Global Journal of Health Science; Vol. 9, No. 4; 2017
ISSN 1916-9736 E-ISSN 1916-9744
Published by Canadian Center of Science and Education

Investigation the Effects of Metformin versus Insulin on Neonatal and Maternal Outcomes in Women with Gestational Diabetes Mellitus: A Randomized Clinical Trail

Mahin Najafian[1], Mojgan Barati[1], Sara Masihi[1], Ailin Fardipor[1] & Zeinab Shajirat[1]

[1] Fertility Infertility and Perinatology Research Center, School of medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Correspondence: Ailin Fardipor, Fertility Infertility and Perinatology Research Center, School of medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. Tel: 98-613-221-6104. E-mail: ailinfardipor@gmail.com

Received: July 3, 2016 Accepted: August 27, 2016 Online Published: September 28, 2016

doi:10.5539/gjhs.v9n4p272 URL: http://dx.doi.org/10.5539/gjhs.v9n4p272

Abstract

The aim of this study was to evaluate the effectiveness of metformin versus insulin in the glycemic control and to investigate the maternal and neonatal outcomes in in women with gestational diabetes mellitus. Pregnant women with gestational diabetes were randomized to either receive metformin (n=70) or insulin (n=70). Inclusion criteria were singleton pregnancy, following healthy diet and performing exercise for at least one week without satisfactory blood glucose level, no risk factor contributing to lactic acidosis, and no anatomic and/or chromosome anomalies. Two patients were excluded from the study due to lost to follow-up. The mean score of BMI and FBS after treatment was similar between two groups. But, the mean score of 2 hours blood sugar in insulin group (104.38±7.06 mg/dl) was significantly higher than metformin group (97.5±5.98 mg/dl) (P<0.0001). The weight gain in metformin group was slightly lower than insulin group. (P=0.123). The proportion of neonatal hypoglycemia in insulin group was higher than metformin group (20 vs 3, P=0.002). Other neonatal outcomes such as IUGR, IUFD, fetal anomaly, polyhydramnios, macrosomia, oligohydramnios, and NICU stay did not differ significantly between two groups. In conclusion, metformin had compatible effect with insulin in decreasing adverse maternal and neonatal outcomes even in some parameters such as neonatal hypoglycemia it works better. Totally, metformin is safe and effectiveness in controlling the gestational diabetes mellitus.

1. Introduction

Gestational diabetes mellitus (GDM) incidence has risen over the last few decades in the consequence of increasing in obesity-induced insulin resistance (Hunt & Schuller, 2007). Its incidence varies between 7% and 18% of pregnancies depending on the diagnostic methods used and the population studied (Coustan, Lowe, Metzger, & Dyer, 2010). It is associated with higher risk of neonatal outcomes such as fetal macrosomia and hypoglycemia and maternal outcomes including preeclampsia and cesarean section. All these complications significantly decrease when glucose levels are controlled by diet and exercise or through medication when the first approach fails to gain satisfactory results (Spaulonci, Bernardes, Trindade, Zugaib, & Francisco, 2013).

Standard treatment for achieving adequate glucose levels is insulin therapy (American Diabetes Association, 2012). However, insulin requires multiple daily injections mostly reducing patient adherence. Moreover, high cost of insulin drug prevents treatment for some patients. Oral antidiabetic agents have been investigated as an alternative to insulin therapy because of their ease of use and lower cost (Su & Wang, 2014). Biguanide metformin is an anti-glycemic medication that forces the hepatic to reduce gluconeogenesis and increases peripheral insulin sensitivity (Pellonpera & Ronnemaa, 2016). Recently, some studies have investigated the use of metformin for the treatment of gestational diabetes mellitus, of those two randomized trials have shown similar neonatal results when comparing insulin with metformin which demonstrating metformin seems to be a comparable alternative agent for the treatment of GDM (Cheung, 2009; Dhulkotia, Ola, Fraser, & Farrell, 2010; Silva, Pacheco, Bizato, de Souza, Ribeiro, & Bertini. 2010). Some other studies have shown different outcomes with metformin in women with GDM. One study evaluating the efficacy and safety of metformin treatment in women with pregestational and gestational diabetes raised concerns about a higher perinatal mortality and a higher rate of preeclampsia (Hellmuth, Damm, & Mølsted-Pedersen, 2000).

However, a recent large randomized controlled trial which compared metformin with insulin in the treatment of gestational diabetes (MiG trial) suggested that metformin, alone or with supplemental insulin, is an effective and safe treatment option for women with gestational diabetes (Rowan, Hague, Gao, Battin, & Moore, 2008). However, the effectiveness of metformin over insulin for reducing adverse neonatal and maternal outcomes need more investigations.

Hence, the aim of this study was to compare the effectiveness of metformin versus insulin in glycemic control in women who received metformin or insulin for the treatment of GDM in our population and also we evaluated neonatal and maternal outcomes to evaluate the effectiveness of metformin over insulin.

2. Materials and Methods

This case-control study was conducted on 140 pregnant women who treated by metformin or insulin for glycemic control in women clinics of Imam Khomeini and Razi hospitals between March 2014 and February 2016. The ethical committee approval was obtained. All participants assigned the inform consent. Inclusion criteria were singleton pregnancy, the gestational age between 24-33 weeks, the gestational diabetes was diagnosed for the first time at the study, the FBS level is 92 mg/dl or 2hpp above 120 mg/dl after one week of diet therapy, following healthy diet and performing exercise for at least one week without satisfactory blood glucose level, no risk factor contributing to lactic acidosis, and no anatomic and/or chromosome anomalies. Exclusion criteria were lack of patient's satisfaction, the history of previous diabetes except GDM, multiple pregnancies, underlying disease (cardiovascular disease, coagulant disorders, liver, renal and autoimmune disorders), and the lack of glycemic control even at the maximum dose of metformin.

The maximum dose of metformin was defined as 2 gr per day equal two 4 tabs. Patients in insulin group (n=70) received firstly half-unit per kilogram of body weight subcutaneously twice a day, morning and evening as follows:

Morning: NPH 2/3 + Reg 1/3

Evening: NPH 1/2 + Reg 1/2

If patient need insulin to control blood sugar it is raised on a weekly basis. Patients in metformin group (n=70) received once a day started with 500 mg metformin (1 pill) orally after launch, and if need to achieve the targeted blood glucose level the dose increased 500 mg weekly by 2 gr. Maternal age, BMI, FBS, 2hpp and maternal weight at baseline and end of treatment were measured. Maternal outcomes including preeclampsia, infection and type of delivery (cesarean or vaginal delivery) and neonatal outcomes including neonatal hypoglycemia, IUGR, IUFD, fetal anomalies, macrosomia, polyhydramnious, and NICU hospitalization were recorded.

Clinical properties between two groups were compared using student t-test and chi square test for continuous and categorical variables, respectively. The results are presented as mean± standard deviation (SD) or absolute frequency (percentage). The significance level less than 0.05 was deemed as significance. The SPSS software version 22 was utilized for data analysis.

3. Findings

Table 1 presents baseline and demographic variables. The mean age scores of insulin and metformin group were comparable (30.7±6.4 years and 28.8±5.7 years, respectively, P value=0.49). The minimum and maximum age of whole women were 18 and 47 years old, respectively. The median of parity in insulin group (median=1) was the same as metformin group (median=1). The median of history of abortion was similar in two groups. While, this range in insulin group was 0-4, and in metformin group was 0-2. The mean of BMI at baseline in insulin group (29.82± 4.41 kg/m^2) did not differ significantly with metformin group (29.44± 4.53 kg/m^2) (P=0.68). The mean of FBS at baseline in insulin and metformin group was similar (116.83± 30.5 mg/dl and 114.38± 33.87 mg/dl, respectively) (P=0.64). Moreover, the mean score of FBS was similar between two groups. Similarly, 2 hpp and also maternal weight were matched between two groups of insulin and metformin (174.6±49.1 mg/dl and 171.1±44.9 mg/dl, respectively, P value= 0.79). The mean maternal weight of women in insulin group (77.1±10.6 kg) at baseline did not have significant difference with that in metformin group (77.1±12.1 kg) (P value=0.4).

Table 1. Baseline characteristics in two groups

Variable		Insulin (n=70)	Metformin (n=70)	P value
Age		30.7 ± 6.4	28.8±5.7	**0.49**
Min-max		18-47	20-25	
Parity	Median	1	1	**0.7**
	Min-max	0-6	0-3	
	Interquartile range	2	2	
Abortion	Median	0	0	**0.59**
	Min-max	0-4	0-2	
	Interquartile range	0	1	
BMI (kg/ m)		29.8±4.4	29.4±4.5	**0.68**
Min-max		23-47	21.7-39	
FBS (mg/dl)		116.8±30.5	114.4±33.9	**0.64**
Min-max		72-230	75-232	
2hpp (mg/dl)		174.6±49.1	171.1±44.9	**0.79**
Min-max		90-304	93-275	
Maternal weight (kg)		77.1±10.6	77.1±12.1	**0.4**
Min-max		55-130	58-101	

Table 2 presents the number of Tabs which was used in metformin group. Eighteen patients (26.4%) treated with four tabs, 45 patients (66.7%) treated with three tabs, four patients (5.5%) received only two tabs per day and one patient (1.47%) received one tab per day.

Table 2. The received dose by metformin group

Number of Tabs per day	Number of patients (%)
Four Tabs.	18 (26.4)
Three Tabs.	45 (66.17)
Two Tabs	4 (5.9)
One Tab	1 (1.47)

The values are presented as frequency (percentage).

Some post-treatment measurements are presented in Table 3. The mean score of BMI in insulin group (31.5±4.2 kg/m^2) did not differ significantly with metformin group (30.4±4.3 kg/m^2). The mean score of FBS in metformin group (82.4±3.6 mg/dl) was slightly lower but was not significant than insulin group (83.7±3.32 mg/dl) (P=0.065). The range of FBS in metformin was 74–93 mg/dl and that in insulin group was 75-91 mg/dl. However, the mean score of 2 hpp in metformin group (97.5±5.9 mg/dl) was significantly lower than insulin group (104.4±7.1 mg/dl) (P<0.0001). The maternal weight gain after treatment in insulin group (81.4±11.5 kg) was slightly higher than metformin group (77.9±10.5 kg), however, this difference was not significant (P=0.123).

Table 3. Measurements after treatment

Variable	Insulin (n=70)	Metformin (n=68)	P value
BMI	31.5 ± 4.24	30.4 ±4.3	**0.21**
Min-max	24.2-48.5	22.6-40.5	
FBS	83.7±3.32	82.4±3.6	**0.065**
Min-max	75-91	74-93	
2hpp	104.38 ± 7.1	97.5±5.9	**<0.0001**
Min-max	90-116	85-111	
Maternal weight	81.4±11.5	77.9±10.5	**0.123**
Min-max	63-123	50.6-105	

The values are presented at mean±SD.

The maternal outcomes are presented in Table 4. The incidence of preeclampsia in insulin and metformin groups was 14.2% and 8.8%, respectively (P value=0.7). Of 70 subjects in insulin group 6 cases (6.5%) and of 68 subjects in control group two cases (2.9%) had infection. This difference was significant (P value<0.001). The rate of delivery by cesarean section was high in both insulin (40 of 70 subjects) and metformin groups (38 of 68 subjects).

Table 4. Maternal outcomes in two groups

Variable	Insulin (n=70)	Metformin (n=68)	P value
Preeclampsia	10 (14.2)	6 (8.8)	0.7
Infection	6 (8.5)	2 (2.9)	0.001
Cesarean	40 (57.1)	38 (55.8)	0.54
Vaginal delivery	30 (42.9)	32 (47)	

The values are presented as frequency (percentage).

Table 5. Neonatal outcomes in two groups

Variable	Insulin (n=70)	Metformin (n=68)	P value
Neonatal hypoglycemia	20 (28.2)	3 (4.4)	0.002
IUGR	2 (2.9)	2 (2.9)	1.000
IUFD	9 (12.8)	2 (9/2)	1.000
Fetal anomaly	3 (4.3)	4 (5.8)	1.000
Polyhydramnios	1 (1.4)	0	1.000
Macrosomia	8 (11.4)	5 (7.3)	1.000
Oligohydramnios	2 (2.9)	3 (4.4)	1.000
NICU hospitalization	4 (1.4)	2 (2.9)	0.67

Statistically significance.

Neonatal outcomes in treatment with insulin and metformin are shown in Table 5. Of 70 subjects in insulin group 20 cases and of 68 cases in metformin group only 3 cases were complicated by neonatal hypoglycemia. On the

other words, the rate of neonatal hypoglycemia in metformin group (2.9%) was significantly lower than this rate in insulin group (28.2%) (P value=0.002). Totally, four cases of IUGR, two of those were in insulin arm and two of those were in metformin arm. The incidence of IUFD, fetal anomaly, polyhydramnios, macrosomia, oligohydramnios and NICU hospitalization in insulin group were 12.8%, 4.3%, 1.4%, 11.4%, 2.9% and 1.4%, respectively, while the their incidence in metformin group were 2.9%, 5.8%, no case, 7.3%, 4.4% and 2.9%, respectively. The rates of IUFD, IUGR, fetal anomaly, polyhydramnios, oligohydramnios, and NICU hospitalization were similar between two groups of insulin and metformin.

4. Discussion

In the current trial, we evaluated the effectiveness of metformin over insulin in terms of neonatal and maternal outcomes for the control of blood glucose in the pregnancies complicated by GDM.

Active drug therapy of even mild glucose intolerance has been demonstrated to decrease the incidence of GDM related complications such as death, pre-eclampsia, fetal death and macrosomia (Crowther, Hiller, Moss, McPhee, Jeffries, & Robinson, 2005). When diet and lifestyle modifications are failed to control blood glucose, medication is required. Insulin is the standard medication therapy, but the amount of published information increases about the efficacy and safety of metformin treatment during pregnancy (Mesdaghinia et al., 2013; Moore et al., 2007; Ijas et al., 2011; Rowan et al., 2013; Tertti et al., 2008; Niromanesh et al., 2012; Spaulonci, 2013), encouraging the use of metformin for the GDM treatment.

Metformin is known to reduce the weight gain of women with GDM during pregnancy (Spaulonci, 2013; Gui, Liu, & Feng, 2013). However, the evidence regarding its effect on some obstetric outcomes specifically weight gain during pregnancy is inconclusive.

In the present study, the weight gain in metformin group was slightly lower but not significant in compare to insulin group. In contrast with our findings, in Spaulonci's study, the maternal weight gain from baseline until delivery in metformin group was significantly lower than insulin group (Spaulonci et al., 2013). In similar with Spaulonci's study, the study by Rowan also have been shown that weight gain in metformin group was significantly lower than insulin group (Rowan et al., 2008). In another follow-up study (Pellonpera, & Ronnemaa, 2016), they have demonstrated that short-term therapy with metformin compared with insulin cannot effectively prevent maternal weight gain in GDM pregnancies. One explanation for this inconsistency is the median dose of metformin in the MiG trial and Pellonpera study which were 2500 mg/day and 1500 mg/day, respectively and in our study it was 1500 mg/day. The finding regarding loss weight in Pellonpera's study supports our finding may due to these two studies have similar median daily dose of metformin and consequently similar maternal loss weight finding.

In our study the rate of preeclampsia in metformin group was 8.5% and in insulin group was 14.9%. However, there was not significant difference. In consistent with our finding, Rowan et al. (Rowan et al., 2008), Tertti et al. (Tertti, Ekblad, Vahlberg, & Rönnemaa, 2008) and also Spaulonci et al. (Spaulonci et al., 2013) have been reported similar results. It is notable that despite there was not significant difference in preeclampsia rate between two groups, but its rate was lower in metformin group. In Spaulonci's study the rate of preeclampsia in metformin group was higher in insulin group; however it was not significant (Spaulonci et al., 2013).

Recently, Balsells et al., (Balsells et al., 2015) published a meta-analysis comparing the effects of metformin vs. insulin on fetal and maternal outcomes. They have found that in metformin versus insulin, the maternal weight gain and neonatal hypoglycaemia significantly differed. They have demonstrated that metformin acts slightly better than insulin.

Hypoglycemia is frequently occurs in newborns of women with GDM. In the present study, the rate of neonatal hypoglycemia in metformin group was significantly lower than insulin group. Lowering hypoglycemia can prevent from damage of central nervous system (Glueck, Wang, Kobayashi, Phillips, Harvey, & Sieve-Smith, 2002). We found that other neonatal outcomes including IUGR, IUFD, fetal anomaly, polyhydramnios, macrosomia, oligohydramnios, and NICU hospitalization did not differ significantly between two groups. Similarly, a recent retrospective study on 243 patients with gestational diabetes has reported no significant difference between metformin and insulin group in terms of macrosomia and NICU hospitalization (Knight, Fontaine, Page, Green, & Allwood, 2016).

5. Conclusion

Finally we concluded that in women with gestational diabetes, metformin is comparable with insulin in the glycemic control and consequently reducing adverse maternal and neonatal outcomes even it worked better on some parameters such as neonatal hypoglycemia. Totally, metformin is safe and effectiveness in controlling the

gestational diabetes mellitus.

Acknowledgements

The authors of this study wish to acknowledge participants of the study and also Ahvaz Jundishapur University of Medical Sciences for its financial support.

Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

American Diabetes Association. (2012). Standards of medical care in diabetes. *Diabetes care*, *35*, S11**.**

Balsells, M., García-Patterson, A., Solà, I., Roqué, M., Gich, I., & Corcoy, R. (2015). Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. *BMJ*, *350*, h102. http://dx.doi.org/10.1136/bmj.h102

Cheung, N. W. (2009). The management of gestational diabetes. *Vascular health and risk management*, *5*(1), 153164**.**

Coustan, D. R., Lowe, L. P., Metzger, B. E. & Dyer, A. R. (2010). The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: paving the way for new diagnostic criteria for gestational diabetes mellitus. *American Journal of Obstetrics & Gynecology*, *202*(6), 654.e651-654.e656. http://dx.doi.org/10.1016/j.ajog.2010.04.006

Crowther, C. A., Hiller, J. E., Moss, J. R., McPhee, A. J., Jeffries, W. S., & Robinson, J. S. (2005). Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *The New England journal of medicine, 352*(24), 2477-2486. http://dx.doi.org/10.1056/NEJMoa042973

Dhulkotia, J. S., Ola, B., Fraser, R., & Farrell, T. (2010). Oral hypoglycemic agents vs insulin in management of gestational diabetes: A systematic review and metaanalysis. *American journal of obstetrics and gynecology, 203(5)*, 457. e451-457. e459. http://dx.doi.org/10.1016/j.ajog.2010.06.044

Glueck, C., Wang, P., Kobayashi, S., Phillips, H., & Sieve-Smith, L. (2002). Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome. *Fertility and sterility*, *77*(3), 520-525. http://dx.doi.org/10.1016/S0015-0282(01)03202-2

Gui, J., Liu, Q., & Feng, L. (2013). Metformin vs insulin in the management of gestational diabetes: A meta-analysis. *PLoS One*, *8*(5), e64585. http://dx.doi.org/ 10.1371/journal.pone.0064585

Hellmuth, E., Damm, P., & Mølsted-Pedersen, L. (2000). Oral hypoglycaemic agents in 118 diabetic pregnancies. *Diabetic Medicine*, *17*(7), 507-511. http://dx.doi.org/10.1046/j.1464-5491.2000.00314.x

Hunt, K. J., & Schuller, K. L. (2007). The increasing prevalence of diabetes in pregnancy. *Obstetrics and gynecology clinics of North America, 34*(2), 173-199, vii. http://dx.doi.org/ 10.1016/j.ogc.2007.03.002

Ijas, H., Vaarasmaki, M., Morin-Papunen, L., Keravuo, R., Ebeling, T., Saarela, T., & Raudaskoski, T. (2011). Metformin should be considered in the treatment of gestational diabetes: A prospective randomised study. *BJOG*, *118(7)*, 880-885. http://dx.doi.org/10.1111/j.1471-0528.2010.02763.x

Knight, L., Fontaine, T., Page, J., Green, E., & Allwood, A. (2016). Retrospective analysis of maternal and neonatal outcomes following the introduction of metformin in the treatment of Gestational Diabetes. Paper presented at the *Bjog-An International Journal of Obstetrics and Gynaecology*.

Mesdaghinia, E., Samimi, M., Homaei, Z., Saberi, F., Moosavi, S. G. A., & Yaribakht, M. (2013). Comparison of Newborn Outcomes in Women with Gestational Diabetes Mellitus Treated with Metformin or Insulin: A Randomised Blinded Trial. *International Journal of Preventive Medicine*, *4*(3), 327-333.

Moore, L. E., Briery, C. M., Clokey, D., Martin, R. W., Williford, N. J., Bofill, J. A., & Morrison, J. C. (2007). Metformin and insulin in the management of gestational diabetes mellitus: Preliminary results of a comparison. *The Journal of reproductive medicine, 52*(11), 1011-1015.

Niromanesh, S., Alavi, A., Sharbaf, F. R., Amjadi, N., Moosavi, S., & Akbari, S. (2012). Metformin compared with insulin in the management of gestational diabetes mellitus: A randomized clinical trial. *Diabetes research and clinical practice, 98*(3), 422-429. http://dx.doi.org/ 10.1016/j.diabres.2012.09.031

Pellonpera, O. & Ronnemaa, T. (2016). The effects of metformin treatment of gestational diabetes on maternal weight and glucose tolerance postpartum--a prospective follow-up study. *Acta obstetricia et gynecologica*

Scandinavica, 95(1), 79-87. http://dx.doi.org/10.1111/aogs.12788

Rowan , J. A., Hague, W. M., Gao, W., Battin, M. R., & Moore, M. P. (2008). Metformin versus Insulin for the Treatment of Gestational Diabetes. *New England Journal of Medicine*, *358*(19), 2003-2015. http://dx.doi.org/10.1056/NEJMoa0707193

Silva, J. C., Pacheco, C., Bizato, J., de Souza, B. V., Ribeiro, T. E., & Bertini, A. M. (2010). Metformin compared with glyburide for the management of gestational diabetes. *International Journal of Gynecology & Obstetrics, 111*(1), 37-40. http://dx.doi.org/10.1016/j.ijgo.2010.04.028

Spaulonci, C. P., Bernardes, L. S., Trindade, T. C., Zugaib M., & Francisco R. P. (2013). Randomized trial of metformin vs insulin in the management of gestational diabetes. *American journal of obstetrics and gynecology*, *209(1),* 34.e31-37. http://dx.doi.org/10.1016/j.ajog.2013.03.022

Su, D. F. & Wang, X. Y. (2014). Metformin vs insulin in the management of gestational diabetes: A systematic review and meta-analysis. *Diabetes research and clinical practice, 104*(3), 353-357. http://dx.doi.org/10.1016/j.diabres.2013.12.056

Tertti, K., Ekblad, U., Vahlberg, T., & Rönnemaa, T. (2008). Comparison of Metformin and Insulin in the Treatment of Gestational Diabetes: A Retrospective, Case-Control Study. *The Review of Diabetic Studies RDS*, *5*(2)*,* 95-101.