# Basal bolus insulin regimen with metformin versus carbohydrate insulin ratio with metformin in the management of diabetes mellitus during pregnancy

Dr. Amira Tarabay
Resident of Obstetrics and Gynecology in Mansoura General Hospital, Mansoura, Egypt.

Prof. Dr. Mohamed Tawfik
Prof. of Obstetrics and Gynecology Department, Faculty of Medicine Mansoura University, Mansoura, Egypt.

Dr. Ashraf Ghanem
Associate Prof. of Obstetrics and Gynecology Department, Faculty of Medicine Mansoura University, Mansoura, Egypt.

Dr. Alaa Wageh
Associate Prof. of Obstetrics and Gynecology Department, Faculty of Medicine Mansoura University, Mansoura, Egypt.

**Corresponding author:**
Dr. Alaa Wageh
Associate Prof. of Obstetrics and Gynecology Department, Faculty of Medicine Mansoura University, Mansoura, Egypt.
E-mail wagehalaa@yahoo.com.

## Running Title

Basal bolus insulin regimen versus carbohydrate insulin ratio in diabetes mellitus during pregnancy

## Ethical statement

- Authors declare that there is no conflict of interest
- No funding.
- Accepted by the Ethical Research Committee of the Obstetrics and Gynecology Department and institutional review board (IRB) in the Faulty of Medicine (MS/16.03.03).
- Written informed consent was taken from the participants.

## Abstract

**Background:** Controlling diabetes mellitus (DM) in pregnancy is important to avoid further maternal and fetal complications. This can be achieved by diet regimen, exercise, insulin and oral hypoglycemic agent like metformin. We aimed to compare between basal bolus insulin regimen with metformin and flexible basal bolus regimen according to carbohydrate insulin ratio with metformin on control of blood sugar among pregnant women with diabetes.

**Methods:** Our study is a randomized controlled trial on 60 cases of pregnant women with diabetes who are attending Obstetrics and Gynecology department at Mansoura university hospitals. Cases were randomized into two groups: Group I (basal bolus regimen group) (n = 30) including women who received oral metformin in addition to insulin by the basal bolus insulin regimen; Group II (insulin carbohydrate regimen group) (n = 30) including women who received oral metformin in addition to insulin by insulin carbohydrate regimen.

**Results:** Our result showed that there was 100% control in fasting glucose levels and 100% control in post prandial glucose level in group 1 and 70% control in group 2.

**Conclusion:** the basal bolus regimen is better than insulin carbohydrate ratio in patient with diabetes who are at mid education level with carbohydrate counting.

**Keywords:** Carbohydrate-to-insulin ratio, Diabetes, Insulin, Metformin, Pregnancy.

## Introduction

Egypt is listed among the world's high countries in the number of patients with Diabetes mellitus (DM). The prevalence of DM is around 15.56% among the population between 20 and 79 years of age, accordingly, diabetes that complicates pregnancies is a common problem (1).

Although Insulin is the preferred Antidiabetic treatment agent for the management of diabetes in pregnancy (2), Metformin becomes safe and more effective than insulin in lowering the 2-hour postprandial level (3). Adding metformin to the conventional insulin regimen effectively achieved good glycemic control with a lower dose of insulin (4). This combination is powerful in insulin-resistant DM with pregnancy (5).

Carbohydrate counting has been tried with success in patients with type 1 diabetes as one of the strategies used in Diabetes Control and Complications Trials (DCCT). In this protocol patients adjust their insulin dose according to the amounts of carbohydrate consumed known by frequent blood glucose measurements (6).

Using carbohydrate counting not only makes use of an insulin dose scale according to their pre-prandial blood glucose values; but they also base their dosage titration on insulin/carbohydrate ratios. These ratios allow them to vary their carbohydrate quantity within meals and from day to day, as long as there is adequate insulin to account for the carbohydrate content (7). However, little data on insulin/carbohydrate ratios to control diabetes in pregnancy is present in the literature. To our knowledge, no previous studies compared between insulin carbohydrate ratio and basal bolus regimen after adding the metformin.

Therefore, this study was designed to compare the basal-bolus insulin regimen with metformin and flexible basal-bolus regimen according to carbohydrate insulin ratio with metformin on control of blood sugar among pregnant women with diabetes.

## Patients and Methods

This randomized controlled trial was conducted on 60 pregnant women between 20 and 48 years with Gestational diabetes mellitus (GDM) & type 2 DM who have uncontrolled blood sugar or poor glycemic control (Poor glycemic control is defined as fasting blood glucose > 95 mg/dl and/or 2-h postprandial blood glucose >120 mg/dl) and having a singleton pregnancy between 20 and 34 weeks who were admitted to Mansoura University Hospitals during the period between March 2016 to December 2017.

The study was started after getting signed consent from each patient and being approved by the Ethical Research Committee of the Obstetrics and Gynecology Department, and the institutional review board at Mansoura University (MS/16.03.03). A signed consent from each patient was taken.

Women with type 1 DM and those with secondary diabetes, or had other medical disorders and/or diabetes-related complications such as renal failure, heart failure, chronic liver disease, severe chronic pulmonary disease, coronary insufficiency, history of thromboembolic disorder, gestational hypertension, preeclampsia, fetal growth restriction and fetal macrosomia, fetal anomaly, ruptured membranes in second trimester, contraindications or hypersensitivity to metformin intake like gastrointestinal side effects and altered liver functions with or without jaundice were excluded from the study.

## Randomization

A computer-generated list of numbers sealed in opaque envelopes in a parallel manner was used to randomize the cases into two equal groups.

**Group 1:** The patient was given 50% of the calculated insulin dose as a basal dose of intermediate-acting insulin (where two-thirds of the dose is given AM and one-third at bedtime). The other half of the calculated dose was given as bolus short-acting insulin (where one-third of the dose is given before each meal: breakfast, lunch, dinner) (8).

**Group 2:** The patient was given 50% of the calculated dose as basal dose in group 1 and the bolus dose was given according to insulin carbohydrate ratio (every 10–15-gram carbohydrate covered by 1-unit short-acting insulin). The initial ICR was 1:15 for all participants (9).

At the first visit, all patients were educated on carbohydrate counting and on how to achieve and maintain good metabolic control.

Calculation of insulin dose: Begin with 0.7-0.8 unit/kg insulin (Humulin-R, Humulin –N) in the 1st trimester, 0.8-0.9 unit/kg in the 2nd trimester, and 0.9-1.2 unit/kg in the 3rd trimester. Insulin dose was raised at a rate of 1 IU for every 10 mg/dl higher than the target blood glucose concentration. The target blood glucose concentration was 60–95 mg/dl for fasting and less than 120 mg/dl for 2h postprandial.

Both groups added metformin (Cidophage, 500mg, CID Pharmaceuticals, Egypt) initiated at a dose of 500 mg once daily for two first days to prevent possible gastrointestinal side effects. Then dose was increased to twice daily, 1000mg /day. Metformin was stopped if maternal contraindications (such as liver or renal impairment or sepsis) or fetal growth restriction developed.

All participants were subjected to routine laboratory investigation including urine analysis, ketone tests, urine for glycosuria or ketonuria checked twice daily, blood glucose monitoring, fasting, and three postprandial blood glucose levels 2 hours after breakfast, lunch, and dinner daily and twice weekly or every 48 h. HbA1C was done at study entry and after 1 month. All women had frequent ultrasound assessments of fetal growth and measurement of liquor.

Patients were followed up, and given Iron, calcium, vitamin B12, and folic acid supplements.

Women in group 2 who did not reach the target blood glucose concentrations for 10 days were switched to the conventional insulin metformin group. Outcomes were fasting and 2-h postprandial blood glucose.

Statistical analysis

Data were analyzed with SPSS version 21. The normality of data was tested with a one-sample Kolmogorov-Smirnov test. Qualitative data were described using numbers and percentages. Association between categorical variables was tested using Chi-square and Fischer exact tests. Continuous variables were presented as mean ± standard deviation (SD) for parametric data. The two groups were compared with the Student t-test (parametric data) and Mann–Whitney test (non-parametric data) while paired groups were compared by paired t-test and Wilcoxon signed rank test. P value $<0.05$ was statistically significant.

## Results

The demographic data obstetric history and DM characteristics were comparable between groups. (Table 1)

There was no statistically significant difference between groups in fasting glucose levels at 3, 6, and 9 days. There was a highly significant difference in fasting glucose levels before treatment and after 9 days in both groups ($p<0.0001$). (Table 2)

There was a significant difference in glycemic

control of 2-hour post-prandial glucose. Glycemic control after 3 days in group 1 was in 29 cases and group 2 11 cases only. After 6 days the glycemic control of group 1 was in 30 cases (100%), and 17 cases only in group 2. Group 1 still controlled after 9 days, and group 2 increased to 21 cases about (70%). There was no significant difference between groups regarding the hypoglycemic attacks (Table 3)

In group 2, cases were subdivided according to education level and obesity. The results showed that the mid-educated cases had significantly elevated post-prandial blood glucose levels than the high-educated cases. Moreover, the severe obesity cases had significantly elevated post-prandial blood glucose levels than the moderate obesity cases. (Table 4)

## Discussion

Using carbohydrate-to-insulin ratios during pregnancy is challenging because insulin requirements change so often. In the first trimester, the body is more sensitive to insulin, and insulin requirements drop. During the second half of the pregnancy, insulin resistance causes an increase in the insulin requirement so weekly insulin adjustments are needed (10).

The addition of metformin benefits the patients in group 1 to achieve rapid control

These results are in agreement with the results of Feig et al. showed that adding metformin is associated with proper glycemic control in 76.1 % without increasing the dose of insulin compared with insulin alone (11). The same results were confirmed by another study comparing two groups of pregnant women with type 2 DM, one used insulin alone and the other was insulin with metformin (12).

Only 70% of the second group (21 cases) were controlled for their post-prandial blood glucose and it was a depressing result that was most properly due to low compliance of patients, lack of experience with food, diet control, and self-management, because most of these women were newly diagnosed as GDM the duration of diabetes, was between 12- 84 month.

To our knowledge, no study added metformin to insulin carbohydrate ratio in type 2 DM with pregnancy.

In our study, we add the metformin to insulin carbohydrate ratio by 10-15 gm carbohydrate needed without using sensitivity factor and in type 2 DM and GDM.

A study by Bongiovanni, et al. assessed carbohydrate-to-insulin ratio values in pregnant women with type 1 diabetes. Their result was that the ratio decreased on average from 9.6 to 5.4 at breakfast, from 10 to 8.4 at lunch, and from 12.5 to 6.1 at dinner (13).

In a study, Zagury et al. studied the changes in carbohydrate ratio during the day in diabetic pregnant women with type 1 DM and the result was a progressive reduction at every meal (mean of 8.2 g/IU for breakfast, 7.7 g/IU for lunch and 7 g/IU for dinner) (9).

Both studies tried to adjust of insulin dose during pregnancy and their result was 100% control. These studies are not in agreement with ours, because all of them are dealing with DM type 1, using different rout in the calculation of insulin carbohydrate ratio, and with no addition of metformin.

On the other hand, in carbohydrate counting regimen, weighing foods and initially recording food intake is an extra work that can be burdensome, and most people do not enjoy it. Blood glucose level testing before and after meals can also be difficult, but it is necessary to determine the appropriate dose of treatment (usually insulin) needed to restore normal glucose levels.

The Increasing flexibility in the types and timing of foods provided by carbohydrate counting can make weight management a challenge. Patients may be tempted to take more liberties with their eating. Given

the increased flexibility, this management approach provides in controlling blood glucose. This is an issue that needs to be raised with patients before they start using the carbohydrate calculation method (14).

In our study, we found that the level of education and orientation can affect the control of blood glucose by insulin carbohydrate ratio as patients with primary education only achieved control in 50% of them but in highly educated patients the control was in 92% of the cases. Also, we found that the degree of obesity can have effect, as patients with moderate degree of obesity showed control in 94% of cases, but in those with severe degree of obesity the control was only in 33% and they needed to increase the insulin dose. There were only 3 cases of hypoglycemic bouts during our journey and they were due to missed meals

## Conclusions

The basal bolus regimen is better than the insulin carbohydrate ratio in patients with diabetes who are not educated well with carbohydrate counting. Also, metformin has a beneficial effect on glycemic control without the need to increase the insulin dose more than the calculated dose according to the patient's weight and without increasing the risk of hypoglycemia. It is necessary to teach the patients and their families about carbohydrate counting in their diet.

## Financial support and sponsorship

Nil.

## Conflict of Interest

Nil.

## References

1. Hegazi R, El-Gamal M, Abdel-Hady N, Hamdy O. Epidemiology of and risk factors for type 2 diabetes in Egypt. Ann Glob Health 2015;81(6):814-820.
2. Alzeidan R, Fayed A, Hersi AS, Elmorshedy H. Performance of neck circumference to predict obesity and metabolic syndrome among adult Saudis: a cross-sectional study. BMC Obes 2019; 6:1-8.
3. Beyuo T, Obed SA, Adjepong-Yamoah KK, Bugyei KA, Oppong SA, Marfoh K. Metformin versus insulin in the management of pre-gestational diabetes mellitus in pregnancy and gestational diabetes mellitus at the Korle Bu Teaching Hospital: a randomized clinical trial. PLoS One 2015; 10(5): e0125712.
4. Enkhtuvshin B, Nagashima S, Saito N, Wakabayashi T, Ando A, Takahashi M, et al. Successful pregnancy outcomes in a patient with type A insulin resistance syndrome. Diabet Med 2015;32(6): e16-9.
5. Ibrahim MI, Hamdy A, Shafik A, Taha S, Anwar M, Faris M. The role of adding metformin in insulin-resistant diabetic pregnant women: a randomized controlled trial. Arch Gynecol Obstet 2014; 289(5):959-965.
6. Lachin JM, Bebu I, Gao X, Nathan DM, Zinman B, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Association of estimated time-in-range capillary glucose levels versus HbA1c with progression of microvascular complications in the Diabetes Control and Complications Trial. Diabetes Care 2022;45(10):2445-2448.
7. Krzymien J, Ladyzynski P. Insulin in type 1 and type 2 diabetes—should the dose of insulin before a meal be based on glycemia or meal content? Nutrients 2019;11(3):607.
8. Webber J, Charlton M, Johns N. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period (NG3). Br J Diabetes 2015;15(3):107-111.

9. Zagury RL, Rodacki M, Mello de Oliveira L, Saunders C, de Carvalho Padilha P, Zajdenverg L. Carbohydrate counting during pregnancy in women with type 1 diabetes: are there predictable changes that we should know? Ann Nutr Metab 2017;70(2):140-146.

10. Rasmussen L, Poulsen CW, Kampmann U, Smedegaard SB, Ovesen PG, Fuglsang J. Diet and healthy lifestyle in the management of gestational diabetes mellitus. Nutrients 2020;12(10):3050.

11. Feig DS, Donovan LE, Zinman B, Sanchez JJ, Asztalos E, Ryan EA, et al. Metformin in women with type 2 diabetes in pregnancy (MiTy): a multicentre, international, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2020;8(10):834-844.

12. Feig DS, Murphy K, Asztalos E, Tomlinson G, Sanchez J, Zinman B, Ohlsson A, Ryan EA, Fantus IG, Armson AB, Lipscombe LL. Metformin in women with type 2 diabetes in pregnancy (MiTy): a multi-center randomized controlled trial. BMC Pregnancy Childbirth 2016; 16:1-8.

13. Bongiovanni M, Fresa R, Visalli N, Bitterman O, Suraci C, Napoli A. A study of the carbohydrate-to-insulin ratio in pregnant women with type 1 diabetes on pump treatment. Diabetes Technol Ther 2016;18(6):360-365.

14. Kulkarni KD. Carbohydrate counting: a practical meal-planning option for people with diabetes. Clinical Diabetes 2005;23(3):120-123.

**Table (1): Demographic data, obstetric history and DM characters of the studied groups**

| Variables | Group1 (n=30) | Group2 (n=30) | $\chi^2$ | P value |
|---|---|---|---|---|
| **Age/years** (Mean ± SD) | 30.73±4.60 | 32.73±4.27 | t=1.91 | 0.06 |
| **Gestational age/ weeks** (Mean ± SD) | 29.03±2.83 | 28.86±2.27 | t=0.251 | 0.802 |
| **Gravidity** Median (Min-Max) | 3.00 (1.00- 6.00) | 3.00 (1.00- 7.00) | Z=1.363 | 0.173 |
| **Parity** Median (Min-Max) | 2.00 (0.00- 4.00) | 2.00 (0.00- 5.00) | Z=1.826 | 0.068 |
| **BMI** (Mean ± SD) | 34.44±3.7 | 34.38±4.84 | 0.051 | 0.960 |
| Non-obese No (%) | 2 (6.7 %) | 1 (3.3 %) | 0.351 | 0.554 |
| Obese No (%) | 28 (93.3 %) | 29 (96.7 %) | | |
| **Education** No (%) | | | | |
| Primary | 9 (30.0 %) | 14 (46.7%) | 1.76 | 0.184 |
| Higher | 21 (70.0 %) | 16 (53.3 %) | | |
| **Type of DM** No (%) | | | | |
| Gestational DM | 16 (53.3 %) | 10 (33.3 %) | 2.443 | 0.118 |
| Type 2 DM | 14 (46.7 %) | 20 (66.7 %) | | |
| **Duration of DM (month)** Median (Min-Max) | 36.00 (12- 60) | 36.00 (12- 84) | 0.143 | 0.886 |
| **HbA1c** (Mean ± SD) | 6.48±0.70 | 6.45±0.67 | 0.129 | 0.898 |

Data are presented as mean ± SD, frequency (%), or median (IQR). BMI: Body mass index, DM: diabetes mellites, HbA1c: Hemoglobin A1C. t: student t-test, $\chi 2$: chi square test.

**Table (2): Difference between groups regarding fasting blood glucose**

| Variables | Group1 (n=30) | Group2 (n=30) | t-test | P value |
|---|---|---|---|---|
| FBG day3 | 28 (93.3 %) | 27 (90.0%) | 0.001 | 0.972 |
| FBS day6 | 30 (100.0%) | 30 (100.0%) | 0 | 1 |
| FBS day9 | 30 (100.0%) | 30 (100.0%) | 0 | 1 |
| Paired t-test<br>$P_{before-day9}$ | t=7.27<br>P<0.001** | t=10.4<br>P<0.001** | - | - |

Data are presented as frequency (%). FBG: fasting blood glucose. ** P<0.001is statistically highly significant.

**Table (3): Difference between two groups in post-prandial blood glucose levels and hypoglycemic attacks**

| Variables | Group1 (n=30) | Group2 (n=30) | t-test | P value |
|---|---|---|---|---|
| 2h PP day3 | 28 (93.33%) | 11 (36.7%) | 5.624 | <0.001** |
| 2h PP day6 | 29 (96.6%) | 17 (56.7%) | 4.087 | <0.001** |
| 2h PP day9 | 30 (100.0%) | 21 (70.0%) | 10.59 | 0.002* |
| Paired t-test<br>$P_{before-day9}$ | t=9.59<br>P=<0.001** | t=8.34<br>P=<0.001** | - | - |
| **Hypoglycemia** | | | **$\chi^2$** | **p-value** |
| Yes | 1 (3.3%) | 2 (6.7%) | 2.06 | 0.561 |
| No | 29 (96.7%) | 28 (93.3%) | | |

Data are presented as frequency (%). 2h PP: 2-hour post-prandial glucose. $\chi 2$: chi square test. * Significant p <0.05, **highly significant p <0.001.

**Table (4): Difference between post-prandial blood glucose control in (Group 2) according to the level of education and obesity**

| Variables | Mid educated (n=16) | High educated (n=14) | t-test | P value |
|---|---|---|---|---|
| 2h PP day 9 | 126.87±12.93 | 118±7.1 | 2.2 | 0.030* |
| Control | 8 (50%) | 13 (92%) | 2.79 | 0.009* |
| | **Moderate obesity (n=17)** | **Severe obesity (n=12)** | | |
| 2h PP day 9 | 117.70±5.1 | 130±13.88 | -3.50 | 0.002* |
| Control | 16 (94.11%) | 4 (33.33%) | 4.4 | <0.001** |

Data are presented as mean ± SD. 2h PP: 2-hour post-prandial glucose. frequency (%). * Significant p <0.05, **highly significant p <0.001.