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Efficacy and safety of Metformin in Control of Gestational Diabetes Mellitus

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Abstract: Background and objective: Oral medications are attractive options for gestational diabetes mellitus control, This study aimed to evaluate the safety and efficacy of metformin in comparison to insulin for control of gestational diabetes mellitus. **Patients and Methods:** This was a comparative prospective randomized controlled trial conducted at Obstetrics and Gynecology Department, Al-Azhar University hospital, (New Damietta) during the period from January 2017 to January 2019 and included 106 pregnant women diagnosed with gestational diabetes mellitus using 75-g oral glucose tolerance test (OGTT) and divided randomly into two groups which are subjected to either insulin or metformin treatment, and the results of maternal and neonatal outcome between both groups were compared and statistically analyzed. **Results:** A Total of 106 pregnant women were included in the study,56 of them received metformin drug and the rest 50, received insulin, Glycemic control was statistically significant between the two groups after one week of treatment with higher mean fasting and post prandial among insulin group (92.42±4.933,129.82±7.889) versus (86.88±5.021,117.30±8.848) respectively *(P* value<0.05)., Cesarean delivery was higher in insulin group (81.5% versus57,7%), also mean birth weight was more in insulin than metformin groups (3.52±0.14) versus (2.99±0.12) at dose of 2000 mg with statistically significant differences (p<0.05). **Conclusion:** Metformin was safe, effective and acceptable drug in controlling mild GDM with comparable maternal and neonatal outcomes to insulin therapy.
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1. Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or initial diagnosis during pregnancy, which includes previously undetected type 1 or 2 diabetes mellitus or first presentation of diabetes during pregnancy (1).

Recently, the American Diabetes Association clearly defined GDM as diabetes diagnosed in the second or third trimester of pregnancy (2).

The prevalence of diabetes in pregnancy has been increasing in the united states (U.S). The majority is gestational diabetes mellitus (GDM) with the remainder primarily preexisting type 1 diabetes and type 2 diabetes. The rise in GDM and type 2 diabetes in parallel with obesity both in the U.S. and worldwide is of particular concern. Both type 1 diabetes and type 2 diabetes in pregnancy confer significantly greater maternal and fetal risk than GDM. (3).

In general, specific risks of uncontrolled diabetes in pregnancy include spontaneous abortion, preeclampsia, fetal demise, macrosomia, neonatal hypoglycemia, and neonatal hyperbilirubinemia, among others. In addition, diabetes in pregnancy may increase the risk of obesity and type 2 diabetes in offspring later in life. (4).

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 gynecology supports the use of either oral or injectable medications as acceptable therapies for women with GDM (5).

Insulin may be required to treat hyperglycemia, and its use should follow the guidelines. Both multiple daily insulin injections and continuous subcutaneous insulin infusion are reasonable alternatives, and neither has been shown to be superior during pregnancy. (6).

Oral medication are attractive options for GDM patients given their ease of administration, lower cost, comparable efficacy and improved adherence. **(7)**

Metformin, an oral biguanide, may be a 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 (8)

Insulin therapy has many disadvantages e.g. multiple daily injection, risk of maternal hypoglycemia and weight gain (9). So, the aim of the present study was to evaluate the safety and efficacy of metformin in comparison to insulin as an oral hypoglycemic drug for control of gestational diabetes mellitus.

2. Patients and Methods

This was a comparative prospective randomized controlled trial conducted at Obstetrics and Gynecology Department, Al-Azhar University hospital, (New Damietta) during the period from January 2017 to January 2019 and included 106 pregnant women with risk factors for development of gestational diabetes mellitus and diagnosed using 75-g oral glucose tolerance test (OGTT). Patient is considered diabetic if the plasma glucose (fasting more than or equal 92 mg /dl, or 1-h more than or equal 180 mg/dl, or 2-h more than or equal 153 mg/dl (10).

Inclusion criteria

1. Pregnant women with gestational diabetes mellitus, not controlled by diet.
2. Gestational age 28^{th} to 34^{th} weeks.
3. BMI: 25 - 35 kg/m².
4. Singleton pregnancy.

Exclusion criteria

1. Pregestational diabetes mellitus.
2. Renal or hepatic dysfunction.
3. Fetal congenital anomalies before enrolling in the study.
4. Previous adverse reaction to metformin.

Ethical consent: The nature of the study was clearly explained to each patient; an informed written consent was obtained. Also, an approval from the local ethics committee was taken (ADIM-IRB23032019).

Patients enrolled in the study, were admitted to the hospital for (glycemic control), history taking, general examinations, abdominal examination, laboratory investigations (routine investigations, fasting and post prandial blood glucose level, liver and kidney function tests, urine analysis for proteinuria), obstetric ultrasound (to rule out congenital fetal malformation and polyhydramnios and others).

Interventions

All patients are divided into two groups randomly according to electronic randomization.

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

Group B (metformin Group): included 56 patients**,** received metformin tablet with initial dose of 500 mg once daily with food and increased to 500 mg every one week if blood sugar not controlled up to a maximum dose of 2000 mg in divided doses, those patients are shifted to insulin treatment.

Outcome measures of the study were included are.

A. Maternal outcomes

1. Glycemic control, Good glycemic control is considered if the fasting capillary blood glucose less than 95 mg/dl and1 h postprandial less than 140 mg/dl 2 hours post prandial less than 120 mg/dl. (11).

2. Mode of delivery 3. Development of complications as preterm delivery and hypertension. 4. Maternal weight gain5. Acceptability of treatment.

B. Neonatal outcomes1-. Birth weight2-APGAR score at1 and 5--minutes.

3. Neonatal hypoglycemia, defined as plasma glucose level < 30 mg/dl in the first 24 hours of life and < 45 mg/dl thereafter. (12)

Statistical analysis: Data were analyzed using SPSS (ver. 22.0; IBM, Chicago, IL, USA). Quantitative data were displayed in the form of mean ± standard deviation (SD). $p < 0.05$ was accepted as indicating statistical significance. the following tests were done: Test of normality,. Independent-samples t-test, Paired t-test, A one-way analysis of variance (ANOVA), Chi-square (X^2) test and Fisher exact test.

3. Results

The study were included 106 pregnant women with gestational diabetes mellitus, 56 of them were treated with metformin, and the remaining number (50) were treated with insulin.

Both insulin and metformin groups were comparable with no statistically significant differences as regards age (32.82 ±3.02 versus 31.98 ±3.49) gravidity, parity, gestational age (30.8 ±2.22 versus 30.64 ± 2.068) body mass index (30±52 ±2.49 versus 30.74 ± 2.06841) liver function, kidney function and urine analysis as shown in Table1.

Glycemic control (fasting and postprandial glucose level) were statistically significant between insulin and metformin groups after one week of treatment with higher mean among insulin groups (92.42±4.933, 129.82±7.889) versus (86.88±5.021, 117.30±8.848) respectively *(P* value<0.05). Table (2).

There were statistically significant differences between insulin and metformin groups as regards mode of delivery as insulin group has higher percentage than metformin groups in cesarean delivery 44 (81.5%) versus 30(57.7%) respectively *(P* value<0.05). also, maternal weight gain in insulin group has higher mean of weight gain than metformin

group (5.4±0.5 versus 4±0.5) respectively (*P* value<0.05) Table 3.

There were statistically significant differences between insulin and metformin groups as regards neonatal outcomes as birth weight (3.52±0.14 versus (2.99±0.12), Apgar score at one minute (7.28±0.6 versus 7.45±0.6) and serum glucose level after one hour of delivery (22.34±2.3 versus 28.12±1.7) r espectively (*P* value<0.05) Table 4.

Table (1): Patients characteristics and laboratory investigations

Character	Insulin group N=50	Metformin group N=56	*p*-value
Age (years *Range* *Mean±SD*	28–39 32.82±3.02	25–38 31.98±3.49	0.202[1]
Gravidity *Range* *Median (IQR)*	1–7 3(2)	1–7 3(3)	0.180[2]
Parity *Range* *Median (IQR)*	0–6 2(2)	0–6 2(3)	0.907[2]
G.A (weeks) *Range* *Mean±SD*	28–34 30.8±2.22	28–34 30.64±2.068	0.710[1]
BMI Kg/m^2 *Range* *Mean±SD*	26–34 30.52±2.49	28–33 30.74±2.41	0.654[1]
Liver function tests Normal Abnormal	50(100%) 0(0%)	56(100%) 0(0%)	1.00[2]
Kidney function tests Normal Abnormal	50(100%) 0(0%)	56(100%) 0(0%)	1.00[2]
Urine analysis Normal Proteinuria	48(96%) 2(4%)	50(92%) 6(8%)	0.352[2]

[1] Independent t-test used
[2] 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** **Mean±SD**	85–100 92.42±4.933	80–97 86.88±5.021	0.0001[1]*
Postprandial **Range** **Mean±SD**	110–140 129.82±7.889	105–135 117.30±8.848	0.0001[1]*

*Statistically significant (p<0.05)
[1] Independent t-test use

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 labour	4(7.4%)	7(13.5%)	0.056[1]
Mode of delivery *CS* *VD*	44(81.5%) 10(18.5%)	30(57.7%) 22(42.3%)	0.031[2]*
Maternal weight gain *Mean±SD*	5.4±0.5	4±0.5	0.024[2]*
Acceptability of treatment	100%	92.2%	0.621[1]

*Statistically significant (p<0.05)
[1]Fisher-exact test used [2]Chi-square test used

Table (4):): Comparison of neonatal outcomes between both groups.

Neonatal outcomes	Insulin group N=54	Metformin groups N=52				*p*-value
		500mg N=19	1000mg N=13	1500mg N=12	2000mg N=8	
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[1]*
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[1]*
Apgar 5 min. *Mean±SD*	8.9±1.0	9. 8±0.3	9.6±0.4	9.7±0.6	9.6±0.6	0.0521[1]*
Serum glucose level (mg/dl)						
1 hr *Mean±SD*	22.34±2.3	25.56±2.4	26.31±1.9	27.38±2.7	28.12±1.7	0.035[1]*
2 hr *Mean±SD*	40.54±0.9	43.23±1.1	43.21±1.6	42.38±2.7	43.65±0.9	0.041[1]*

*Statistically significant (p<0.05)
[1] ANOVA test used.

4. Discussion

The majority of guidelines recommend insulin for treatment of hyperglycemia in GDM[10]however, there are several barriers toward insulin use in this population, namely an undesirable route of administration, the potential for weight gain (which may further compound and propagate hyperglycemia and the risk of hypoglycemia (13). Thus, in this present study, comparison between metformin and insulin was done as regard maternal and neonatal outcomes. The study included 106 pregnant women with gestational diabetes mellitus, 56 women were treated with metformin, and the remaining 50women, were treated with insulin, comparison between both groups were done as regard maternal and neonatal outcomes.

In the present study the glycemic control after one week of treatment between both groups as regard fasting and post-prandial mean glucose level was higher in insulin group than metformin group respectively with significant statistical differences and this finding indicate that metformin group reached glucose target sooner, and the reason may be the time used by the pregnant women to adjust the dose of insulin which is consistent with study done by GUI et al (14), which showed metformin is comparable with insulin in glycemic control and also consistent with study done by (15) in their prospective observational study were comparing metformin to insulin for patients with GDM and type 2 DM (T2DM) in pregnancy. They found that glycemic control was better with metformin after 1 week of therapy and also throughout gestation compared to insulin and also found no major complications or perinatal deaths related to metformin uptake. They proved that metformin is clinically efficient, inexpensive, and a harmless alternative to insulin therapy in pregnant diabetic women, metformin reduce hyperglycemia by reduce hepatic gluconeogenesis, increasing insulin sensitivity and enhancing peripheral glucose uptake (16). The results of this current study were comparable to the findings of Glueck et al (17) as we also found

that metformin intake during pregnancy was not associated with increasing rate of preeclampsia or neonatal complications.

In the present study the rate of pre-term delivery was higher in metformin group (13.5%) than insulin group (7.4%) with insignificant statistical differences which is consistent with study done by(18) and this may denote metformin might have unrecognized effect on labor process.

In the present study the rate of caesarean section was higher in insulin group (81.5%) Versus metformin group (57.7%) with significant statistical differences which is consistent with study done by (19).

In the present study the maternal weight gain at the time of enrolment in the study was higher in insulin group (5.4±0.5) versus metformin group (4±0.5) with significant statistical differences which is consistent with study done by (19) that showed significant statistical differences.

In the present study, the mean Birth weight was high in insulin group (3.52±0.14) versus metformin group (2.99±0.12) after 2000 mg with significant statistical differences which is consistent with study done by (19).

In the present study the mean neonatal Serum glucose level (mg/dl) after one hour of delivery was lower in insulin group (22.34±2.3) versus metformin group (28.12±1.7) after 2000 mg with significant statistical differences which is consistent with study done by (18) who found rates of neonatal hypoglycemia were similar in the two groups but sever hypoglycemia less than 28.8 mg/dl occurred less often in infants of women taking metformin.

Also, consistent with study done by (20) had randomized Australian study performed on women with gestational diabetes between 20 and 33 weeks of pregnancy getting metformin or insulin. There was no difference in efficacy between both groups in controlling glucose levels. Infants of metformin group had a lower rate of hypoglycemia compared with infants of insulin group.

A limitation of the present study is the small sample size and the short follow up period that end after patient delivery so the long-term safety data of metformin is absent.

5. Conclusion and Recommendations:

Metformin is safe and effective drug in controlling mild gestational diabetes mellitus and more acceptable, with comparable maternal and neonatal outcomes to insulin therapy, with the benefit of avoiding the drawback of insulin as multiple daily injections, risk of maternal hypoglycemia and weight gain and more acceptable by most of studied patient, and can be prescribed for this purpose by the clinician but the clinicians should carefully balance the risk-benefit profile of different treatments according to various situations. and further large study is recommended to establish the long-term outcomes in exposed offspring to metformin treatment.

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