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RESEARCH ARTICLE

Comparative analysis of fetomaternal outcome in women with gestational diabetes mellitus managed on different modalities

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ABSTRACT

Objectives: To compare fetomaternal outcome in women of gestational diabetes mellitus (GDM) managed on different modalities. **Methods**: A retrospective observational study was conducted in department of obstetrics and gynaecology at Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi. All case records of 352 women with singleton pregnancy diagnosed with GDM in the hospital managed on different modalities, over a period of 18 month, were reviewed. Diagnosis of GDM was made according to guidelines of diabetes in pregnancy study group of India (DIPSI). They were divided into four groups, group A - MNT (medical nutrition therapy) (140 patients), group B - MNT plus metformin (90 patients), group C - MNT plus insulin (90 patients), group D - MNT plus metformin plus insulin (32 patients). Fetomaternal outcomes of GDM women managed on different modalities were recorded. **Results:** All the 4 groups of the patient in this study were demographically matched. There was no statistically significant difference in total weight gain during pregnancy ($p = 0.6012$), mode of delivery ($p = 0.420$), preterm delivery ($p = 0.059$), urinary tract infection ($p = 0.387$), hypertensive disorder in pregnancy ($p = 0.773$), and postpartum haemorrhage ($p = 0.2656$) between insulin v/s metformin group and MNT v/s metformin group. But incidence of polyhydramnios was significantly ($p = 0.0230$) higher in metformin group than in MNT group. **Conclusion:** Our study concluded that metformin seems to be an effective oral hypoglycemic drug in the treatment of GDM and does not appears to be associated with increased maternal and neonatal complications compared to insulin.

Keywords: Gestational diabetes mellitus, medical nutrition therapy, metformin, insulin, fetomaternal outcome.

The incidence of gestational diabetes mellitus (GDM) is increasing worldwide with prevalence of 1-14%.[1,2] GDM is associated with higher fetomaternal risks as it increases the occurrence of preeclampsia, caesarean delivery and type 2 diabetes later on, in the mother.[3] Whenever a women is diagnosed with GDM, she receives advice regarding medical nutrition therapy (MNT) and lifestyle modification. Pharmacological therapy is initiated only when target blood glucose levels are not attained with these modifications.[4] Proper control of blood sugars in GDM, has been shown to significantly improve perinatal outcomes, with decreased occurrence of macrosomia, birth injury and neonatal death.[5]

A large number of previous studies have concluded that treatment of GDM with metformin leads to adequate glycemic control without increasing the risk of adverse perinatal outcomes.[6,7] Metformin acts by suppressing hepatic gluconeogenesis and by increasing insulin sensitivity, leading to control of hyperglycaemia.

Metformin may be a more favourable alternative to insulin, as it does not increase maternal weight and is also not associated with hypoglycaemia, with additional advantages of avoiding need for injections and also makes maternal follow-up much simpler.[8] Use of metformin from 12 to 18 weeks of gestation, reduces gestational weight gain

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in obese women, without any effect on the development of GDM or neonatal birth weight.[9]

A prospective clinical trial that randomised women with GDM to insulin or metformin found that, metformin therapy was not associated with an increased risk of perinatal complications.[10] Previous meta-analyses have also found that there is no difference in perinatal outcomes, for women with GDM, treated with metformin versus insulin.[11,12] Some women managed first with metformin, may require additional therapy with insulin to achieve euglycemia, but the dose of insulin needed along with it is much less than, when managed with standalone insulin therapy.[13]

A recent study concluded that metformin treatment in the first trimester of pre-gestational diabetes was associated with an increased risk of birth defects and pregnancy loss but these increased risks were attributed to hyperglycaemia rather than metformin therapy.[14] Needle phobia, life threatening hypoglycemia, weight gain, daily injections, and psycho-social stigma, makes injectable therapy with insulin unwelcomed in pregnant women with GDM.[15]

At our institution, the use of metformin for the treatment of GDM has been adopted as an alternative approach to insulin therapy. Thus, the aim of the present study was to carry out an audit to assess and compare the maternal characteristics and perinatal outcomes of women with GDM treated with metformin (with or without supplemental insulin), in comparison to those treated solely with insulin or MNT and lifestyle modification alone in tertiary care hospital settings.

Materials and methods

This study was conducted at department of obstetrics and gynaecology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi. In this retrospective observational study, fetomaternal outcome of all women with singleton pregnancy diagnosed with GDM, managed on different modality of treatment, was analyzed from inpatient clinical records from January 2018 to June 2019, over a period of 18 months. Women with GDM with multiple pregnancy, chronic hypertension, overt diabetes, bad obstetric history and PCOS patients on metformin, were excluded from the study.

All study women were divided into groups based on modality of treatment on which their fasting blood sugar was <95mg/dl and postprandial 2 hours blood sugar <120mg/dl. The four study groups were as follows: Group A - MNT, Group B - MNT plus metformin, Group C - MNT plus insulin and Group D - MNT plus metformin plus insulin.

Diagnosis of GDM was made on guidelines of diabetes in pregnancy study group of India (DIPSI). DIPSI is done as a single step procedure irrespective of the last meal. Pregnant women attending the antenatal OPD were given 75g anhydrous glucose in 250-300ml of water and plasma glucose was estimated after 2 hour. A 2 hours plasma glucose ≥ 140 mg/dl was taken as GDM and a value of ≥ 200 mg/dl as DM. If the DIPSI value at first visit was normal then test was further repeated at 24-28 weeks and at 32-34 weeks in high risk women.

GDM women managed on different modality of treatment were considered to have controlled blood sugar when fasting sugar was less than or equal to 95mg/dl and post prandial blood sugar, 2 hours after meals less than or equal to 120 mg/dl. Case records were studied to record various fetomaternal outcomes. Maternal outcome studied, in all the study groups, were mode of delivery, period of gestation, occurrence of polyhydramnios, urinary tract infection (UTI), hypertensive disease in pregnancy and postpartum haemorrhage (PPH). Neonatal outcome studied were birth weight, gestational age at birth, macrosomia, fetal growth restriction (FGR), shoulder dystocia, NICU admission, jaundice, birth injury, neonatal death, still birth and Apgar score at birth.

Statistical analysis: Statistical package for social sciences (SPSS) software version 23.0 was used for analysis. The data was entered in Microsoft excel spreadsheet. Categorical variables presented in number and percentage and continuous in mean ± SD and median. Normality of data was tested by Shapiro- wilk test. Comparison of variable, quantitative and qualitative using paired/ unpaired t-test and chi square test respectively and P value of <0.05 was considered statistically significant.

Results

In this retrospective study on women with GDM in singleton pregnancy, a total of 352 women were included as per inclusion criteria. Out of these, 90 patients (25.57%) each were in metformin only and insulin only group, thirty two (9%) were managed with metformin plus insulin and majority, 140 women (39.77%) were managed with MNT.

The metformin dose varied from 500mg to 2gm a day with a mean dose of 1gm a day. In the insulin treated group (n=90), 27 patients were treated with short acting insulin only, 19 patients were treated with intermediate acting insulin only, and 44 patients were treated with both short and intermediate acting insulin.

All the 4 groups of the women in this study were matched for various variables. Glucose values in OGTT at

2hrs were significantly higher ($p < 0.0001$) in the insulin group than in metformin group which when compared with the MNT were also significantly higher ($p < 0.0001$) in metformin group.

There were no statistically significant difference between the metformin and insulin only group with respect to maternal age (p=0.3621), total weight gain during pregnancy (p=0.6012), mode of delivery (normal, assisted, caesarean) (p=0.420), prematurity (p=0.059), UTI (p=0.387), hypertension (p=0.773), PPH (p=0.2656), and polyhydramnios (p = 0.329) (table 1).

There were also no statistically significant difference between the metformin and medical nutritional therapy with respect to maternal age (p = 0.8617), total weight gain during pregnancy (p = 0.7311), mode of delivery (normal, assisted, caesarean) (p = 0.254), prematurity (p = 0.125), UTI(p = 0.471), hypertension (p = 0.283), and PPH (p = 0.303), but polyhydramnios was significantly higher (p = 0.0230) in metformin group than in MNT group.

There were no statistically significant difference between the metformin group when compared to insulin only, in relation to birth weight (p = 0.4936), gestational age (p = 0.207), occurrence of macrosomia (p = 0.732), FGR (p = 1.000), shoulder dystocia (p = 0.560) and need for NICU admission (p = 0.755). Similarly occurrence of jaundice (p = 0.798), stillbirth (p = 0.650) and Apgar score at 5 mins (p = 0.0914) were also not significant between the metformin group and insulin group. No incidence of birth injury and neonatal death were documented in both the groups (table 2).

There were no statistically significant difference between the metformin group when compared to MNT only group in relation to birth weight (p = 0.0975), gestational age (p = 0.2194), occurrence of macrosomia (p = 0.847), FGR (p = 0.835), shoulder dystocia (p = 0.653) and NICU admission (p = 0.659). Similarly occurrence of jaundice (p = 0.933), stillbirth (p = 0.325) and Apgar score at 5 min (p = 1.000) were also not statistically significant between the metformin group and MNT only group. No incidence of birth injury and neonatal death were documented in both the groups.

Table 1: Showing maternal parameters

Parameters		Metformin (n=90)	Insulin (n=90)	MNT (n=140)	Metformin + insulin (n = 32)	Met.vs. Ins. (p value)	Met. vs. MNT (p value)
Age (yrs)		26.2 ± 4.6	26.8 ± 4.2	26.3 ± 4.0	27.6 ± 4.1	NS (0.3621)	NS (0.8617)
Total weight gain (kg)		10.8 ± 4.6	11.2 ± 5.6	10.6 ± 4.1	11.8 ± 4.1	NS (0.6012)	NS (0.7311)
OGTT (2hrs) (mmol / l)		8.8 ± 1.2	10.4 ± 1.8	7.8 ± 0.8	10.9 ± 1.0	SS (<0.0001)	SS (<0.0001)
Gestational age (OGTT)		22.3 ± 1.2 week	22.1 ± 1.1 week	22.2 ± 1.4 week	22.1 ± 2.0 week	NS (0.2454)	NS (0.5771)
Mode of delivery	Caesarean section	28	21	30	10		
	Assisted vaginal	6	7	10	4	NS (0.420)	NS (0.254)
	Vaginal	56	62	100	18		
Prematurity		4	11	14	3	NS (0.059)	NS (0.125)
Polyhydramnios		30	24	28	13	NS (0.329)	NS (0.0230)
UTI		5	8	5	4	NS (0.387)	NS (0.471)
Hypertension		6	7	5	13	NS (0.773)	NS (0.283)
PPH		5	9	4	1	NS (0.2656)	NS (0.303)

MNT – Medical nutritional therapy, OGTT – Oral glucose tolerance test, UTI – Urinary tract infection, PPH – Postpartum haemorrhage, NS – Nonsignificant.

Table 2: Showing neonatal parameter

Parameters	Metformin (n = 90)	Insulin (n =90)	MNT (n = 140)	Met+ Ins (n = 32)	Met. vs. Ins. (p value)	Met.vs. MNT (p value)
Birth weight (gms)	2880 ± 210	2900 ± 180	2830 ± 230	3160 ± 110	NS (0.4936)	NS (0.0975)
Gestational age (weeks)	38.1 ± 1.2	37.8 ± 1.9	38.4 ± 2-1	37.0 ± 0.8	NS (0.207)	NS (0.2194)
Macrosomia	4	5	7	2	NS (0.732)	NS (0.847)
FGR	1	1	2	1	NS (1.000)	NS (0.835)
Shoulder dystocia	2	1	2	1	NS (0.560)	NS (0.653)
NICU admission	5	6	6	4	NS (0.755)	NS (0.659)
Jaundice	8	9	12	3	NS (0.798)	NS (0.933)
Birth injury	0	0	0	0	NS	NS
Neonatal death	0	0	0	0	NS	NS
Still birth	2	3	1	2	NS (0.650)	NS (0.325)
Apgar score at 5 mins	8.9 ± 1	8.7 ± 0.5	8.9 ± 0.5	8.4 ± 0.4	NS (0.0914)	NS (1.000)

FGR – Fetal growth restriction, NICU – Neonatal intensive care unit, NS – Nonsignificant

Discussion

Metformin use in GDM has not gained widespread acceptance because the evidence of safety and efficacy has largely been derived from inadequately powered study.

Data from our study was similar to study done by Kristiina et al[16], as there were no statistically significant difference in maternal weight gain during pregnancy, gestational week at the time of performing OGTT, mode of delivery, prematurity, postpartum haemorrhage (PPH)

between the metformin group and insulin only group. Glucose levels in OGTT at 2 hrs in our study were consistent with the study by Kristina et al[16], as in both the study there was significant difference between blood sugar level, in women who were controlled on metformin versus insulin.

In contrary to our study, the maternal weight gain during pregnancy was less in metformin group than insulin group, both groups were comparable according to obstetrics and neonatal complications in the study done by Shirin N et al[17]. The occurrence of gestational hypertension, in our study, was also not statistically significant between metformin and insulin group, and same had been also observed by Balani et al[18]. Incidence of UTI and polyhydramnios was also not statistically significant between maternal data from metformin versus insulin only group of women and metformin versus and MNT group. But incidence of polyhydramnios was significantly higher in metformin group in comparison to MNT group.

A small randomized pilot study of 30 patients with GDM found that neonatal outcomes were not different between patients treated with metformin and those on standard insulin therapy.[19] Similarly, analysis of neonatal data in our study showed no statistical significance when compared between metformin and insulin only group of the patients in relation to birth weight, Apgar score at 5 min, macrosomia, FGR, NICU admission, and jaundice. These analytical findings also were similar to the study by Kristina et al[16]. Incidence of shoulder dystocia was also not clinical significant when compared to metformin versus insulin only as well as metformin versus MNT and similar was reported by Balani et al[18]. No serious adverse effect of metformin was reported in our study.

The limitation of this study is that it is a retrospective study hence randomization was not possible. Its possible that insulin treated patients were having more hyperglycemia than metformin treated patients as evident by OGTT at 2 hrs. Similarly the metformin treated patients were more hyperglycemic in comparison to MNT only group of the patients as shown by OGTT values at 2 hrs.

Conclusion

In the present study, metformin was observed to be an effective oral hypoglycemic drug in the treatment of gestational diabetes mellitus (GDM). Metformin was not found to be associated with increased maternal and neonatal complications in comparison to insulin. Before making any final recommendation for GDM management, further sufficiently powered prospective randomized study of larger number of women is required, including long term follow up of their children, so that we determine the role of metformin as an effective alternative treatment to insulin in their management.

Conflict of interest: None. **Disclaimer:** Nil.

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