

COMPARISON OF DIET, METFORMIN AND INSULIN IN THE TREATMENT OF GESTATIONAL DIABETES MELLITUS

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Introduction: During pregnancy, an increase in insulin resistance occurs¹. GDM develops if there is inadequate insulin secretion to compensate insulin resistance.

GDM increases the risk of pregnancy complications. Prospective randomized studies demonstrated that effective treatment of hyperglycemia in women with GDM can reduce adverse perinatal outcomes². The treatment is with diet, metformin or insulin. The disadvantages of insulin for pregnant women are: need to give injections, risk of hypoglycemia, risk of excessive weight gain, and cost¹. Theoretically, metformin is an alternative to insulin in the treatment of hyperglycemia during pregnancy. It does not induce hypoglycemia and it is not associated with increased weight gain. Also metformin reduces insulin resistance and hepatic gluconeogenesis, which could be beneficial for preservation of β cell function¹.

The number of studies reporting on the use of metformin in women with type 2 diabetes during pregnancy or GDM is small. They provide conflicting information about the safety of metformin use in type 2 diabetes or GDM pregnancies¹.

Objective: The aim of the study was to compare maternal and neonatal outcomes in patients with gestational diabetes mellitus (GDM) treated with metformin versus those with insulin, or diet alone.

Material and methods: 62 women with GDM attending Outpatient department of University Clinic of Endocrinology Diabetes and Metabolic Disorders. 24 GDM women were treated with metformin, 21 with insulin, and 17 without pharmacological treatment, only on diet. All were with singleton pregnancies.

Criteria for GDM were at least two out of three abnormally high plasma glucose value measurements in the 75 g OGTT (a fasting level $\geq 5,1$, 1-hour level $\geq 10,0$, 2-hour level $\geq 8,5$ mmol/l)³. They were taught self-monitoring of plasma glucose, with instructions to measure fasting and postprandial values at 60 min after main meals at least four times a day during three consecutive days. The mode of treatment, based on self-monitored plasma glucose values, was determined within a week after starting monitoring. Metformin was given at a dose of 500 mg three times a day to a maximum of 2000 mg/day based on glycemic profile.

The outcome measures studied were glycemic control, maternal and neonatal outcome.

Statistical analysis: Statistical analyses were performed using SAS software for Windows, version 11.0. For analysis, t-test, Anova test, and Chi-square test were used.

Results:

Table 1. Maternal Characteristics at Baseline

	Diet (N=17)	Metformin (N=24)	Insulin (N=21)	Metformin vs. diet P	Metformin vs. insulin P	Diet vs. insulin P
Age (years)	32,5±4,1	33,2±5,1	33±5,2	NS	NS	NS
Pre-pregnancy BMI (kg/m ²)	27,6±7,7	29,1±5,7	29±5,0	NS	NS	NS
Weight gain (kg)	3,2±1,6	2,7±1,8	3,4±2,7	NS	NS	NS
Gestational week at enrolment (wk)	29,2±5,4	29±5,5	24,7±6,1	NS	< 0,05	< 0,01
Smoking cigarettes (%)	2 (11,7%)	3 (12,5%)	2 (9,5%)	NS	NS	NS
Familial history for diabetes (%)	8 (47,1%)	14 (58,3%)	11 (52,4%)	NS	NS	NS

Table 3. Neonatal primary outcomes

	Diet (N=17)	Metformin (N=24)	Insulin (N=21)	Metformin vs. diet P	Metformin vs. insulin P	Diet vs. insulin P
Birth weight (gr)	3712±565	3452±482	3378±741	NS	NS	NS
prematurity	0	2 (8,3%)	6 (28,6%)	-	NS	-
LGA (> 2SD/%)	4 (23,5%)	4 (16,7%)	5 (23,8%)	NS	NS	NS
SGA (< 2SD/%)	0	1 (4,2%)	2 (9,5%)	NS	NS	NS
Neonatal glycaemia (mean, % with hypoglycaemia)	3,3±0,9 (17,6%)	2,6±0,8 (33,3%)	2,4±1,0 (52,4%)	< 0,05	< 0,05	< 0,05
Apgar score at 5'	8,4±0,5	8,3±0,6	8,1±0,7	NS	NS	NS

Although mean birth weight in diet and metformin groups was higher, no statistically differences between the groups were observed (Table 3, Graphic 3).

The incidence of neonatal hypoglycemia (s-gluc < 2.6 mmol/l) was statistically significant higher in insulin group compared with those treated with metformin or diet, but the difference between mean values between metformin and insulin groups did not reach statistical significance (Table 3, Graphic 4).

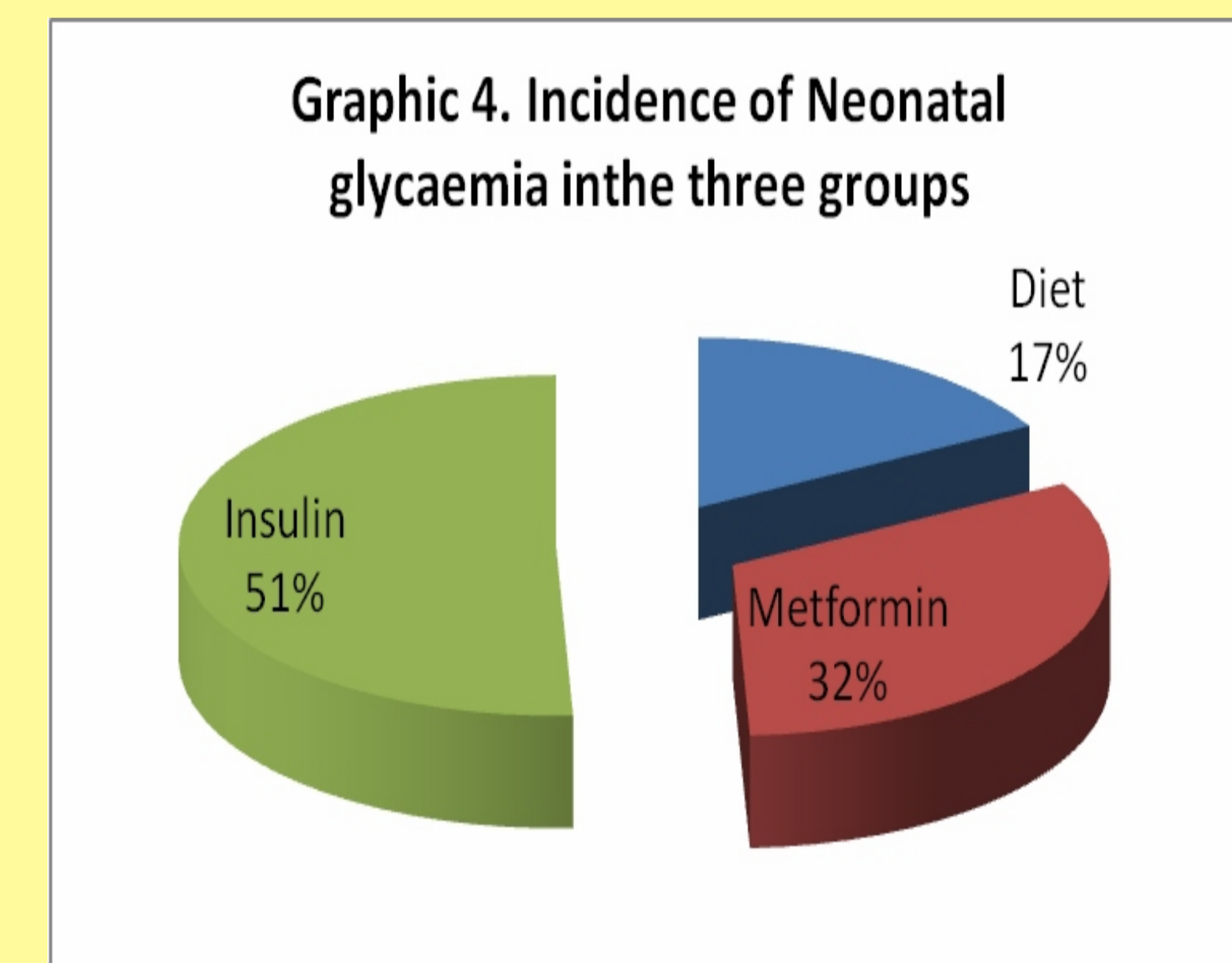
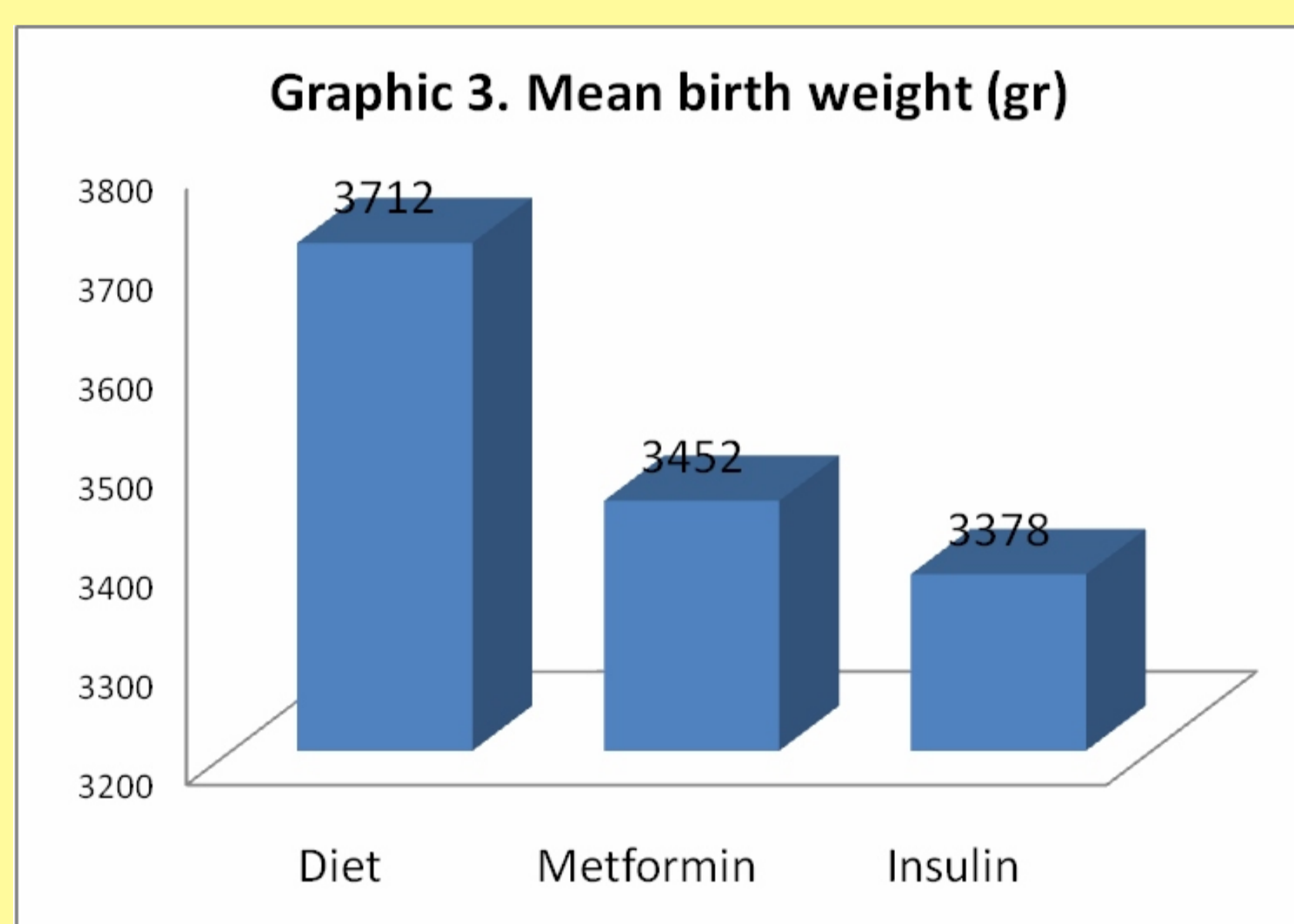
There were no major complications or perinatal deaths in this study. One neonate had asphyxia, whose mother belongs to insulin group.

LGA- large for gestational age, SGA- small for gestational age, SD- standard deviation;

Mean glycosylated haemoglobin (HbA1c) at 37 gestation week was lower in diet and metformin groups than in insulin group (Table 2, Graphic 1). Mean postprandial glycaemia (PPG) statistically significant differed in diet from metformin group and in diet as to insulin group (Table 2, Graphic 2).

Table 2 Maternal primary outcomes

	Diet (N=17)	Metformin (N=24)	Insulin (N=21)	Metformin vs. diet P	Metformin vs. insulin P	Diet vs. insulin P
HbA1c at 37 g.w. (mean)	4,5±0,9	5,3±0,7	6,1±1,3	< 0,05	< 0,05	< 0,01
Fasting glycaemia mmol/l	5,4±1,3	5,4±0,7	5,9±1,5	NS	NS	NS
Postprandial glycaemia (PPG) mmol/l	6,2±2,1	7,5±1,1	8,3±2,3	< 0,05	NS	< 0,05
preeclampsia	1 (5,9%)	2 (8,3%)	2 (9,5%)	NS	NS	NS
Gestational age at delivery (wk)	39,1±2,2	38,7±1,6	37,3±2,4	NS	< 0,05	< 0,05
Mode of delivery						
-spontaneous	7 (41,2%)	10(41,7%)	7 (33,3%)	NS	NS	NS
- assisted	1 (5,9%)	0	0	NS	NS	NS
- caesarean section	9 (52,9%)	14(58,3%)	14 (66,7%)	NS	NS	NS



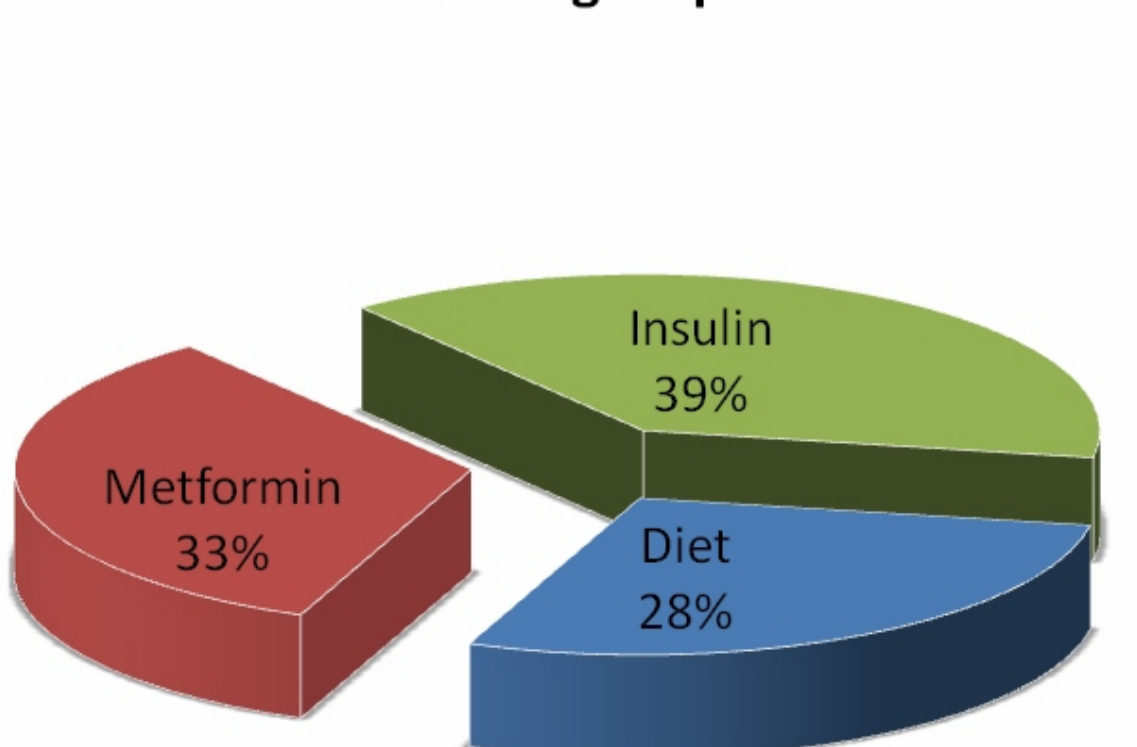
Discussion: According to HbA1c, glycemic control in diet and metformin group were significantly better compared to insulin group. Also PPG was lower (without statistical significance) in metformin group then in insulin group. As others conclude^{4,5}, metformin can be effective in controlling the GDM.

We found significantly fewer neonates with hypoglycemia in the metformin group compared with the insulin group (p = 0,04), although mean values did not differ statistically significant. These data are consistent with results of Tertti et al.⁵, and observations in PCOS patients treated with metformin⁶, but are inconsistent with the results obtained by Hellmuth et al.⁷ In the latter study, increased rates of preeclampsia and perinatal loss were observed in mothers treated with metformin, but the groups were not well matched for age or body mass index. In this study, the groups were well matched and did not differ in the rates of preeclampsia, mode of delivery, apgar score at 5 minutes, birth weight, LGA and SGA. Also there was not perinatal loss. Few studies which included randomized 751 women with GDM into treatment with insulin or metformin, indicated that there were no serious adverse events associated with use of metformin. Even some PCOS studies, where metformin was used, reported a reduction in spontaneous abortion in the first trimester⁸. As others conclude^{5,9}, metformin is safe in GDM pregnancies. Also metformin is more acceptable to women with GDM then insulin¹.

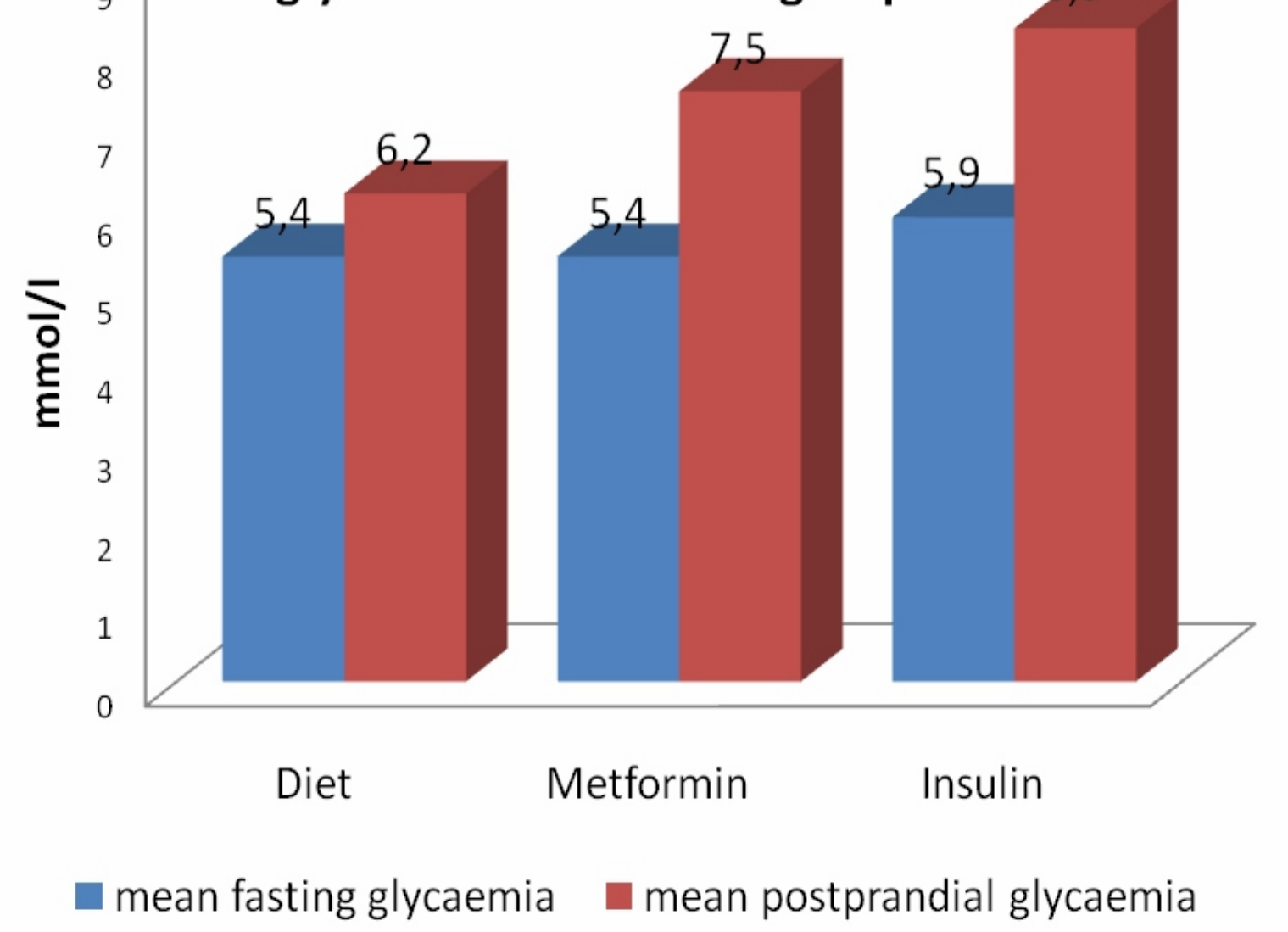
If metformin had any unanticipated adverse effect on fetal growth or well-being, there would be more iatrogenic preterm births¹. But, the frequency of preterm births was higher in the insulin group then in metformin group.

Conclusions: Maternal and neonatal outcomes were similar in metformin and insulin group. So, metformin appears to be effective and save in the treatment of GDM patients and may have its place as first line GDM therapy. However, further clinical long-term follow-up studies are needed to determine the role of metformin as an alternative treatment to insulin in GDM patients.

Graphic 1. Mean levels of HbA1c (%) in the three groups



Graphic 2. Maternal fasting and postprandial glycaemia in the three groups



1. Wah Cheung N. The management of gestational diabetes. *Vascular Health and Risk Management*. 2009; 5: 153-164.
 2. Crowther C, Hillier J, Moss J, McPhee A, Jeffries W, Robinson J. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005; 352:2477-2486.
 3. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. 2010; 33(3):676-82.
 4. Rowan J, Hague W, Gao W, Battin M, Moore M, MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med* 2008; 358:2003-2015.
 5. 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) 5:95-101.
 6. Glueck C, Bornovalli S, Prankoff J, Goldenberg N, Dharashivkar S, Wang P. Metformin, pre-eclampsia, and pregnancy outcomes in women with polycystic ovary syndrome. *Diabet Med* 2004; 21:829-836.
 7. Hellmuth E, Damni P, Molsted-Pedersen L. Oral hypoglycaemic agents in 118 diabetic pregnancies. *Diabet Med* 2000; 17(7):507-511.
 8. Jacobowicz D, Iuorno M, Jacobowicz S, Roberts K, Nestler J. Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2002; 87:524-529.
 9. Rai L, Meenakshi D, Kamath A. Metformin - A convenient alternative to insulin for Indian women with diabetes in pregnancy. 2009; 63(11):491-497.