Comparative study between the use of long-acting insulin versus multiple dose regimen in control of Gestational Diabetes Mellitus: a randomized controlled trial

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Abstract

Objective : The aim of our work is the comparison between long-acting insulin and multiple dose regimens in control of gestational diabetes.

Patients and Methods : This prospective randomized controlled trial included 128 Pregnant women with gestational DM who required insulin treatment after failure of diet control in Ain Shams maternity hospital from September 2019 to December 2020. Patients were randomized into two groups; Group A: received long-acting insulin analogs as a single dose once daily at bedtime, while Group B received intermediate-acting insulin (NPH) besides short-acting insulin (lispro) in divided doses.

Results: Group B showed a shorter statistically significant time to control blood sugar than Group A (10+1 vs 14+2 days, respectively). ▪ There was no statistically significant difference between groups regarding Maternal hypoglycemia ($P<0.05$). Group A had a non-significant higher rate of obstetric complications as PIH, Preterm delivery, Shoulder dystocia, and CS delivery rate and lower Polyhydramnios rate than group B. Group (A) had a non-significant higher rate of fetal/Neonatal complications such as fetal macrosomia, congenital anomalies, IUFD, NICU admission, and Neonatal death than group (B) by Per protocol (PP) analysis ($P<0.05$).

Conclusion: We can conclude that there is no clinical difference between using a multiple-dose regimen and using long-acting insulin analogs to control gestational diabetes regarding maternal and fetal outcomes. However, a multiple-dose regimen needs a shorter time for blood glucose control than long-acting insulin. It is to be noted that long-acting insulin is more expensive.

Key Words: long-acting insulin, multiple-dose regimen, Gestational Diabetes Mellitus.

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INTRODUCTION

Gestational Diabetes Mellitus (GDM) is defined as any degree of glucose intolerance to be first diagnosed during pregnancy. (1) Risk factors for GDM are previous GDM, increase maternal BMI, family history of DM, advanced maternal age, previous history of macrosomia, recurrent abortions, and congenital fetal malformations. (2)

GDM can lead to severe complications in pregnancy, including gestational hypertension, preeclampsia, and eclampsia. It can also cause preterm labor, macrosomia, shoulder dystocia, and an increased rate of Caesarean deliveries. (3) Adopting the criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) has increased the prevalence of GDM by 2-3 folds. (4-5) The IADPSG recommends universal screening for GDM and requires one single glucose value above the cut-off value during the oral glucose tolerance test (OGTT) for diagnosis (4).

There have been several changes in the management of diabetes during pregnancy, including the use of insulin analogs. Antibody-free human insulin is to be considered by most practitioners to be the gold standard for use in pregnancy because it does not cross the placenta and is highly effective (6).

Insulin analogs offer some advantages that may reduce "resistance" to using insulin during pregnancy. Currently, available insulin analogs include rapid-acting mealtime insulins: lispro and aspart, intermediate-acting insulin: Neutral Protamine Hagedorn (NPH), and long-acting basal insulin: glargine(longer-lasting insulin analog; the basal level of insulin will be maintained up to 24 hours) all are considered safe in pregnancy as are included in Food and Drug Administration(FDA) (7).

Commonly prescribed regimens consisting of combined short-acting (Regular) and intermediate-acting insulins have been used to mimic endogenous insulin response. However, these regimens are sometimes incapable of adequately simulating the basal or meal-stimulated components of normal insulin secretion. (8).

AIM:

The aim of our work is the comparison between long-acting insulin and multiple dose regimens in control of gestational diabetes.

Patients and Methods:

This study is a Prospective randomized controlled trial Study conducted in Ain Shams University - Maternity Hospital from September 2019 to December 2020. The study had been approved by the ethical and research committee of the Obstetrics and Gynecology Department, Ain Shams University, and the Faculty of Medicine Research Ethics Committee with number M S 323/ 2019. The study was registered in the clinicaltrial.gov (NCT04674332)

We included pregnant women with gestational diabetes from the Ain Shams Maternity Hospital antenatal clinic who required insulin therapy after diet and medical therapy failed.

Women with pregestational DM or patients with complicated diabetes such as neuropathy, nephropathy, or retinopathy were excluded from the study. Other exclusion criteria included patients with endocrine abnormalities or medical diseases (hypertension, cardiac problems, hepatic diseases, renal disorders, and systemic lupus). Patients with bad obstetric history (intrauterine growth retardation, previous intrauterine fetal death, threatened preterm labor) were also excluded from the study.

◊ **Method of randomization:** A computer-developed randomization sheet contains 148 patients randomly assigned into two groups (group A & group B), each group of 74 patients. The randomization had been concealed using the sequentially

numbered opaque sealed envelope (SNOSE). 148 opaque easy-opening envelopes had been numbered serially; in each envelope, the corresponding letter in the randomization sheet had been put. Participant women had been allocated to each group according to the letter inside the envelope.

- ***Group A:*** patients receiving long-acting insulin analogs as a single dose (insulin glargine), one daily injection of long-acting insulin at an initial dose of (0.44 IU/kg) once daily at bedtime (11, 12).
- ***Group B:*** patients receiving intermediate-acting insulin (NPH) and short-acting insulin (lispro) in divided doses. (13).

The study purpose and methods had been explained to all enrolled women, and written informed consent had been obtained from all participants before enrolment.

Our hospital protocol for initial insulin requirements is based on a woman's body weight and gestational age; the total daily insulin requirement in the second trimester is 0.8 units/kg/day (9-10, 14).

Our patients were admitted to the hospital for insulin treatment until they reached normal glycemic values and were discharged. Follow-up after discharge was done by regular visits twice monthly in high-risk clinics and weekly from the 36th gestational week for patients who had the facility for that or by regular phone calls or internet messaging for patients who didn't have the facility to attend the regular visits.

> **Primary outcome:** The time needed to reach target levels of plasma glucose; fasting ≤ (90-95 mg/dl) and two h post-prandial ≤ (120 mg/dl). The duration was determined after being controlled for three consecutive days. (9):

◊ **Secondary outcomes:** Maternal hypoglycemia, PIH, polyhydramnios, Shoulder dystocia PTL, CS, GA, Birth Weight, macrosomia, Congenital anomalies, IUFD, neonatal death, NICU admission

◊ **Sample size justification**

The required sample size has been calculated using the G*power software (Universitat Dusseldorf, Germany). Currently, there is no adequate information regarding the difference between both methods for glycemic control on the outcome measures; therefore, the present exploratory study would target clinically relevant effect size. So, it is estimated that a sample size of 148 patients, after calculating a 15% anticipated drop-out ratio, equally randomized into either study group (74 per group) would achieve a power of 80% (type II error, 0.2) to detect a statistically significant difference between the two groups as regards the quantitative outcome measures (e.g.; FBS, PPBS, HbA1C or birth weight) for a medium effect size corresponding to a Cohen d coefficient of 0.5 using a two-sided unpaired t-test and the targeted test confidence set at a level of 95% (type I error, 0.05). The effect size ***(d)*** is calculated as follows): d = (m1 – m2) sd, where m1 and m2 are the means of group I and group II, respectively, and sd is the common standard deviation (17).

◊ **Statistical Methods**

Data were analyzed using IBM© SPSS© Statistics version 26 (IBM© Corp., Armonk, NY). Categorical variables are presented as numbers and percentages, and intergroup differences are compared using Fisher's exact test. Ordinal data are compared using linear by-linear association. Numerical data are presented as mean, standard deviation, and between-group differences are compared using the independent-samples t-test. The time-to-event analysis uses the Kaplan-Meier (KM) method by comparing KM curves with the log-rank test. Two-sided P- values <0.05 are considered statistically significant.

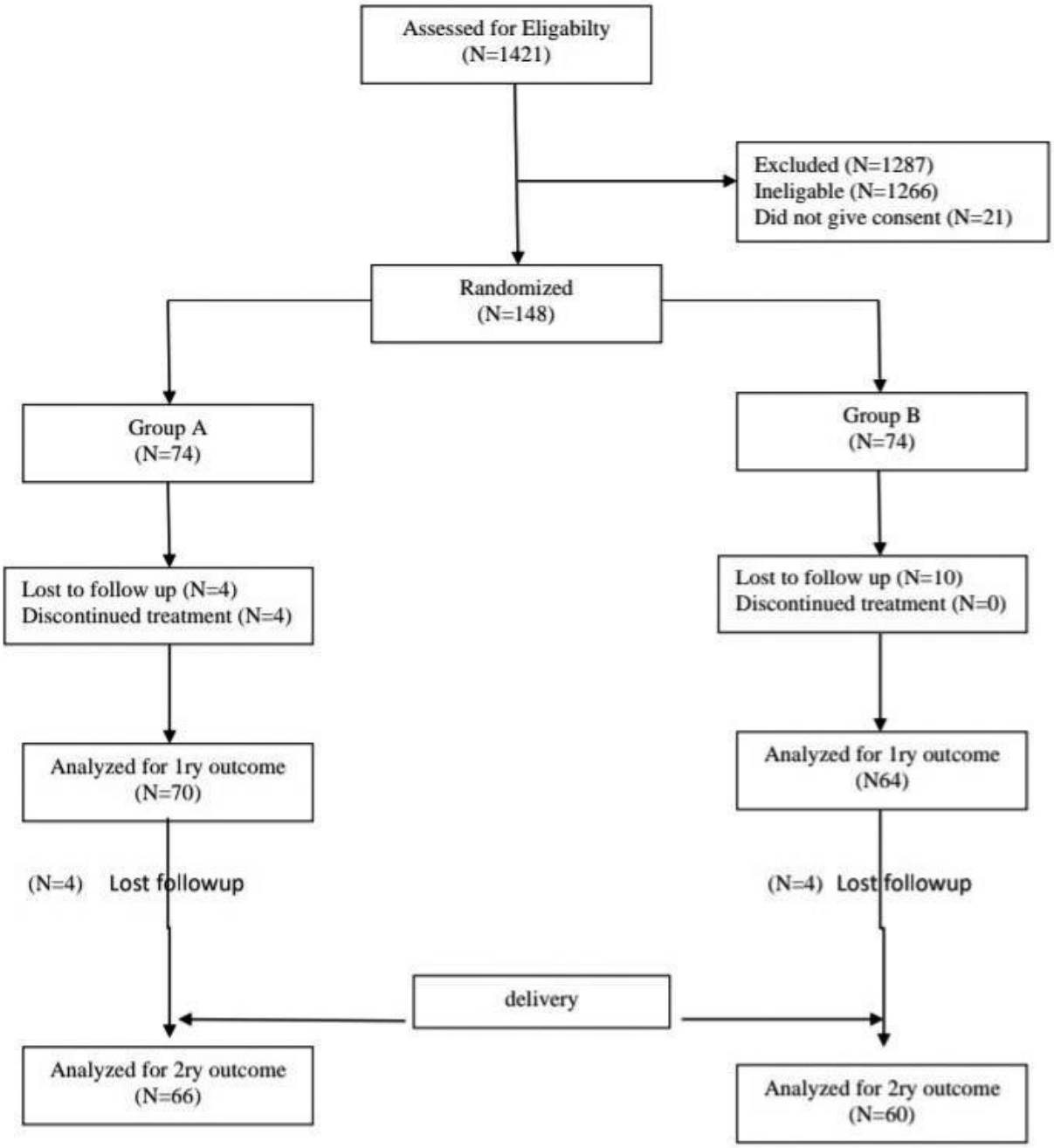

Figure 1. CONSORT flow chart showing patient recruitment and follow up.

Results

As regards demographic characteristics of patients in both study groups, mean age was (26.3±5.2 SD), BMI (29.1±2.1 SD), and GA at recruitment (25.3±1.5 SD). No statistically significant difference exists between the two groups regarding age (P=0.172), BMI (P=0.172), or GA at recruitment (P=0.321). There is no statistically significant difference between the two groups regarding parity and Previous abortions, **with P values of** 0.603 0.941, **respectively** (Data not tabulated).

The Means of Pre-treatment FBS, 2h-PPBS, and HbA1c are near in both groups with no statistically significant difference. (Table 2)

As shown in Table 3, the means of Pre-treatment FBS, 2h-PPBS, and HbA1c in both groups show no statistically significant differences. In contrast, group B shows a lower statistically significant time to control blood sugar than group A (10+1 vs 15+2 days, respectively). Fig 1. Show **Kaplan-Meier curves that show a statistically significant difference between both KM curves (log-rank test chi-squared = 104.251, df = 1, P-value < 0.001).**

Regarding secondary outcomes, there is no statistically significant difference between the studied groups regarding the **Incidence and frequency of maternal hypoglycemia in both study groups, with P values of 0.518 and 0.206, respectively** (Data not tabulated). Table 4 and Figure 2 show the obstetric outcomes by Per protocol (PP) analysis. Group A has a non-significant higher rate of obstetric complications such as PIH, Preterm delivery, Shoulder dystocia, and CS delivery rate and a lower Polyhydramnios rate than group B.

Group (A) has a higher non-significant mean of Birth weight than group (B) 3517+351 gm vs. 3427+305 gm with a P value of 0.128, and both groups have the same mean of GA at delivery 37.2+1.1 vs. 37.2+1.0 with a P value 0.782 (Data not tabulated). Table 6 shows that group (A) has higher nonsignificant Fetal/Neonatal outcomes, Fetal macrosomia, Congenital anomalies, IUFD, NICU admission, and Neonatal death than group (B) by Per protocol (PP) analysis.

Table 1. Measures of glycemic control before treatment in both study groups

	Group A		Group B						
Variable	Mean	SD	Mean	SD	Mean	SE	Lower 95% CI	Upper 95% CI	P-value†
Pre-treatment FBS (mg/dl)	156.5	7.8	158.8	12.0	-2.3	1.8	-5.8	1.2	0.192
Pre-treatment 2h-PPBS (mg/dl)	175.0	13.7	178.6	14.9	-3.5	2.5	-8.4	1.3	0.154
Pre-treatment HbA1c (%)	6.1	0.5	6.2	0.5	-0.1	0.1	-0.3	0.0	0.13

SD = standard deviation, SE = standard error, 95% CI = 95% confidence interval.
†. Independent-samples t-test.

Table 2. Measures of glycemic control after treatment in both study groups

	Group A		Group B						
Variable	Mean	SD	Mean	SD	Mean	SE	Lower 95% CI	Upper 95% CI	P-value†
Post-treatment FBS (mg/dl)	84.1	10.3	81.1	8.5	3.1	1.6	-0.2	6.3	0.064
Post-treatment 2h-PPBS (mg/dl)	110.3	12.4	114.3	11.1	-4.0	2.0	-8.0	0.1	0.053
Post-treatment HbA1c (%)	5.3	0.4	5.4	0.5	-0.1	0.1	-0.2	0.1	0.319
Time to control blood sugar (days)	15	2	10	1	4.7	0.3	4.1	5.4	<0.001

SD = standard deviation, SE = standard error, 95% CI = 95% confidence interval.
†. Independent-samples t-test.

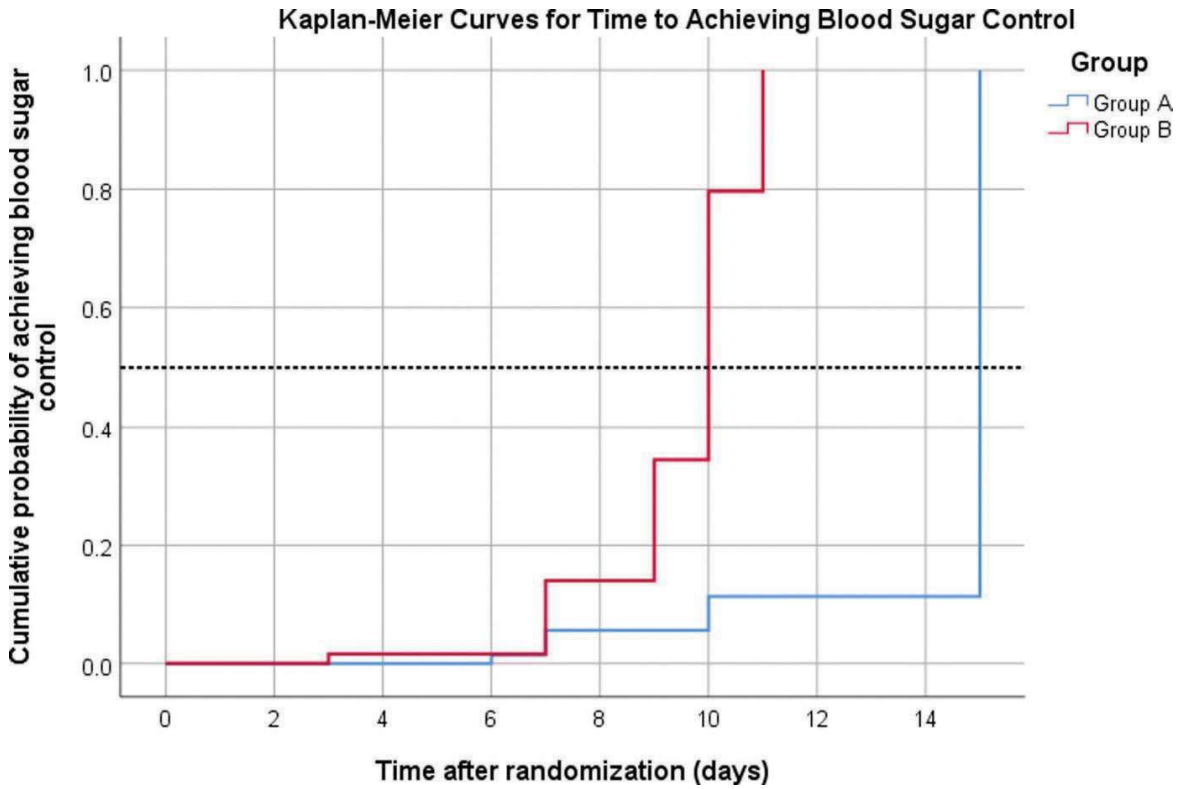

Figure 1. shows Kaplan-Meier curves for time to achieve blood sugar control. Median time to achieve control of blood sugar = 15 days in Group A versus ten days in Group B. Difference between both KM curves is statistically significant (log-rank test chi-squared = 104.251, df = 1, P-value < 0.001).

Table 3. Obstetric outcomes in both study groups: Per protocol (PP) analysis

	Group A		Group B		
Variable	n	%	n	%	P-value†
PIH	3	4.5%	2	3.3%	1.000
Polyhydramnios	5	7.6%	7	11.7%	0.548
Preterm delivery	15	22.7%	10	16.7%	0.503
Shoulder dystocia	5	7.6%	2	3.3%	0.503
CS delivery	32	48.5%	27	45%	0.724

n = number. †. Fisher's exact test

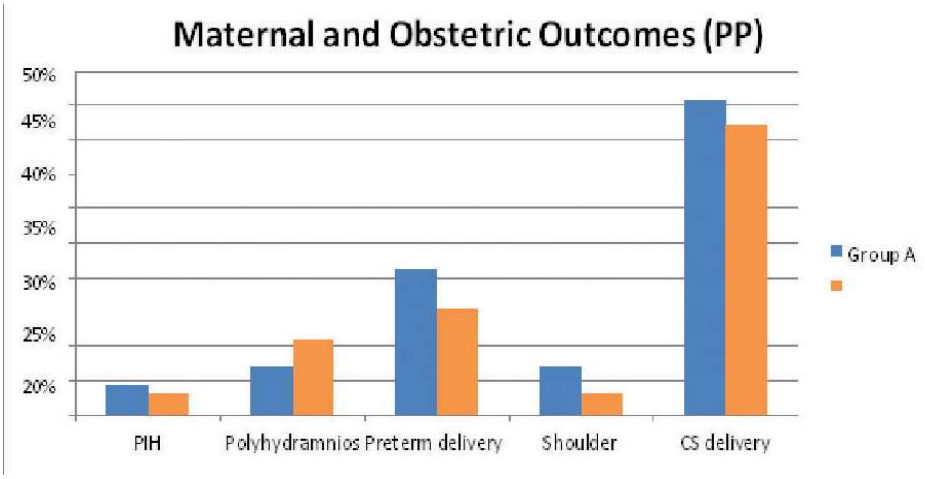

Figure 2 Maternal and obstetric outcomes in both study groups by per protocol (PP) analysis.

Table 4. Risk analysis for main maternal/obstetric outcomes (PP)

	Group A		Group B			
Maternal hypoglycemia	0.61		0.807	0.420	25.4	8.2 (Harm) to 7.5 (Benefit)
PIH	1.36	0.18 to 2.04	0.346	0.729	82.5	12.4 (Harm) to 17.8 (Benefit)
Polyhydramnios	0.65	0.24 to 1.94	0.774	0.439	24.4	6.3 (Harm) to 7.0 (Benefit)
Preterm delivery	1.36	0.66 to 2.80	0.845	0.398	16.5	5.0 (Harm) to 12.8 (Benefit
Shoulder dystocia	2.27	0.46 to 11.28	1.004	0.315	23.6	8.2 (Harm) to 26.8 (Benefit)
CS delivery	1.08	0.741 to 1.5666	0.391	0.696	28.7	4.8 (Harm) to 7.2 (Benefit)

95% CI = 95% confidence interval

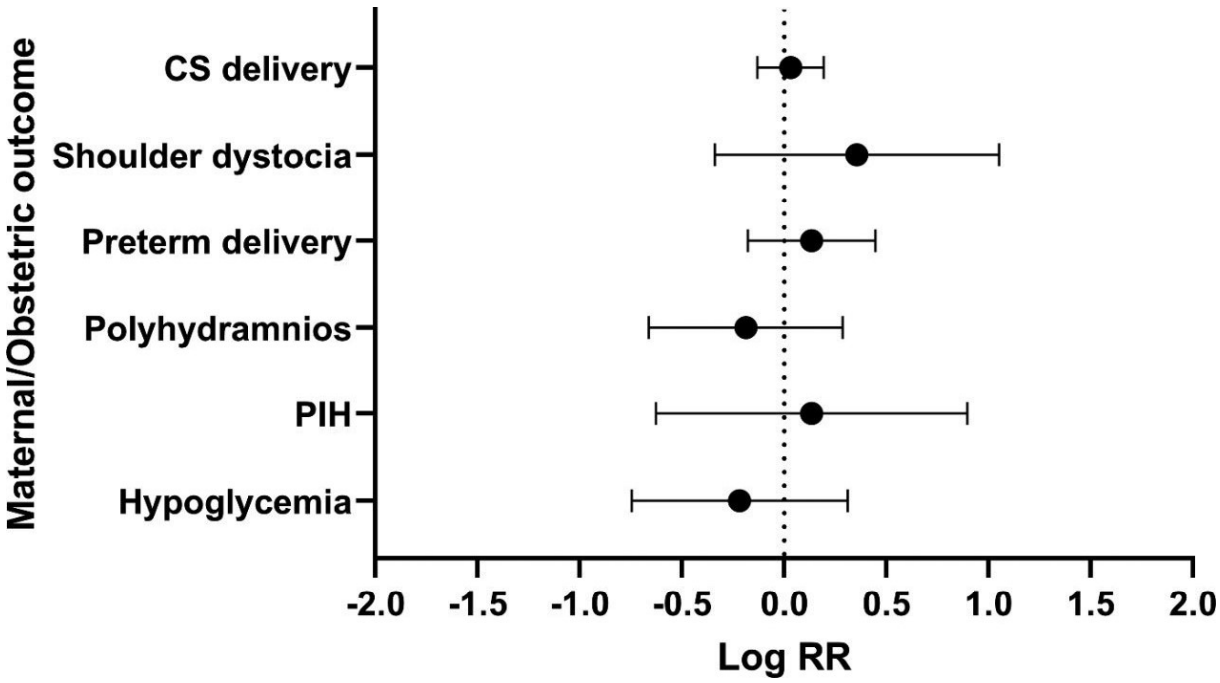

Figure 3. Relative risk (RR, rounded marker) with 95% confidence limits (95% CI, error bars) for maternal and obstetric outcomes in both study groups by per protocol (PP) analysis. There is no statistically significant difference between long-acting or intermediate-acting insulin regarding maternal or obstetric outcomes.

Table 5. Fetal/Neonatal outcomes in both study groups: Per protocol (PP) analysis

	Group A		Group B		
Variable	n	%	n	%	P- value†
Fetal macrosomia	8	12.1%	2	3.3%	0.099
Congenital anomalies	2	3.0%	1	1.7%	1.000
IUFD	2	3.0%	2	3.3%	1.000
NICU admission	7	10.6%	5	8.3%	0.766
Neonatal death	3	4.5%	2	3.3%	1.000

n = number. †. Fisher's exact test.

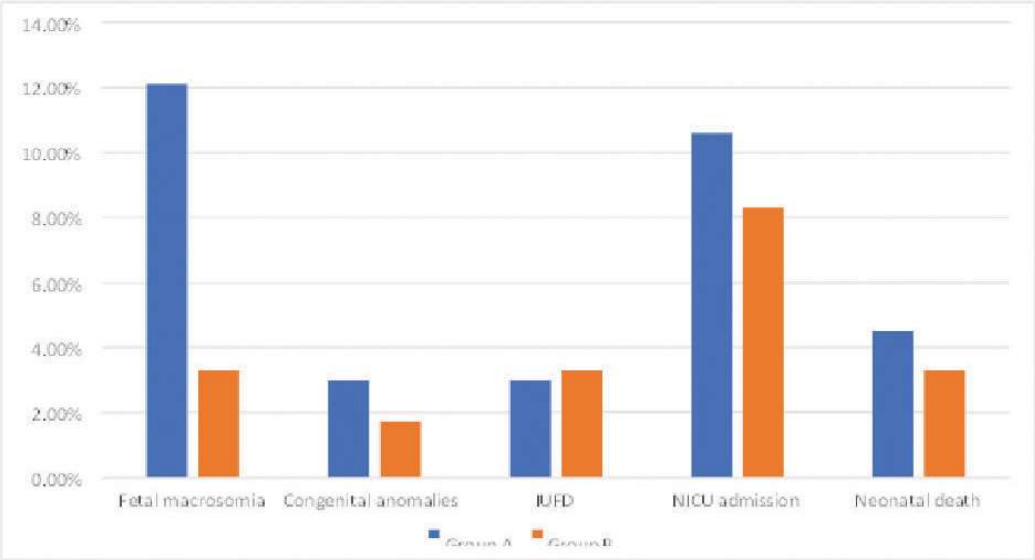

Figure 4. Fetal/Neonatal outcomes in both study groups: Per protocol (PP) analysis.

Table 6. Risk analysis for main fetal/neonatal outcomes: Per protocol (PP) analysis

	Group A					
Feta macrosomia	3.64	0.80 to 16.45	1.676	0.094	11.4	5.5 (Harm) to 186.2 (Benefit)
Congenital anomalies	3.64	0.80 to 16.45	1.676	0.094	11.4	5.5 (Harm) to 186.2 (Benefit)
IUFD	3.64	0.80 to 16.45	1.676	0.094	11.4	5.5 (Harm) to 186.2 (Benefit)
Low Apgar 5	3.64	0.80 to 16.45	1.676	0.094	11.4	5.5 (Harm) to 186.2 (Benefit)
Low Apgar 10	1.27	0.80 to 16.45	0.432	0.665	44.0	8.0 (Harm) to 12.5 (Benefit)
NICU admission	1.36	0.43 to 3.80	0.346	0.729	82.5	12.4 (Harm) to 17.8 (Benefit)
Neonatal death	3.64	0.80 to 16.45	1.676	0.094	11.4	5.5 (Harm) to 186.2 (Benefit)

95% CI = 95% confidence interval, NNT = number needed to treat.

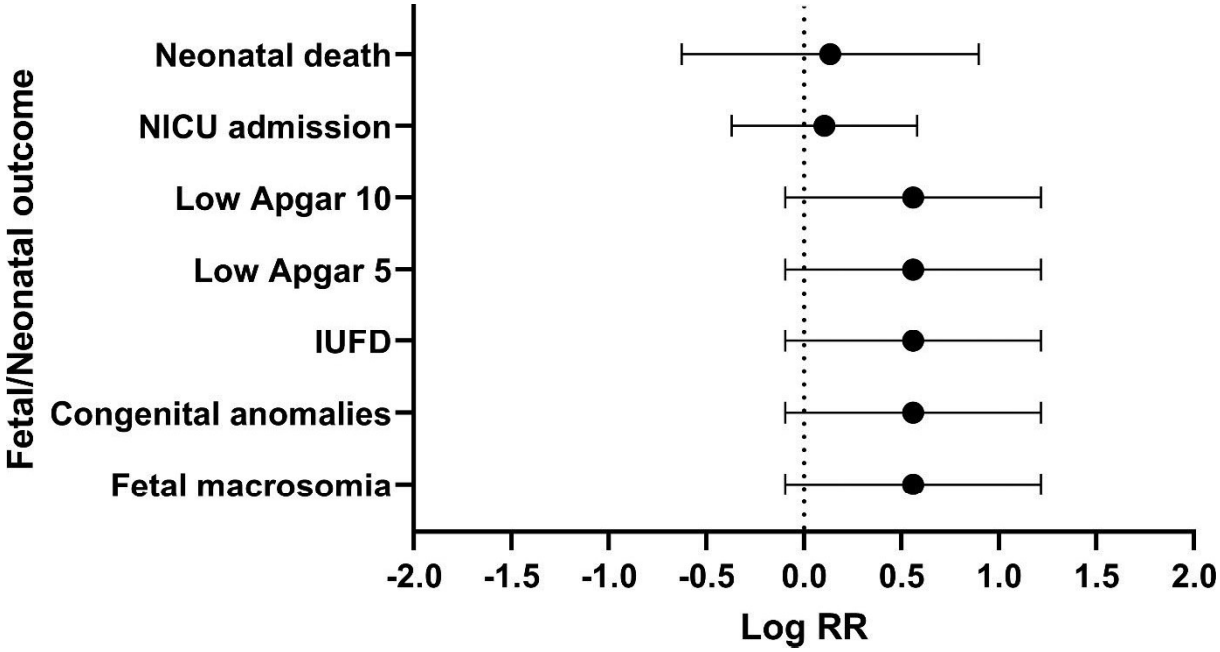

Figure 5. Relative risk (RR, rounded marker) with 95% confidence limits (95% CI, error bars) for fetal and neonatal outcomes in both study groups by per protocol (PP) analysis. There is no statistically significant difference between long-acting or intermediate-acting insulin regarding maternal or obstetric outcomes.

Discussion

Pregnancy is a potentially glucose-intolerant condition. Insulin sensitivity decreases as the pregnancy advances. Some women develop GDM due to inadequate insulin secretion, particularly in obese women with pre-existing insulin resistance (18-20).

The standard therapy for gestational diabetes is insulin. On the other hand, Insulin has several disadvantages, including daily injections, the risk of hypoglycemia, and maternal weight gain (21-22). Different types of insulin have different time for control of blood glucose levels due to different pharmacological composition, and that cause difference in the total time needed for reaching normal glycemic levels and difference in the number of hypoglycemic attacks occurring to the patients during the time to reach normal glucose levels. (23-25) GDM causes higher risks for polyhydramnios and excessive fetal growth, increasing the risk of shoulder dystocia. All these factors cause higher rates of caesarian section in patients with gestational diabetes (9).

Our Results and their interpretation

Our work aimed to compare the long-acting insulin injected once daily at bedtime and multiple-dose regimens of NPH and short-acting insulin to control gestational diabetes.

There was no statistically significant regarding patients' demographic characteristics in both study groups (age, BMI, and GA at recruitment). There was no statistically significant difference between studied groups regarding Parity or previous abortions.

Regarding glycemic control, there was no statistically significant difference between groups regarding pre-medication glucose and HbA1C level. Regarding post-treatment measures:

In Group A, long-acting insulin had a better effect on mean 2h-PPBS than Group B but

didn't reach statistical significance. While in Group B: patients showed better control in mean FBS than in Group A (not yet statistically significant). Group B showed a shorter time to achieve blood sugar control in the studied patients.

Our patients had a mean HbA1c of 6.53 +/− 1.05%; we observed an improvement in metabolic control throughout the gestation, regardless of the type of insulin treatment. Our data confirm other reports (26). Also, no significant difference between both groups regarding HbA1c post-treatment. These results declared that a multiple-dose regimen better controls GDM than long regimens.

Comparison of our results to similar studies

The study of Pöyhönen-Alho et al., 2002, compared the effect of short-acting insulin and long-acting insulin on perinatal outcomes in insulin-requiring gestational diabetes mellitus. Similar to our results, they concluded that GDM is better to be treated with short-acting insulin and using long-acting insulin doesn't differ in controlling GDM (12).

In another study that agreed with our results, Lv et al., 2013, examined the potential differences between multiple daily injections (MDI) regimens based on new long-acting insulin analogs (glargine or detemir) and continuous subcutaneous insulin infusion (CSII) by insulin aspart. They included 119 patients; 48 males, 71 females) with poorly controlled type 2 diabetes of a duration exceeding five years were randomly assigned into three groups: Group A treated with CSII using insulin aspart, Group B treated with glargine-based MDI, and Group C treated with detemir-based MDI. Good glycemic control was achieved by patients in Group A in a relatively shorter duration (4 days) than patients in Groups B and C (7 days). (27) This study correlates with our results as it declares the good control of diabetes with long-acting insulin analogs yet over a longer duration to achieve control.

Similar to our results, A study by López-Tinoco et al., 2019, compared the effect of different insulin therapies on obstetric-fetal Outcomes. They evaluated the effectiveness of the different insulin therapies on obstetrics-fetal outcomes in women with pregestational diabetes mellitus. They enrolled 147 pregnant women with pre-existing type 1 or 2 diabetes mellitus. Clinical and biochemical parameters were analyzed for obstetric and fetal outcomes. A percent of 14.2% of the patients received treatment with Neutral Protamine Hagedorn insulin and short-acting insulin analogs; 19% with premixed human insulin; 40.1% with insulin glargine and lispro, 6.2% with detemir and aspart and 20% with continuous subcutaneous insulin infusion. All five types of treatment achieved a reduction of the mean HbA1c during pregnancy (p=0.01). They reported that no significant difference was observed between all regimens regarding episodes of hypoglycemia or obstetric outcomes. (28)

Strength and weakness points in our study:

Our study is a prospective one. Our patients were strictly followed up during hospitalization. Most of the patients were followed up till delivery through regular follow-up visits or other contacting methods as taking more than a phone number for the patient and internet contacting this helped us to collect more data about the obstetric and fetal outcomes of our patients.

We believe that the weak point in our study is that it didn't prescribe other lines of treatment for gestational diabetes as oral hypoglycemic drugs for the patients. This is to avoid undesirable side effects of oral hypoglycemic drugs. also to avoid a lack of patient compliance to oral treatment that will surely affect the accuracy of the results. So,

we preferred to use insulin as the patient will have precise and accurate follow-up and good compliance during hospitalization. Also, We didn't include patients with pregestational diabetes because that would increase the heterogenicity of the sample of patients causing inaccurate results.

Implication for the clinical practice

We can introduce long-acting insulin as a protocol for treating gestational diabetes mellitus as long as the patient has no obstetric complication or emergency or fetal risk, is aware of the number of injections, and can afford the price of long-acting insulin.

Recommendations for future research

After recognizing the safety and efficacy of insulin analogs, we recommend treating them with long-acting analogs, especially if there is a risk of nocturnal hypoglycemia. Also, further studies are required to demonstrate the benefits over the rest of insulin therapies,

Conclusion

e can conclude that there is no clinical difference between using a multiple-dose regimen and using long-acting insulin analogs to control gestational diabetes regarding maternal and fetal outcomes. However, a multiple-dose regimen needs a shorter time for blood glucose control than long-acting insulin. It is to be noted that long-acting insulin is more expensive.

Ethics approval

Study approved by Ethical Committee

Consent for publication

Nonapplicable

Availability and data material

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

Competing interests

The author reports there are no competing interests to declare

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