Original Article

Comparison of Metformin Versus Insulin for Glycemic Control in GDM

Farah Deeba[1], Bushra Khan[2], Saima Anwar[3]

[1,2]Senior Registrar, [2]Senior Registrar, [3]Women Medical Officer
Holy Family Hospital, Rawalpindi Medical University, Rawalpindi

Correspondence: *Dr. Bushra Khan*
Senior Registrar, Holy Family Hospital, Rawalpindi Medical University
bushrakhandr@yahoo.com

Abstract

Objective: To compare the efficacy of Metformin versus Insulin for glycemic control of pregnant women with GDM.

Study Design: A randomized controlled trial.

Place and Duration: Department of Obstetrics & Gynaecology Unit I, Holy Family Hospital Rawalpindi, duration of study was 6 months from January 2017 to June 2017.

Methodology: Total 160 patients were included in the study divided into two groups, each having 80 fulfilling the inclusion criteria. All potential diabetics, who were all those with previous macrosomic babies wt>4 kg, previous pregnancy complicated by GDM, family history of DM, and obese women with BMI >30 were included in this study.75g oral glucose tolerance test (OGTT) was done according to NICE criteria at 24-28 weeks of pregnancy to diagnose GDM. Group A had those treated with Tab. Metformin and Group B comprised those who were given inj. Insulin (subcutaneously).

Results: It was found out that Metformin was effective in 71(88.8%) patients whereas Insulin was effective in 74(92.5%) patients.

Conclusion: Both Metformin and Insulin are equally effective in controlling hyperglycemia in pregnant women with diabetes.

Key words: GDM, Hyperglycemia, Metformin.

Cite this article as: Deeba F, Khan B, Anwar S. Comparison of Metformin Versus Insulin for Glycemic Control in GDM. J. Soc. Obstet. Gynaecol. Pak. 2018; Vol 8(2):81-85.

Introduction

Pregnancy is potentially glucose intolerant condition, and in all pregnancies, insulin sensitivity decreases as the pregnancy advances. This predisposes to the development of Gestational Diabetes Mellitus, particularly in obese women with pre existing insulin resistance.[1] The incidence of Gestational Diabetes Mellitus is approximately 3-5% and 1 in 250 will be complicated by pre existing diabetes.[2]

Diabetes Mellitus increases the risk of certain pregnancy complications like congenital malformations, pre eclampsia, macrosomia, increased rate of operative deliveries, intrauterine deaths, fetal hypoglycemia, and bad perinatal outcome[2], it is also associated with development of type II Diabetes Mellitus.[2] Hyperglycemia exerts its teratogenic effects during period of organogenesis[3], once HbA1C is >10%in early pregnancy, risk of congenital malformation is 8%.

Optimal glycemic control is of utmost importance to achieve the best possible outcome of a pregnancy complicated by Diabetes.[4,2] Insulin has been the main therapeutic agent for treatment of Diabetes Mellitus in

Authorship Contribution: [1]Conceptualized study design Article writing, [2]Supervised and review the study. Data analysis, Interpretation, Data Collection

Funding Source: none
Conflict of Interest: none

Received: Mar 29, 2018
Accepted: June 07, 2018

pregnancy for last many years. But now Oral hypoglycemic agents like metformin have been found effective and safe for the treatment of Diabetes in pregnancy.[3]

Insulin therapy is considered best because it is very effective, safe and does not cross the placenta. Disadvantages of Insulin are a risk of hypoglycemia, cost and frequent injections that simulated interest in trials of Oral hypoglycemic agents use during pregnancy.[3] Women who begin insulin therapy require education to ensure the safe administration of insulin.[5] Use of insulin is also associated with weight gain.[5] Insulin therapy controls blood sugar levels very effectively but it has no effect on insulin resistance which is an important feature of pregnancy.[3]

Metformin is a cheap, effective and safe alternative to Insulin.[5,3] It decreases hepatic glucose production, decreases intestinal glucose absorption, improves insulin sensitivity and peripheral glucose uptake and utilization.[3] Blood sugar levels control during pregnancy and the number of women attaining blood sugar levels control are significantly better with metformin as compared to Insulin.[3] Dose adjustment is required less often with metformin despite longer duration of action.[3] Metformin crosses placenta but no adverse perinatal outcome has been reported with its use during pregnancy.[6]

Recent studies have shown the equivalence to insulin of both glyburide and metformin in terms of pregnancy outcomes in Gestational diabetes mellitus[7,8,9]. Efficacy of metformin is 82% and of insulin is 54% in achieving maternal glycemic goals.[3]

The aim of the study is to explore the efficacy of Metformin versus Insulin and to find out the better drug for glycemic control of pregnant women.

Methodology

A randomized controlled trial was conducted at Obstetrics and Gynaecology Department at Holy Family Hospital. A total of 160 patients were selected. Patients irrespective of age and parity, who gave informed consent were divided into two groups randomly i.e. based on a computer-generated table of random numbers, Group A received Metformin and Group B received Insulin.

In all potential diabetics, who were all those with previous macrosomic babies wt>4 kg, previous pregnancy complicated by GDM, family history of DM, and obese women with BMI >30,75g oral glucose tolerance test (OGTT) was done according to NICE criteria at 24-28 weeks of pregnancy. For OGTT, patients were instructed not to restrict carbohydrate intake in the days or weeks before the test. After an overnight fast of at least 8 hrs., patient's venous blood sample for fasting blood sugar level (BSF) was taken, then she was given 75g glucose solution to drink. After 2 hrs, another venous sample was taken. Criteria for diagnosing GDM was BSF >100mg/dl and /or 2 hrs pp >140mg/dl. Women diagnosed with gestational diabetes were recruited to receive either insulin or metformin.

In group A, Metformin was given as 500-750 mg once a day for one week,500-750 mg twice a day for 2nd week,500-750 mg thrice a day from 3rd week onwards based on blood sugar levels. In group B, Insulin was started and titrated against blood sugar levels, short acting insulin (Regular) was used initially, and intermediate acting insulin (NPH) was added whenever required.

The glycemic profile was done daily. The goal of therapy was to have BSF <100 mg/dl and 2 hrs postprandial <140 mg/dl at 3 weeks of starting tab. metformin or insulin.

Maternal glycemic control was the primary outcome measure at 3 weeks. Patients were monitored for side effects of insulin and metformin e.g. nausea, vomiting, hypoglycemia and lactic acidosis.

Data Analysis Procedure: Data was collected in form of variables and was stored and analyzed on SPSS ver.10. Mean and standard deviation was calculated for quantitative data including variables as maternal blood sugar levels(mg/dl), maternal age (yrs), parity, gestational age(wks). Frequency and percentage were calculated for the efficacy of the drug. Chi-square test was applied to compare the efficacy of both drugs. P value of less than 0.05 was taken as significant.

Results

Descriptive statistics were calculated for Age of patient in terms of years in both the groups, in which mean$\pm$SD of age of patient in Group A (Metformin) was 32.46$\pm$4.696 with ranges 20 to 42 years where as mean$\pm$SD of age of patient in Group B (injection insulin) was 31.95$\pm$31.00 with ranges from 24 to 45 years as shown in Table no. I

Similarly, parity of patients were also compared in both the groups in which mean+SD of parity in both the groups were 3.29$\pm$1.794 and 4.06$\pm$1.885 respectively whereas mean$\pm$standard deviation of gestational age in both the groups were 28.20$\pm$2.341 and 26.95$\pm$2.433

respectively. Body Mass Index in Group A (metformin) was 35.84±3.763 and in Group B (insulin), the mean±SD of BMI was 35.55±4.432 as shown in Table. no. II

Table no I: Descriptive Statistics of Age (yrs) of patients in both the groups

	Two Groups		Statistic
Age of patient	Metformin	Mean	32.46
		Std. Deviation	4.696
		Minimum	20
		Maximum	42
	Injection Insulin (subcutaneous)	Mean	31.95
		Std. Deviation	4.922
		Minimum	24
		Maximum	45

Table no II: Comparison of Parity, Gestational Age and BMI of patients in both the groups

	Two Groups	N	Mean	Std. Deviation
Parity	Metformin	80	3.29	1.794
	Injection Insulin	80	4.06	1.885
Gestational Age	Metformin	80	28.20	2.341
	Injection Insulin	80	26.95	2.433
BMI	Metformin	80	35.84	3.763
	Injection Insulin	80	35.55	4.432

Fasting glucose in GTT at presentation and at 2 hours were compared in both the groups in which mean+SD at 2 hrs Glucose in OGTT in both the groups were 186.73+43.92 and 182.10+47.38 respectively as shown in Table. no. III

Table no III: Comparison of Glucose in OGTT of patients in both the groups

	Two Groups	N	Mean	Std. Deviation
Fasting Glucose in OGTT	Metformin	80	131.11	16.736
	Injection Insulin (subcutaneous)	80	123.66	15.358
2 hr Glucose in OGTT	Metformin	80	186.73	43.924
	Injection Insulin (subcutaneous)	80	182.10	47.383

Frequency and percentages of Blood Sugar Levels with treatment after 3 wks were also compared in both the groups in which 70 (87.5%) patients were controlled Blood Sugar Levels with treatment after 3 wks in Group A (Metformin) and 74 (92.5%) patients were controlled in Group B (insulin) as shown in Table. no. IV

Comparison of efficacy of both the groups was the outcome of the study, in which 71 (88.8%) patients were effective in Metformin Group whereas 74 (92.5%) patients were effective in Group B (insulin). Chi-square test was used to compare the efficacy in both the groups which were statistically not significant (p-value 0.416) as shown in the Table. no. V which showed that there was no difference between the efficacy of metformin and insulin.

Table no IV: Comparison of Blood Sugar Levels with treatment after 3 wks of patients in both the groups

		Two Groups	
		Metformin	Injection Insulin (subcutaneous)
Blood Sugar Levels with treatment after 3 wks	Controlled	70	74
		87.5%	92.5%
	not controlled	10	6
		12.5%	7.5%
Total		80	80
		100.0%	100.0%

Table no V: Comparison of Efficacy in both the groups

		Two Groups	
		Metformin	Injection Insulin (subcutaneous)
Efficacy	yes	71	74
		88.8%	92.5%
	no	9	6
		11.3%	7.5%
Total		80	80
		100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.662	1	.416
N of Valid Cases	160		

Discussion

Diabetes complicating pregnancy is becoming more common worldwide. The majority of complications due

to diabetes in pregnancy are seen in fetal growth, development, labour and delivery.[10] These complications can be prevented with good glycemic control of mother during pregnancy and postnatal period.[11] It is important to note, that many of the medical complications of diabetes affect success and outcome of pregnancy and pregnancy itself may contribute to deterioration in the long-term health of the mother.[12]

Adverse outcomes related to diabetes in pregnancy is divided into short term and long-term complications. Short term risk to the mother is particularly from hypoglycemia. Maternal hypoglycemia may be due to a combination of medical as well as patient`s herself attempt to maintain low blood sugar levels during pregnancy. Long term complications include deterioration of retinopathy and nephropathy. Obesity is also common in patients with GDM.[13] The medical and surgical complications of obesity can be superimposed onto the existing complications of hyperglycemia in pregnancy.

Incidence of gestational diabetes is increasing in association with increasing incidence of obesity in the population at large and the increase in age specific maximum fertility.[14] It is becoming increasingly recognized that a proportion of women diagnosed GDM on OGTT during pregnancy are infact previously unrecognized cases of type 2 diabetes mellitus and this proportion might be as high as 20%, and is increasing.[15]

Gestational diabetes mellitus should be recognized not only to prevent its adverse effects on pregnancy, it is also important to diagnose this because, after delivery interventions such as dietary modifications, pharmacologic drugs and lifestyle modifications may reduce the risk of a subsequent pregnancy being complicated by diabetes.[16] It will also improve long term health of women potentially by reducing her risk of developing chronic type 2 diabetes and its complications.

The first principle of treatment of diabetes in pregnancy is to correctly diagnose the type of diabetes. The second and perhaps even more important principle is to understand the potential vulnerability of the fetus and mother to disease and its treatment. Insulin and oral hypoglycemic agents both are used for the treatment of diabetes in pregnancy. Insulin and oral hypoglycemic agents both are categorized as “Category C.”Insulin does not cross placenta. Metformin crosses placenta but no teratogenic affects have been observed so far. Both drugs are considered safe for the baby.

Insulin has long been the preferred drug for treating diabetes in pregnancy, but side effects are hypoglycemia, and in country like ours where compliance is poor and most of the people are uneducated, it is very difficult to educate women and their families regarding storage of insulin, injection technique, signs and symptoms of hypoglycemia and its treatment, that's why oral hypoglycemic agents are gaining popularity.[17]

In our study Insulin and metformin both were effective in controlling hyperglycemia in pregnant females.

A systematic review of observational studies and randomized controlled trials of neonatal and maternal outcome in pregnant women with Diabetes Mellitus treated with oral hypoglycemic agents compared with insulin was conducted by Nicholson W et al. Two trials compared insulin to oral hypoglycemic agents; one trial compared insulin to metformin, and one trial compared insulin to glyburide. No significant difference was found in maternal blood sugar levels control and cesarean sections rate between insulin and glyburide groups. No substantial neonatal and maternal outcome differences were found when metformin or glyburide was compared to insulin in women with GDM.[18]

Hickman MA et al, compared the tolerability and safety of metformin to insulin for blood sugar levels control among pregnant women with GDM and type II DM. No difference was found in achieving glycemic targets between the two groups. Women treated with metformin had comparatively fewer episodes of hypoglycemia compared with those using insulin.[19]

Another study conducted by Ijas H,et al found that there were no significant differences in mean cord artery pH, mean birthweight and neonatal morbidity between metformin and insulin groups. Fifteen out of 47 women (31.9%) women randomized to metformin needed supplemental insulin. These women had higher fasting blood sugar levels in OGTT (6.1 versus 5.0 mmol/l), were more obese (with a body mass index (BMI) of 36Kg/m^2 versus 30Kg/m^2) and needed medical treatment for gestational diabetes mellitus earlier (26 weeks versus 31 weeks of gestational age) than women who were normoglycemic with metformin. Cesarean section rate was higher in the metformin group than in the insulin group. They concluded that metformin is effective for the prevention of fetal macrosomia, especially in moderately overweight and lean women developing gestational diabetes mellitus in

late gestation. Women with high fasting blood sugar levels, obesity and an early need for medical treatment may be more suitable for insulin therapy. [6]

Balani J et al observed that Women treated with insulin had significantly greater mean weight gain from enrolment to term (2.72 ± 0.4 vs. 0.94 ± 0.3 kg). There was no difference between the metformin and insulin groups, respectively, comparing gestational hypertension (6 vs. 7%), pre-eclampsia (9 vs. 2%) induction of labour (26 vs. 24%) or rate of Caesarean section (48 vs. 52%). No perinatal loss occurred in either group. Neonatal morbidity was improved in the metformin group; prematurity (0 vs. 10%), neonatal jaundice (8 vs. 30%) and admission to neonatal unit (6 vs. 19%).[20]

Study conducted by Rai L et al in India concluded that glycemic control was better and quicker with metformin than with insulin. When compared with insulin they found metformin cheap, practical and a useful first-line therapy in resource-poor settings.[3]

Conclusion

Both Metformin and Insulin are equally effective in controlling hyperglycemia in pregnant women with diabetes. In group A Metformin was effective in 71 (88.8%) patients, whereas in 74 (92.5%) patients insulin was effective in Group B. Metformin has advantage of easy administration,less cost,less frequent daily blood sugar levels monitoring and less risk of hypoglycemia,so metformin is better choice in developing countries like Pakistan where hospitals are overcrowded, patients are poor,have large families can not afford prolong and repeated hospital admissions.

References

1 Tertti K,Ekblad U,Vahlberg T,Rönnemaa T.Comparison of metformin and insulin in the treatment of gestational diabetes: a retrospective,case-control study. Rev Diabet Stud 2008;5(2):95-101.

2 Fraser R and Farrell T,Diabetes. in A Anthony,A Janet,A John,A Domenico,A Vincent T,A George,Hi Risk management option,4th ed Philadelphia,United Kingdom,Book power 2011;795-811.

3 Rai L,Meenakshi D, Kamath A. Metformin - A convenient alternative to insulin for Indian women with diabetes in pregnancy. Indian J Med Sci. 2009;63:491-7

4 Baker PN,Obstetrics by Ten Teachers.London;Book Power 2011

5 Rowan JA, Hague WM, Gao W, Battin MR, Moore MP; MiG Trial Investigators Metformin versus Insulin for the Treatment of Gestational Diabetes.N Engl J Med. 2008;358(19):2003-15

6 Ijas H,Vaarasmaki M,Morin-Papunen L,Keravuo R,Ebeling T,Saarela T and Raudaskoski T.Metformin should be considered in the treatment of gestational diabetes:a prospective randomized study;BJOG.2011;118(7):880-885.

7 Paglia MJ, Coustan DR The use of oral antidiabetic medications in gestational diabetes mellitus. Curr Diab Rep. 2009;9(4):287-90.

8 Dhulkotia JS, Ola B, Fraser R, Farrell T Oral hypoglycemic agents vs insulin in management of gestational diabetes: a systematic review and metaanalysis. Am J Obstet Gynecol. 2010;203(5):457.e1-9.

9 Refuerzo JS Oral hypoglycemic agents in pregnancy Obstet Gynecol Clin North Am. 2011;38(2):227-34,

10 Capula C, Chiefari E, Vero A, et al., "Predictors of Postpartum Glucose Tolerance Testing in Italian Women with Gestational Diabetes Mellitus," ISRN Endocrinology.,2013;182505: 6

11 Wahabi HA, Esmaeil SA and Alzeidan RA .Pre-existing diabetes mellitus and adverse pregnancy outcomes BMC Res Notes.2012;496(5)

12 Bell R, Bailey K, Cresswell T, Hawthorne G, Critchley J and Barned NL Northern Diabetic Pregnancy Survey Steering Group. Trends in prevalence and outcomes of pregnancy in women with pre-existing type I and type II diabetes.BJOG:2008;115(4):445-452.

13 Deveer R,Deveer M, Akbaba E, Engin-Üstün Y,Aydoğan P,Çelikkaya H, Danişman N,Mollamahmutoğlu L.*The effect of diet on pregnancy outcomes among pregnants with abnormal glucose challenge test:2013;17(9):* 1258-1261

14 Chyad M, Noaemi A, Radenkovic M , Helmy M and Shalayel F. Pathophysiology of Gestational Diabetes Mellitus: The Past, the Present and the Future, Gestational Diabetes, (Ed.), (2011) ISBN: 978-953-307-581-5,

15 Harlev A, Wiznitzer A. New Insights on Glucose Pathophysiology in Gestational Diabetes and Insulin Resistance**;** Current Diabetes Reports. 2010;10(3): 242-247

16 Piotr M, Agnieszka B, Katarzyna H. The Common C49620T Polymorphism in the Sulfonylurea Receptor Gene SUR1 (ABCC8) in Patients with Gestational Diabetes and Subsequent Glucose Metabolism Abnormalities, Experimental Diabetes Research. 2012,712617: 7

17 Cho Y, Kim T, Lim S, Choi S, Shin H, Lee H, et al. Type 2 diabetes-associated genetic variants discovered in the recent genome-wide association studies are related to gestational diabetes mellitus in the Korean population. Diabetologia.2009;52:253–261.

18 Nicholson W, Bolen S, Witkop CT, Neale D, Wilson L, Bass E,Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes: a systematic review. Obstet Gynecol. 2009;113(1):193-205

19 Hickman MA, McBride R, Boggess KA, Strauss R.Metformin compared with insulin in the treatment of pregnant women with overt diabetes: a randomized controlled trial. Am J Perinatol. 2013;30(6):483-90

20 Balani J, Hyer SL, Rodin DA, Shehata H. Pregnancy outcomes in women with gestational diabetes treated with metformin or insulin: a case-control study. Diabet Med. 26:2009;798–802.