ORIGINAL ARTICLE

Bali Medical Journal (*Bali MedJ)* 2022, Volume 11, Number 3: 1234-1242
P-ISSN.2089-1180, E-ISSN: 2302-2914

Pregnancy outcomes in pregnant women with diabetes treated with insulin alone and insulin with metformin

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Received: 2022-01-09
Accepted: 2022-07-14
Published: 2022-09-22

ABSTRACT

Introduction: The goal of this study was to compare maternal and neonatal results in diabetic pregnant ladies who were treated either insulin and metformin or insulin only.
Methods: 220 pregnant diabetic women with type 1, 2 or gestational diabetes were randomisely assigned into two groups .each group is 110 pregnant diabetic women. One group takes insulin and metformin treatment to achieve glycemic targets and other take insulin only treatment. Pregnancy results in 110 ladies who stayed solely on insulin have been compared to pregnancy results in 110 pregnant diabetic ladies treated with insulin and metformin who were matching for age, weight, as well as ethnicity.
Results: Inulin only group gained significantly more weight but no statistical differences were found in gestational hypertension, pre-eclampsia, vaginal delivery, elective Caesarean section, and perinatal loss despite significantly lower insulin dosage. Combination of insulin and metformin significantly lower rate of neonatal morbidity such as neonatal hypoglycemia, respiratory distress, and neonatal jaundice. The lower macrosomia rate and incidence of polyhydramnios were also observed.
Conclusions: Diabetic pregnant women who were treated with insulin plus metformin who had equal baseline risk factors for unfavourable pregnancy outcomes gained less weight and needed less insulin to maintain glycemic control but with significant improvement in prenatal morbidit compared with those treated with insulin alone.

Keywords: Pregnant Diabetic Women, Insulin and Metformin, Insulin, Maternal, Perinatal Outcome.
Cite This Article: Elsaeed, U.A., Riad, R.I., Taher, A., Elnokeety, M., Elanwary, S. 2022. Pregnancy outcomes in pregnant women with diabetes treated with insulin alone and insulin with metformin. *Bali Medical Journal* 11(3): 1234-1242. DOI: 10.15562/bmj.v11i3.3082

INTRODUCTION

Diabetes is becoming more common among pregnant women. GDM (gestational diabetes mellitus) accounts for most preexisting type 1 and 2 diabetes cases. Globally, the growth in GDM, type 2 diabetes, and obesity is a cause for concern. Types 1 and 2 diabetes increase maternal and fetal risk much more than GDM in pregnancy, including some variances depending on the type of diabetes. Spontaneous abortion, fetal abnormalities, preeclampsia, fetal mortality, macrosomia, neonatal hypoglycemia, and neonatal hyperbilirubinemia are all dangers of uncontrolled diabetes in pregnancy.[1] Diabetes during pregnancy raises a child's chance of obesity and type 2 diabetes later in life.[1]

Diabetes detected before pregnancy is "preexisting diabetes in pregnancy." Preexisting diabetes has been more common in the last decade[2], owing mostly to the rise in type 2 diabetes.[3] According to studies, perinatal death, congenital abnormalities, high blood pressure, preterm birth, large-for-gestational-age (LGA) newborns, cesarean birth, and other neonatal comorbidities are all higher in women with preexisting diabetes than in the general population.[2]

Diabetes mellitus (DM) is a metabolic condition caused by abnormalities in insulin secretion, insulin action, or both. It is characterized by persistent hyperglycemia and carbohydrate, lipid, and protein metabolism disturbances.

Insulin therapy has long been the go-to treatment for gestational diabetes that hasn't responded well to diet and exercise.

Despite its effectiveness, insulin has significant drawbacks, including the inconvenient nature of regular injections, high cost, storage issues, and hypoglycemia. In one Indian investigation, insulin was ten times more expensive than metformin.[4]

Metformin has been demonstrated to improve glycemic control, restrict body weight changes, minimize hypoglycemia occurrence, and lower insulin requirement (sparing action), resulting in a 15 to 25% decrease in overall insulin dose.[5,6]

The addition of metformin to insulin treatment has been linked to a reduced insulin dose required in type 1 diabetes .[7,8]

This trial aimed to see if adding metformin to a pregnant woman with diabetes would lower insulin dosages and improve maternal, fetal, and neonatal outcomes.

PATIENTS AND METHODS

This was a prospective randomized controlled study of 220 pregnant diabetic women (gestational and pregestational

diabetes type 1 and type 2) who attended 20 weeks gestation at kasr el ainy hospital from August 2016 to February 2020 and were given informed written consent before enrolment in this research. Two groups of 220 patients were randomly assigned: group I received insulin and metformin, while group II received only insulin.

Sample size calculation

The sample size was estimated according to a previous study measuring the undesired perinatal outcomes to be 19% and 6% for groups I & II, respectively.[9] So, the estimated sample size in each arm according to the previously mentioned measures at type I (α) error 0.05 and type II (β) error 0.2 was 98 subjects. Then, the estimated sample size was increased by 20% to overcome the dropouts. The final recruited subjects were 120 individuals in each arm. Finally, those who met the inclusion and exclusion criteria and not drop out were 110 subjects in each arm. For statistical analyses, MedCalc Statistical Software version 14.8.1 (MedCalc Software, Ostend, Belgium) was utilized; http://www.medcalc.org.

After an overnight fast, a plasma glucose concentration of (126 mg/dl) is used to diagnose pregestational diabetes mellitus. Fasting is described as consuming no calories for at least eight hours if the blood glucose concentration is ≥ (200 mg/dl) two hours following a 75g glucose drink or with randomized plasma glucose of 200 mg/d in a patient with normal hyperglycemia or hyperglycemic crises.[10,11]

At 24 -28 weeks of pregnancy, we used the American Diabetes Association 2015 recommendation for diagnosing GDM, which is a one-step strategy: do a 75-g OGTT with plasma glucose measurement when the patient is fasting and at 1 and 2 hours in women who have not previously been diagnosed with overt diabetes. The OGTT should be done in the morning following a fast of at least 8 hours the night before. When any of the following plasma glucose readings are reached or exceeded, GDM is diagnosed: FBS > (92 mg/dl); 1HPG > (180mg/dl) or 2HPG > (153 mg/dl).[11] Newly diagnosed clients were managed on a diet (Women with diabetes should consume a balanced diet throughout their pregnancy, and low-glycaemic-index meals should be substituted for high-glycaemic-index foods) and exercise (walking for 30 minutes after a meal) for 1 week. They were recruited into the research and put on the therapy protocol when their glycemic control was inadequate. Women diagnosed with pregestational diabetes and taking medication were not allowed to participate in the OGTT.

Inclusion criteria

- Age: 18 to 45 years.
- Gestational age: single fetus at 20 weeks gestation.
- GDM not controlled by diet and excercise for starting insulin therapy
- Pregestational diabetes (type 1 and type 2) taking insulin.
- Absence of lactic acidosis risk factor e.g. Liver diseases

Exclusion criteria

- Patients with allergies to metformin.
- Twin pregnancy or higher order pregnancy
- Pregnancy with fetal structural abnormalities
- Chemical-induced diabetes such as with glucocorticoid use, after organ transplantation
- Patients with chronic medical disorders such as hypertension, systemic lupus erythematosus, and kidney or liver diseases.

Two hundred twenty patients were randomly assigned to two groups using blocked randomization: group I was given insulin plus metformin, and group II was given insulin only. The block size and assignment ratio (the number of participants in one group vs. the other) were set at 110, and participants were assigned randomly to each block with an allocation ratio of (1:1).

All participants signed a written consent form before enrolment, and those who did not do so were disqualified. Basic demographic data were recorded, such as age, parity, obstetric history, weight, height, and BMI. Subjects were followed through their pregnancy by measuring blood pressure, proteinuria, weight and the dose of metformin or insulin each patient needs for optimal glycemic control.

By obstetric and diabetes clinic follow-up for achieving glycemic targets, insulin, both soluble and premixed, is prescribed. There was no restriction on the type of brand. Insulin was delivered subcutaneously in the deltoid region, both premixed and soluble. At the time of beginning, the total daily dose of premixed insulin for most patients was determined to be 0.3 IU/kg body weight. On the other hand, patients admitted with high blood glucose levels were treated with soluble insulin on a sliding scale, with starting doses dependent on total daily requirements. Two-thirds of the daily dose was taken 30 minutes before breakfast in the morning, and one-third of the dose was given 30 minutes before supper in the evening.

To meet the glycemic objectives, each patient's total insulin dose was titrated. Glycemic targets of FBS < (95 mg/dl) but and 2HPG < (120mg/dl) in addition to avoiding hypoglycemia not less than (60mg/dl) recommended by American Diabetes Association 2015 was selected for the study.[11] A few patients used a combination of soluble insulin given 3 times a day before meals and premixed insulin given once daily to accomplish their glycemic control targets. Patients who failed to meet their glycemic objectives on their outpatient doses after two titration attempts were hospitalized in the ward and managed with soluble insulin to identify their new optimal insulin needs. Before discharge, all patients were trained about the condition and how to self-administer the proper dosages of insulin by both nurses and doctors. In group I, the starting dose of metformin with the same trade name was 500 mg once a day, which was subsequently increased to three times a day over two weeks. Per the trial protocol, the maximum daily dose authorized was 2000 mg. During pregnancy, diabetic pregnant women should test their blood glucose levels at various times, including fasting, pre-meal, 2-hour post-meal, and bedtime.

Every two weeks, all patients were required to attend follow-up sessions.

During each inspection visit, scheduled every two weeks (and once a week throughout the latter weeks of pregnancy)

till the due date, they were urged to come in sooner if their blood glucose levels were high. The recorded data by the patient was recorded in the patient's medical file.

The treatment monitoring method was carried out using SMBG during the study period (self-monitoring of blood glucose) for both groups using a glucometer (ACCU-CHEK ACTIVE) .OGTT and HbA1c were checked monthly during the pregnancy.

To establish the level of risk for pregnancy, at the start of the trial, we measured HbA1c levels in all pregnant ladies who had diabetes. At the time of diagnosis, we assessed HbA1c levels in all women with gestational diabetes to see if any had type 2 diabetes previously.

Statistical analysis

The "Microsoft Office Excel Software" application (2010) for Windows was used to enter the data on the computer. The data was then statistically evaluated using the Statistical Package of Social Science Software program, version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). For quantitative variables, range, mean, and standard deviation are used; for qualitative variables, frequency and percentage are used. A qualitative variable comparison was carried out through a Chi-square test, while a comparison of quantitative variables was performed through a t-test with independent samples. Statistical significance was defined as a P value of less than 0.05.

RESULTS

The demographic specifications of the group I and group II indicated no statistically significant difference between patients joining the study regarding age, BMI, family history of DM, parity, mode of delivery, glycemic state and type of DM with pregnancy (Table 1).

At the start of therapy and throughout the research, there have been no statistically significant differences between the two groups' FPG levels or 2 hr PG. Furthermore, no statistically significant variations in FPG, 2 hr PG, or HbA1C were found between the two groups during the therapy period until delivery. But decreased insulin dosage was required to reach the glycemic target in group I, which reached a highly significant value (tables 1 and 2).

Maternal outcomes are shown in (Table 2). Weight gain from enrolment to delivery was (4.3 ±0.49 kg) in group I patients receiving insulin and metformin and was (5.9 ±0.72 kg) in group II patients receiving insulin. The difference was highly statistically different, p =0.000.

Prenatal daily insulin dosage was (39.5 ±16.5 units) in group I and was (55.4 ±17.5 units) in group II, with a highly statistically significant difference (p =0.000). Gestational hypertension was 14.5% in group I and 19.1% in group II, with no statistically significant difference between groups I and II. (p =0.367).

Preeclampsia was 7.27 % in group I and 9.09 % in group II, with no statistically significant difference (p =0.622). Vaginal delivery was 41.8 % in group I and 47.3% in group II, with no statistically significant difference (p =0.416).

Primary CS in group I was 16.3 % and was 10 % in group II, with no statistically significant difference (p =0.162).

Emergency cesarean section was 19.1 % in group I and 20 % in group II, with no statistically significant difference (p =0.865).

Elective cesarean section was 39.1 % in group I and 32.7 % in group II, with no statistically significant difference (p =0.325).

Preterm delivery was 16.63 % in group I and 24.55 % in group II, with no statistically significant difference (p =0.417).

FPG after treatment was 89.9 ±2.2 mg/dl in group I and 90.2 ±2.8 mg/dl in group II, with no statistically significant difference (p =0.444).

2hour post prandial was 119.9 ±1.6 in group I and 120.1 ±2.2 in group II, with no statistically significant difference (p =0.529). HbA1C was 6.3 ±0.4 in group I and 6.3 ±0.5 in group II, with no statistically significant difference (p =0.587).

Perinatal outcomes

Table 3 shows the results of perinatal outcomes.

Neonatal jaundice requiring phototherapy was 13.6 % in group I patients receiving insulin and metformin and 33.6 % in group patients receiving insulin, and the difference was highly statistically significant (p =0.000).

Neonatal hypoglycemia was 7.3 % in group I and 24.5 % in group II, with a highly statistically significant difference (p =0.000).

Neonatal respiratory distress was 13.6 % in group I and 30 % in group II, with a statistically significant difference (p =0.003).

Birth weight < 90th birthweight centile was 16.4% in group I and 29.1% in group II, with a statistically significant difference (p =0.024).

Birth weight from 10th to 90th birthweight centile was 67.2 % in group I and 48.1 % in group II, with a statistically significant difference (p =0.004).

Polyhydramnios was 13.6 % in group I and 32.7 % in group II, with a statistically significant difference (p = 0.001).

Special care unit admission was 24.5 % in group I and 35.4 % in group II, with no statistically significant difference. (p =0.077).

Birth weight > 10th birthweight centile was 16.4 % in group I and 22.7 % in group II, with no statistically significant difference (p =0.234).

Shoulder dystocia was 2.7 % in group I and 4.5 % in group II, with no statistically significant difference (p =0.721).

The perinatal loss was 2.7 % in group I and 3.6 % in group II, with no statistically significant difference (p =0.701).

DISCUSSION

Certain characteristics, such as patient age, BMI, and family history of diabetes mellitus, were similar between the two groups in our study, glycemic state at the entry of study, types of diabetes mellitus denoting proper randomization, which added to the worth of the results obtained as suggesting that insulin and metformin have comparable efficiency in regulating blood glucose levels compared to insulin and achieving glycemic targets, in addition to the proper interpretation of maternal and fetal outcome in both groups.

The current study found no statistically significant difference in glycemic control between the two groups, which is in line with earlier research.[12,13] Still, in our study, we reached the glycemic target with less

Table 1. Baseline characteristics comparison between group I (Insulin and metformin) and group II (insulin only).

Variables	Group		P- value
	Group I (n=110)	Group II (n=110)	
Age			
Range	25 – 34	23 - 34	
Mean ± SD	28.8 ± 2.3	29.1 ± 2.5	0.460
BMI			
Range	28 – 35	27 - 38	
Mean ± SD	31.1 ± 2.2	30.7 ± 2.6	0.328
BMI			
Overweight (25-30)	27 (24.5)	39 (35.5)	0.077
Obese (< 30)	83 (75.5)	71 (64.5)	
Family history of diabetes			
Yes	41 (37.3)	42 (38.2)	0.889
No	69 (62.7)	68 (61.8)	
Parity			
Range	0 – 3	0 - 4	
Mean ± SD	1.4 ± 1	1.6 ± 1	0.205
Previous caesarean section			
Yes	46 (41.8)	47 (42.7)	0.891
No	64 (58.2)	63 (57.3)	
Number of Previous caesarean section			
0	64 (58.2)	63 (57.3)	0.783
1	33 (30)	32 (29.1)	
2	10 (9.1)	9 (8.2)	
3	3 (2.7)	6 (5.5)	
FPG at treatment onset(mg/dl)			
Range	143 – 199	123 - 191	
Mean ± SD	162.2 ± 12.4	164.3 ± 14.4	0.253
2Hr PG at treatment onset (mg/dl)			
Range	160 – 230	156 - 218	
Mean ± SD	192.8 ± 15.3	190.1 ± 13.4	0.166
HbA1c at entry %			
Range	5.8 – 8.3	5.6 – 8.2	
Mean ± SD	7.1 ± 0.8	7.3 ± 0.6	0.080
DM type			
T1DM	19 (17.3)	25 (22.7)	0.312
T2DM	39 (35.5)	36 (32.7)	0.670
GDM	52 (47.3)	49 (44.5)	0.685

Group I= Insulin + Metformin, Group II= Insulin only.* = P value <0.05% statistically significant.

insulin dosage in group I than group II and the difference was highly statistically significant between the two groups.

Several studies have examined the effects of metformin compared to insulin on GDM patients' outcomes, including research by Saleeh et al.[14] and 75 people divided into 2 groups, and research by Waheed et al.[15] In each of the two groups, 34 participants were assigned, research by Tertti et al.[16] two groups of 45 sufferers were recruited and another by Goh et al.[23] including two groups of 80 people. The findings of these researches concluded metformin and insulin have a similar effect on achieving glycemic control, but in our study, we used metformin as an adjunct to insulin which showed glycemic control with less insulin dosage

While reporting on the similar effects of the two drugs, some authors have indicated the necessity for supplemental insulin in a few sufferers where FPG couldn't have been sufficiently controlled by Goh et al.[23], but in our study, we did not examine the use of metformin alone, we used it combined with insulin in group I.

In terms of glucose monitoring, the results of the FPG and 2hr PG clinical controls indicate that the therapy strategy was successful in lowering plasma glucose concentrations below 95 and 120 mg/dl, respectively. In this regard, there was no statistically significant difference between the two groups apart from a highly significant difference in insulin dosage within group I as Insulin does not improve insulin resistance but improves glycemic profile, an important feature of pregnancy, GDM and T2DM consistent with the previous study.[4]

In the current investigation, no

Table 2. Comparison between both groups regarding maternal outcomes.

	Group		P- value
	Group I (n=110)	Group II (n=110)	
Weight gain from enrolment to delivery (kg)			
Range	3.5 – 5	4.5 - 7	
Mean ± SD	4.397 ± 0.49	5.905 ± 0.721	0.0000*
Prenatal daily insulin dosage (unit)			
Range	20 – 85	35 - 100	
Mean ± SD	39.5 ± 16.5	55.4 ± 17.5	0.000*
Gestational hypertension			
Yes	16 (14.5)	21 (19.1)	0.367
No	94 (85.5)	89 (80.9)	
Preeclampsia			
Yes	8 (7.27)	10 (9.09)	0.622
No	102 (92.73)	100 (90.91)	
Mode of delivery			
Vaginal delivery	46 (41.8)	52 (47.3)	0.416
Elective cesarean section	43 (39.1)	36 (32.7)	0.325
Emergency cesarean section	21 (19.1)	22 (20)	0.865
Primary Caesarean section	18 (16.3)	11 (10)	0.162
Delivery			
Preterm delivery	22 (16.63)	27 (24.55)	0.417
Term delivery	88 (83.64)	83 (75.45)	0.417
FPG(mg/dl)			
Range	86 – 95	85 - 95	
Mean ± SD	89.9 ± 2.2	90.2 ± 2.8	0.444
2Hr PP (mg/dl)			
Range	116 - 124	114 - 124	
Mean ± SD	119.9 ± 1.6	120.1 ± 2.2	0.529
HbA1C %			
Range	5.5 – 7.1	5.6 – 7.3	
Mean ± SD	6.3 ± 0.4	6.3 ± 0.5	0.587
Perinatal metformin dose mg/dl			
1000	14 (12.7)		
1500	75 (68.2)		
2000	21 (19.1)		

Group I= Insulin + Metformin, Group II= Insulin only. *= P value <0.05% statistically significant.

statistically significant differences in fasting glucose levels, HbA1c levels, or 2hr PG levels were shown between the two therapy groups (I vs. II), but with a great advantage to the insulin and metformin group as less insulin dosage was needed to reach this glycemic control which is highly statistically significant than insulin group.

Our study showed lower maternal weight gain from enrolment in the study until delivery in group I, which is highly statistically significant and aids in decreasing insulin resistance in those patients. Moreover, Balani et al.[9] were in line with our results with statistically significant value, which can be explained by insulin sensitivity improvement and may explain why people lose weight when they take metformin. However, the particular pathomechanisms are still unknown.[18,19]

As far as birth weight is concerned, in our study, there is a statistically significant difference between group I versus group II regarding there were more large-for-gestational-age neonates in group II which can be explained by the placental passage of metformin causing decreased fetal hyperinsulinemia.[20]

But In the insulin group, some investigations have found a discrepancy between baby weights and gestational age. For example, Mesdaghinia et al.[21] reported that the insulin group of the trial had a higher number of large gestational age babies than the metformin group, even though the differences were not statistically significant. Similarly, other research found no statistically significant differences.[16,22]

Our study revealed a large for gestational age in group I compared to group II (16.4% vs. 29.1%). A study conducted by Goh et al.[23] involving 1,269 women found that 18.5% of those in the

Table 3. Comparison between both groups regarding perinatal outcomes.

	Group		P- value
	Group I (n=110)	Group II (n=110)	
Jaundice			
Yes	15 (13.6)	37 (33.6)	0.000*
No	95 (86.4)	73 (66.4)	
Hypoglycemia			
Yes	8 (7.3)	27 (24.5)	0.000*
Polyhydramnios			
Yes	15 (13.6)	36 (32.7)	0.001*
No	95 (86.4)	74 (67.3)	
Birth weight >90% birth weight centile			
Yes	18 (16.4)	32 (29.1)	0.024*
No	92 (83.6)	78 (70.9)	
Respiratory distress			
Yes	15 (13.64)	33 (30)	0.003*
No	95 (86.36)	77 (70)	
Special care baby unit admission			
Yes	27 (24.55)	39 (35.45)	0.077
No	83 (75.45)	71 (64.54)	
Birth weight from 10^{th} to 90^{th} birth weight centile	74 (67.2)	53 (48.1)	0.004*
Birth weight <10% birth weight centile			
Yes	18 (16.4)	25 (22.7)	0.234
No	92 (83.6)	85 (77.3)	
Shoulder dystocia			
Yes	3 (2.7)	5 (4.5)	0.721
No	107 (97.3)	105 (95.5)	
Perinatal loss			
Yes	3 (2.7)	4 (3.6)	0.701
No	107 (97.3)	106 (96.4)	

Group I= Insulin + Metformin, Group II= Insulin only.* = P value <0.05% statistically significant.

insulin group had macrosomia vs. 12.5% of the neonate belonging to the metformin group, which showed no significant difference, and this difference was due to the high sample size in the latter study.

On the other hand, Ghomian et al.[24] showed that the measurement of birth weight in both groups insulin versus metformin demonstrated that the neonates' mean weights were normal in both groups and that there were no statistically significant differences between the two groups in that regard, but in contrast to our study, there was no combined therapy of insulin and metformin and GDM only enrolled in that study, which is in line with the findings of a study conducted by Mesdaghinia et al.[21]

In our study showed high incidence of polyhydramnios in group II which showed significant difference that can be explained by macrosomia and fetal hyperinsulinemia in that group. In contrast to our study Saleh et al.[14] showed high incidence in metformin group which did not reach significant value and that is explained by enrolment of GDM only patients and comparing insulin vs. metformin group in that study dislike our study.

In our study higher incidence of respiratory distress in group II which showed statistical significant difference and that could be clarified by increased prematurity and macrosomia in that group

In our research, the metformin group had a decreased incidence rate of hypoglycemia, but it was statistically significant at a high level in the whole group. Agreeing with our study, The findings of the two GDM treatment approaches have been described in the literature.[13,16,22,25] Rowan et al.[22] studied two groups of patients (insulin versus metformin) and found that those who took metformin had a decreased rate of severe hypoglycemia. Between the two groups, there were statistically significant differences. Spaulonciet al.[26] cited the reduced occurrence rate of hypoglycemia as evidence of metformin's favorable efficacy in lowering blood glucose levels in the moms included. According to Ghomian et al.[24], the metformin group had a decreased incidence rate of hypoglycemia, although this did not achieve statistical significance.

In our study, a higher incidence of neonatal jaundice in group II showed highly statistically significant differences, which may be explained by increased prematurity and large gestational age in that group, and Mesdaghinia et al.[21] also showed similar results.

The greater rate of premature labor

among patients in the insulin group, which was also highlighted in earlier research[9,21], could explain the discrepancy in the results. Moreover, NICU admission with metformin use was also lower in George et al.[20] which could be attributable to a decrease in newborn hypoglycemia rates.

Our study showed higher incidence of shoulder dystochia in group II but did not reach a statistically significant value, which can be explained by a higher rate of large for gestational age in that group. In contrast to our study, Balani et al.[9] showed a higher incidence in the metformin group, which is explained by lacking randomization.

In our study, maternal outcomes regarding preeclampsia and gestational hypertension showed lower incidence in group I but did not reach a statistically significant difference, which is in line with our study and that can be explained as Metformin use has also been linked to a significant decrease in maternal weight gain, and this could have an impact on a potential reduction in the risk of preeclampsia and gestational hypertension.[19] Although the pathophysiology of pregnancy-induced high blood pressure is still being researched, our findings of lower pregnancy-induced high blood pressure with metformin usage could be due to reduced inflammation, and the lesser pregnancy excess weight in ladies who took metformin could have compensated for their risk of pregnancy-induced high blood pressure.[27]

Furthermore, it was demonstrated that the risk of preeclampsia doubles with every 5-7 kg/m2 rise in pre-pregnancy BMI.[28] In addition, In women with polycystic ovary syndrome (PCOS), BMI is the most important factor in determining interleukin-6 (IL-6) and C-reactive protein (CRP) levels. Metformin has been shown to help with this chronic inflammatory condition[29] IL-6 and CRP levels have also been reported to be greater in preeclampsia patients.[30] Metformin may help by acting on pathophysiological processes similar to those studied in PCOS women. Furthermore, it has been suggested that metformin's effect on the anti-angiogenic state may help to prevent preeclampsia.[31]

In terms of glycosylated hemoglobin testing performed during pregnancy, the results showed HbA1c values in both group I and group II (6.3±0.4 vs. 6.3±0.5), respectively, and the difference between the two groups is not statistically significant. The metformin group had reduced levels of HbA1c, according to the results of the study[21], which may be due to investigating in pregnant women with gestational diabetes taking metformin only versus women taking insulin. Before 16 weeks of pregnancy,[32] examined total glycosylated hemoglobin in 105 insulin-treated women. They discovered that mothers with normal babies had considerably lower glycosylated haemoglobin levels than those with deformed babies. In the current investigation, HbA1c values showed no statistical difference between groups, and newborns had no obvious congenital abnormalities.

Regarding gestational age, in the current study, premature births did not differ statistically significantly between the two groups, but with increased incidence in group II, which may be explained by an increased rate of polyhydramnios in that group.

On the contrary, several randomized controlled trials have found a higher rate of premature deliveries in metformin-treated individuals compared to insulin-treated patients.[23,25] In a study published in 2008, Rowan et al.[22] found that individuals on metformin had a greater rate of preterm birth than those taking insulin (12.1 percent vs. 7.6%), respectively. This conflict may be due to our combined usage of metformin and insulin in our study.

The current study evaluated two groups' cesarean section rates and discovered no statistically significant difference. In 2016, a randomized controlled trial indicated no statistically significant differences between the metformin and insulin groups in the number of cesarean section cases.[14] In addition, a study conducted by Moore et al.[33] on 32 metformin-treated and 31 insulin-treated patients, there were no statistically significant differences in the incidence of the cesarean section between the two groups.

In contrast, a study conducted by Goh et al.[23], included 3 therapy groups: insulin (399 ladies), metformin (465 ladies, 249 of who received metformin alone and 216 of whom received metformin in conjunction with insulin), and a diet regimen (371 ladies), found that the insulin group had a statistically significant higher rate of cesarean section than the other two groups and this result may be explained by adopting high sample size. In contrast, 34. Ijäs et al.[34] randomly allocated 50 patients to insulin and 47 patients to metformin; and found that the metformin group had a greater rate of cesarean section. This result can be explained by the usage of metformin alone in treatment dislike our study and its small sample size.

This investigation's findings back up. We discovered no increase in unfavorable perinatal effects for newborns exposed to metformin, as we found in that trial. Similarly, maternal weight growth and birth weight centiles were significantly lower in the metformin-treated group. In contrast to the MiG trial, we discovered that premature birth was more likely in group II. Rather than a higher induction rate, this was due to an increase in spontaneous preterm labor. The greater incidence of neonatal jaundice, respiratory distress, and hospitalizations in the Special Care Baby Unit in group II are likely due to the rise in preterm found in this statistically significant study.

CONCLUSION

Data on fasting glucose levels that used in this investigation, 2hr PG and HbA1c levels, revealed no statistically significant differences between the two therapy groups (group I and group II). As a result, because metformin is easier to use, less expensive, and does not require injections, it can be recommended as a good complement to insulin in the treatment of diabetic pregnant women with the great advantage of decreasing insulin dosage to achieve glycemic control.

The findings of this study imply that metformin may have an advantage over insulin in respect of maternal weight growth and neonatal birth weight modified for gestational age. With the expected advantages of improved glycemic control in diabetic women, metformin should be encouraged to be used as an adjuvant or substitute for insulin. The results of this study support this recommendation.

Furthermore, metformin will be extremely cost-effective, saving both time and money for specialists and patients.

Furthermore, further studies on type 1 DM with a suitable sample size are required to clarify its benefits regarding decreasing the insulin dosage required for glycemic control and improving maternal and fetal outcomes.

In addition, large RCTs should be conducted in the future before advocating the usage of metformin in obese, non-diabetic women who are pregnant to improve the quality of the evidence. Future trials must also determine the best dosage and evaluate how additional therapies could benefit this group of women. Long-term monitoring of the kids must also be considered, and mothers should be conscious of the unknowns surrounding the long-term implications of transplacental passage on metabolic results.

ACKNOWLEDGMENTS

Conflict Of Interest

The authors declare that there is no conflict of interest regarding the manuscript.

Ethics Consideration

The Ethical committee has approved this study by the Faculty of Medicine, Cairo University.

Funding

The authors are responsible for the funding without the involvement of grants, sponsorship, or other funding sources.

Author Contribution

All of the authors equally contributed to the study from the conceptual framework, data gathering, and data analysis until reporting the study results.

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