COMPARISON OF METFORMIN AND INSULIN IN THE TREATMENT OF GESTATIONAL DIABETES MELLITUS: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: For the past few decades, Insulin has been the first line of treatment for gestational diabetes mellitus. Even though Metformin is being increasingly used for the same, however sufficient data on its efficacy for glycaemic control, specially in high-risk ethnic groups is still lacking. Hence an unequal dichotomous opinion is observed in clinical practice.

Objective: Our study aimed to compare glycaemic control achieved by insulin and metformin respectively, in women with gestational diabetes mellitus that were not controlled with 2 weeks of lifestyle changes and medical nutrition therapy.

Materials and Methods: This study was an open labelled, randomised control trial carried out at a tertiary care centre in India. Women aged between 18 to 45 years, presenting within 24 to 28 weeks of gestational age, diagnosed as GDM were randomised into two groups to receive either insulin or metformin. The glycaemic control of the two groups were compared. This Study was conducted from September 2019 to June 2021 at Department of OBSTETRICS AND GYNAECOLOGY, PRADYUMNA BAL MEMORIAL HOSPITAL, KIMS, BBSR.

Result: Between september 2019 and june 2021, 142 participants were recruited and 120 were randomised with 60 each in the insulin and metformin groups.Venous blood was used collected for laboratory blood glucose profile analysis. Analysis of Fasting Blood Plasma Glucose (FPG) and two-hour postprandial glucose (2HPG) was done. Glycemic profile measurement included glycosylated hemoglobin (HbA1c) levels at enrollment and at 36-37weeks of period of gestation as well. Distribution of mean Capillary glucose level af overnight last 2 wk bf delivery with Group was not statistically significant (p=0.7826). .Distribution of mean 2-Hr capillary glucose last 2 wk before delivery with Group was not statistically significant (p=0.1095).

Conclusion: The major problem of repeated injections of insulin could be solved with metformin, our study concluded that glycemic control in GDM can be achieved by using metformin orally as an alternative to insulin.

Keywords: gestational diabetes, insulin, metformin, OGTT and hypoglycemia.

INTRODUCTION

Gestational diabetes mellitus (GDM) is currently defined as a condition in "women who have carbohydrate intolerance, the onset or recognition of which takes place during pregnancy" [1].GDM currently affects 3-25% of pregnancies worldwide constituting a significant global healthcare burden[2].

40–60% of GDM cases have chance of developing diabetes mellitus over the 5–10 years after pregnancy[3].

Recent studies suggest that the incidence of GDM has increased in the past decade and that rates may be higher in specific ethnic or racial subgroups. The clinical effects of GDM can range from asymptomatic to severe hyperglycemia.

Complications of GDM are manifold, as both mother and fetus are affected. The main adverse perinatal outcomes of GDM in fetuses are macrosomia, large for gestational age (LGA) babies while shoulder dystocia, birth trauma and birth asphyxia can occur during labour.[4] In addition, such infants are prone to disease conditions such as delayed motor development, obesity and diabetes in later life [5].

Furthermore, women with a history of macrosomia at birth have an up to five-fold increased risk for the development of premenopausal breast cancer. Similarly, LGA births are also reported to have increased risk of breast cancer [6].

When lifestyle changes do not decrease hyperglycemia enough to achieve the glycemic target, pharmacological therapy is indicated. There is no universal agreement on when to begin GDM pharmaceutical therapy. If glycemic control is not obtained after 1–2 weeks of lifestyle management, the Canadian Diabetes Association (CDA) and NICE guidelines both

advocate starting pharmaceutical therapy. The disadvantages of insulin for the mother include the need to give injections, frequent daily testing for monitoring and risks of hypoglycemia, increase in appetite, weight gain and high cost.[7] Metformin, an oral biguanide, may be a more acceptable alternative to insulin for women with GDM. It is presently classified as an FDA category B medication for use during pregnancy, implying that animal studies have found no danger to the foetus, but no appropriate and well-controlled trials in pregnant women have been conducted.

AIMS AND OBJECTIVE:

To compare the efficacy and safety of metformin with insulin on

- glycemic control
- maternal outcome

in patients with gestational diabetes mellitus (GDM)

MATERIALS AND METHODS

The place of study was the department of Obstetrics and Gynaecology, Pradyumna Bal Memorial Hospital, Kalinga Institute of Medical Sciences, Bhubaneshwar. It was conducted from September 2019 to June 2021.The study design was a randomised Controlled open labelled trial of about 120 (expected) antenatal cases presenting to OPD.

STUDY SUBJECTS-Antenatal cases presenting to OPD for regular ANC or various other indications.

INCLUSION CRITERIA-

Women were eligible for inclusion if they were

1. Pregnant women attending O&G OPD who are within 24th to 28th weeks of gestation
2. Between 18 and 45 years of age,
3. Those patients with diagnosis of gestational diabetes mellitus (according to the criteria of the DIPSI) and requiring medication for glycaemic control
4. Having singleton pregnancy

EXCLUSION CRITERIA-

The exclusion criteria were

1. Pre-pregnancy diagnosis of diabetes,
2. Any contraindication to metformin,
3. Any fetal anomaly,
4. Ruptured membranes.
5. Multifetal gestation
6. ANC presenting for the first time in the 3rd trimester of pregnancy
7. Patients who have had to switch from metformin to insulin during the trial for better glycemic control
8. Patients who do not give consent.

The patients were randomized in two groups.

For a set of four patients seen at the clinic for the first time, they were randomised by letting them pick one paper with an inscription each from an opaque envelope. This assigned participants to one of the two treatment groups —insulin and metformin. The sequence of picking was in the

order in which they reported to the clinic; "first to report, first to pick".

RESULT AND DISCUSSION

In both the groups, age distribution was similar. In Insulin Group, the mean BMI At enrollment (mean± s.d.) of patients was 28.3958± 1.7206.

In Metformin Group, the mean BMI At enrollment (mean± s.d.) of patients was 28.6083± .9876. In Insulin Group, the mean 2hr OGTT after 75gm glucose (mean± s.d.) of patients was 164.9333± 11.5727. In Metformin Group, the mean 2hr OGTT after 75gm glucose (mean± s.d.) of patients was 164.8500± 6.5038. In Insulin Group, the mean Capillary glucose level af overnight fast 2 wk (mean± s.d.) of patients was 89.5000± 7.0266.

In Metformin Group, the mean Capillary glucose level after overnight fast 2 wk (mean± s.d.) of patients was 90.0167± 7.6546.

Our study showed that there was no difference in the HbA1c values at 35 to 37 weeks of gestational age. **Picón-César Et Al[8](2021)** found that there was no significant difference observed ,between the groups in their RCT, for mean fasting and post-prandial glycemic values at 2 weeks of randomisation and at 36-37 weeks of gestational age. This was similar to our results. Their study found lower C-section rates in the metformin treated group while in our study the rates of C-section and normal labour were similar in both the groups.

Distribution of mean Capillary glucose level after overnight fast 2 wk with Group was not statistically significant (p=0.7008). In Insulin Group, the mean Postprandial capillary glucose level after 2 wk (mean± s.d.) of patients was 117.7167± 19.5275. In Metformin Group, the mean Postprandial capillary glucose level after 2 wk (mean± s.d.) of patients was 122.4000± 3.0654. Distribution of mean Postprandial capillary glucose level after 2 wk with Group was not statistically significant (p=0.0690).

In Insulin Group, 35 (58.3%) patients had Lower segment Cesarian section delivery and 25 (41.7%) patients had vaginal delivery In Metformin Group, 30 (50.0%) patients had Lower segment Cesarian section delivery and 30 (50.0%) patients had vaginal delivery. Association of Mode of delivery vs Group was not statistically significant (p=0.3596). In Insulin Group, the mean Capillary glucose level after overnight last 2 wk before delivery (mean± s.d.) of patients was 89.7333 ± 5.9057.

Huhtala MS et al [9](2020) conducted a randomised control trial comparing metformin (n-110) and insulin (n=107) as treatment of GDM. In this trial, both the metformin and insulin groups were similar in inclusion criteria like OGTT values, HbA1c at enrollment and pre-pregnancy BMI. This was similar to our inclusion criteria in both the groups. In their study, There were no differences between the metformin and insulin groups regarding pregnancy outcomes, except for higher labor

induction rates in the insulin group compared to the metformin group (54.2% vs. 37.6%, p = 0.014). We found the mode of delivery to be similar in both arms of the study.

Galal M et al [10](2019) found that after 1 week of treatment with insulin or metformin there was statistically significant differences regarding the fasting and post prandial blood glucose level (92.42±4.93, 129.82±7.88 vs. 86.88±5.02, 117.30±8.84) in insulin and metformin group respectively with better glycemic control in the metformin group. In our study, the mean FBS and PPBS values after two weeks of enrolment in the respective groups , did not show any significant difference statistically. Also, their trial concluded that the rate of c-section was higher in insulin group as compared to metformin (81.5% vs 57.7%) . However, in our study, the mode of delivery was similar in both groups.

In Metformin Group, the mean Capillary glucose level after overnight last 2 wk bf delivery (mean± s.d.) of patients was 89.3833 ± 7.8224. Distribution of mean Capillary glucose level af overnight last 2 wk bf delivery with Group was not statistically significant (p=0.7826)..In Insulin Group, the mean 2-Hr capillary glucose last 2 wk before delivery (mean± s.d.) of patients was 122.1833± 7.7972.In Metformin Group, the mean 2-Hr capillary glucose last 2 wk before delivery (mean± s.d.) of patients was 124.1000± 4.8945.Distribution of mean 2-Hr capillary glucose last 2 wk before delivery with Group was not statistically significant (p=0.1095).In Insulin Group, the mean Glycated hemoglobin at wk 36–37 (mean± s.d.) of patients was 5.4733± .3296.In Metformin Group, the mean Glycated hemoglobin at wk 36–37 (mean± s.d.) of patients was 5.4167± .3489. Distribution of mean Glycated hemoglobin at wk 36–37 with Group was not statistically significant (p=0.3623).

In the study by **Mahmood OA et al [11](2019)** the demographic characteristics like age (in years) and pre-pregnancy BMI during enrollment in each group were similar. This was alike the demographic characteristics that we have enrolled in our trial. According to the study conducted by them, the number of cesarean section in the insulin treatment group (60%) was higher than in the metformin treatment group (46%). This outcome was not reflected in our study as the mode of delivery (c-section vs normal labour) was statistically insignificant in our study between the insulin and metformin group, which was similar to results obtained by **Ali AE et al [12](2018).** They found that blood sugar control was better in the metformin group than in insulin treated group where the mean blood sugar was 111mg/dl in metformin vs 145mg/dl in insulin group. In our trial, we found that the values of FBS and PPBS were similar in both groups.

Limitations of our study were a relatively small sample size, having been

conducted at a single centre and it being tertiary must have introduced hospital bias.

CONCLUSION

- Insulin has been the first line of treatment for GDM for the past few decades. Though it was successful in achieving strict glycemic control to avoid pregnancy complications, insulin came at a cost of patient's acceptance.
- Incidences of hypoglycemia in mothers, the difficulties of storage, travel, and repeated insulin injections were the common problems faced by GDM patients.
- Metformin, an oral hypoglycemic agent, has been used as the first line therapy in the management of Type-2 diabetes mellitus but the drug's role during pregnancy remained controversial.
- The major problem of repeated injections of insulin could be solved with metformin. The cost effectiveness, the logistics of storage and travel could be taken care of with metformin. Incidences of hypoglycemia were also lower with metformin.
- Our study concluded that glycemic control in GDM can be achieved by using metformin orally as an alternative to insulin. Metformin does not increase the risk of maternal hypoglycemia.

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Table 1: Association between Mode of delivery (VD/LSCS)

	GROUP				
Mode of delivery (VD/LSCS)	**INSULIN**	**METFORMIN**	**TOTAL**	**Chi-square**	**p-value**
LSCS	35	30	65	0.8392	0.3596
Row %	53.8	46.2	100.0		
Col %	58.3	50.0	54.2		
VD	25	30	55		
Row %	45.5	54.5	100.0		
Col %	41.7	50.0	45.8		
TOTAL	60	60	120		
Row %	50.0	50.0	100.0		

Col %	100.0	100.0	100.0		

Table 2: Distribution of mean Capillary glucose level af overnight fast 2 wk, Postprandial capillary glucose level after 2 wks of randomisation, Capillary glucose level af overnight last 2 wk bf delivery, Glycated hemoglobin at wk 36–37

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Capillary glucose level af overnight fast 2 wk	INSULIN	60	89.5000	7.0266	72.0000	99.0000	92.0000	0.7008
	METFORMIN	60	90.0167	7.6546	80.0000	109.0000	90.0000	
Postprandial capillary glucose level after 2 wk	INSULIN	60	117.7167	19.5275	16.0000	129.0000	120.0000	0.0690
	METFORMIN	60	122.4000	3.0654	118.0000	130.0000	124.0000	
Capillary glucose level af overnight last 2 wk bf delivery	INSULIN	60	89.7333	5.9057	74.0000	100.0000	90.0000	0.7826
	METFORMIN	60	89.3833	7.8224	72.0000	98.0000	90.0000	
Glycated hemoglobin at wk 36–37	INSULIN	60	5.4733	.3296	4.9800	6.0000	5.6000	0.3623
	METFORMIN	60	5.4167	.3489	4.8000	5.8000	5.3000	