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Metformin compared to insulin for the management of gestational diabetic

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ABSTRACT

A prospective comparative two arms study done in Al Kadhimiya teaching hospital for 1 year duration from January 2017 till January 2018, this study included 150 women with singleton pregnancies diagnosed with gestational DM. The primary endpoints were neonatal outcomes which include; neonatal hypoglycemia (≥2 neonatal glucose values 46.8 m/dL), respiratory distress (admission to neonatal care unite NUC), need for phototherapy (neonatal jaundice), 5-minute Apgar scores below 7, or premature birth (<37 weeks of gestation). The maternal outcome includes the rate of gestational hypertension, preeclampsia, mode of delivery and Polyhydramnios. Metformin offer less risk for the neonate to have an episode of blood glucose level <28.8 mg/dl compared to insulin RR (95%CI): 0.598 (0.457 – 0.999) and it was significant, metformin also offer less risk for the neonate to have recurrent blood glucose level <46.8 mg/dl RR (95%CI): 0.820 (0.586 – 1.289) but it was not statistically significant, metformin had slightly increased risk for preterm birth compared to insulin, the rest of the variables did not show a significant difference between both drugs. There was no significant difference in the maternal outcome between both drugs. There was no significant difference between metformin and insulin in their FPG and HbA1c after commencing therapy. In conclusion, metformin is an effective and safe treatment option for women with GDM, and that metformin comparable with insulin in glycemic control, there is no a significant risk of maternal or perinatal adverse outcome with the use of metformin compared with insulin in GDM.

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INTRODUCTION

Treatment of gestational diabetes can improve pregnancy outcome. Many women can achieve euglycemia with nutritional therapy alone, but up to 30 percent will require drug therapy (2018b).

Pregnancy is accompanied by insulin resistance, mediated primarily by placental secretion of diabetogenic hormones including growth hormone, corticotropin-releasing hormone, placental lactogen, and progesterone. These and other metabolic changes ensure that the fetus has an ample supply of nutrients (Lloreda-García *et al.,* 2016). Gestational diabetes mellitus develops during pregnancy in women whose pancreatic function is insufficient to overcome the insulin resistance associated with the pregnant state. Among the main consequences are increased risks of preeclampsia, macrosomia, and cesarean delivery, and their associated morbidities (Catalano *et al.,* 2003).

The prevalence of gestational diabetes mellitus as traditionally defined is approximately 6 to 7 percent in the United States (range 1 to 25 percent)

(Hartling *et al.,* 2012, Moyer, 2014). The prevalence varies worldwide and among racial and ethnic groups, generally in parallel with the prevalence of type 2 diabetes. In the United States, prevalence rates are higher in African American, Hispanic American, Native American, Pacific Islander, and South or East Asian women than in white women (Ferrara, 2007). Women at low risk of gestational diabetes mellitus are younger (<25 years of age), non-Hispanic white, with normal BMI (<25 kg/m2), no history of previous glucose intolerance or adverse pregnancy outcomes associated with gestational diabetes mellitus, and no first-degree relative with diabetes (Hartling *et al.,* 2012).

There are two pharmacologic options in pregnant patients who require medical therapy aimed at controlling blood glucose: insulin (and some insulin analogues) and selected oral antihyperglycemic agents (like metformin, glyburide). Insulin is the treatment of choice, but oral antihyperglycemic agents are a reasonable alternative for women who fail nutritional therapy and refuse to take, or are unable to comply with, insulin therapy. Systematic reviews of studies of pregnancy outcome in women with gestational diabetes mellitus treated with oral antihyperglycemic agents or insulin have generally found that both approaches can be effective (Nicholson *et al.,* 2008, Nicholson *et al.,* 2009, Dhulkotia *et al.,* 2010, Balsells *et al.,* 2015, Brown *et al.,* 2017a). There is a trend toward more frequent hypoglycemia with use of insulin (Brown *et al.,* 2017a) and some women on oral agents need supplemental insulin to achieve and maintain euglycemia (Brown *et al.,* 2017b). However, it difficult to draw firm conclusions about the optimal approach because of inconsistencies in criteria for gestational diabetes, glucose targets, patient adherence to treatment, and clinical outcome measures across studies, as well as lack of data regarding long-term outcomes in offspring (Brown *et al.,* 2017a). We aimed in this study to assess the maternal and neonatal outcomes in pregnant women with gestational diabetes treated with either insulin or metformin.

Methods

A prospective comparative two arms study done in Al Kadhimiya teaching hospital for 1 year duration from January 2017 till January 2018. This study included 150 women with singleton pregnancies diagnosed with gestational DM, written informed consent was taken from all participant after ethical approval taken from the Al Farahidi University, college of pharmacy. Women were eligible for inclusion if they were between 18 and 45 years of age. The exclusion criteria were a prepregnancy diagnosis of diabetes, a contraindication to metformin, a fetal anomaly, gestational hypertension, preeclampsia, fetal growth restriction, and ruptured membranes.

50 gram one-hour glucose screen test used for routine screening women with gestational age (GA) between 24 – 28 weeks, positive results suggest the diagnosis of gestation DM (GDM), with the following procedure: A 50-gram oral glucose load is given without regard to the time elapsed since the last meal and plasma glucose is measured one hour later. Glucose concentration measured in venous plasma with the following thresholds to define a positive screen: ≥140 mg/dL (7.8 mmol/L).

To confirm the diagnosis 100-gram two-hour oral glucose tolerance test used and positively confirm the diagnosis (see table 1) (2018a), 100-gram oral glucose load is given in the morning to a patient who has fasted overnight for at least 8 hours. Glucose concentration greater than or equal to these values at two or more time points is generally considered a positive test (Metzger *et al.,* 2010).

After the diagnosis of GDM al women offered nutritional counselling to achieve goals of medical nutritional therapy: normoglycemia, prevent ketosis, provide adequate gestational weight gain based on maternal body mass index (BMI) and contribute to fetal well-being. The meal plan includes: three small- to moderate-sized meals and two to four snacks, For women who are at ideal body weight during pregnancy, the caloric requirement is 30 kcal/kg/day; for women who are overweight, the caloric requirement is 22 to 25 kcal/kg/day; and for morbidly obese women, the caloric requirement is 12 to 14 kcal/kg/day (present pregnant weight), but obese women should consume a minimum of 1800 cal/day to prevent ketosis (2004).

Women were divided into two groups 75 treated with insulin and 75 with metformin; women measure daily their fasting glucose levels to assess their medication effectiveness and reported their measure to the antenatal clinic, the follow up at the outpatient clinic at 4 weeks interval.

Metformin initially 500 mg once daily, for the 1st week twice daily for the 2nd week and three-time daily in the 3rd week to a maximum of 2500 mg, the increase in dose and frequency dependent on the glycemic control reached by the women and the side effect that occur by the medication, women that did not achieve sufficient glycemic control by metformin or insulin alone were excluded from the study and offered additional treatment according to the hospital policy.

Women that offered insulin received a combination of bedtime NPH insulin (intermediate-acting insulin) and pre-meal short-acting insulin analogue with the aim to normalized postprandial glucose concentration.

Table 1: Diagnostic criteria for the 100-gram three-hour GTT to diagnose gestational diabetes mellitus (2018a)

Time	Plasma or serum glucose level	
	mg/dL	mmol/L
Fasting	95	5.3
One hour	180	10
Two hours	155	8.6

Table 2: Maternal characteristics at baseline

Variables	Insulin	Metformin	p-value
Number	75	75	-
Age (years), mean ± SD	33.7 ± 6.1	35.1 ± 4.3	0.106
BMI (kg/m^2), mean ± SD	35.9 ± 2.3	35.2 ± 3.1	0.118
Baseline HbA1 (%), mean ± SD	5.6 ±0.4	5.5 ± .5	0.178
Nulliparous, n (%)	56 (37.3%)	51 (34.0%)	0.547
Preintervention 100-g oral GTT			
FPG after an overnight fast	103.8 ±19.6	106.8 ± 20.3	0.359
2-Hr postprandial FPG	178.3 ±40.2	172.9 ±36.9	0.393

FPG: fasting plasma glucose, SD: standard deviation

The primary endpoints were neonatal outcomes which include; neonatal hypoglycemia (≥2 neonate al glucose values 46.8 m/dL), respiratory distress (admission to neonatal care unite NUC), need for phototherapy (neonatal jaundice), 5-minute Apgar scores below 7, or premature birth (<37 weeks of gestation). The neonates were monitored for hypoglycemia by measuring blood glucose levels within 2 hours after birth and before each feeding until consecutive glucose values of ≥46.8 mg/dL were achieved. Readings <46.8 mg/dL and < 28.8 mg/dL were also recorded as was treatment for hypoglycemia (Rowan *et al.,* 2008). While maternal outcome includes the rate of gestational hypertension, preeclampsia, mode of delivery and Polyhydramnios.

Statistical analysis

Continuous data presented as mean ± standard deviation while categorical variables presented as number (%), independent t-test used to assess the difference two continuous variables, while chi-square used the difference between categorical variables, relative risk used to calculate the association between exposure to drug and outcome while the confidence interval of the relative risk using the Koopman asymptotic score (Koopman, 1984). Prism version 7.00 for Windows (GraphPad Software, La Jolla California USA), a software package used to make the statistical analysis, p-value considered when appropriate to be significant if less than 0.05.

RESULTS

A total of 150 patients included in this study (75 patients received insulin and 75 patients received metformin), there was no significant difference in maternal age, BMI, baseline HbA1c, pre-interventional 100 gm oral GTT, as illustrated in table 2.

Metformin offer less risk for the neonate to have an episode of blood glucose level <28.8 mg/dl compared to insulin RR (95%CI): 0.598 (0.457 – 0.999) and it was significant, metformin also offer less risk for the neonate to have recurrent blood glucose level <46.8 mg/dl RR (95%CI): 0.820 (0.586 – 1.289) but it was not statistically significant, metformin had slightly increased risk for preterm birth compared to insulin, the rest of the variables did not show a significant difference between both drugs, as illustrated in table 3. There was no significant difference in the maternal outcome between both drugs, as illustrated in table 4. There was no significant difference between metformin and insulin in their FPG and HbA1c after commencing therapy, as illustrated in table 5.

DISCUSSION

The management of GDM is important because appropriate therapy can decrease adverse pregnancy and neonatal outcomes, Effective treatment regimens consist of dietary therapy, exercise, self-blood glucose monitoring, and administration of insulin if target blood glucose values are not met with diet alone.

In the current study, we found that mean fasting plasma glucose level after 1 and 2 weeks and HbA1c level at delivery were similar in both groups throughout GDM treatments, which is in agreement with previous studies (Rowan *et al.,* 2008, Balani *et al.,* 2009, Niromanesh *et al.,* 2012).

In the current study we found no significant difference between metformin and insulin in the maternal outcome, while in term of neonatal outcome only hypoglycemic episode was higher in insulin group compared to metformin in which severe hypoglycemia (<28.8 mg/dl glucose) occurred signif-

Table 3: Neonatal outcome

Variables	Insulin	Metformin	RR (95% CI)	p-value
Number	75	75	--	--
Recurrent blood glucose level <46.8 mg/dl	13 (8.7%)	9 (12.0%)	0.820 (0.586 – 1.289)	0.356
Any blood glucose level <28.8 mg/dl	8 (10.7%)	2 (2.7%)	0.598 (0.457 – 0.999)	0.049
Respiratory distress	3 (2.0%)	1 (0.7%)	0.658 (0.475 – 1.659)	0.311
Phototherapy	8 (5.3%)	9 (12.0%)	1.070 (0.694 – 1.965)	0.797
5-Min Apgar score <7	2 (1.3%)	1 (0.7%)	0.745 (0.494 – 2.412)	0.560
Preterm birth (<37 weeks of gestation)	9 (12.0%)	15 (23.1%)	1.517 (0.956 – 2.740)	0.083

All data presented as n (%); RR: relative risk; CI: confidence interval

Table 4: Maternal outcomes

Variables	Insulin	Metformin	RR (95% CI)	p-value
Number	75	75		-
Gestational hypertension	4 (5.3%)	6 (8.0%)	1.268 (0.711 – 3.054)	0.513
Preeclampsia	2 (2.7%)	3 (4.0%)	1.259 (0.631 – 4.315)	0.649
Mode of delivery				
Vaginal	61 (81.3%)	63 (84.0%)	-	0.666
C/S	14 (18.7%)	12 (16.0%)	-	
Polyhydramnios	20 (26.7%)	23 (30.7%)	1.105 (0.784 – 1.643)	0.588

All data presented as n (%); RR: relative risk, CI: confidence interval

Table 5: Assessment of fasting plasma glucose levels and HbA1c after treatment

Variables	Insulin	Metformin	p-value
Number	75	75	-
FPG after 1st week	91.4 ±8.6	92.6 ± 7.6	0.367
FPG after 2nd week	85.3 ± 7.6	86.1 ± 8.1	0.534
HbA1c (%) at 36 – 37 weeks	4.1 ±0.4	4.2 ± 0.3	0.085

Data presented mean ± SD

icantly less often in infants of women taking metformin, our findings were in agreement with Ro wan et al., in which severe neonatal hypoglycemia was significantly lower in metformin group RR (95%CI) 0.41 (0.21–0.78) (Rowan *et al.,* 2008), while in Niromanesh et al. study there was no significant difference in the hypoglycemic episode between insulin and metformin RR (95% CI) 1.5 (0.3–8.7) (Niromanesh *et al.,* 2012).

Metformin had a slightly higher rate of preterm birth however it was not statistically significant RR (95%CI) 1.517 (0.956 – 2.740), this was in agreement with Niromanesh et al. with RR (95%CI) 2.2 (0.7–7.0) (Niromanesh *et al.,* 2012), and in agreement with Rowan et al 1.60 (1.02–2.52) (Rowan *et al.,* 2008), while Balani et al. previously showed that preterm delivery was more common in the insulin group (Balani *et al.,* 2009). This inconsistency could be due to chance or unrecognized effete of metformin on the labor (Niromanesh *et al.,* 2012).

In the current study there was no significant difference in the rate of gestational hypertension and preeclampsia, our findings in agreement with other studies (Niromanesh *et al.,* 2012, Balani *et al.,* 2009), but in disagreement with Hellmuth et al. in which a combined cohort of GDM and type 2 diabetes mellitus examined, they observed increased rates of preeclampsia and perinatal loss in mothers treated with metformin (Hellmuth *et al.,* 2000), a possible expiation that their study was retrospective, and the control groups were inadequately matched, and the metformin group had other increased risk factors for preeclampsia such as older age and obesity. It is now believed that metformin may reduce preeclampsia in GDM women by reducing the endothelial activation and maternal inflammatory response of insulin resistance (Niromanesh *et al.,* 2012).

CONCLUSION

Our findings suggest that metformin is an effective and safe treatment option for women with GDM and that metformin comparable with insulin in glycemic control, there is no a significant risk of maternal or perinatal adverse outcome with the use of metformin compared with insulin in GDM.

Conflict of interest

There are no conflicts of interest.

Author contributions

All authors contribute equally

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