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Original Article

Ground breaking concept for prediction and prevention of gestational diabetes mellitus and its sequelae

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Abstract. The global prevalence of diabetes is increasing, prompting a shift in focus towards the primordial prevention of diabetes. Gestational diabetes mellitus (GDM) presents an ideal opportunity for this prevention. First time NIH study in 2018 suggested HbA1c 5.3 (2hr PPBS>110mg/dl) in the 10th week of gestation predicts GDM, hence for prevention Blood sugar has to be brought to <110mg/dl, at 10th week, as fetal beta cells start secreting insulin around 11thweek. Therefore, at 8th week itself post prandial blood sugar (PPBS) has to be estimated because in case PPBS is >110 mg at 8th week, the grace period of 2 weeks is available to attain 2hr PPBS < 110mg at the 10th week. The objectives of this study were: 1. To determine the risk for GDM in the first trimester at 8 Weeks; 2. To manage the risk for GDM (BG between 110 to 119) at 8-10 weeks of gestation by MNT and metformin; and 3. To compare the maternal-fetal outcomes in both groups. At 8 weeks of gestation, pregnant women were recruited and divided into 2 groups. Group A included those with 2-hour PPBS of < 110 mg/dL, they received no intervention (82 participants). Group B ((69 Participants) included women with 2-hour PPBS of 110-119 mg/dL and they received Medical Nutrition Therapy (MNT) and Metformin intervention. The prediction of GDM is based on a 2-hour PPBS ≥110 mg/dL at 10weeks. Therefore, at the 8th week, the 2-hour PPBS need to be estimated. In group A, one (1.2%) of the subjects got GDM in the third trimester due to being grand multipara, while in group B, one (1.4%) developed GDM in the third trimester due to non- adherence to management measures. In conclusion, screening for early gestational glucose intolerance (EGGI) at 8 weeks of pregnancy and intervention will benefit in preventing GDM and its sequelae.

Keywords: Metformin, gestational diabetes mellitus, primordial prevention, post prandial blood sugar, impaired glucose tolerance, oral glucose challenge test, medical nutrition therapy, antenatal women, early gestational glucose intolerance.

Introduction

Diabetes mellitus presents a pressing global health challenge, affecting millions of people worldwide [1]. Efforts are being made globally to detect diabetes early and prevent complications. In clinical practice, screening for high blood sugar and detecting diabetes in its early stages are essential for "primary prevention." Treating patients and managing complications are crucial for "secondary prevention" and "tertiary prevention," [2].

NIH study in 2018 [3] suggested that blood glucose screening will identify gestational diabetes mellitus (GDM) risk and HBA1c 5.3 (2hr post prandial blood glucose; PPBG> 110mg/dl) in the 10th week predicts GDM [4]. No evidence-based trials were performed so far. Hence it has been conceptualized that maternal 2 hr PPBG should not exceed110 mg/dl by 10thweek.If it is >110 it indicates a risk of GDM. Therefore, it is crucial to bring down the glucose to<110 mg to prevent GDM [5]. Hernandez also suggested 2hr PPBS 99+/- 10 (fig1) [6]"Fuel-mediated teratogenesis:" In pregnant women, insulin does not pass through the placenta freely, whereas maternal glucose does. In response, when maternal glucose is high, the fetal pancreas attempts to balance by secreting more insulin, which increases fetal size by increasing growth hormone and becomes responsible for promoting growth and adiposity [10].

Ideally, to achieve this effect toward the primordial prevention of diabetes, the peak maternal PPBG should be

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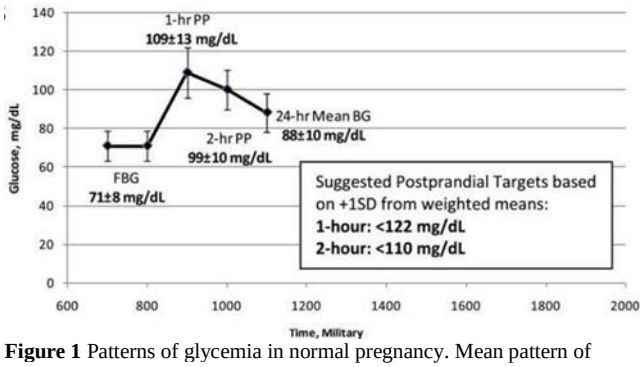

Figure 1 Patterns of glycemia in normal pregnancy. Mean pattern of glycemia across 12 studies [6]. Credit: Hernandez TL

< 110 mg/dl from preconception through the early weeks of pregnancy.

The target blood glucose levels should fall within the range of 99±10 mg/dl, and the goal should further work towards ensuring that the newborn offspring have their weight within the suitable range of 2.5-3.5 kg early gestational glucose intolerance (EGGI) should be diagnosed in all pregnant women to avoid its complications as much as possible. It is, therefore, essential to reduce the cut-off for glucose intolerance detection, especially in the first trimester of pregnancy (Table 1). With this backdrop, we recommend a pragmatic sub-classification of Gestational Diabetes Mellitus (GDM) [7].

Materials and Methods

A cross-sectional survey was conducted in the Department of Obstetrics and Gynecology, Madras Medical College, Chennai, Tamil Nadu, India. The study participants were pregnant women in their 8th to 10th week of pregnancy, and the study received ethical approval from the Ethics Committee of Madras Medical College. All eligible women were included after obtaining their written informed consent. A comprehensive history and physical examination were conducted following standard protocol. Gestational period was estimated based on the last menstrual period or ultrasound findings. All women underwent standardized testing for post- prandial blood glucose levels, two hours after breakfast, using Accuchek Performa glucometer. Subsequently, they received regular follow-up at the antenatal clinic and were monitored for GDM by diabetes in pregnancy study group India (DIPSI) test at 14-16, 24-28, and between 32-34 weeks' gestation.

All expectant mothers underwent testing for 2-hour PPBS at their 8th week of pregnancy and grouped into A and B. Group A consists of 82 participants with their 2hr PPBS<110mg/dl called euglycaemic group and Group B, 69 participants if PPBS levels exceed ≥110 mg/dl in the 8th week and called interventional group. The Group B (interventional) women were provided with a comprehensive treatment plan involving medical nutrition therapy (MNT), exercise, and the administration of Metformin which is a safe drug [8] during pregnancy and dosage used is 250 mg twice daily until the completion of their pregnancy. They also should ensure that their postprandial blood glucose levels are below 110 mg/dl (mean 99 +/- 10), other than their routine antenatal care.

Women, who were detected to have GDM, were given treatment as per standard protocol. All recruited women were monitored carefully up to delivery. The new-born's weight and maternal and neonatal outcomes were observed at delivery.

Sample Size

The sample size was calculated on the prevalence of gestational diabetes at 12% with a power of .80 at a confidence interval of 95% percentile.

Inclusion criteria were all pregnant women around 8 weeks with singleton pregnancy. Exclusion criteria included known diabetic (Type 1 or Type 2) or pre-diabetes, any women on metformin for Polycystic ovary syndrome (PCOS) and women beyond 10 weeks of pregnancy and with features of threatened abortion, pregnant women with PPBG 2-hour with ≥120 mg/dl were excluded from the study. For the study 2hr PPBS between 110 (+1SD) and 119 (+2SD) only is taken as PPBS 120 and above is gestational glucose intolerance which is a different category.

Statistical Method

Data analysis is an essential part of our overall approach when conducting research. For data encoding, we used MS Excel; for statistical analysis, we used Statistical Package for Social Science (SPSS) 21.0. The continuous data was well analyzed for the means and Standard Deviation (SD) or Median and Interquartile range (IQR). Categorical data was expressed in terms of percentage. Sample t-tests were used to compare the means or medians of two independent groups. The chi-square was used to define the strength of categorical variables associated with high stringency. The format used included presenting discrete variables as proportions and continuous variables as mean and standard deviation. Moreover, we used the independent t-test to determine whether the observed mean differences between distinct groups are statistically significant. All tests were conducted at two-tailed, and $p < 0.05$ was consideredstatistically significant.

Results

In the primary outcome, out of 82 pregnant women in Group A, only one developed (1.2%) GDM and she was grand multipara and in Group B again one developed (1.4%) GDM as she discontinued Metformin at 22 weeks of gestation. Gestational week at delivery: only 4.2% delivered preterm in the interventional group and 9.8 % in the non-interventional group. 96% in interventional group and 90% in the non- interventional delivered at term indicating the intervention has reduced the preterm deliveries. Birth weight of babies between 2.5 to 3.5 kg was 84% in the interventional group and 74% in the euglycemic group. The incidence of caesarean was 35% in interventional group and 37% in euglycemic group. And the indications for LSCS are same in both the groups.

The BS values at 8, 9, 10, 11 were estimated to make sure the PPBS remains <110mg/dl. Metformin was started if it is >110mg/dl, in the intervention group. Though the PPBS had come down to < 110, it is not to the extent of

TABLE 1
CHARACTERISTICS OF THE PARTICIPANTS AT BASELINE AT POST PRANDIAL AT 8-11 WEEKS GESTATION.

Variable	**PPBS at 8-11 wks>=110(mg/dl)** (Mean ± SD) N = 69 (%)	**PPBS at 8-11 wks<110(mg/dl)** (Mean ±S D) N = 8 (%)	**P-value**
Age(years)	28.0 ± 4.5	25.6 ± 4.7	0.005
Gestational week			0.059
<37	3(4.2)	8(9.8)	
37+	6(8.7)	19(23.2)	
38+	35(50.7)	28(34.1)	
39+	16(23.2)	19(23.2)	
40	9(13.0)	8(9.8)	
Gravida			0.574
Primi	28 (40.6)	41 (59.4)	
Multi	37 (45.1)	45 (54.9)	
Past history of fetal waste			0.132
Present	16(43.2)	13(28.9)	
Absent	21(56.8)	32(71.0)	
Type of delivery			0.943
NVD	41 (65.1)	46 (63.0)	
LSCS	22 (34.9)	27 (37.0)	
Term of delivery			1.000
Pre term	4 (6.3)	4 (5.5)	
Term	59 (93.7)	69 (94.5)	
Family history of DM			0.518
YES	34 (49.3)	35 (42.7)	
NO	35 (50.7)	47 (57.3)	
BMIkg/m2 (EarlyI trimester)	25.9 ± 4.1	24.2 ± 3.4	
BMI category			0.148
Normal (18.5-22.9)	18(26.1)	29(35.4)	
Over weight (23.0-24.9)	17(24.6)	22(26.8)	
Obese (25.0-29.9)	22(31.9)	26(31.7)	
Morbid obese (30-40)	12(17.4)	5(6.1)	

glycemic level in the euglycemic group necessitating the adjustment of metformin dosage.

Discussion

In this study, 69 women (PPBS ≥110mg/dl) participated in the intervention group (B Group) and 82 women with PPBS <110 mg/dl in the euglycemic group (A Group). It is observed that the mean age between the groups were statistically significant (P<0.05). The other basic characteristics, such as Gravida, history of previous Fetal waste, type of delivery, term of delivery, family history of DM, and BMI, are not statistically significant (P>0.05), indicating these characteristics are similar in both the groups (Table 1).

Table 2 enumerates the primary and secondary outcomes of the study. Regarding the primary outcome, the difference in the mean PPBS values between the groups in the initial week from 8 to 11 weeks is statistically significant. A gradual decrease in mean PPBS value was observed in the intervention group, and an almost similar OGCT values were noticed in the later weeks of 16, 24, and 32; the difference in the mean value of OGCT is not significant (P>0.05) between the groups. The mean OGCT value converged at 32 weeks in both groups, indicating

TABLE 2
PRIMARY AND SECONDARY PREGNANCY OUTCOMES.

Outcome	**PPBS>=110 mg/dl Fetal-maternal outcomes** Metformin Mean ± SD N = 69 (%)	**PPBS<110 mg/dl Fetal-maternal outcomes** No intervention Mean ± SD N = 82 (%)	**P-value**
Primary pregnancy Outcomes			
PPBS– 8 weeks	111.6 ± 6.2	97.6 ± 6.8	0.000
PPBS– 9 weeks	109.3 ± 6.6	97.6 ± 6.5	0.000
PPBS – 10 weeks	107.1 ± 4.7	97.3 ± 7.0	0.000
PPBS – 11weeks	105.8 ± 3.8	97.2 ± 7.7	0.000
OGCT – 16 weeks	110.2 ± 12.0	108.3 ± 11.9	0.353
OGCT – 24 weeks	112.4 ± 11.7	109.1 ± 14.6	0.133
OGCT – 32 weeks	110.8 ± 10.8	110.8 ± 7.9	0.976
Secondary outcome			
Birth weight (kg.)	**3.0 ± 0.4**	**2.9 ± 0.4**	0.360
<2.5 kg	4(6.3)	10(13.7)	
2.5 – 2.99	29(46.0)	34(46.6)	
3.0 – 3.49	24(38.1)	20(27.4)	
≥3.5	6(9.5)	9(12.3)	
Indication of LSCS			0.633
No indication	48(69.6)	61(74.4)	
CPD	4(5.8)	3(3.7)	
FD	2(2.9)	2(2.4)	
MSL	0(0.0)	3(3.7)	
MSFD	2(2.9)	2(2.4)	
PROM	2(2.9))	2(2.4)	
Breech	3(4.3)	3(3.7)	
Previous LSCS	6(8.7)	6(7.3)	

that the intervention significantly impacts the glycemic level in the intervention group.

In the secondary outcome, the mean birth weight of babies in the groups is not statistically significant (P>0.05). The incidence of LSCS in the intervention group is 35%, and in the non-intervention group 37%; however, the incidence of LSCS is higher in the non-intervention group, and the difference is not significant (P>0.05). One grand multi developed GDM in euglycemic group(A) and one pregnant woman developed GDM in the interventional group(B) as she discontinued the metformin regarding the use of metformin during pregnancy, it has been proven to be safe from conception to delivery [9]. Not only does it help reduce the risk of pregnancy-induced hypertension and preeclampsia, but it has also been linked to the absence of significant differences in children's weight, height, head circumference, and waist circumference when compared to a placebo [10]. Exposure to metformin in utero is not associated with a higher body mass index (BMI) for children of women with diabetes. Use of metformin after 8 weeks of pregnancy is safe for intervention if the 2hr PPBG is >110mg/dl and also the embryonic stage is over by 8weeks. It is vital to note, however, that starting metformin after the 12th week will not effectively prevent GDM [11].

Limitation of Study

Given that our study was conducted at a single center, it is essential to utilize a larger sample size and a multicenter approach to robustly validate our findings on pregnancy outcomes. However, our results provide a valuable framework for researchers eager to implement

early pregnancy dysglycemia interventions as early as 8 to 10 weeks. By doing so, we can potentially make a significant positive impact on the course of the disease.

Highlights and Conclusion

Before getting pregnant, it is crucial to plan for a better outcome for the fetus. It is essential to improve metabolic control early in pregnancy. Gestational diabetes can be predicted if the 2-hour postprandial blood glucose (PPBG) level is equal to or greater than 110 mg/dl in the 10th week. Preventive measures must be implemented by the eighth week to ensure the mother's PPBG remains below 110 mg/dl and throughout the pregnancy. Medical nutrition therapy (MNT) and Metformin will be continued until childbirth. The priming of the fetal beta cells around the 11th week may contribute to the persistence of fetal hyperinsulinemia throughout pregnancy. Preventing diabetes from developing is well-established, applicable, and achievable. Early Gestational Glucose Intolerance (EGGI) is a 2-hour PPBG in the early weeks of pregnancy equal to or greater than 110 mg/dl. We hope to achieve a generation free of diabetes shortly, if not in the coming year. Therefore, we are committed to achieving the "Primordial Prevention of Diabetes."

"The Womb is more important than the home." It all starts in utero. Hence, for the “Diabetes-Free Generation," we should concentrate on offspring development." Focus on the Fetus for the Future. “We hope to achieve a generation free of diabetes in the near future, if not in the coming year. Therefore, we are committed to achieving the "Primordial Prevention of Diabetes."

Conflict of interest

The authors declare no conflicts of interest.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: 2021. Available at: https://www.diabetesatlas.org.

2. Briana Mezuk, Julie Ober Allen; Rethinking the Goals of Diabetes Prevention Programs. Diabetes Care 44: 2457–2459, 2021.

3. NIH analysis 16th August 2018. Centers for Disease Control and Prevention. National Diabetes Statistics Report 2021; website.https://www.cdc.gov/diabetes/data/statistics-report/index.html.

4. Hinkle SN, Tsai MY, Rawal S, Albert PS, Zhang C. HbA1c Measured in the First Trimester of Pregnancy and the Association with Gestational Diabetes. Sci Rep 8:12249, 2018.

5. Seshiah, V. Primordial prevention: a futuristic approach to intervene in gestational diabetes and its sequelae Int J. Diabetes Dev Ctries 43:483–484, 2023.

6. Hernandez TL, Friedman JE, Van Pelt RE, Barbour LA: Patterns of glycemia in normal pregnancy: should the current therapeutic targets be challenged? Diabetes Care. 34:1660-1668, 2011.

7. Seshiah V, Sahay BK, Das AK, Shah S, Banerjee S, Rao PV, Ammini A, Balaji V, Gupta S, Divakar H, Misra S, Thanawala U. Gestational diabetes mellitus--Indian guidelines. J Indian Med Assoc 107: 799-802, 804-806, 2009.

8. Brand KMG, Sarelainen L, Sonaalg et al. Metformin in pregnancy and risk of adverse long- term Outcomes: A register-based cohort study. BMJ Open Dia Res Care 10:e002363, 2022.

9. Seshiah V, Bronson SC, Balaji V, Jain R, Anjalakshi C: Prediction and Prevention of Gestational Diabetes Mellitus and Its Sequelae by Administering Metformin in the Early Weeks of Pregnancy. Cureus 15:31532, 2022

10. Krishnaveni GV, Veena SR, Hill JC, Kehoe S, Karat SC, Fall CH: Intrauterine exposure to maternal diabetes is associated with higher adiposity and insulin resistance and clustering of cardiovascular risk markers in Indian children. Diabetes Care 33:402-4, 2010.

11. Valdés E, Sepúlveda-Martínez A, Candia P, Abusada N, Orellana R, Manukian B, Cuellar E. Metformin as a prophylactic treatment of gestational diabetes in pregnant patients with pregestational insulin resistance: A randomized study. J Obstet Gynaecol Res 44(1):81-86, 2018.