FASTING PLASMA GLUCOSE AS A PRIMARY SCREENING TEST FOR THE DIAGNOSIS OF GESTATIONAL DIABETES MELLITUS

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ABSTRACT

Background: Gestational Diabetes Mellitus (GDM) is often encountered during pregnancy. The gold standard for diagnosing GDM is oral glucose tolerance test but it is inconvenient, unpleasant and time consuming process. On the other hand, measuring fasting plasma glucose level is easy, cost effective and may be used to diagnose GDM. **Aim:** To see the diagnostic efficacy of fasting plasma glucose (FPG) compared to oral glucose tolerance test (OGTT) during pregnancy. **Materials and Method**: In this cross-sectional study, we enrolled 542 pregnant women 18 years or older by consecutive sampling irrespective of gestational age. Three-sample 75-gm OGTT was done and categorized into either normal glucose tolerance (NGT) ,abnormal glucose tolerance (AGT) according to WHO (World Health Organization) 2013 criteria. **Results:** The sensitivity of FPG with a threshold of 5.1 mmol/L was 47.3% among the study subjects, which was very low but specificity was very high (99.7%). However, changing the cut- off value to 4.7mmol/L and 4.5mmol/L significantly increased the sensitivity to 64.8% and 73.3% with modestly decreased specificity to 86.2% and 73.2% respectively. In pregnant women with gestational age 24 to 28 weeks, FPG with a threshold of 4.5mmol/L could identify 75% of Gestational Diabetes Mellitus (GDM) subjects with specificity of 76.8%. Furthermore, it has the highest sensitivity in detecting AGT in all three trimesters (80%, 74.4% and 68%) compared to 4.7 mmol/L (80%, 68.9% and 50%) and 5.1 mmol/L (80%, 47.8% and 30%) in 1st, 2nd and 3rd trimester respectively. FPG had a positive correlation with maternal age (r=0.138, p=0.001), and body mass index (BMI) (r=0.164, p<0.001) but a negative correlation with weeks of gestation (r= -0.242, p<0.001). **Conclusion**: FPG with cut-off value of 4.5mmol/L may be used as an initial screening test for GDM to reduce the need for OGTT.

Keywords: Gestational Diabetes mellitus, Screening Test, Fasting Plasma Glucose.

INTRODUCTION

Gestational Diabetes Mellitus (GDM) is one of the most typically encountered endocrine issues in pregnancy. About one in six women globally and one in four women in Southeast Asia has been suffering from some form of hyperglycemia in pregnancy (HIP), and GDM contributes about 80% of cases of HIP[1]. It is associated with many complications for both mother and off spring reported from many well-established studies from different parts of the world [2-6]. Screening for GDM is essential as a high prevalence of GDM is observed in Southeast Asia. Although screening for GDM with an oral glucose tolerance test is a gold standard and ideal procedure, but it is inconvenient, unpleasant, time-consuming, and unsuitable for large-scale screening.

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Furthermore, oral glucose load is not well accepted by many patients. One study reported that nearly half of the pregnant women were extremely bothered with having to drink the glucose solution[7]. Conversely, FPG is inexpensive, reproducible, and suitable for a screening test. In the hyperglycemia and pregnancy outcome (HAPO) study, 51% of GDM was diagnosed by an FPG > 5.1 mmol/L[8].In China, Due to complexity of Chinese vast geography and population, they have adapted a two steps strategy for GDM screening with FPG. They selectively do OGTT in pregnancy if FPG value is found between 4.4 to 5.0 mmol/L. This simplicity of test procedure ensures universal screening of GDM in low resource setting [9].In one study from South Africa reported, FPG of ≥5.1 mmol/L identified 87.8% of GDM patients and the sensitivity and specificity of FPG ≥4.5 mmol/L were 98% and 80%, respectively[10]. Our study aimed to see the sensitivity and specificity of FPG with different cut-off values as a screening test for GDM in different trimesters.

MATERIALS AND METHOD

Study design and Study subjects

This cross-sectional study included 542 pregnant women with an age ≥18 years. Pregnant women with gestational age ≥ 6 to 37 weeks, irrespective of presence or absence of risk factors for GDM were recruited between February 2014 and January 2017 by consecutive sampling from the Antenatal clinic, department of Gynecology and Obstetrics, Bangladesh Medical University (BMU), Dhaka, after approval by the Institutional Review Board (IRB) of the same institution. OGTT was done at the GDM clinic, department of Endocrinology, BSMMU. Any women with prior history of GDM or DM, or currently using steroids at supraphysiological dose for any illnesses were excluded from the study. Three-samples 75-gm OGTT was done and categorized into either NGT (normal glucose tolerance) or AGT (abnormal glucose tolerance) according to WHO 2013 criteria. AGT comprises both GDM and DIP (diabetes in pregnancy). Demographic and clinical variables including height, weight, BMI (kg/m^2), and blood pressure (mm Hg) were recorded in structured data collection sheet for analysis.

Analytic method

After collection of blood samples, it was centrifuged at the collection site within 15 minutes and transported to biochemistry laboratory within one hour of collection for analysis. Plasma glucose was assayed by the glucose oxidase method with an automated analyzer [RA-50 analyzer (Dade Behring, Germany)].

Statistical analysis

All data were processed in IBM SPSS Statistics for Windows version 23.0 (IBM Corp, Armonk, NY, USA) and expressed as frequencies or percentages as well as mean (± SD) as applicable. The frequency of AGT was assessed by descriptive statistics and comparison of different variables between NGT and AGT were done by using chi-square test and independent sample t-test as applicable. The p values ≤ 0.05 were considered statistically significant. Correlation of FPG with various maternal factors was done by Pearson correlation. Sensitivity, specificity, positive predictive value and negative predictive value of FPG were assessed in relation to three samples OGTT status according WHO 2013 criteria using following formulas (formula 1).

Formula 1: Accuracy of a diagnostic test (FPG)

Diagnostic Test (FPG)	WHO 2013 Criteria	
	Affected	**Unaffected**
Positive test	True positive (a)	False positive (b)
Negative test	False negative (c)	True Negative (d)

Sensitivity (%) = (a/ a+c) × 100
Specificity (%) = (d/ b+d) × 100
Positive predictive value = a/ a+b
Negative predictive value = d/c+d

RESULTS

Our study population were mainly from housewife occupational category (69%) and majority of them were multigravida (59%). About half of the study population (49.1%) were from second trimester and only 16% of them from first trimester (Table 1). Based on WHO 2013 criteria, 30.5% of the study population had AGT, of which GDM were 26.4% and DIP were 4.1% as depicted in Figure 1. The sensitivity of FPG as a screening test for GDM compared to three samples 75g OGTT was 47.5% among the study subjects, which was very low but it's specificity, positive predictive value, negative predictive value seemed to be good (99.73%, 98.73% and 81.21% respectively). However, changing the cut off value of FPG from 5.1mmol to 4.7mmo/L and 4.5mmol/L significantly increased the sensitivity to 64.8% and 73.3% respectively (Figure 2). Selecting the study population between 24-28 weeks of gestation mildly increased the diagnostic sensitivity and specificity of FPG and a threshold of 4.5mmol/L could identify 75% of GDM subjects with specificity of 76.8% (Figure 3). Trimester specific analysis of efficacy of FPG revealed that the FPG has the highest sensitivity for diagnosis of GDM in first trimester (80%) regardless of the cut-off value used for diagnosis, but its sensitivity progressively declined in subsequent trimesters (Table 2). Among different cut off value of FPG, 4.5mmol/L had the highest sensitivity in all three trimesters for diagnosis of GDM (Table 2). Pearson correlation revealed FPG had positive and significant correlation with maternal age and BMI. However it was negatively correlated with gestational weeks (Table 3).

Table 1: Socio-demographic characteristics of study subjects (N=542)

| Characters/variables	Frequency (%)
Age (mean ± SD, yr)	26.23±4.98
BMI (mean ± SD, kg/m^2)	25.23±4.15
Systolic BP (mean±SD, mmHg)	106±11
Diastolic BP (mean±SD, mmHg)	68±9
Family history of DM	
Present	205(37.8)
Absent	337(62.2)
History of abortion	
Present	160(29.5)
Absent	382(70.5)
Gravida	
Primigravida	222(41)
Multigravida	320(59)
Trimester	
1st Trimester	87(16.1)
2nd Trimester	266(49.1)
3rd Trimester	189(34.8)
Occupation	
Housewife	374(69)
Service holder	121(22.3)
Students	47(8.7)

(Within parenthesis, percentages are over column total)
BMI=body mass index; BP= Blood pressure; DM=Diabetes mellitus; SD: Standard deviation
N= Total number subjects;

Glycemic stutus among the study subjects (N=542)
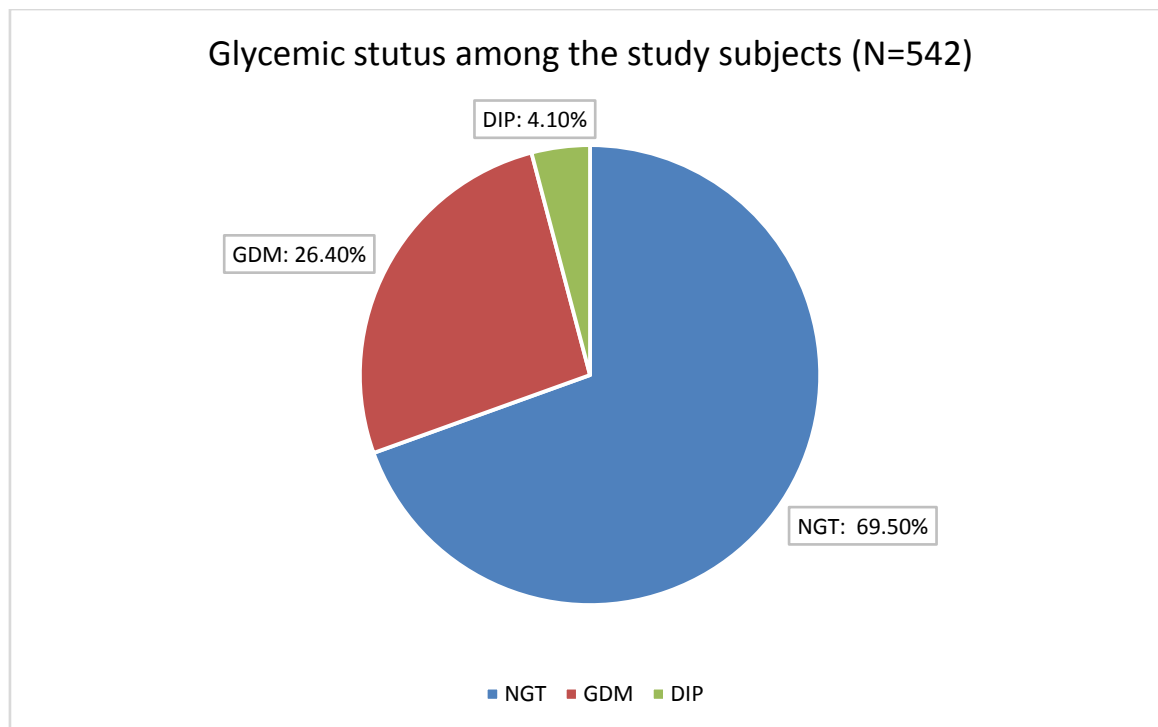
Figure 1: Glycemic status among the study subjects according to WHO 2013 criteria. (NGT= Normal Glucose Tolerance, DIP = Diabetes in Pregnancy, GDM= Gestational Diabetes mellitus)
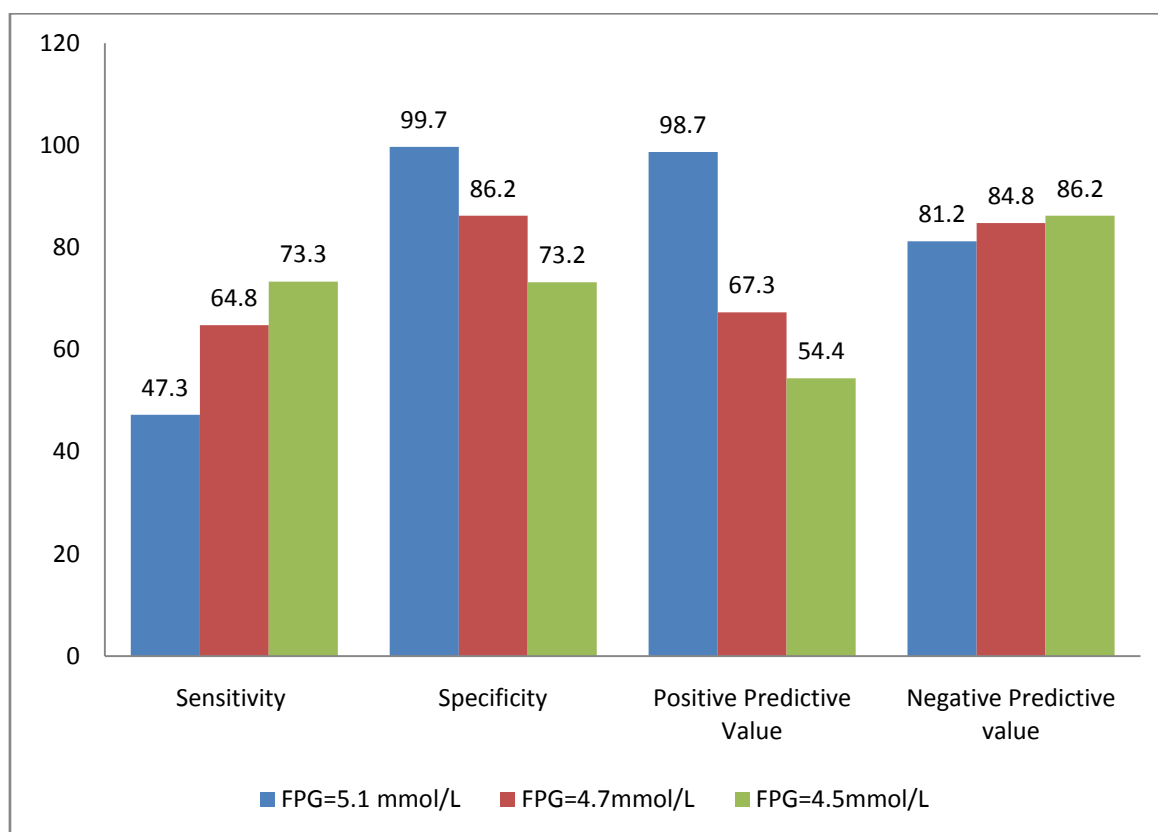
Figure 2: Diagnostic efficacy of Fasting Plasma Glucose in study subjects of all trimesters (n=542) with different cut off value (5.1, 4.7 and 4.5 mmol/L)
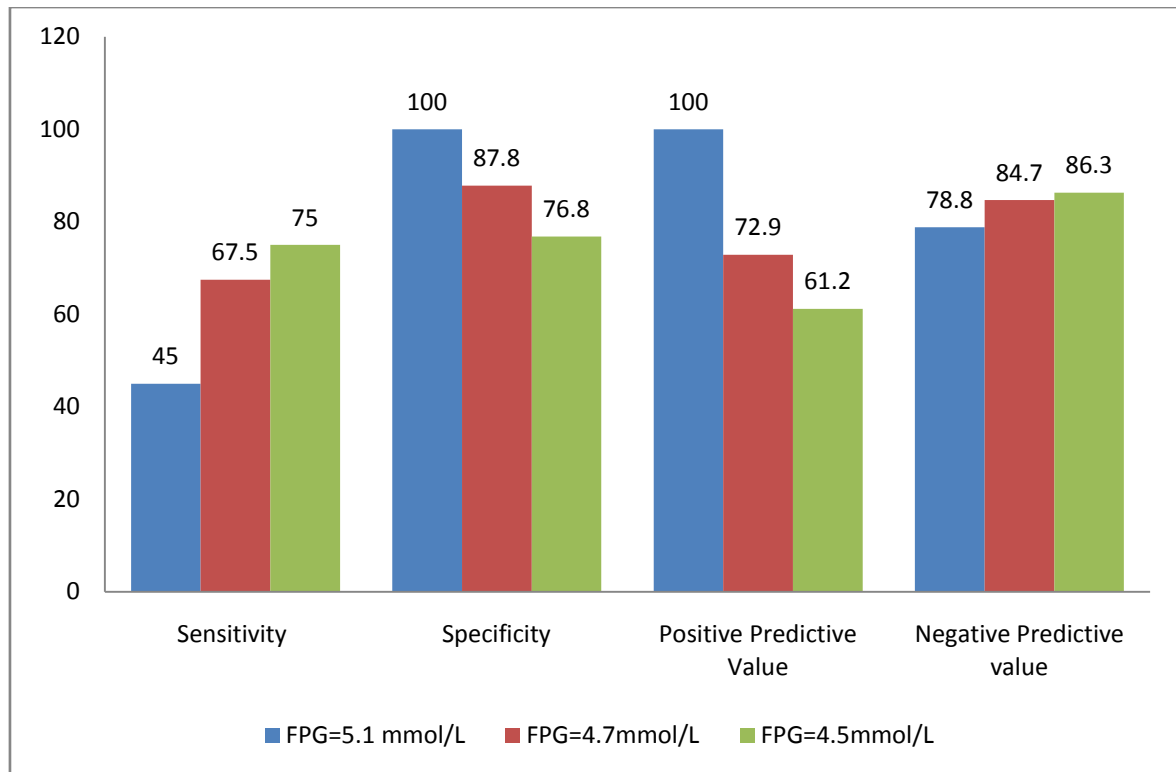
Figure 3: Diagnostic efficacy of Fasting Plasma Glucose in pregnant women with gestational age 24-28 weeks (n=122) with different cut off value (5.1, 4.7 and 4.5 mmol/L)

Table 2: Diagnostic efficacy of Fasting Plasma Glucose with cut off value of 5.1, 4.7 and 4.5 mmol/L for diagnosis of Abnormal Glucose Tolerance at different trimester (N=542)

Parameters	Trimesters	FPG diagnostic efficacy at different cut off values		
		FPG=5.1 mmol/L	FPG=4.7mmol/L	FPG=4.5mmol/L
Sensitivity (%)	1st	80	80.0	80.0
	2nd	47.78	68.9	74.4
	3rd	30	50	68
Specificity (%)	1st	100	75.8	62.9
	2nd	99.4	84.0	68.7
	3rd	100	94.2	83.4
Positive Predictive Value (%)	1st	100	57.14	46.5
	2nd	97.7	68.1	55
	3rd	100	75.7	59.6
Negative Predictive value (%)	1st	92.5	90.4	71.3
	2nd	78.8	84.0	84
	3rd	79.9	84.0	87.8

N= Total number subjects; FPG: Fasting Plasma Glucose

Table 3: Pearson correlations of FPG with various patient factors

Determinant	Study Subjects (n=542)	
	r	*p*
FPG vs. Age	0.138	0.001
FPG vs. BMI	0.164	<0.001
FPG vs. Weeks of gestation	-0.242	<0.001

FGP= Fasting plasma glucose, BMI= Body mass index (kg/m^2)
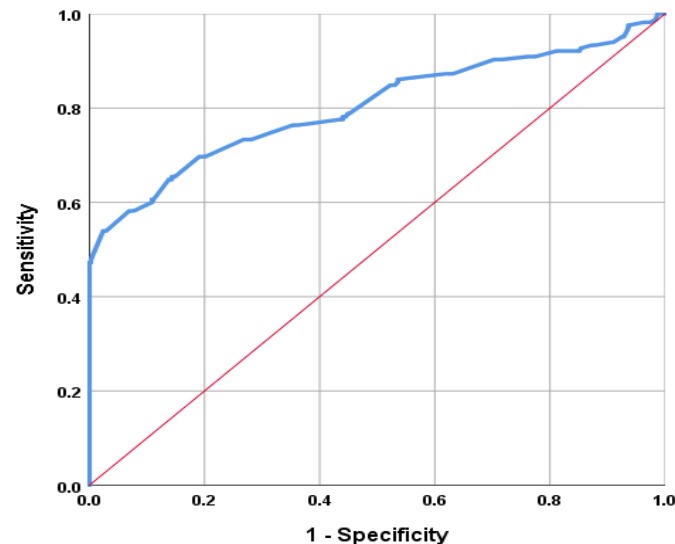
Figure 4: The Receiver Operating Characteristic (ROC) curve showing the performance of FPG in diagnosing AGT in pregnancy among the study subjects (N=542)

FPG = fasting plasma glucose; AGT = abnormal glucose tolerance (includes gestational diabetes mellitus and diabetes in pregnancy)

Figure 4 shows the receiver operating characteristic (ROC) curve showing the performance of FPG in diagnosing AGT of pregnancy (AUC 0.80; 95% CI: 0.76-0.85; *p*<0.001). The Youden index was 0.56 at the FPG cut-off 4.59 mmol/L with a sensitivity of 70% and specificity 81%.

DISCUSSION

It is well established from pregnancy outcome based study that the OGTT is a gold standard for diagnosis of GDM[11]. However many pregnant women feel distressed during oral glucose load for OGTT[7] .The use of FPG as a screening test to avoid OGTT was studied by many researchers in different countries with very positive result[10,12-16]. In our study, FPG could identify only 47.5% pregnant women with GDM with the same cut off value used in WHO 2013 criteria and international association of diabetes in pregnancy study group (IADPSG) criteria, which is similar to a study done by Agarwal et al. [17] to certain extent. However, changing the cut off value of FPG from 5.1mmol/L to 4.5 mmol/L significantly increased the sensitivity to 73.3% and specificity to 73.2%. A study done among the Mexican population reported that the FPG threshold of 4.5 mmol/L had the higher sensitivity (97%), but the specificity was very poor (50%)[13]. This significant

difference in sensitivity and specificity may be attributed to the socio-demographic characteristics of study population. Mean age of our study population was 26 years, whereas their study only included adolescent women with the mean age of 16 years. Maternal age has significant impact on overall prevalence of GDM as well as the FPG during pregnancy. Another study reported that the addition of maternal age to FPG increase the sensitivity of FPG for diagnosis of GDM [14].Our study also reported significant positive correlation of maternal age with fasting plasma glucose.

Şevket et. al reported the higher sensitivity (93.4%) of FPG cut-off value of ≤4.5 mmol/l with almost similar specificity (67.6%) like our study[15].A study from South Africa reported very high sensitivity and specificity (98% and 80% respectively) with the same FPG cut off value[10], this may be due to the gestational age of the study population, they included only the pregnant women with gestation age 24-28 weeks whereas our study population were from all three trimesters. The subgroup analysis with pregnant women of 24-28 weeks of gestation in our study population revealed relatively lower sensitivity and specificity. Ethnicity may also contribute to the sensitivity which needs to be explored by multinational study including the population of different ethnicity.

Since 2000, the UAE (United Arab Emirates) has been using two thresholds for "rule-in and rule-out" of GDM based on multiple studies which significantly reduce the number of OGTT. They used FPG cut-off of 5.0 mmol/L for "rules-in" GDM with 100% specificity and another cut-off of 4.4 mmol/L for "rules-out" GDM with variable sensitivity. Use of this approach successfully avoided up to 70% OGTT during pregnancy. Similar results were observed from studies in China and Brazil[18]. Our study also observed similar result; using FPG with a threshold of 4.5mmol/L could potentially identify about 70% pregnant women with GDM and reduce the need for oral glucose load in a significant number of patients.

LIMITATIONS

Pregnant women in all trimesters were included in our study, whereas most of the studies included only pregnant women with gestational age 24 to 28 weeks, using IADPSG or WHO criteria. Relatively lower number of study population of this specific gestational week's category may attribute to relatively lower sensitivity and specificity of FPG as a screening test in our study. Asian population typically has lower FPG with sharp rise of post prandial plasma glucose which is not usually seen in Caucasian counterparts [19].Therefore, sensitivity of FPG may vary in different regions of the world.

CONCLUSION

FPG may be used as a screening test for selecting the ideal patient for OGTT.Using a protocol adapted in the UAE and China may be a suitable alternative and cost effective strategy for universal screening of GDM.

Financial Disclosure

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethical approval

This study was approved by the Institutional Review Board (IRB) of BMU, Reg: No. BSMMU/2013/14269 and BSMMU/2016/2746.All procedures performed in studies involving human participants were in accordance with the ethical standards of the IRB and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed written consent was obtained from each of the participants included in the study.

CONFLICT OF INTEREST

There is no conflict of interest.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas-10th edition. Available from: www.diabetesatlas.org [(Accessed on 25th January 2023)]

2. Sheiner E. Gestational Diabetes Mellitus: Long-Term Consequences for the Mother and Child Grand Challenge: How to Move on Towards Secondary Prevention? Front Clin Diabetes Healthc 2020;1:546256.doi:10.3389/fcdhc.2020.546256.

3. Hartling L, Dryden DM, Guthrie A, Muise M, Vandermeer B, Donovan L. Benefits and harms of treating gestational diabetes mellitus: A systematic review and meta-analysis for the U.S. Preventive Services Task Force and the National Institutes of Health Office of Medical Applications of Research. Ann Intern Med. 2013; 159(2):123–129. doi: 10.7326/0003-4819-159-2- 201307160-00661.

4. Shah BR, Retnakaran R, Booth GL. Increased risk of cardiovascular disease in young women following gestational diabetes mellitus. Diabetes Care. 2008;31(8):1668–69. doi: 10.2337/dc08-0706.

5. Lawlor DA, Fraser A, Lindsay RS, Ness A, Dabelea D, Catalano P, et al. Association of existing diabetes, gestational diabetes and glycosuria in pregnancy with macrosomia and offspring body mass index, waist and fat mass in later childhood: Findings from a prospective pregnancy cohort. Diabetologia. 2010;53(1):89-97.doi: 10.1007/s00125-009-1560-z.

6. Jayasinghe IU, Koralegedara IS, Agampodi SB. Early pregnancy hyperglycaemia as a significant predictor of large for gestational age neonates. Acta Diabetol. 2022;59(4):535-43. doi: 10.1007/s00592-021-01828-1.

7. Alecrim MJ, Mattar R, Torloni MR. Pregnant women's experience of undergoing an oral glucose tolerance test: A cross-sectional study. Diabetes Res Clin Pract. 2022;189:109941.doi: 10.1016/j.diabres.2022.109941.

8. HAPO Study Cooperative Research Group; Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358(19):1991-2002. doi: 10.1056/NEJMoa0707943.

9. Juan J, Yang Hui-Xia, Su Ri-Na, Kapur A. Diagnosis of Gestational Diabetes Mellitus in China: Perspective, Progress and Prospects. Maternal-Fetal Medicine. 2019; 1(1):31-37. doi: 10.1097/ FM 9.0000000000000008.

10. Dickson LM, Buchmann EJ, Janse van Rensburg C, Norris SA. Fasting plasma glucose and risk factor assessment: Comparing sensitivity and specificity in identifying gestational diabetes in urban black African women. S Afr Med J. 2019; 110(1):21-26. doi: 10.7196/SAMJ.2019.v110i1.14089.

11. Chatzakis C, Eleftheriades A, Demertzidou E, Dinas K, Vlahos N, Sotiriadis A, et al. Pregnancy outcomes in the different phenotypes of gestational diabetes mellitus based on the oral glucose tolerance test. A systematic review and meta-analysis. Diabetes Res Clin Pract. 2023;204:110913. doi: 10.1016/j.diabres.2023.110913.

12. Trujillo J, Vigo A, Reichelt A, Duncan BB, Schmidt MI. Fasting plasma glucose to avoid a full OGTT in the diagnosis of gestational diabetes. Diabetes Res Clin Pract. 2014;105(3):322-6. doi: 10.1016/j.diabres.2014.06.001.

13. Reyes-Muñoz E, Sandoval-Osuna NL, Reyes-Mayoral C, Ortega-González C, Martínez-Cruz N, Ramírez-Torres MA, et al. Sensitivity of fasting glucose for gestational diabetes mellitus screening in Mexican adolescents based on International Association of Diabetes and Pregnancy Study Groups criteria: a diagnostic accuracy study based on retrospective data analysis. BMJ Open. 2018;8(4):e021617.doi:10.1136/bmjopen-2018-021617.

14. Tai YY, Lee CN, Kuo CH, Lin MW, Chen KY, Lin SY, et al. Simplifying the screening of gestational diabetes by maternal age plus fasting plasma glucose at first prenatal visit: A prospective cohort study. PLoS One. 2020;15(8):e0237224. doi: 10.1371/journal.pone.0237224.

15. Şevket O, Ateş S, Kılıç G, Molla T, ÖzkalF,Dansuk R, et al. Using an initial fasting plasma glucose to decrease the need for the Oral Glucose Tolerance Test during FPG as primary screening test of GDM 120.

16. Saeedi M, Hanson U, Simmons D, Fadl H. Characteristics of different risk factors and fasting plasma glucose for identifying GDM when using IADPSG criteria: a cross-sectional study. BMC Pregnancy Childbirth. 2018;18(1):225. doi: 10.1186/s12884-018-1875-1.

17. Agarwal MM, Dhatt GS, Punnose J, Koster G. Gestational diabetes in a high-risk population: using the fasting plasma glucose to simplify the diagnostic algorithm. Eur J Obstet Gynecol Reprod Biol. 2005;120(1):39-44. doi: 10.1016/j.ejogrb.2004.07.034.

18. Agarwal MM. Gestational diabetes mellitus: Screening with fasting plasma glucose. World J Diabetes . 2016;7(14):279-289. doi:10.4239/wjd.v7.i14.279

19. Balaji V, Balaji M, Anjalakshi C, Cynthia A, Arthi T, Seshiah V. Inadequacy of fasting plasma glucose to diagnose gestational diabetes mellitus in Asian Indian women. Diabetes Res Clin Pract. 2011; 94:21-23. doi: 10.1016/j.diabres. 2011. 07.008