy in women initially treated with metformin.

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