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Metformin compared with diet or insulin in the management of gestational diabetes in clinical practice

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ABSTRACT

This study involved 150 women with singleton pregnancies diagnosed with GDM, and they were divided into three groups (50 women managed with diet, 50 women managed with insulin and 50 women managed with metformin). The study aimed to compare the maternal and neonatal outcome according to different treatments. The study carried out in Baghdad Medical city, from the period of March 2013 to July 2014. The rate of cesarian delivery was higher in those treated with insulin compared to those on metformin and diet (46%, 26%, and 22% respectively), also insulin receiving women had higher rate of preterm birth compared to

those on metformin and diet (20%, 4%, and 8% respectively), neonatal admissions (20%, 4% and 6%, respectively), neonatal intravenous dextrose use (22%, 6%, and 8%) compared to metformin and diet. In conclusion, the use of metformin was associated with fewer adverse outcomes compared with insulin.

Keywords: insulin, metformin, diet, gestational diabetic, outcomes

1. 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 (2018). Identifying women with gestational diabetes mellitus is important to minimize maternal and neonatal morbidity. A 2013 systematic review and meta-analysis of randomized trials for the US Preventive Services Task Force found that appropriate management of gestational diabetes (nutritional therapy, self-blood glucose monitoring, administration of insulin if target blood glucose concentrations are not met with diet alone) resulted in reductions in Preeclampsia (relative risk [RR] 0.62, 95% CI 0.43-0.89; 72/1001 [7.2 percent] versus 119/1013 [11.7 percent], three trials), Birth weight >4000 g (RR 0.50, 95% CI 0.35-0.71; five trials), and Shoulder dystocia (RR 0.42, 95% CI 0.23-0.77; three trials) (Hartling et al., 2013).

There are two pharmacologic options in pregnant patients who require medical therapy aimed at controlling blood glucose: insulin (and some insulin analogs) and selected oral antihyperglycemic agents (metformin, glyburide). 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, Ola, Fraser & Farrell, 2010, Mohammed et al., 2018, Mohammed, Kadhim, Jasim & Fawzi, 2018, Mohammad Zubair et al. 2019). There is a trend toward more frequent hypoglycemia with use of insulin (Brown, Grzeskowiak, Williamson, Downie & Crowther, 2017), and some women on oral agents need supplemental insulin to achieve and maintain euglycemia (Brown, Martis, Hughes, Rowan & Crowther, 2017). In the current study, we aimed to compare maternal and neonatal outcomes in women with GD treated with diet, metformin, and insulin in clinical practice in a single center.

2. PATIENTS AND METHODS

Study design

A prospective study carried out in Baghdad teaching hospital, Baghdad Medical city from March 2013 till July 2014, the study was approved by the Arabic board for medical specialization.

Setting

The study involved 150 women with singleton pregnancies diagnosed with GDM, and they were divided into three groups (50 women managed with diet, 50 women managed with insulin and 50 women managed with metformin). The diagnosis of GDM was made after the 24 weeks of gestation, written informed consent was taken from all the patients participated in the study. Metformin was initiated at a dose of 500 mg once daily for the first week, then twice daily for the second week, and three times daily from the third week, and titrated up to 2500 mg daily, until glycaemic control achieved. The medication was continued if significant side effects were observed.

Statistical analysis

Discrete variables presented using their number and percentage, chi-square test used to analyze the discrete variable, one way ANOVA used to analyze the differences between more than two groups (if they follow normal distribution with no significant outlier), GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, software package used to make the statistical analysis, p-value considered when appropriate to be significant if less than 0.05.

3. RESULTS

The rate of CS delivery was significantly higher in women on insulin therapy compared to both those on diet and metformin treatment, as illustrated in table 1.

Table 1 maternal characteristics and outcomes

Variables	Diet	Insulin	Metformin	p-value
Number	50	50	50	-
Age (years), mean ± SD	34.2 ± 5.2	33.9 ± 5.0	34.2 ± 5.2	0.945
Hypertension, n (%)				
Chronic	2 (4.0%)	3 (6.0%)	3 (6.0%)	0.876
Gestational	3 (6.0%)	3 (6.0%)	4 (8.0%)	0.898
Preeclampsia, n (%)	2 (4.0%)	2 (4.0%)	2 (4.0%)	0.999
Mode of delivery, n (%)				
Vaginal	39 (78.0%)	27 (54.0%)	37 (74.0%)	0.021 [S]
CS	11 (22.0%)	23 (46.0%)	13 (26.0%)	
Polyhydramnios, n (%)	7 (14.0%)	9 (18.0%)	7 (14.0%)	0.814
CS: Caesarian section, S: significant, n: number				

Preterm labor, LGA, NICU admission, and IV dextrose therapy were significantly higher in women receiving insulin therapy, compared to both those diet and metformin therapy, as illustrated in table 2 and Fig 1.

Table 2 neonatal characteristics and outcomes

Variables	Diet	Insulin	Metformin	p-value
Number	50	50	50	-
Preterm (<37 weeks), n (%)	4 (8.0%)	10 (20.0%)	2 (4.0%)	0.026 [S]
Preterm (<32 weeks), n (%)	1 (2.0%)	2 (4.0%)	0 (0.0%)	0.360
Birth weight, mean ± SD	3167±635	3176±701	3221±541	0.902
SGA, n (%)	6 (12.0%)	6 (12.0%)	4 (8.0%)	0.756
LGA, n (%)	5 (10.0%)	12 (24.0%)	4 (8.0%)	0.043 [S]
NICU admission, n (%)	3 (6.0%)	10 (20.0%)	2 (4.0%)	0.015 [S]
Blood glucose <2.3 mmol/L, n (%)	5 (10.0%)	7 (14.0%)	6 (12.0%)	0.828
APGAR score at 5 minutes, mean ± SD	9.0 ± 0.7	8.9 ± 0.7	9.0 ± 0.8	0.735
IV dextrose treatment	4 (8.0%)	11 (22.0%)	3 (6.0%)	0.027 [S]
SGA: small for gestational age (<10th percentile), LGA: large for gestational age (>90th percentile), NICU: neonatal intensive care unit, S: significant				

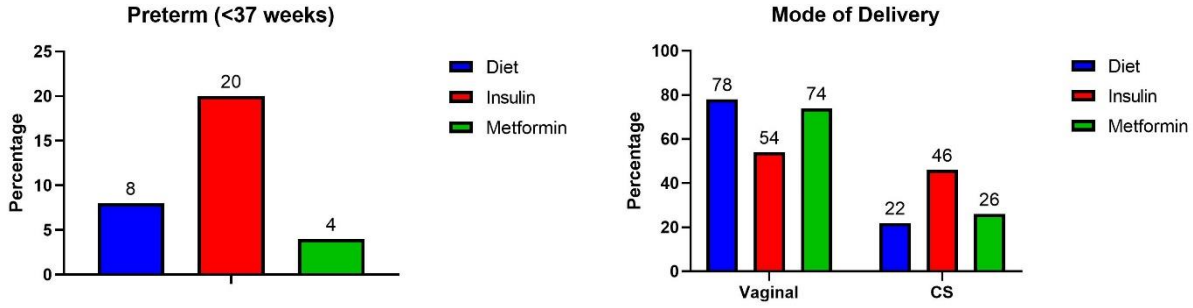

Figure 1 histogram of mode of delivery and preterm labor according to type of treatment

4. DISCUSSION

This Prospective study showed that metformin is a safe and clinically relevant medical alternative for treating GDM. The incidence of adverse pregnancy or neonatal outcomes was not increased in women treated with metformin compared with women treated with insulin. Metformin was found to be especially suitable for women with postprandial hyperglycemia in the latter half of pregnancy.

The key findings were that women treated with metformin had similar outcomes to those treated with diet alone (apart from fewer preterm births before 32 weeks in metformin-treated women) and, compared with women treated with insulin, they had significantly fewer preterm birth, Caesarean deliveries, large-for-gestational-age babies and neonatal intensive care unit admissions, and fewer infants were treated with intravenous dextrose. Two prospective randomized studies (MiG trial) reported the proportions of LGA newborns with birth weights over the 90th percentile (Balani, Hyer, Rodin & Shehata, 2009, Rowan, Hague, Gao, Battin & Moore, 2008). The incidence of LGA in this study was 8% in the metformin group and 24% in the insulin group, was similar to earlier retrospective Finnish study (15.6 and 22.2%, respectively) (Tertti, Ekblad, Vahlberg & Ronnemaa, 2008). These are observational data and, although they show that metformin use (With supplemental insulin as required) is associated with better outcomes than insulin alone, it is likely that other factors contributed to these outcomes. One potential factor is that women with a fetal abdominal circumference $<10^{th}$ percentile at the initiation of treatment were not offered the option of metformin, although, anecdotally, this was an uncommon situation and it did not result in higher rates of small-for-gestational-age infants at birth in the insulin group (Tertti, Ekblad, Vahlberg & Ronnemaa, 2008).

In the MiG trial and in the Finnish cohort study like our study the incidence of severe neonatal hypoglycemia was significantly higher in the insulin-treated group than in the metformin-treated group (Tertti, Ekblad, Vahlberg & Ronnemaa, 2008, Rowan, Hague, Gao, Battin & Moore, 2008). Overall, metformin treatment does not increase the risk of neonatal complications, and may even decrease the risk of neonatal hypoglycemia as compared with insulin.

In this study, the rate of preterm births was lower in women treated with metformin compared with insulin and the rate in the metformin was no different from women treated with diet. There was no difference in spontaneous preterm birth between the treatment groups. After excluding the small-for-gestational-age infants, preterm births were not significantly different between the metformin and insulin groups. This is in contrast to the MiG trail, where preterm births were significantly higher in the metformin group (12.1% vs. 7.6%, p-value = 0.04) (Rowan, Hague, Gao, Battin & Moore, 2008).

5. CONCLUSION

In clinical practice giving women with a gestational diabetic who requires medication the choice of treatment with metformin or insulin is associated with fewer preterm births and improved neonatal outcomes in those treated with metformin.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of The Arabic Board for Medical Specializations and written informed consent was provided by each patient. All methods were performed in accordance with relevant guidelines and regulations.

Patient consent for publication

Written informed consent was provided by each patient.

Competing interests

The authors declare they have no competing interests.

Author's contribution

Tagreed Hamood Hatem: Conceived and designed the analysis, data analysis, wrote the initial paper

Nisreen Ali Hussein: collected data, data analysis, wrote the initial paper

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