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ORIGINAL ARTICLE

Demystifying Glycemic Variability in GDM Pregnancies: A Cross-Sectional Observational Study

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Abstract

Aim To study glycemic variability (GV) and 24-h ambulatory glucose profile (AGP) in gestational diabetes mellitus (GDM) patients who were apparently controlled on drugs and their correlation with fetomaternal outcomes.

Methodology In this cross-sectional observational study, 40 gestational diabetic pregnancies on pharmacotherapy were recruited. Flash glucose monitor was used to record AGP between 32 and 36 weeks of gestation. A total of 600 patient days with 58,600 glucose values were analyzed.

Results Variables of GV: Mean amplitude of glycemic excursion ($p = 0.001$), standard deviation ($p = 0.001$), Continuous Overall Net Glycemic Action ($p = 0.002$) and High Blood Glucose Index ($p = 0.001$) were significantly high in GDM group when compared to normoglycemic patients and these were well correlated with poor fetomaternal outcome in this group. Time in range was also significantly altered in GDM group. ($p < 0.001$).

Conclusion High GV and time in range are the important parameters which get altered in GDM pregnancies despite apparent control of blood glucose, and this can be a reason of adverse fetomaternal outcomes in these pregnancies.

Keywords Glycemic variability · Time in range · Glucose excursion · Pregnancy · Gestational diabetes mellitus

Background

Gestational diabetes mellitus (GDM) is defined as any degree of hyperglycemia that is detected for the first time in pregnancy. This definition includes cases of undiagnosed type 2 diabetes mellitus (T2DM) identified early in pregnancy and true GDM, which develops later. Once GDM is diagnosed, glucose monitoring is the mainstay of checking glycemic control, dose adjustment and treatment compliance. Most common method of glucose monitoring in GDM is self-monitoring of blood glucose (SMBG). Despite apparent control on SMBG, the fetomaternal outcome is not optimum in many of these GDM cases. Other glucose monitoring tools, i.e., CGM (Continuous Glucose Monitoring) and FGM (Flash Glucose Monitoring) appear to be good option for finding out the reason of suboptimal outcome with added advantage of measuring glycemic variability (GV), 24-h ambulatory glucose profile (AGP) and time in range (TIR). GV is characterized by extreme glucose excursions which includes both inter- and intra-day hypo- and hyperglycemia. Time in range can be defined as the time spent in an individual's target glucose range.

GV & TIR have not been adequately studied in pregnancies complicated by GDM, and very little is known about the relationship between GV and TIR with maternal–fetal outcomes. Therefore, we aim to study GV, TIR and 24-h AGP in GDM women who were apparently controlled on drugs (as evidenced by SMBG) in third trimester and its correlation with fetomaternal outcomes.

Design

It was a cross-sectional observational study conducted between January 2021 and July 2022 in Department of Obstetrics and Gynaecology of Hamdard Institute of Medical Sciences and Research and associated HAH Centenary

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Hospital, New Delhi, after obtaining permission from the Ethics Committee (EC/new/inst/2020/961).

Setting

All pregnant women between 19 and 35 years were screened for GDM on basis of oral glucose tolerance test (OGTT) using IADPSG (International Association of Diabetes Study Group) criteria between 24 and 28 weeks. A written informed consent was obtained from all study participants.

The inclusion criteria included singleton pregnancy between 28 and 36 weeks taking Metformin/Insulin for the control of GDM.

Exclusion criteria were GDM women on diet only, twin pregnancy, patient with autoimmune disease, patient with current tuberculosis, patient with diabetes diagnosed before pregnancy, and patients on steroids.

The control group comprised of low-risk singleton pregnancies with normal OGTT and no other high-risk factor.

Sample Size Calculation

Sample size was calculated assuming GDM prevalence to be 14% [1] in North India and 44.8% among them requiring pharmacotherapy [2] making prevalence of 5% pregnant women with GDM on Pharmacotherapy.

$$N = \frac{Z\alpha^2 P(1-P)/d^2}{}$$

Where n is sample size, P = prevalence, p = 5%, $Z\alpha$ = confidence level according to the standard normal distribution (For a level of confidence of 95%, $z = 1.96$), d = precision (tolerated margin of error), i.e., 10%

Accordingly, 40 pregnant women with GDM on drugs were taken as the study group and 20 pregnant women with normal OGTT were taken as a control group. The study group was further divided on the basis of pharmacotherapy. There were 28 women who were controlled on Metformin, 7 were on Insulin, and 5 were on both insulin and metformin.

Method

Abbott FreeStyle Libre Pro Flash Glucose Monitoring System was inserted between 32 and 34 weeks for 2 weeks. FGM recorded 96 data points per day making 960 data points for every patient for 10 days. Total 400 days with 38,400 glucose values in the study group and 200 days with 19,200 glucose values in control group were analyzed.

Patient was called on 7th and 14th day to check for the functioning of the monitor, and removal was done after day 14. The treatment was not modified according to the readings. SMBG was advised as per hospital protocol, i.e., twice a week.

All the patients were followed till delivery, and the feto-maternal outcome was noted, i.e., mode of delivery, difficult labor/shoulder dystocia, baby weight, baby outcome—Apgar score, NICU admission, postpartum complications.

Main Outcome Measure

The collected data were tabulated on SPSS version 20. Data were evaluated descriptively and arranged graphically for a better understanding of the variation in blood glucose profile in 24-h time intervals. GV was calculated using GV Easy Version 9.0.R2 provided following measures of GV: standard deviation (SD), Continuous Overall Net Glycemic Action(CONGA), High Blood Glucose Index (HBGI), J index and MAGE (mean amplitude of glycemic excursion). Another important parameter analyzed through FGM was time in range (TIR) for which target range was taken between 65 and 140 mg/dl. $P < 0.05$ was taken as significant.

Result

The characteristics of the 60 women recruited into the study are depicted in Table 1

Table 1 Baseline characteristics of study participants

	Study group($n = 40$)	Control group($n = 20$)	P value
Age (years)	29.65 (4.38)	28.15 (3.57)	0.190
BMI (kg/m2)	30.25	24.82	**0.001**
Family history of GDM	60% (24)	20% (4)	**0.001**
Period of gestation at which FGM inserted (weeks)	33.15	32.6	
History of GDM in previous pregnancy	32%	0	
Multigravida	85%(34)	70%(14)	
Primigravida	15% (6)	30%(6)	
OGTT (0/1/2 h values) in mg/dl	115.03/200.60/162.18	74.35/118.90/97.25	**0.001**

Bold indicates $p < 0.05$

Table 2 delineates the blood glucose parameters in relation to meals, and it shows a significant difference in all parameters despite apparent control of blood sugar in the study group. Table 3 compares 24-h blood glucose among subgroups.

The 24-h mean glucose value in women with GDM was 18% higher ($p < 0.001$).

Mean daytime glucose (108.63 ± 17.49 versus 72.51 ± 5.37 mg/dl, $p < 0.001$) and mean nocturnal glucose (96.74 ± 12.58 mg/dl versus 70.38 ± 4.86 mg/dl, $p = 0.001$) was significantly higher in women with GDM.

The area under curve (Fig. 1) for 24-h, daytime and nocturnal periods, was also significantly higher in women with GDM.

There was significant rise in blood sugar post-meal when compared to women with normoglycemia. Average post-meal rise was 22.46 ± 8.28 versus 7.51 ± 4.27 mg/dl ($p < 0.001$).

Tables 4, 5 compare measures of glycemic variability of 3 subgroups. Figure 2 depicts AGP of the 3 subgroups. These were significantly high in GDM when compared to normoglycemic women.

Table 6 delineates TIR, hypo- and hyperglycemic excursions which is significantly higher in GDM group and this

Table 2 Comparison of 24-h glycemic profile between study and control group

AGP values in Mg/dl	Mean (SD)		*p* value
	Cases($N=40$) 400 days (38,400 glucose values)	Controls($N=20$) 200 days (19,200 glucose values)	
Fasting at 6 AM	73.76 (12)	59.51 (7.29)	**0.001**
Before breakfast	87.35 (19.24)	63.98 (9.07)	**0.001**
Post breakfast after 1 h	115.35 (16.68)	73.85 (9.3)	**0.001**
Post-breakfast after 2 h	95.69 (14.15)	71.86 (11.93)	**0.001**
Pre-lunch	86.64 (15.61)	72.08 (9.34)	**0.001**
Post-lunch after 1 h	109.87 (18.4)	79.46 (10.41)	**0.001**
Post-lunch after 2 h	94.42 (16.86)	77.56 (9.43)	**0.001**
Evening at 6 PM	87.46 (16.48)	74.64 (9.41)	**0.002**
Pre-dinner	98.24 (21.05)	75.94 (8.51)	**0.001**
Post-dinner after 1 h	114.41 (19.18)	81.6 (12.62)	**0.001**
Post-dinner after 2 h	98.72 (20.23)	78.23 (10.43)	**0.001**
2 am	78.68 (15.95)	67.73 (5.51)	**0.004**
24-h mean blood glucose	87.27 (13.45)	71.33 (7.25)	**0.001**

Bold indicates $p < 0.05$

Table 3 Comparison of average blood glucose from ten-day AGP between GDM subgroup according to treatment. ($N=40$)

Timing of various blood sugar levels in relation to meals(mg/dl)	Metformin-mg/dl $N=28$ (280 days DP*-26,800)	Metformin + insulin mg/dl $N=5$ (50 days, DP*-4800)	Insulin mg/dl $N=7$ (70 days, DP*-6720)	*P* value
6am	71.21 (9.88)	85.84 (12.48)	75.32 (15.41)	0.035
Pre-breakfast	86.72 (19.11)	101.54 (24.45)	79.74 (11.29)	0.147
1 h after breakfast	95.54 (13.73)	112.42 (18.15)	110.24 (22.14)	0.054
2 h after breakfast	88.96 (11.03)	98.1 (14.34)	96.03 (22.36)	0.178
Pre-lunch	83.53 (13.3)	97.62 (18.16)	91.28 (19.96)	0.121
1 h post-lunch	98.51 (15.89)	119.54 (18.33)	114.14 (19.46)	0.013
2 h post-lunch	96.52 (14.88)	105.56 (16.61)	102.05 (20.6)	0.074
Pre-dinner	94.33 (18)	103.11 (37.94)	100.42 (14.57)	0.65
1 h post-dinner	98.54 (19.53)	110.23 (24.09)	105.48 (15.21)	0.58
2 h post-dinner	95.43 (19.83)	108.85 (24.97	104.06 (19.89)	0.037
2 am	76 (10.6)	84 (12.96)	81.36 (13.59)	0.062

Bold indicates $p < 0.05$

*Data points (total 400 days of monitoring with 38,400 data points)

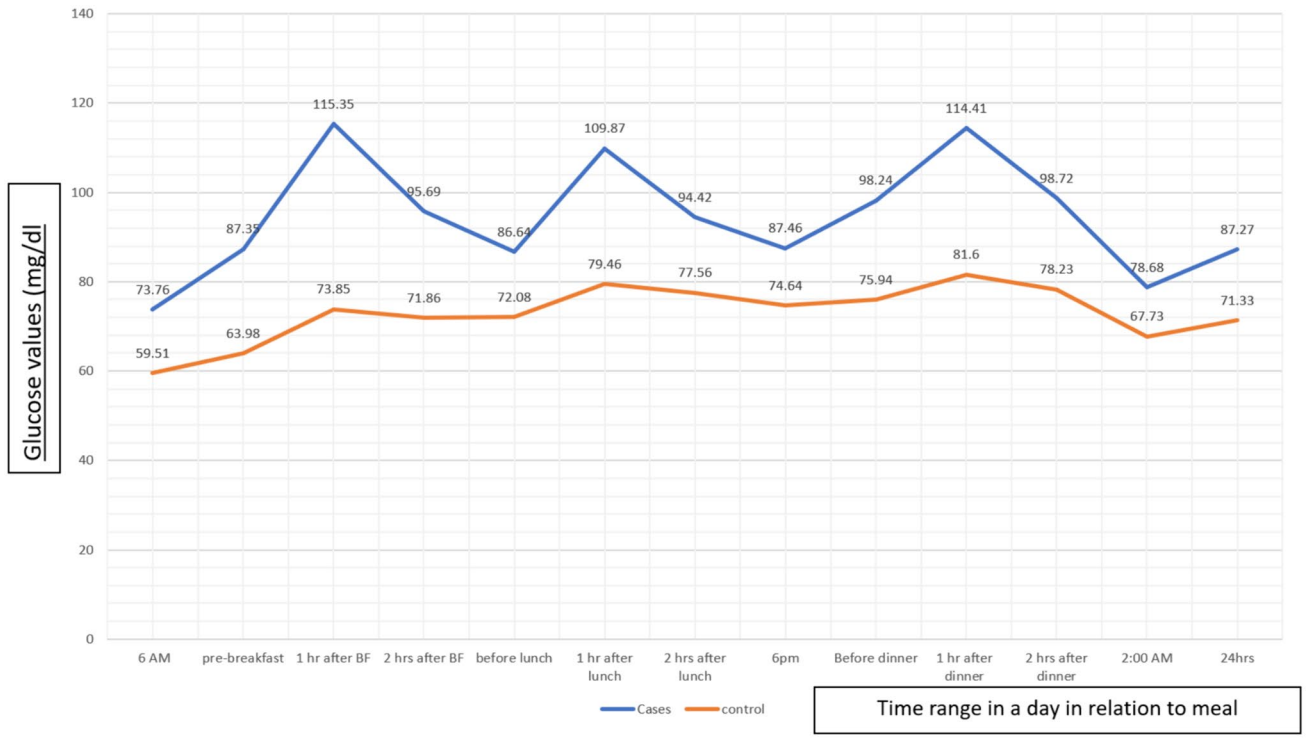

Fig. 1 Comparison of 24-h ambulatory glucose profile between cases and controls

Table 4 Comparison of glycemic variability between cases and controls

Measure of GV(mg/dl)	Mean (SD)		*P* value
	Cases (*N* = 40)	Controls (*N* = 20)	
SD	20.63 (6.06)	10.99 (2.79)	0.001
CONGA	68.12 (11.3)	49.05 (7.14)	0.002
J INDEX	3813.99(1248.76)	2376.29 (445.74)	0.001
MAGE	58.66(14.3)	35.72 (7.63)	0.001
HBGI	244.88 (27.66)	211.09 (17.31)	0.001

Bold indicates $p < 0.05$

SD standard deviation, *CONGA* continuous overall net glycemic action, *MAGE* mean amplitude glycemic excursion, *HBGI* high blood glucose index

can be correlated with poor fetomaternal outcomes in GDM group [poor fetal outcome (FGR, LGA, macrosomia) in 17.5% compared to nil in control group; poor maternal outcome (Antepartum hemorrhage, Postpartum hemorrhage, Preterm, Preeclampsia, Surgical site infection) in 20% compared to nil in control group].

Discussion

The current study provides evidence regarding GV, TIR and other glucose-related parameters evaluated using FGM in pregnant women with GDM on pharmacotherapy. There is dearth of literature on these parameters in GDM

Table 5 Comparison of glycemic variability between the three groups. (*N* = 40)

Measures of GV (mg/dl)	Metformin (*N* = 28)	Metformin + insulin (*N* = 5)	Insulin (*N* = 7)	*P* value
SD	18 (4.9)	21.89 (6.42)	25.39 (7.67)	0.034
CONGA	67.02 (9.31)	76.31 (10.83)	67.90 (12.95)	0.182
J index	3539.92 (1033.66)	4775.39 (1437.54)	4389.56 (1540.82)	0.050
MAGE	52.25 (12.44)	56.94 (16.69)	62.95 (14.73)	0.167
HBGI	240.82 (25.03)	269.53 (30.74)	259.94 (32.65)	0.098

Bold indicates $p < 0.05$

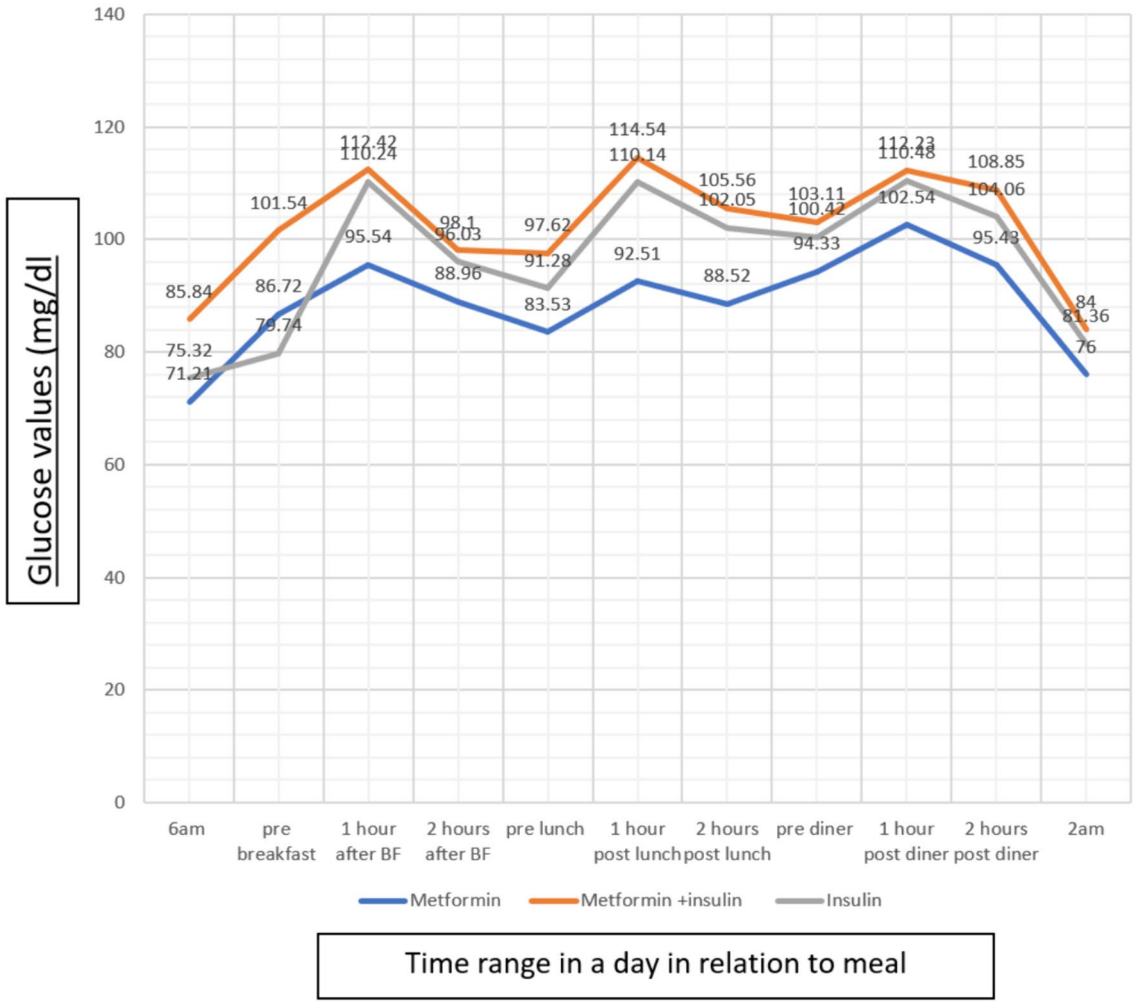

Fig. 2 Comparison of average blood glucose from ten days AGP between cases according to treatment

Table 6 Comparison of TIR (time in range), hypoglycemia % and hyperglycemia% between cases and controls

	Mean (SD)		*p* value
	cases ($N=40$)	Controls ($N=20$)	
TIR %	44.89 (18.15)	79.80 (8.40)	**< 0.001**
Hypo %	45.15 (21.68)	20.15 (8.40)	**< 0.001**
Hyper %	9.96 (4.83)	0 (0)	**< 0.001**

Bold indicates $p < 0.05$

pregnancies, and current data help us to understand cause of complications in these apparently controlled GDM pregnancies who are on pharmacotherapy.

In 2017, the International Consensus on the Use of Continuous Glucose Monitoring defined and standardized CGM metrics which were revised in 2019. The consensus panel concluded that TIR, when used as a measure of glycemic control in addition to HbA1c, provided better and more actionable information than HbA1c alone. TIR measures glucose in the context of patients' glycemic variability and exposure to hypoglycemia and hyperglycemia [4].

Pregnancies complicated by diabetes should have TIR between 65 and 140 mg/dL. In our study, GDM group spend only 48.89% time in target range, while it was 78% in control group. Time below range (TBR) was 42.15%, and time above range (TAR) was 9.96% in GDM group. This reflects that while being controlled on drugs, GDM group patients spent less than 50% time in euglycemic range and achieving recommended goals is a real challenge in treating GDM.

Apart from hyperglycemia, another major concern in GDM women is risk of hypoglycemia. The need to avoid hypoglycemia is a limiting factor to achieve target glucose values in GDM patient. Tightening glycemic control may increase the risk of asymptomatic as well as symptomatic hypoglycemia, with potential adverse maternal outcomes including coma and seizures.

Yogel et al. [9] conducted a study enrolling 117 patients (82 GDM vs. 35 normoglycemic pregnant) and found that there were frequent asymptomatic hypoglycemic episodes detected by using CGM in the GDM group compared to the controls ($P < 0.001$).

Our study had similar findings with GDM patient spending on an average 9.96% time in hyperglycemic state and 42.15% time in hypoglycemic state, of which most episodes were asymptomatic. Control group spent only 20.15% time in hypoglycemic state while they had no hyperglycemic episodes even post-meals. ($p < 0.001$).

The study found significant differences in mean 24-h, nocturnal and diurnal glucose values between women with normoglycemia and GDM. Besides, significant differences were also observed for fasting glucose, mean preprandial glucose and various meal-related parameters (1-h and 2-h postprandial glucose values, 1-h postprandial glucose excursion and peak glucose values) between the two groups, all being higher in women with GDM.

Studies have shown that fluctuating blood glucose levels increase free radicals and endothelial dysfunction. Reece and Homko postulated an association between maternal hyperglycemia-induced oxygen-free radical overproduction and fetal abnormalities, with the onset of diabetes-related embryopathy [3]. This fluctuation is measured by GV that can be used as a new tool to anticipate and prevent poor fetal outcomes as shown in the study. Intrauterine hyper- and hypoglycemia may result in metabolic imprinting of the fetus and may be responsible for fetal origin of adult diseases like childhood obesity and metabolic syndrome.

The largest study of FGM in pregnancy is Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT). CONCEPTT trial found that continuous use of real-time CGM in women with T1D in pregnancy was linked with a greater reduction in HbA1c, more time spent in the target range, less time spent above the target range, and reduced GV. Additionally, neonatal outcomes were improved, including a lower incidence of LGA infants and a decrease in neonatal hypoglycemia. [4] There is paucity of studies on GDM population, especially in Indian population.

Monnier and Colette [5] proposed that the target level of GV should not be more than 40 mg/dl. In our study, in normoglycemic pregnant females, GV was 35.722 mg/dl and SD was 10.98 mg/dl. Similar results were found by Nigam et al. [6] where GV in healthy pregnant women was between 20 and 35 mg/dl.

Other studies have also demonstrated that continuous glucose monitoring during pregnancy and improved GV is associated with improved glycemic control in the third trimester, lower birth weight, and reduced risk of macrosomia [7].

Current study shows a stark difference between post-meal rise in GDM group when compared to control group. It has been observed that post-meals blood glucose values increase gradually, reaching a peak after 50–60 min, and then gradually decrease after 2 h. Similar post-meal rise in glucose was seen in other studies [8]. Average rise in blood glucose levels after meal was 20–25 mg/dl in GDM group. On the contrary in control group post-meal rise in blood glucose was minimal and the rise was on average less than 10 mg/dl.

Episodes of hypo- and hyperglycemia that occurs throughout the day in GDM women are often missed by SMBG. These episodes are captured by FGM because of continuous and real-time glucose measurement. Postprandial, nocturnal and diurnal fluctuations are detected by FGM, and necessary interventions can be taken.

Although there are no guidelines that management during pregnancy can be changed on the basis of FGM data, modifications in meals, drug dose and drug timings according to real-time glucose data generated by FGM can be considered to give a better outcome.

Therefore, it can be concluded from the current study that there is a significant difference in the glycemic variability and 24-h glycemic profile in apparently controlled GDM women on pharmacotherapy as compared to euglycemic healthy pregnant women. FGM can be of distinct clinical utility to detect GV, episodes and duration of asymptomatic or nocturnal hypoglycemia.

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Declarations

Conflict of interest There is no conflict of interest.

Ethical Approval Ethical approval was taken from Institutional Ethical Committee vide letter no EC/new/inst/2020/961.

Informed Consent Informed written consent was obtained from all the study participants.

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