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Neonatal outcomes in case of euglycemic control in gestational diabetes using insulin *vs.* metformin: Randomized controlled trial

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SUMMARY

AUTHORS' CONTRIBUTION: (A) Study Design · **(B)** Data Collection . **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** Funds Collection

Background: Gestational diabetes mellitus (GDM) is a major global public health issue, with prevalence increasing in recent years due to the epidemic of obesity and type 2 diabetes. Aim of the Work: to compare different neonatal outcomes according to the different treatment modalities used in the management of GDM. Our hypothesis was that Metformin is as effective and safe as insulin in patients with gestational diabetes.

Patients and Methods: The current non inferiority-Randomized controlled trial was conducted at Ain Shams Maternity hospital between June 2020 to February 2021. The study included 140 outpatient cases or admitted patients for antenatal care: Group A: women were given Metformin (Total 70) and Group B: Women were given insulin. (Total 70).

Results: there was no significant difference between Metformin and Insulin groups regarding age, enrolment BMI, parity and family history of DM. There was no significant difference between Metformin and Insulin groups regarding gestational age at enrolment and delivery as well as pregnancy duration after intervention. BMI at delivery, BMI increase as well as BMI increase rate were significantly lower in Metformin group.

There were no significant differences between Metformin and Insulin groups regarding fasting, two-hour postprandial and HbA1c blood glucose at enrollment and throughout treatment as well as their reduction after intervention. Maternal complications as hypoglycemia, hyperglycemia and preeclampsia were non-significantly less frequent among Metformin group than among Insulin group. Compliance to treatment was significantly more frequent among Metformin group than among Insulin group. Cesarean delivery was non-significantly less frequent among Metformin group than among Insulin group. There was no significant difference between Metformin and Insulin regarding birth weight APGAR-1, but APGAR-5 was significantly higher in Metformin group. Neonatal complications as IUFD, IUGR, macrosomia, congenital anomalies, neonatal hypoglycemia, respiratory distress and NICU admission were non-significantly less frequent among Metformin group.

Conclusions: From the results of current study we can conclude that: Oral metformin was effective as insulin injection in control and management of GDM. BMI was controlled with oral metformin better than insulin injection. Maternal and neonatal complications specially birth weight were the same with both types of treatment. Women had better compliance to metformin treatment. Type of delivery wasn't affected by type of treatment.

Keywords: Neonatal outcomes; Euglycemic control; Gestational diabetes; Insulin; Metformin

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INTRODUCTION

Gestational diabetes mellitus is a major global public health issue, with prevalence increasing in recent years due to the epidemic of obesity and type 2 diabetes [1,2].

Gestational diabetes mellitus is defined as a condition in which a woman without diabetes develops the glucose intolerance resulting in hyperglycemia of variable degree during pregnancy [3].

Risk factors of developing Gestational diabetes mellitus include being overweight, polycystic ovary syndrome, maternal age, and a family history with type 2 diabetes. Gestational diabetes mellitus generally exhibit no symptoms, but it increases the risk of preeclampsia, depression, and the incidence of cesarean section. Moreover, children born to mothers with badly treated Gestational diabetes mellitus are at higher risk of LGA, hypoglycemia, jaundice or at increased risk of being overweight and developing type 2 diabetes [4].

So the management of Gestational diabetes mellitus is primarily aimed at glycemic control to reduce the incidence of adverse pregnancy outcomes [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 Gestational diabetes mellitus, 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 Gestational diabetes mellitus 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 there are more than 10 studies assessing metformin safety and efficacy [8].

The largest study was known as Metformin in Gestational Diabetes (MiG) study and involved 751 pregnant women with Gestational diabetes mellitus. 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

The purpose of this study to compare different neonatal outcomes according to the different treatment modalities used in the management of Gestational diabetes mellitus..

PATIENTS AND METHODS

This Non Inferiority-Randomized controlled trial was conducted at Ain Shams Maternity Hospital between September 2020 to February 2021. The study included 140 outpatient cases or admitted patients for antenatal care. Subjects of the study were divided into 2 groups:

Group A: women were given Metformin (Total 70). Metformin was started at dose of 500 mg and increased up to 2500 mg in 3 divided doses as tolerated until glycemic control is achieved. Target blood glucose levels for glycemic control are FBS <95 mg/dl and 1 hour post parandial <140 mg/dl. If blood glucose levels are higher than the cut off values 1 week after treatment with maximum dose of metformin, insulin was added according to American Diabetes Association recommendations.

Group B: Women were given insulin (Total 70).

Total daily requirement of insulin: 0.9 units/Kg/day

It was divided into:

1. 50% intermediate acting insulin twice per day (at breakfast and bedtime).
2. 50% short acting insulin three times per day (before each meal).

The study included patients diagnosed with gestational diabetes by using Fasting (>95 mg/dl)and 2 hrs postprandial (>120 mg/dl), singleton pregnancy and Low risk patient should be screened and diagnosed with GDM between 24 to 28 weeks, and high risk patient (History of GDM or Macrosomic baby, obesity, first degree relative with diabetes) at first antenatal visit.

While pre-existing type 1 or type 2 diabetes as it affects the neonatal and maternal outcomes., HbA1C > or =6.5 in first trimesteric as it is considered of having type 2 diabetes. Treatment interfering with glucose metabolism as steroids as it affects the glycemic control of the patient. Allergies to one of the components of the treatment as it may lead to anaphylaxis shock and adverse outcomes. Underlying diseases such as severe chronic hypertension, thyroid disease, chronic renal insufficiency, hepatic disease, thrombophilia, systemic lupus erythromatosis and history of intrauterine growth retardation as it affects the fetal growth which lead to controversy between the effect of drug used in the treatment or the actual disease, and their effect on drug clearness and the possibility of using the drugs. Macrosomia as its considered one of the side effects of the used medications, congenital fetal malformation to identify the adverse outcomes from the used medications were excluded from the study.

Study procedures

All women in this research 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), and 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 was done by measuring fasting and 2 hrs postprandial glucose level test -after an overnight fast of 8-14 h. Diagnosis of GDM was made with elevated plasma glucose levels fasting glucose >95 mg/dl (5.3 mmol/1), 2 hr >120 mg/dl (6.7 mmol/1). 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.

Investigations: All subjects had routine laboratory work up: CBC, KFT, LFT, urine analysis, urine culture, and HbA1C.

Performing HbA1c to evaluate the patient status and the outcomes of the treatment: Outside of pregnancy, HbA1c has been shown to be a useful biomarker for diagnosing type 2 diabetes and monitoring glucose control among individuals with diabetes. Its current application in pregnancy has been limited to screening for overt type 2 diabetes and it remains unclear if it has utility for GDM screening.

In accordance with current American Diabetes Association recommendations, we considered women to have had overt diabetes if their first trimester HbA1c was ≥ 6.5% (48 mmol/mol) and were excluded from the study analyses. Then the patients were randomized after data analysis to choose the ideal therapy for treatment.

6-Follow up: Follow up visits was arranged in-the same antenatal clinic every 2 weeks till 36 weeks then weekly tills 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 were advised to measure fasting blood glucose and 1 hr postprandial after each meal. Our goals was to keep fasting glucose <= 95 mg/dL, and 1hr postprandial values <= 140 mg/dL.

Patients who can't monitor and record their blood glucose levels were tested using glucose monitors at each antenatal visit. Fasting and post prandial blood glucose levels 1 h after breakfasts 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 performed at first visit at 16-19 weeks (anomaly scan) and then monthly. Follow up was continued till delivery to evaluate the pregnancy outcome.

1. All subjects who participated in this study were informed by the purpose of the study, and were provided by a written informed consent before their participation.
2. All subjects were assured that refusal to participate in this study would not in any way compromise further therapy or provided medical service or contact with medical staff, and that all the data collected from them are confidential. This confidentiality was never breached.

Outcomes: Outcomes of interest were divided into 2 categories: neonatal outcomes and maternal outcomes. Our primary outcome included the neonatal increase in birth weight

Other neonatal outcomes: APGAR score, NICU, IUGR, neonatal hypoglycemia, mean birth weight, RDS, gestational age at delivery, IUFD.

Maternal outcomes: The maternal outcomes included glycohemoglobin (HbA1c), FBG, 2HBG, weight gain hypoglycemia, hyperglycemia, compliance and preeclampsia.

Ethical Considerations: The study was presented for approval from the ethical committee of the department of Obstetrics and Gynecology, faculty of medicine, Ain Shams University. Informed consent after explaining the study purpose and methods to the subjects. Data presentation was not by the patient name but by diagnosis.

Statistical methods: 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 was done for quantitative data as minimum& maximum of the range as well as #mean ± SD (standard deviation) for quantitative normally distributed data, median and 1st & 3rd inter-quartile range for quantitative non-normally distributed data, while it was done for qualitative data as number and percentage.

Inferential analyses were done for quantitative variables using Shapiro-Wilk test for normality testing, ANOVA test and Kruskal Wallis test for more than two independent groups with non-normally distributed data. In qualitative data, inferential analyses for independent variables was be done using Chi square test for differences between proportions and Fisher's Exact test for variables with small expected numbers. Log rank test was used to test survival functions. The level of significance was taken at P value <0.050 is significant, otherwise is non-significant.

RESULTS

No significant difference between Metformin and Insulin groups regarding age, parity and family history of DM (Tab. 1.).

No significant differences between Metformin and Insulin groups regarding Gestational age at enrollment and delivery as well as pregnancy duration after intervention (Tab. 2.).

No significant differences between Metformin and Insulin groups regarding enrollment BMI. BMI at delivery, BMI increase as well as BMI increase rate were significantly lower in Metformin group (Tab. 3.).

No significant differences between Metformin and Insulin groups regarding fasting blood glucose at enrollment and throughout treatment as well as its reduction after intervention (Tab. 4.).

No significant differences between Metformin and Insulin groups regarding two-hour postprandial blood glucose at enrollment and throughout treatment as well as its reduction after intervention (Tab. 5.).

No significant differences between Metformin and Insulin groups regarding HbA1c at enrollment and

Tab. 1. Demographic characteristics among the studied groups.

Items	Measures	Metformin (N=70)	Insulin (N=70)	P-value
Age (years)	Mean ± SD	29.3 ± 4.2	30.1 ± 3.6	^0.250
	Range	19.0-38.0	21.0-36.0	
Parity, (n, %)	Nulli	23 (32.9%)	20 (28.6%)	#0.583
	Multi	47 (67.1%)	50 (71.4%)	
Family history of DM		22 (31.4%)	25 (35.7%)	#0.591

^ Independent t-test, #Chi square test.

Tab. 2. Demographic characteristics among the studied groups.

Time	Measures	Metformin (N=70)	Insulin (N=70)	^ P-value	Effect size Mean ± SE 95% CI
Enrollment	Mean ± SD	27.3 ± 3.8	27.5 ± 2.3	0.665	-0.2 ± 0.5
	Range	21.0-34.0	21.0-34.0		-1.3-0.8
Delivery	Mean ± SD	38.6 ± 0.7	38.3 ± 0.9	0.075	0.2 ± 0.1
	Range	36.0-40.0	36.0-40.0		0.0-0.5
Duration	Mean ± SD	11.3 ± 3.9	10.8 ± 2.4	0.389	0.5 ± 0.5
	Range	4.0-18.0	4.0-18.0		-0.6-1.5

^ Independent t-test. *Significant. CI: Confidence Interval

Tab. 3. BMI (kg/m^2) at enrollment and delivery.

Time	Measures	Metformin (N=70)	Insulin (N=70)	^ P-value	Effect size Mean ± SE 95% CI
Enrollment	Mean ± SD	29.1 ± 2.5	28.8 ± 2.2	0.427	0.3 ± 0.4
	Range	23.0-34.1	24.7-34.6		-0.5-1.1
Delivery	Mean ± SD	33.0 ± 2.5	34.5 ± 2.2	<0.001*	-1.5 ± 0.4
	Range	27.0-37.8	30.4-40.1		-2.3-0.7
Increase	Mean ± SD	3.9 ± 0.2	5.7 ± 0.3	<0.001*	-1.8 ± 0.0
	Range	3.2-4.5	5.1-6.4		-1.9-1.7
BMI change rate per week	Mean ± SD	0.4 ± 0.2	0.6 ± 0.2	<0.001*	-0.2 ± 0.0
	Range	0.2-1.0	0.3-1.4		-0.2-0.1

^ Independent t-test. *Significant. CI: Confidence Interval

Tab. 4. Fasting blood glucose (mg/dL) at enrollment and throughout treatment.

Time	Measures	Metformin (N=70)	Insulin (N=70)	^ P-value	Effect size Mean ± SE 95% CI
Enrollment	Mean ± SD	139.1 ± 12.5	140.6 ± 13.4	0.482	-1.5 ± 2.2
	Range	106.0-160.0	113.0-159.0		-5.9-2.8
Throughout treatment	Mean ± SD	104.9 ± 13.6	108.2 ± 14.8	0.180	-3.2 ± 2.4
	Range	74.0-137.0	78.0-138.0		-8.0-1.5
Reduction	Mean ± SD	34.1 ± 8.6	32.4 ± 8.7	0.247	1.7 ± 1.5
	Range	4.0-53.0	15.0-53.0		-1.2-4.6

^ Independent t-test. *Significant. CI: Confidence Interval

Tab. 5. Fasting blood glucose (mg/dL) at enrollment and throughout treatment.

Time	Measures	Metformin (N=70)	Insulin (N=70)	^ P-value	Effect size Mean ± SE 95% CI
Enrollment	Mean ± SD	192.1 ± 28.8	195.4 ± 32.6	0.536	-3.2 ± 5.2
	Range	134.0-258.0	134.0-256.0		-13.5-7.1
Throughout treatment	Mean ± SD	117.5 ± 11.1	121.0 ± 12.6	0.087	-3.5 ± 2.0
	Range	89.0-144.0	97.0-161.0		-7.4-0.5
Reduction	Mean ± SD	74.6 ± 21.1	74.4 ± 23.6	0.952	0.2 ± 3.8
	Range	23.0-124.0	32.0-123.0		-7.3-7.7

\^ Independent t-test. *Significant. CI: Confidence Interval

throughout treatment as well as its reduction after intervention (Tab. 6.).

Maternal complications were non-significantly less frequent among Metformin group than among Insulin group (Tab. 7.).

Compliance to treatment was significantly more frequent among Metformin group than among Insulin group (Tab. 8.).

Cesarean delivery was non-significantly less frequent among Metformin group than among Insulin group (Tab. 9.).

No significant differences between Metformin and Insulin regarding birth weight APGAR-1, but APGAR-5 was significantly higher in Metformin group. Neonatal complications were non-significantly less frequent among Metformin group (Tab. 10.).

DISCUSSION

GDM generally exhibit no symptoms, but it increases

Tab. 6. HbA1c (%) at enrollment and throughout treatment.

Time	Measures	Metformin (N=70)	Insulin (N=70)	^ P-value	Effect size Mean ± SE 95% CI
Enrollment	Mean ± SD	6.1 ± 0.1	6.1 ± 0.1	0.840	0.0 ± 0.1
	Range	5.7-6.2	5.7-6.3		-0.2-0.1
Throughout treatment	Mean ± SD	5.6 ± 0.1	5.7 ± 0.1	0.17759	-0.1 ± 0.1
	Range	5.3-5.9	5.4-5.9		-0.2-0.1
Reduction	Mean ± SD	0.5 ± 0.2	0.4 ± 0.2	0.483	0.1 ± 0.1
	Range	0.1-0.7	0.1-0.8		-0.2-0.1

^Independent t-test. *Significant. CI: Confidence Interval

Tab. 7. Comparison regarding maternal complications.

Outcomes	Metformin (N=70)	Insulin (N=70)	#P-value	Effect size RR (95% CI)
Hypoglycemia	11 (15.7%)	14 (20.0%)	0.508	0.79 (0.38-1.61)
Hyperglycemia	6 (8.6%)	10 (14.3%)	0.288	0.60 (0.23-1.56)
Preeclampsia	10 (14.3%)	13 (18.6%)	0.494	0.77 (0.36-1.64)

#Chi square test. RR: Relative Rate. *Significant. CI: Confidence Interval

Tab. 8. Comparison regarding maternal compliance to treatment.

Status	Metformin (N=70)	Insulin (N=70)	#P-value	Effect size RR (95% CI)
Compliant	61 (87.1%)	43 (61.4%)	<0.001*	1.42 (1.15-1.74)
Not	9 (12.9%)	27 (38.6%)		

#Chi square test. RR: Relative Rate. *Significant. CI: Confidence Interval

Tab. 9. Comparison regarding mode of delivery.

Mode	Metformin (N=70)	Insulin (N=70)	#P-value	Effect size RR (95% CI)
Cesarean	32 (45.7%)	39 (55.7%)	0.237	0.82 (0.59-1.14)
Vaginal	38 (54.3%)	31 (44.3%)		

#Chi square test. RR: Relative Rate. *Significant. CI: Confidence Interval

Tab. 10. Comparison regarding neonatal condition and complications at delivery.

Findings		Metformin (N=70)	Insulin (N=70)	P-value	Effect size Mean ± SE 95% CI
Birth weight (kg)	Mean ± SD	3.4 ± 0.5	3.3 ± 0.6	^0.486	0.1 ± 0.1
	Range	2.0-4.8	2.1-4.8		-0.1-0.3
APGAR 1	Mean ± SD	6.9 ± 1.2	6.7 ± 1.3	^0.269	0.2 ± 0.2
	Range	4.0-9.0	4.0-9.0		-0.2-0.6
APGAR 5	Mean ± SD	7.7 ± 1.1	7.3 ± 1.3	^0.037*	0.4 ± 0.2
	Range	5.0-9.0	5.0-9.0		0.1-0.8
					RR (95% CI)
IUFD		0 (0.0%)	1 (1.4%)	§0.999	--
IUGR		3 (4.3%)	8 (11.4%)	#0.116	0.38 (0.10-1.36)
Macrosomia		7 (10.0%)	10 (14.3%)	#0.438	0.70 (0.28-1.73)
Congenital anomalies		1 (1.4%)	2 (2.9%)	§0.999	0.50 (0.05-5.39)
Hypoglycemia		9 (12.9%)	15 (21.4%)	#0.178	0.60 (0.28-1.28)
Respiratory distress		2 (2.9%)	4 (5.7%)	§0.681	0.50 (0.09-2.64)
NICU admission		11 (15.7%)	17 (24.3%)	#0.205	0.65 (0.33-1.28)

^Independent t-test. #Chi square test. §Fisher's Exact test. RR: Relative Rate. *Significant. CI: Confidence Interval

the risk of preeclampsia, depression, and the incidence of cesarean section. Moreover, children born to mothers with badly treated GDM are at higher risk of LGA, hypoglycemia, jaundice or at increased risk of being overweight and developing type 2 diabetes [4].

Munshi and Khandaker [9] assessed the efficacy of metformin in the management of Gestational Diabetes Mellitus (GDM) and to compare maternal fetal outcome between metformin and insulin in GDM. It is a prospective comparative study performed in a tertiary centre. 100 women diagnosed with gestational diabetes mellitus according to Diabetes in Pregnancy Study group of India (DIPSI) criteria at booking and/or between 24-28 weeks of gestation. These women were divided randomly into two groups, 50 patients in each group and they are subjected to pharmacological treatment with either insulin or metformin. Optimum glycemic control between the two groups is studied along with maternal and fetal outcome. They agreed with current results and stated that there was no significant difference between both groups as regard age distribution parity and gravidity.

Wang et al., [10] compared between metformin *vs.* insulin for pregnancy outcomes in gestational diabetes. They systematically searched PubMed, Embase, Medline, ClinicalTrials.gov, and the Cochrane database (from database inception to 10 February 2020) for randomized

controlled trials (RCTs) that treatment with metformin *vs.* insulin for GDM. They agreed with us and stated that there were no significant differences in maternal age and body mass index before treatment in any of the included studies.

Ahmed et al., [11] compared the efficacy of oral metformin therapy *vs.* insulin treatment in patients with gestational diabetes mellitus in term of maternal glycemic control, maternal outcome and fetal outcome. A total of 156 patients who have the diagnosis of gestational diabetes were enrolled after fulfilling certain inclusion and exclusion criteria. They were randomly assigned to two groups of treatment with either insulin or metformin. Serial ultrasound examination and blood glucose level were assessed at enrolment and at follow-up visits. The outcomes were fetal and maternal outcomes. They agreed with us and stated that there was insignificant difference between both groups regarding baseline characteristics at enrollment at the study, the range of age in Metformin group was 24-43 years (mean ± SD=31.8 ± 5.1), while those in Insulin group were with range of age 23-43 years (mean ± SD=30.6 ± 4.5). According to weight (mean ± SD) in Metformin group was 78.6 ± 7.4 and in Insulin group was 78.1 ± 6.8. Only 4 (5.12%) of the Metformin group have Family history of GDM while 10 (12.8%) of the insulin group have this history.

Bao et al., [12] performed a systematic review and meta-analysis about metformin *vs.* Insulin in management of gestational diabetes. They systematically searched PubMed, Embase, and the Cochrane database (last search was updated on 1 May 2019) for randomized controlled trials comparing metformin with insulin. Two reviewers extracted the data and calculated pooled estimates by use of a random effects model. They agreed with us and stated that there were no significant differences before treatment in maternal age (p=0.49; MD=0.14; 95%CI (-0.26, 0.54); I2=26%) and body mass index (BMI) (p=0.61; MD=0.14; 95%CI (-0.38, 0.65); I2=49%).

Mahmood [12] compared the efficacy of metformin in controlling hyperglycemia in GDM or their effect on the pregnancy outcome *vs.* insulin therapy. This study was carried out at the Obstetrics and Gynecology Department of Al-Zahraa Teaching Hospital in Al-Najaf from February 2015 to November 2015, as 100 pregnant ladies from (20 to 32) weeks of gestational age were already diagnosed to have GDM or we diagnosed them by formal 75 g oral glucose tolerance test. They disagreed with us and stated that women were older, with higher parity in metformin group than insulin one but there was no difference regarding BMI.

Ali et al., [14] compared the efficacy of metformin with that of insulin in treatment of gestational diabetes mellitus (GDM). The study included 94 pregnant women who have been diagnosed as gestational diabetics at 25-33 weeks gestation with singleton pregnancy. They had fasting blood glucose (FBG) level ranging from 95-120 mg/dl or 2-hour postprandial blood glucose (PPBG) level ranging from 120-190 mg/dl. The exclusion criteria include pregnant women with preexisting DM and underlying diseases known to affect fetal growth or drug clearance. All patients were randomized to receive metformin (n=47) or insulin (n=47). They agreed with us and stated that there were no significant differences between the two groups regarding maternal age, gravidity, parity and BMI at time of diagnosis.

Statistical analysis of current study showed that there was no significant difference between Metformin and Insulin groups regarding gestational age at enrollment and delivery as well as pregnancy duration after intervention.

Munshi and Khandaker [9] agreed with current results and stated that gestational age at the time of diagnosis of GDM between metformin and insulin group were comparable.

Wang et al., [10] agreed with us and stated that there was no significant difference in gestational age before treatment in any of the included studies.

Bao et al., [12] agreed with us and stated that there were no significant differences before treatment in gestational age (p=0.48; MD=0.11; 95%CI (-0.19, 0.41); I2=32%). But they disagreed with us regarding gestational age of delivery and stated that in Seven studies involving 847 GDM patients were included in the analysis of gestational age at delivery, and there was a significant difference between the two groups (p=0.00; MD=-0.29; 95% CI (-0.46, -0.11); I2=0%). The result might suggest that metformin can shorten the pregnancy and induce premature delivery. But in the analysis of premature delivery which include 10 studies, there was no significant difference (p=0.11; RR=1.28; 95% CI (0.95, 1.73); I2=3.6%).

Ali et al (2018) their results was the same with us and stated that there were no significant differences between the two groups regarding GA at time of diagnosis and GA at beginning of treatment.

Statistical analysis of current study showed that BMI at delivery, BMI increase as well as BMI increase rate were significantly lower in Metformin group.

Bao et al., [12] their results went along with our results and stated that in twelve studies reported the outcome of maternal weight gain including eight studies (involving 978 GDM patients) of total weight gain and four studies (involving 1098 GDM patients) of weight gain after randomization. Total maternal weight gain during pregnancy was statistically lower in the women who received metformin (p=0.00; MD=-1.31; 95%CI (-2.08, -0.54); I2=91%), Maternal weight gain after randomization was statistically lower in the women who received metformin (p=0.00; MD=-1.23; 95% CI (-1.75, -0.71); I2=63%).

Ali et al., [14] admitted our results and stated that maternal weight gain was less in the metformin treated group. It was found that women who required supplemental

insulin had higher BMI, earlier gestational age at the start of treatment and higher levels of FBG and 2 hours glucose level at time of diagnosis.

Statistical analysis of current study showed that there were no significant differences between Metformin and Insulin groups regarding fasting, two-hour postprandial and HbA1c blood glucose at enrollment.

Statistical analysis of current study showed that there were no significant differences between Metformin and Insulin groups regarding fasting, two-hour postprandial and HbA1c blood glucose throughout treatment as well as their reduction after intervention.

Munshi and Khandaker [9] agreed with current results and stated that there was no significant difference in the use of metformin or insulin regarding glycemic control (P = 0.15). 84% of insulin group had good glycemic control whereas in metformin group, 72%, achieved euglycemic state. Of the 50 women assigned to metformin, 84% continued to receive metformin until delivery and 16% received supplemental insulin.

Ahmed et al., [11] showed comparable results with ours and stated that there was no significant difference in the maternal glycemic control between the two groups and also shows no significant difference in the risk of development of hypoglycemia between patients used metformin and those who used insulin.

Bao et al., [12] disagreed with us and stated that in five studies involving 1378 GDM patients were included in the analysis of HbA1c at 36/37 week, and there was a significant difference between the two groups (p=0.25; MD=0.09; 95% CI (-0.06, 0.25); I2=87%). Metformin had potential benefits over insulin in controlling of HbA1c.

Ali et al., [14] differs with us and stated that women in the metformin treated group reached sooner to the glucose targets.

Statistical analysis of current study showed that maternal complications as hypoglycemia, hyperglycemia and preeclampsia were less frequent among Metformin group than among Insulin group but it was non-significant.

Munshi and Khandaker [9] had different results from ours and stated that there was no difference between both groups regarding maternal complications, 4 patients developed mild preeclampsia in the metformin group; whereas there was no patient developing preeclampsia in insulin group p= 0653.

Wang et al., [10] their results contradicted with us and stated that in Twelve studies (n=2885 patients) were included in the analysis of preeclampsia. Metformin reduced the risk of preeclampsia (p<0.00001; RR=0.52; 95% CI (0.40, 0.67); I 2=31%).

Ahmed et al., [11] agreed with us and stated that there was no significant difference between the two groups regarding the associated maternal hypertensive complications. There were no cases of pre-eclampsia in both groups.

Bao et al., [12] concurred with us and stated that in five studies involving 1457 GDM patients were included in the analysis of PIH and nine studies involving 1813 GDM patients were included in the analysis of preeclampsia. Metformin slightly reduced the risk of PIH (p=0.03; RR=0.64; 95% CI (0.44, 0.95); I2=0%). But metformin did not reduce the risk of preeclampsia (p=0.45; RR=0.89; 95% CI (0.65, 1.21); I2=0%).

Statistical analysis of current study showed that compliance to treatment was significantly more frequent among Metformin group than among Insulin group.

Munshi and Khandaker [9] agreed with current results and stated that More women in the metformin group than in the insulin group stated that they would choose to receive their assigned treatment again (76% vs. 18%). 5% were not sure of the type of treatment they want in their next pregnancy. 80% of patients felt that that the repeated injection was the most difficult part of the treatment while 8% felt diet control was the most difficult. 64% of the entire study group felt taking oral medications was the easiest part of the study.

Ahmed et al., [11] their results matched ours and stated that there was significant difference between the two groups in maternal compliance to treatment as 89.7% of patients using metformin were compliant to the use of it while only 39.7% who received insulin therapy were compliant to it.

Statistical analysis of current study showed that Cesarean delivery was non-significantly less frequent among Metformin group than among Insulin group.

Munshi and Khandaker [9] agreed with current results and stated that there was no difference between both groups regarding Cesarean delivery, during the intranatal period it was seen that equal number of cases from each group (14 cases in each group) underwent emergency caesarean section.

Bao et al., [12] agreed with us and stated that in fourteen studies involving 2537 GDM patients were included in the analysis of caesarean delivery. There was no significant difference between two groups (p=0.20; RR=0.94; 95% CI (0.85, 1.04); I2=11.2%).

Zhao et al., [15] determined the association between metformin use and CS and delivery of a large-for-gestational age (LGA) infant compared to insulin use for GDM. The Swedish population health registers were linked to identify pregnant women from 2012 to 2016 without preexisting diabetes and with a first filled prescription of insulin or metformin in trimester 2 or 3 (n=2467), categorized into those treated with insulin only (88%), metformin only (7.6%), or both insulin and metformin (4.3%). Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI). Analyses were adjusted for relevant covariates and stratified by history of CS. They agreed with us and stated that there was no evidence

of a higher association of metformin use alone with CS compared to insulin use for treatment of GDM but a protective effect for delivery of a LGA infant was shown.

Mahmood [13] on the contrary they disagreed with us and stated that the number of cesarean section in the insulin treatment group (60%) was higher than in the metformin treatment group (46%).

Statistical analysis of current study showed that there was no significant difference between Metformin and Insulin regarding birth weight APGAR-1, but APGAR-5 was significantly higher in Metformin group. Neonatal complications as IUFD, IUGR, macrosomia, congenital anomalies, neonatal hypoglycemia, respiratory distress and NICU admission were non-significantly less frequent among Metformin group. We had one sudden IUFD case in woman who was suffered from GDM on insulin treatment. We had also 9 cases of IUGR less than 2.5kg (3 cases in metformin group and 6 cases in insulin group) and 19 cases of macrosomia ≥ 4kg (8 cases in metformin group and 11 cases in insulin group).

Munshi and Khandaker [9] agreed with current results and stated that there was no difference between both groups regarding maternal complications, 12% in metformin group developed polyhydramnios whereas only 8% in insulin group showed polyhydramnios on growth scan. 20% in metformin group developed Abdominal Circumference (AC) >90th percentile and 24% metformin group developed AC >75th percentile, p= 0.51, 0.63, 0.09, 0.14. During postnatal period, it was seen that 2 babies expired in the neonatal period in the insulin group only. Both the babies were low birth weight and were admitted in NICU and developed sepsis. No such mishap occurred in the group which received metformin. Hypoglycemia developed in 4 babies of insulin group and 2 cases in metformin group. Even the number of neonatal jaundice was fewer (36%) in metformin group. They disagreed with us and stated that APGAR score at 5 min and neonatal jaundice were similar.

Wang et al., [10] they went along with us and stated that in Six studies (n=2738 patients) were included in the analysis of prematurity. Metformin can't increase the risk of preterm delivery (p=0.14; RR=1.22; 95% CI (0.94, 1.58); I 2=3%). We compared the incidence of macrosomia in the two groups. Eighteen studies (n=2920 patients) were included in the analysis of macrosomia, the results showed that macrosomia was lower by 38% in the metformin group than in the insulin group (RR 0.62, 95% CI (0.51, 0.76), I 2 = 0%, p <0.00001). Eight studies (n=1751 patients) were analyzed the incidence of SGA. There was no difference in the incidence of SGA (p=0.72; RR=1.06; 95% CI (0.76, 1.49), I2 = 0%). Metformin reduces the incidence of macrosomia without increasing the risk of SGA infants. Twenty studies (n=3340 patients) were included in the analysis of the incidence of neonatal hypoglycemia, and there was a difference between the two groups (p<0.00001; RR=0.56; 95% CI (0.48, 0.64); I2=0%), suggesting that metformin can significantly reduce the incidence of neonatal hypoglycemia compared with insulin. Fifteen studies also revealed that metformin can significantly reduce both the incidence of neonatal respiratory distress (p=0.003; RR=0.61; 95% CI (0.44, 0.85); I2=12%) and the incidence of neonatal NICU admission (p=0.001; RR=0.78; 95% CI (0.67, 0.91); I 2=19%).

Ahmed et al., [11] agreed with us and stated that there was no significant difference between the two groups regarding neonatal complications, the amniotic fluid index Mean ± SD in Metformin group and Insulin group was respectively 13.3 ± 3.0 and 13.3 ± 2.9. In insulin group there were 9 patients with fetal weight of more than 4000gm before delivery while only 7 patients in the Metformin group, with no significant difference. There was no significant relation between the two groups regarding the primary neonatal out-come; Gestational age at birth, Birth weight, Pre-term birth and 1 minute Apgar score. They disagreed with our result regarding 5 minute Apgar score only.

Bao et al., [12] differs with us and stated that Birth weight reported by 14 studies involving 2529 GDM was statistically lower in the women who received metformin compared with insulin (p=0.00; MD=-115.45; 95%CI (-196.18, -34.71); I2=83.6%). Metformin lowered the risk of macrosomia based on 10 studies (p=0.01; RR=0.63; 95% CI (0.45, 0.90); I2=0%). Moreover, treatment with metformin slightly lowered the risk of LGA based on eight studies (p=0.04; RR=0.82; 95% CI (0.68, 0.99); I2=0%). Metformin did not increase the risk of SGA based on seven studies (p=0.95; RR=0.99; 95%CI (0.69, 1.42); I2=0%). Fifteen studies reported on neonatal hypoglycemia and 13 studies reported on NICU admission. Metformin lowered the risk of neonatal hypoglycemia (p=0.001; RR=0.72; 95%CI (0.59, 0.88); I2=0%) and NICU admission (p=0.01; RR=0.74; 95%CI (0.58, 0.94); I2=35.8%). They disagreed with us and stated that there was no significant difference in Apgar score (<7) at 5min (six studies) (p=46; RR=1.24; 95% CI (0.71, 2.17); I2=0%).

Mahmood [13] disagreed with us and stated that the number of neonate admitted to the NCU higher in the insulin-treated group (58%) than in metformin-treated group (6%). There were high percentages of complications among insulin group as RDS, hypoglycemia, seizure, jaundice, hypocalcemia and PTL) which lead to admission to NCU. The total number of complication differs from total number of patients in each group because some patients had more than one complication.

CONCLUSION

From the results of current study we can conclude that: Oral metformin was effective as insulin injection in control and management of GDM. BMI was controlled with oral metformin better than insulin injection. Maternal and neonatal complications specially birth weight were the same with both types of treatment. Women had better compliance to metformin treatment. Type of delivery wasn't affected by type of treatment.

REFERENCES

1. **Ferrara A.** Increasing prevalence of gestational diabetes mellitus: A public health perspective. *Diabetes care*. 2007;30:S141-6.
2. **Coustan DR.** Gestational diabetes mellitus. *Clin Chem.* 2013;59(9):1310-21.
3. **American Diabetes Association**. Medical management of type 2 diabetes. Alexandria, Va: American Diabetes Association; 1998.
4. NIDDK/NIH/International Conference on Diabetes and Depression 2014. Available from http://www2.niddk.nih.gov/News/Calendar/DiabetesDepression12.htm. Accessed 2014.
5. **Coetzee EJ.** Pregnancy and diabetes scenario around the world: Africa. *Int J Gynaecol Obstet.* 2009;104:S39-41.
6. **Kelley KW, Carroll DG, Meyer A.** A review of current treatment strategies for gestational diabetes mellitus. *Drugs Context.* 2015;4.
7. **Nicholson G, Hall GM.** Diabetes mellitus: New drugs for a new epidemic. *Br J Anaesth*. 2011;107(1):65-73.
8. **Marques P, Carvalho MR, Guerra S.** Metformin safety in the management of gestational diabetes. *Endocr Pract.* 2014;20(10):1022-31.
9. **Munshi S, Khandaker S.** Evaluation of metformin *vs.* Insulin in the management of gestational diabetes mellitus: A prospective comparative study. *Int J Reprod Contracept Obstet Gynecol*. 2017;3:357-61.
10. **Wang TH, Zhou XF, Ni Y, et al.** Health information needs regarding diabetes mellitus in China: An internet-based analysis. *BMC Public Health.* 2020;20(1):1-9.
11. **Ahmed SS, Laila RT, Thamilselvam P, et al.** Knowledge of risk factors and complications of diabetes in the Indian ethnic population of Malaysia undiagnosed to have diabetes. *Int J Diabetes Res.* 2019;8(1):4-8.
12. **Bao X, Borné Y, Muhammad IF, et al**. Growth differentiation factor 15 is positively associated with incidence of diabetes mellitus: The Malmö diet and cancer–cardiovascular cohort. *Diabetologia.* 2019;62(1):78-86.
13. **Mahmood OA.** Metformin *vs.* Insulin in the management of gestational diabetes mellitus. *Med J Babylon.* 2019;16(4):346.
14. **Ali AE, Mohamed ME, Ahmed MA**. Oral metformin *vs.* Insulin in treatment of gestational diabetes mellitus. *Zagazig Med J.* 2018;24(5):437-48.
15. **Zhao L, Cesta CE, Pazzagli L.** The role of socioeconomic factors on discontinuation of insulin during pregnancy—methodological challenges from a Swedish register-based study. *J Public Health*. 2020:1-8.