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Original article

Randomized Controlled Trial in the Libyan Population: Comparing Fetal Outcomes in Gestational Diabetes Mellitus Patients Treated with Metformin *versus* Insulin

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Abstract
The study aimed to evaluate the neonatal outcomes in patients with gestational diabetes mellitus (GDM) treated with metformin versus those treated with insulin. 140 participants diagnosed with GDM were included in this study. They were randomized into two groups: one group received metformin, and the other group received insulin. There were no adverse neonatal outcomes such as intrauterine growth retardation, premature labor, birth asphyxia, birth trauma, placental abnormalities, perinatal death, low birth weight, or any neonatal ward admission in patients treated with metformin. The incidence of premature labor and fetal distress was higher in patients treated with insulin.
Keywords. Fetal Distress, Gestational Diabetes Mellitus, Insulin, Metformin, Premature Labor.

Introduction

Worldwide, the prevalence of gestational diabetes mellitus (GDM) is on the rise due to an increase in risk factors such as obesity [1,2]. GDM is defined as glucose intolerance first occurring during pregnancy [3]. The risk factors of developing GDM include obesity, polycystic ovary syndrome, higher maternal age, and a family history of type 2 diabetes mellitus. Patients with a high risk of GDM should be screened at 24-28 weeks of gestation. Generally, patients with GDM are asymptomatic, since common symptoms of diabetes, such as polyuria and lethargy, are also associated with pregnancy. However, GDM is associated with an increased risk of preeclampsia, depression, and the incidence of cesarean section. Also, poor glycemic control in patients with GDM increases the risk of large for gestational age (LGA), hypoglycemia, jaundice, or increased risk of being overweight in the neonate [4]. Therefore, optimum glycemic control is recommended to reduce the incidence of adverse neonatal outcomes [5].

Patients with GDM are recommended lifestyle modification consisting of a healthy diet and regular exercise, which is sufficient for glycemic control in many cases. In patients with poor glycemic control despite lifestyle modification, management with insulin is considered the gold standard for GDM [6,7]. However, insulin treatment is associated with several disadvantages, such as frequent injections, increased risk of hypoglycemia, and higher cost [8]. In addition, the dose of insulin requires titration depending on the body mass index (BMI), glucose control levels, and lifestyle. Ultimately, there is a reduction in patients' compliance, further diminishing glycemic control.[9] In comparison, oral agents such as metformin are advantageous since they are cheaper alternatives and also easier to consume, making them an attractive alternative to insulin with better patient compliance resulting in good glycemic control [10,11]. Metformin is a biguanide that achieves euglycemia primarily by suppressing hepatic gluconeogenesis and enhancing peripheral glucose uptake [12]. The present study aimed to compare the neonatal outcomes in patients with GDM treated with metformin versus those treated with insulin.

Methods

Study design and setting

This study was a randomized, open-label, parallel-group trial to evaluate the neonatal outcome of metformin versus insulin treatment in patients with GDM. Patients registered at a clinic specialized in care for diabetes in pregnancy were enrolled for this study. The follow-up of the enrolled participants was done at any public or private clinic allocated for patient follow-up and service delivery, free of charge. Contact information of the patient and her husband/birth service plan of the patient (public, private) were collected to ensure follow up. The desired number of cases was selected over a period of 45 days. The participants were followed up once every 15 days up to gestational period of 37 weeks and once a week thereafter till delivery. The participants were followed up to 48 hours post-delivery. All participants were given a data sheet, and a history was taken from each participant during the first visit. Clinical examination and diagnostic test results were evaluated to ensure that the participants satisfied the selection criteria. The participants were given a serial number, and random allocation of the participants was done to the two treatment arms.

Subjects

The total number of participants in this study was 140, diagnosed as GDM, and all of them were followed from 28 weeks to 42 weeks, and each participant visited approximately 9 times during the study period. All participants were residents of Benghazi, Libya, aged between 18 and 44 years, with a gestational age of 28-32/40 weeks, with a single fetus diagnosed with GDM with no commencement of treatment. Most of them had a clear obstetric history with a parity of 2-5. None of them had prior insulin dependent diabetes mellitus (IDDM) or non-insulin dependent diabetes mellitus (NIDDM) and also

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did not have extremes of BMI (<18.5 kg/m^2 or ≥40 kg/m^2 [morbid obesity]); overweight and obese participants (BMI 25.0–39.9 kg/m^2) were eligible for inclusion. None of the participants were diagnosed with any other medical condition and there was no pregnancy-related complications earlier. Since this study was to evaluate monotherapy, patients requiring more than one anti-diabetic agent were excluded from the study.

Clinical assessment

Fetal/gestational product outcomes evaluated at every follow-up visit were antepartum bleeding, low fetal movements, intra-uterine death, intra- uterine growth retardation, premature rupture of membranes, premature labor and polyhydramnios. At the end of the study i.e. 48 hours postpartum, the fetal/gestational product outcomes measured were intra-uterine death/still birth, premature rupture of membranes, premature labor, early neonatal death occurring within 24 hours of birth, admission in neonatal care unit, birth weight more than 4000 gm or less than 2000 gm, meconium at labor, slow fetal heart at labor /signs of fetal distress, cesarean/assisted delivery, dysmorphic features of the baby /reported anomalies, neonatal hypoglycemia and birth trauma.

Ethical considerations

The participants were explained about the objectives and impact of the study, and written informed consent was obtained from all the participants.

Results

Baseline characteristics

One hundred and forty participants were enrolled in this study. The median age was 38 years (quartile interval; 32.5 – 40.0 years) (Figure 1). The median body mass index was 31.2 kg per m2 (Interquartile interval; 29.6 – 32.6 kg/m2) (Figure 2). All the participants were either overweight or obese (Figure 3). The participants were assigned randomly to either the metformin arm or the insulin arm. Only 77 cases continued with their starting regimens (55%); 35 (25%) changed from metformin to insulin, and 28 (20%) from insulin to metformin (see Table 1 and Figure 4).

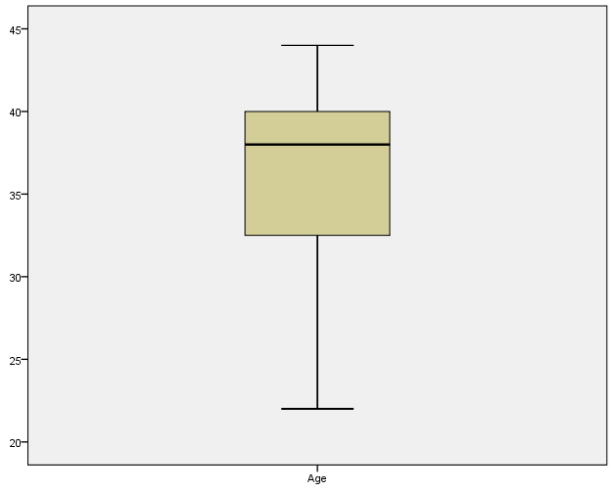

Figure 1. Descriptors of Age in GDM Treatment Trial

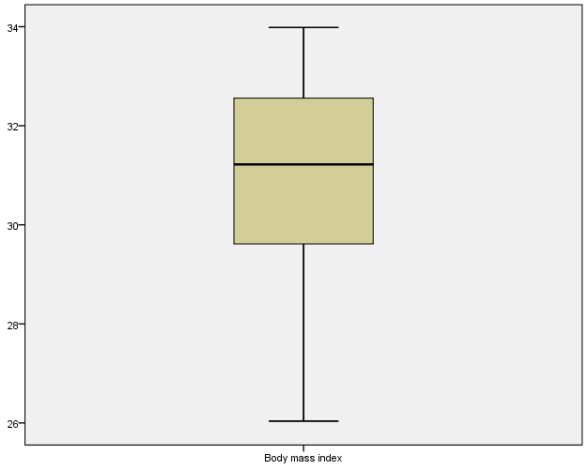

Figure 2. Descriptors of BMI in GDM Treatment Trial

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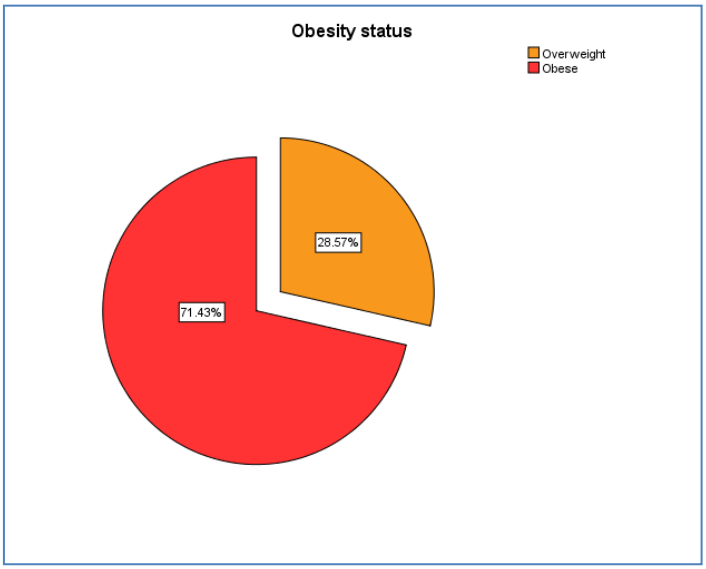

Figure 3. Distribution of Obesity among Cases in GDM Treatment Trial

Table 1. Change in Treatment Plan in GDM Treatment

Treatment plan	Number	Rate
Metformin to insulin	35	25.0
Insulin to metformin	28	20.0
Metformin only	35	25.0
Insulin only	42	30.0
Total	140	100.0

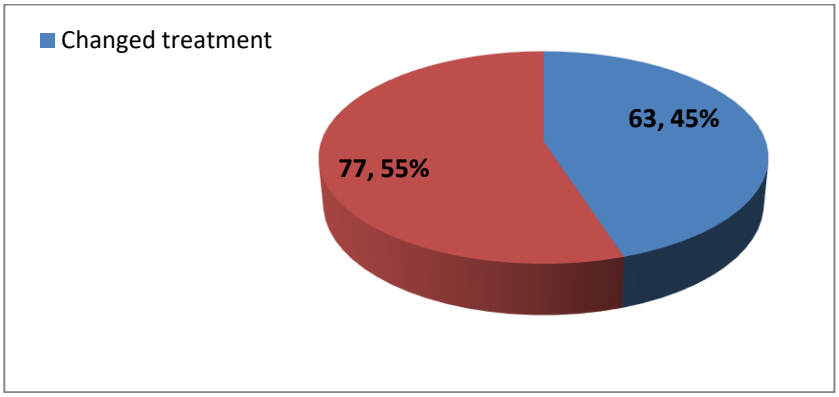

Figure 4. Change in Treatment Plan in GDM Treatment Trial

Fetal outcome

The most frequent fetal complications were polyhydramnios, neonatal hypoglycemia, and fetal distress. Dysmorphic body features and macrosomia were next in ranking, with macrosomia occurring in one out of every four cases. Low birth weight was also evident with a rate of 14.3%. Median birth weight was 3.7 kg (Interquartile interval; 3.2 – 3.98). See (Figures 5 and 6).

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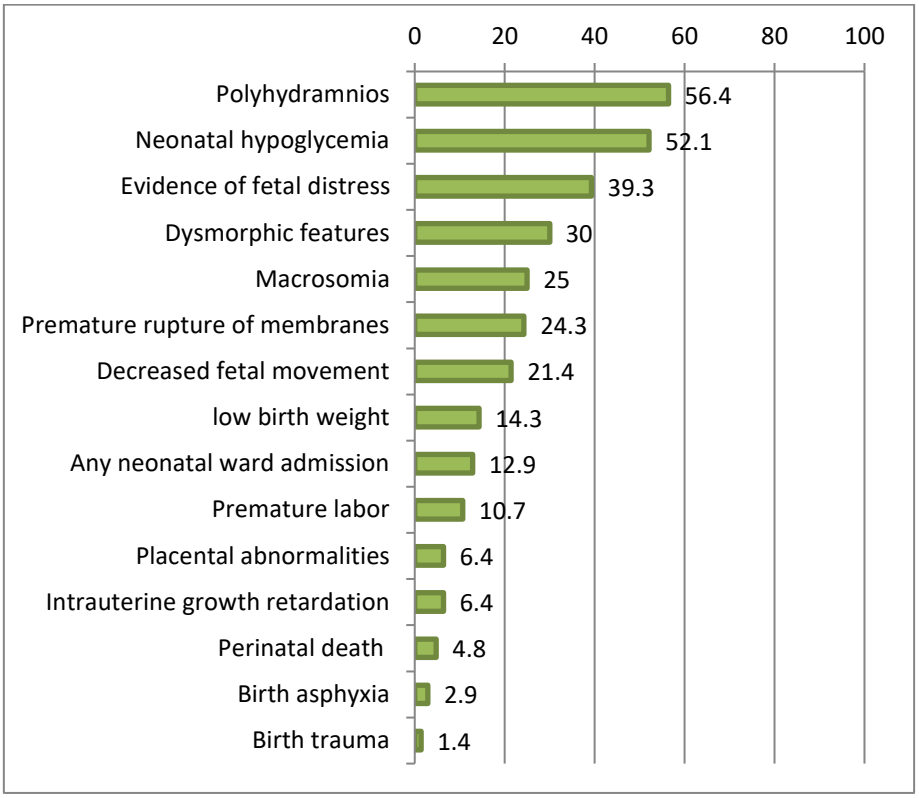

Figure 5. Percentages of Fetal Adverse Outcomes in GDM Treatment Trial

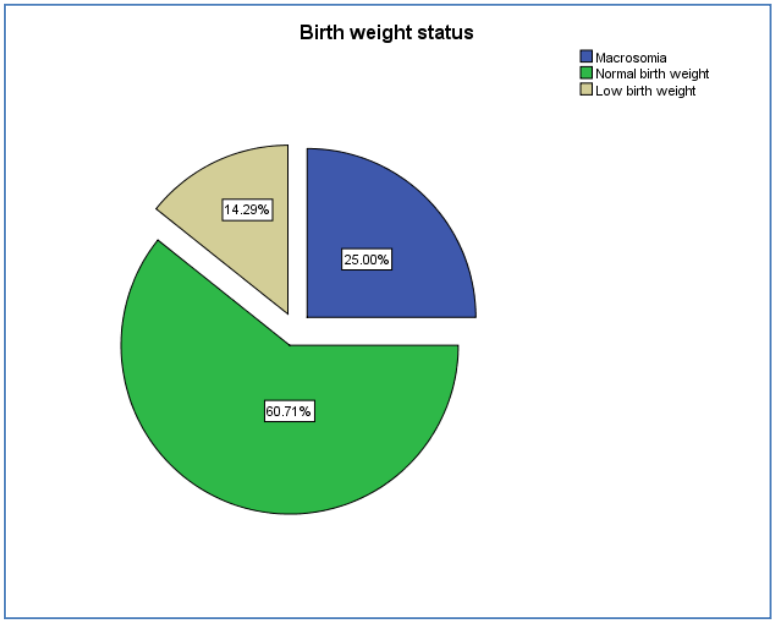

Figure 6. Distribution of Cases in GDM Treatment Trial According to Birth Weight Status

Adverse fetal outcomes such as intrauterine growth retardation, premature labor, birth asphyxia, birth trauma, placental abnormalities, perinatal death, low birth weights, and any neonatal ward admission didn't exist in the metformin treated group. The only statistically significant findings were the occurrence of premature labor and higher rate of fetal distress in the insulin-treated group. It was observed that more than half of pregnancies on insulin treatment experienced fetal distress as compared to more than a quarter in patients in the metformin group. See (Table 2). These findings didn't change on matching for obesity status (Figures 7 and 8).

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Table 2. Analysis of Fetal Outcome in Treatment Groups in GDM Treatment Trial

Outcome or dependent variable (parameter)	Estimate (CI or quartile interval for median		Test used (value)	P value (is association significant?)
	Insulin treated	Metformin treated		
Polyhydramnios (rate)	48% (32%-63%)	34% (18%-51%)	LR chi (1.406)	0.236 (No)
Decreased fetal movement (rate)	19% (7%-31%)	17% (4%-30%)	LR chi (0.047)	0.829 (No)
Intrauterine growth retardation (rate)	5% (0%-11%)	0% (0%-0%)	Fisher exact	0.294 (No)
Premature rupture of membranes (rate)	14% (3%-25%)	23% (8%-37%)	LR chi (0.94)	0.332 (No)
Premature labor (rate)	12% (2%-22%)	0% (0%-0%)	Fisher exact	0.043 (Yes)
Evidence of fetal distress (rate)	52% (37%-68%)	26% (10%-41%)	LR chi (5.771)	0.016 (Yes)
Birth asphyxia (rate)	5% (0%-11%)	0% (0%-0%)	Fisher exact	0.294 (No)
Birth trauma (rate)	2% (0%-7%)	0% (0%-0%)	Fisher exact	0.545 (No)
Neonatal hypoglycemia (rate)	50% (34%-66%)	40% (23%-57%)	LR chi (0.772)	0.38 (No)
Dysmorphic features (rate)	31% (16%-46%)	20% (6%-34%)	LR chi (1.208)	0.272 (No)
Placental abnormalities (rate)	2% (0%-7%)	0% (0%-0%)	Fisher exact	0.545 (No)
Any neonatal ward admission (rate)	10% (0%-19%)	0% (0%-0%)	Fisher exact	0.083 (No)
Perinatal death (rate)	4.8% (0%-11%)	0% (0%-0%)	Fisher exact	0.294 (No)
Birth weight in kg (median)*	3.77 (3.45– 4.0)	3.7 (3.3 – 3.9)	Mann-Whitney U	0.58 (No)
Low birth weight (rate)	10% (0%-19%)	0% (0%-0%)	Fisher exact	0.083 (No)
Macrosomia (rate)	29% 14%-43%)	23% (8%-37%)	LR chi (0.326)	0.568 (No)
Abnormal birth weight (rate)	38% (23%-53%)	23% (8%-37%)	LR chi (2.1)	0.147 (No)
Any fetal adverse outcome (rate)	86% (75%-97%)	69% (52%-85%)	LR chi (3.272)	0.07 (No)

** the distribution of the variable was not normal*

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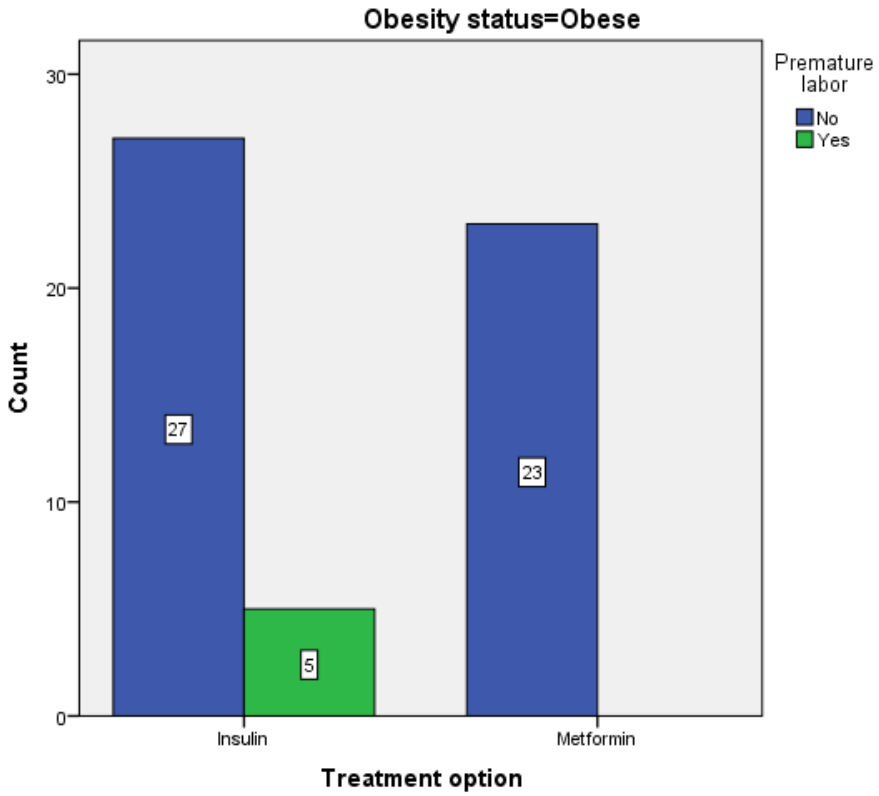

Figure 7. Premature Labor According to Group in Obese Mothers in GDM Treatment Trial

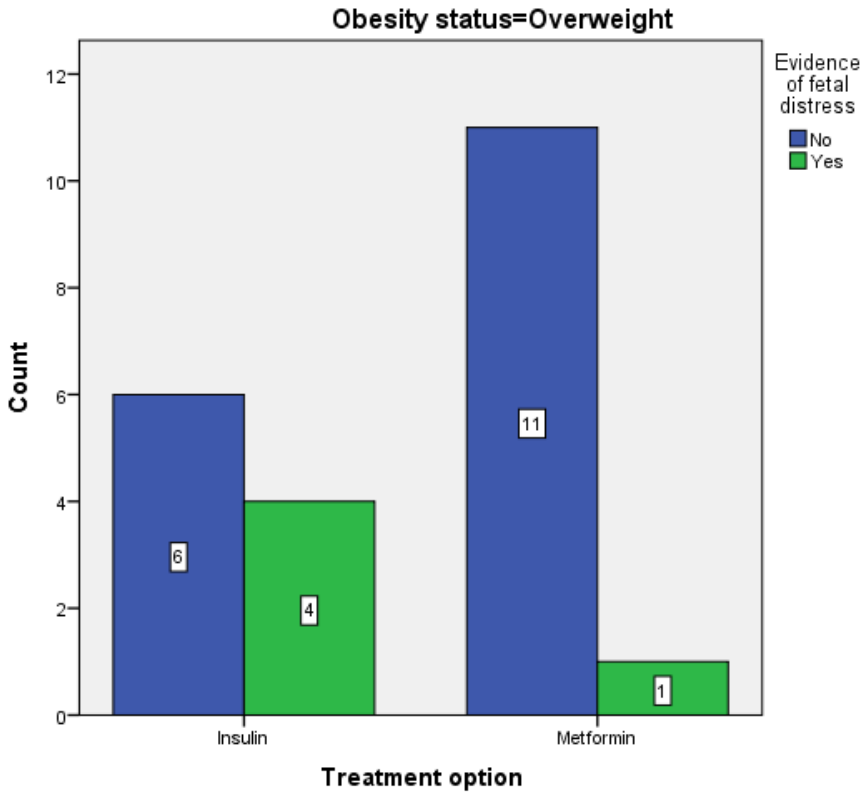

Figure 8. Fetal Distress According to Group in Overweight Mothers in GDM Treatment Trial

Statistical analysis

Cases with a change in treatment (N=63, 45%) were excluded from analysis. Only cases that continued the initial treatment of GDM were considered in our analysis. Likelihood ratio chi-square (2-sided) was used to analyze the significance of the association between the dependent variable (treatment option) and the categorical outcomes. Fisher's exact (1 sided) was reserved for outcomes with expected values that don't fit the requirement of chi-square test. t – test and Mann–Whitney U test were used to test the significance of the association of the treatment option with numerical

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variables. Bivariate analysis exhibited no significant differences in population characteristics between groups (Table 3). A per-protocol analysis was therefore used, restricted to the 77 participants (55%) who remained on their originally allocated treatment throughout the study; treatment changes among the excluded 63 participants (45%) were driven by inadequate glycemic control on the initial agent rather than by non-adherence, and this crossover precluded a meaningful comparison against the original allocation. We acknowledge that excluding nearly half of the enrolled cohort narrows the generalizability of these findings and introduces potential selection bias, as participants who failed initial monotherapy may differ systematically from those who did not. An Intent-to-Treat analysis, in which all participants are analyzed according to their original random allocation regardless of subsequent treatment changes, was not performed in this study; we recommend that future trials in this area report both per-protocol and Intent-to-Treat analyses to allow a fuller assessment of comparative safety and efficacy.

Table 3 Analysis of General Characteristics in Treatment Groups in GDM Treatment Trial

Outcome or dependent variable (parameter)	**Estimate (CI or quartile interval for median)**		**Test used (value)**	**P value (is association significant?)**
	Insulin	Metformin		
Age in years (median)*	38 (33 – 40)	38 (33 -42.5)	Mann-Whitney U	0.66 (No)
Body mass index in kg/m2 (mean)	31.3 (30.7–31.8)	30.6 (30.0-31.2)	t – test (1.69)	0.096 (No)
Obesity (rate)	76% (63%-90%)	66% (49%-82%)	LR chi (1.024)	0.312 (No)

** The distribution of the variable was not normal*

Discussion

There was no substantial fetal outcome differences found with the use of metformin compared to the use of insulin in women with GDM. Therefore, metformin can be recommended as an effective substitute for insulin in the treatment of GDM. In patients with GDM requiring insulin, metformin alone or with supplemental insulin can be recommended as an effective and safe treatment. Due to the oral route of administration, metformin is more acceptable than injectable insulin in patients with GDM, thereby improving patient compliance [13,14]. The results of the present study were consistent with the study by Hamid et al., which reported that there was no significant difference between the two groups concerning the birth delivery method, the cause of cesarean section, birth trauma, Apgar score, birth weight, admission to the neonatal intensive care unit, and neonatal hypoglycemia [15]. Metformin can significantly improve the sensitivity of liver and peripheral tissue to insulin and reduce the output of liver glucose and the level of plasma glucose through direct and indirect effects on liver and muscle [16], and it is not associated with major complications or perinatal death [17]. Although metformin can pass through the placenta, it is not related to fetal malformations when used in the first three months of pregnancy [18]. Several studies have reported the safety and efficacy of metformin in patients with GDM. A randomized controlled study conducted by Rowan et al on patients with GDM comparing metformin and insulin reported that infants born to women given metformin had a lesser incidence of hypoglycaemia as compared to the insulin-treated group [14].

Another study comparing maternal and neonatal outcomes between patients with GDM treated with metformin versus insulin versus diet alone also reported that the rate of neonatal hypoglycemia was substantially lower in the metformin and diet control group versus the insulin group. Also, the birth weight and neonatal macrosomia were comparable in all three groups [19]. A recent study in India reported that metformin effectively controls blood sugar levels in GDM. It is also linked to fewer pregnancy complications and better neonatal outcomes. These findings are consistent with the current study and support metformin as a safe and effective option for GDM management [20]. However, another study conducted in Iran indicated that both insulin and metformin have nearly similar effects on maternal and neonatal pregnancy outcomes while effectively controlling blood glucose levels in Iranian women with gestational diabetes [21].

Conclusion

Due to its advantages in terms of economy and convenience, metformin has been gradually used in the treatment of GDM. Since there is no evidence suggesting poor neonatal outcomes in patients treated with metformin as compared to insulin, metformin is a safe and effective option for the management of GDM. However, several clinical studies, particularly those assessing long-term outcomes, are required in order to conclusively state that metformin can be used for the treatment of GDM instead of insulin.

Conflict of interest. Nil

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