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ORIGINAL ARTICLE

Frequency of Post-partum Persistence of Glucose Intolerance in GDM Patients is Strikingly High at a Tertiary Care Hospital in Bangladesh

Sharmin-Jahan, M Fariduddin,Nusrat-Sultana,Yasmin-Aktar,
Mashfiqul-Hasan, Sandesh-Panthi, M Atiqur-Rahman, M A Hasanat.
Department of Endocrinology,Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, Bangladesh.
For Correspondence: Prof. M A Hasanat, Professor of Endocrinology, Department of Endocrinology, D Block, Room No. 1620, BSSMU, Shahbag, Dhaka, Bangladesh. Email: hasanatdr@yahoo.com

Abstract

Objectives: *The study was aimed to observe the frequency of persistence of glucose intolerance in patients with gestational diabetes mellitus (GDM) at 6-12 weeks post-partum & to compare the efficacy of 75g- 2-hr-oral glucose tolerance test (OGTT) with the indices derived from fasting plasma glucose (FPG) in this respect.*

Methods: *This study encompassed 108 subjects [age (year, 29.4±5.3); BMI (Kg/m^2, 26.4±4.97) mean±SD] diagnosed as GDM during their index pregnancy by standard criteria. At 6-12 week post-partum, 75g-2hr-OGTT following World Health Organization (WHO) criteria was done to know their glycemic status. Results were also analyzed in light of American Diabetes Association (ADA) criteria. Plasma glucose was measured by glucose-oxidase method within 2 hour of sampling.*

Results: *Frequencies of glycemic status defined by WHO and ADA criteria were- normal glucose tolerance (NGT): 57.4% and 50%; impaired fasting glucose (IFG): 0.9% and 8.3%; impaired glucose tolerance (IGT): 23.1% and 12% and diabetes mellitus(DM): 14.8% and 14.8% respectively. Highest frequency of abnormal glucose tolerance (AGT) was found in age-group 30-35 year (50%, 23/46) and the commonest glucose abnormality was IGT (54.3%, 25/46) followed by DM (34.8%, 16/46). There was a strong concordance between the magnitudes of FPG and 02-h values ($\chi 2$=11.115, p<0.001). Holding 02-hr-OGTT as gold standard, sensitivity of FPG at 6.1 mmol/l cut-off was 48.48% for predictability over the persistence of AGT at 6-12 weeks post-partum.*

Conclusion: *It is concluded that about one-half of GDM subjects show persistence of glucose intolerance-mostly IGT anda significant number are diabetic at 6 to 12 weeks post-partum.*

Key words: *GDM, post-partum glucose intolerance.*

Introduction

Gestational diabetes mellitus (GDM) affects 3% to 15% of pregnancies, depending on the population studied (1). Soon after giving birth, 90% to 95% of women with hyperglycemia in pregnancy are diabetes-free by 75g-oral glucose tolerance test (OGTT). By 6-12 weeks post-partum, 4% to 9% are diagnosed with type-2 DM, more than 20% have impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) or both (2). It has been observed that one third to one half of women with a history of GDM develop type-2 DM within 3 to 5 years and 70% will develop type-2 DM over 10 years having cumulative incidence of 2.6% to 70% (3). The effect of GDM extends beyond pregnancy for both the mother and child. Women with a history of GDM are not only at a substantially higher risk of type 2 DM, but also small and large vessel vascular dysfunction, cardiovascular disease

and metabolic syndrome and its components, including hypertension (4). Multiple studies have linked prenatal exposure to GDM with a higher risk of development of several conditions later in life; most notably overweight or obesity and type 2 DM, in addition to potential delays or impairment to neurologic function (5). Screening recommendations for post-partum management of GDM varies considerably-some suggest FPG, whereas other recommends complete 75g-2hr-OGTT. American Diabetes Association (ADA) recommends screening at 6-12 wk. after delivery, and the World Health Organization (WHO) recommends screening at least 6 wk. after delivery. Both organizations suggest a 75-g OGTT. The United Kingdom's National Institute for Health and Clinical Excellence (NICE) recommends screening with a fasting glucose at the 6 wk. postpartum visit. There are currently no official guidelines for the use of hemoglobin A1c(HbA1c) as a screening test in the postpartum period, when the impact of pregnancy and perinatal blood loss on red cell turnover could alter glucose-A1c relationship (6). American College of Obstetrics and Gynecology (ACOG) and the 5th international workshop on GDM strongly recommended that 75g-2hr-OGTT in place of FPG to be done 6-12 weeks post-partum since this confirms impaired glucose tolerance. FPG is quick but poor in sensitivity; though OGTT is expensive and time-consuming is the preferred method because of higher sensitivity. If a woman is found diabetic by above criteria then she should be referred for diabetic management, but if indicates pre-diabetic then HbA1c test is recommended annually, if within normal limit, then every 3 years. The purpose of this study was to detect the rate of persistence of glucose intolerance in GDM patients during 6 to 12 weeks post-partum follow-up as well as to compare the performance of FPG and 75g-2hr-OGTT in this respect.

Methods

Study subjects

This study encompassed 108 patients diagnosed with GDM during their index pregnancy, as confirmed by the report of 75/100-gm-OGTT done at any week of gestation. Informed written consent for participation in the study was taken from each of them. Those having history or clinical manifestation of diabetes or use of anti-diabetic drugs before pregnancy, history or clinical manifestation of cardiovascular disease or other co-morbidities (judged on clinical assessment) or having a BMI ≥40 kg/ m2 were excluded from the study. Characteristics of the study subjects are shown in Table-I.

Table-I: Characteristics of studied subjects

Character	Value (%)
Number	108
Age (mean±SD, year)	29.4±5.3
BMI (Kg/m2, mean±SD)	26.4±4.7
Parity	
0	Nil
1	34 (31.5)
2	36 (33.3)
≥3	38 (35.2)
Family H/O DM	64 (59.3)
Gestational age at detection of GDM	
<20 week	34 (31.5)
≥ 20 week	74 (68.5)
Insulin use during pregnancy	23 (21.3)

(Within parenthesis are percentages over grand total)
BMI= Body Mass Index
DM= Diabetes Mellitus
GDM= Gestational Diabetes Mellitus

Study design

It was across-sectional study carried out at the GDM Clinic, Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University (BSMMU) from December, 2011 to June, 2013.Subjects were enrolled consecutively on the basis of the OGTT results during index pregnancy. A proforma containing general information on demographic characteristics, parity, family history of diabetes, OGTT report and insulin use during pregnancy etc. was filled up. Clinical evaluation including estimation of height, weight, BMI (kg/m2) and BP (mmHg) were measured by calibrated instrument. These women had been on unrestricted carbohydrate diet for 3 days, and came to GDM Clinic after observing overnight fast (at least 8 hr but not more than 14 hr) for 75-g-OGTT. All the subjects underwent a formal 75-g 2-h OGTT between 6-12 weeks post-partum. After taking 3ml blood for FPG all participants were subjected to OGTT with 75-g anhydrous glucose powder properly dissolved in 250-300ml water consumed within 5 minutes. While waiting after intake of 75-g glucose, the women were asked to avoid physical activity during next 2 hr. Exactly 2 hr later second sample of blood for post glucose load plasma was taken and centrifuged.

Prior to commencement of this study the research

Table-II: Frequency of glucose intolerance among various age groups (n=46)

Age group (year)	IFG	IGT	IFG-IGT	DM	Total
< 20 year	0	1 (50.0)	0	01 (50.0)	02 (4.3)
20-24 year	0	01 (33.3)	0	02 (66.7)	03 (6.5)
25-29 year	0	06 (60.0)	01 (10)	03 (30)	10 (21.7)
30-35 year	0	12 (52.2)	02 (8.7)	09 (39.1)	23 (50.0)
>35 year	01(12.5)	05 (62.5)	01 (12.5)	01 (12.5)	08 (17.4)
Total	**01(2.2)**	**25 (54.3)**	**04 (8.7)**	**16 (34.8)**	**46**

(Within parenthesis are percentages over row total except last column which is over column total).
Subjects with normal glucose tolerance are excluded.
IFG = Impaired fasting glucose IFG-IGT = Impaired Fasting Glucose-Impaired Glucose Tolerance IGT = Impaired Glucose Tolerance
DM= Diabetes Mellitus

Table-III: Glycemic status on basis of FPG and 02hr-75 gm OGTT

Status of fasting glucose	Status of 2hr-75 gm OGTT		Total	p
	≥ 7.8	< 7.8		
≥ 6.1	17 (81.0)	04 (19.0)	21	
< 6.1	22 (25.3)	65 (77.7)	87	<0.001
Total	39	69	108	

(Within parenthesis are percentages over row total)
McNemar's test $\chi^2 = 11.115$
FPG= Fasting Plasma Glucose OGTT= Oral Glucose Tolerance Test

AGT/NGT by 2h-OGTT	If 6.1 cut-off of FPG (mmol/L)		Total
	≥ 6.1	< 6.1	
AGT	20	26	46
NGT	0	62	62
Total	46	88	108

Sensitivity:48.48%

protocol was approved by Institutional Review Board (IRB).Permission was also taken from the department concerned for this study.

Analysis methods

The samples were transported to laboratory in pre-labeled test tubes preferably within 30 min, where plasma was assayed immediately by glucose-oxidase method in Dade Behring machine. The result was deducted from computerized calculation utilizing standard curve derived from known concentrations used by the system. Samples of different subjects were run on different days in different assay runs (63 runs). A fixed known concentration for low level (5.21 mmol/l) as well as high level (16.1 mmol/l) was used in every assay run. Inter-assay Co-efficient Variance (CV) for low level was 5.78%, and for high level were 5.59%.

Statistical analysis

All data were analyzed by the use of SPSS program (version 22.0) and expressed as mean ± SEM or in frequency or percentage unless mentioned otherwise. The efficacy of detecting glucose intolerance by fasting and 02 hr value of OGTT were compared by McNemar's test. P values ≤ 0.05 was considered statistically significant.

Results

The frequency of various categories of glucose intolerance as defined by WHO and ADA criteria were NGT: 57.4% vs. 50%, IFG: 0.9% vs. 8.3%, IGT: 23.1% vs. 12%, DM: 14.8% vs. 14.8% respectively. Frequency of AGT cases was 46 (42.59%) by WHO criteria which was 54 (50.0%) by ADA criteria (Figure 1&2). Highest frequency of glucose intolerance was found in age group 30-35 year (50%, 23/46; Table-II) and the commonest glucose abnormality was IGT in nature (54.3%, 25/46) followed by DM (34.8%, 16/46).Assessment of concordance or discordance between FPG and 2-hr-OGTT values of post-partum testing and their role in determining glycemic status is shown in Table-III holding the cut-off value for FPG at 6.1 mmol/L and 2-hr-OGTT value at 7.8 mol/L. It was observed that there was a strong concordance between the magnitudes of these two values ($\chi 2=11.115$, $p<0.001$). Holding 02-hr OGTT status as gold standard, sensitivity of FPG at 6.1 mmol/l cut-off was 48.48% over predictability of persistence of glucose intolerance at 6-12 weeks post-partum.

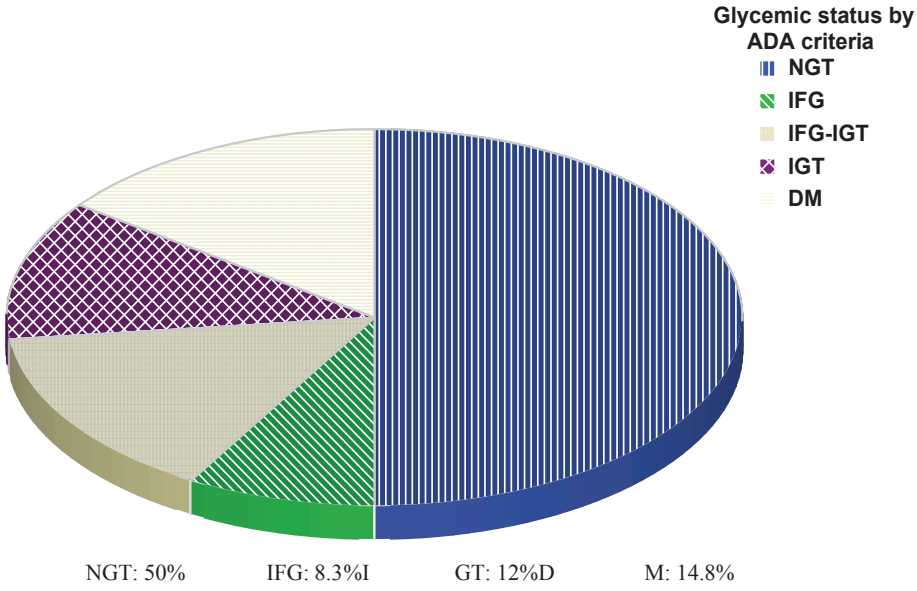

Fig-2.Glycemic status as defined by ADA criteria
NGT: normal glucose tolerance IFG: impaired fasting glucose
IGT: impaired glucose tolerance DM: diabetes mellitus

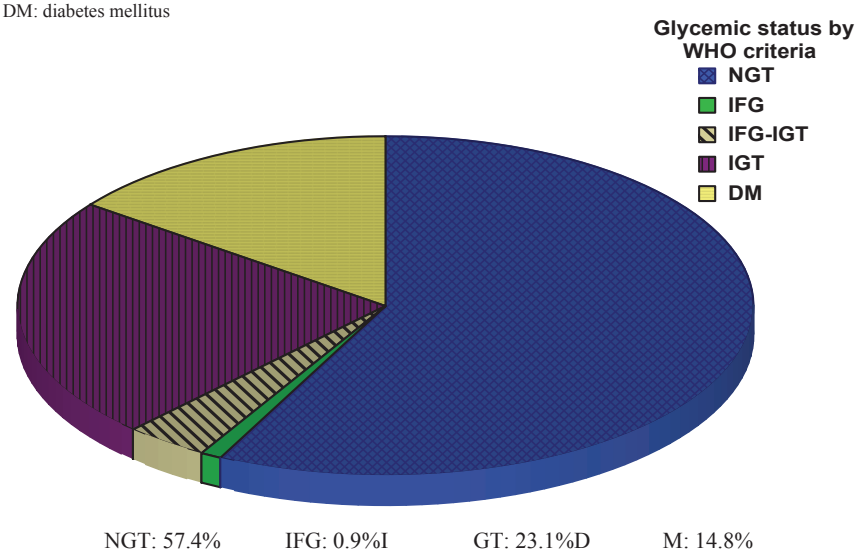

Fig-1. Glycemic status as defined by WHO criteria
NGT: normal glucose tolerance IFG: impaired fasting glucose
IGT: impaired glucose tolerance DM: diabetes mellitus

Discussion

The present study revealed that the rate of persistence of glucose intolerance at 6-12 week post-partum is remarkably high.More than 40% of the subjects exert persistence of glucose intolerance; and the commonest category of AGT is IGT followed by DM.FPG is less sensitive than a formalcomplete 2hr-75g-OGTT in predicting over post-partum AGT.

When the results of OGTT were compared in light of WHO and ADA criteria, there was significant discrepancy between the two criteria. Agarwal et al reported this classification discrepancy between WHO and ADA criteria - 21.5% of female among his study population showed such discordance (7). Causal factors for the apparent increase in GDM and post-partum persistence of AGT are likely to be multiple, including the prevalence of obesity, particularly in youth and improved survival of female infants having birth weights at the extremes of the normal range. As adults, the latter individuals have altered insulin action and/or insulin secretory capacity that may predispose them to the development of GDM and later type-2 DM (8). Petit et al. described the "U" shaped relationship between birth size and prevalence

of the disease in pregnant and post-pregnant subjects in comparison to the "Inverse" relationship in other adults (9). Sivaraman et al. suggested that, ethnicity as one of the key determinants in cumulative risk of persistence which varies from 70% in Sioux Indians, 13% in Chinese and 3.4% in Swedish Caucasians (10). The relatively high rate of persistence among Indo-Asians may be due to the inheritance of the "Thrifty phenotype" in this subset of population. The significantly high prevalence of persistence reinstates the fact that our ethnicity as Southeast Asian confers the greatest risk of DM among our pregnant and post-pregnant population (11). So, universal screening of GDM among our pregnant population with mandatory post-partum follow-up should be the rule wherever feasible. One third to one half of women with a history of GDM will develop type 2 DM within 3 to 5 years and 70% will develop type 2 DM if followed over 10 years. Cumulative incidence rate of type 2 DM varied from 2.6% to 70% (3). Kwak et al. studied 843 Korean GDM mothers and reported a 12.5% rate of persistence at 2 months postpartum (early converter) and 23.8% at 1 year (late converter) (12). Keeping this natural history of GDM in mind, and the observation by other studies, it is logical to recommend periodic follow-up later, as it would pick up the late converters. Thus, it is assumed, if the study subjects were followed–up over further period of time, the frequency of persistence would have increased.

Interestingly, IGT was the commonest category of persistence, constituting nearly one- fifth of AGT cases as observed by others (13, 14). This is very important because IGT is the harbinger of future diabetes. So, this group as well as others represents an ideal target for the development, testing and implementation of the clinical strategies for primary diabetes prevention program (15). Various randomized controlled trial (RCT) have shown that lifestyle modification with or without anti-diabetic medication were effective in prevention/ delay of type 2 DM in women with history of GDM. In the Troglitazone in the prevention of DM (TRIPOD) trial, treatment with Troglitazone reduced the incidence of DM by over 50%. Subgroup analysis among Diabetes Prevention Program (DPP) women with a history of GDM demonstrated that intensive lifestyle intervention and metformin both reduced the risk of type 2 DM by approximately 50%. The subjects with AGT at post-partum are on regular follow-upwith dietary and lifestyle modification advice. We have not yet reached the time point to comment on improvement/ deterioration of their glycemic status over time.

Despite the largest number of subjects being in the age group of 25-29 year, highest frequency of AGT occurred in 30-34 year age group. This finding re-emphasizes the age based risk screening (age≥30 year) of GDM cases as well as their post-partum testing (16).As might be expected that, highest prevalence would occur in the oldest age group (35 year) was not reflected in this study. This area could be made clearer by encompassing a large number of subjects that would help increase the number of mothers in all age group.

One of the important objectives of the study was to determine the efficacy of FPG against full 2-hr-75g-OGTT in detection of AGT at 6-12 week post-partum and to find out a simple, cost-effective yet a reliably sensitive method of post-partum screening in GDM patients. It was seen that if only FPG was used for screening purpose, only 45.6% of total AGT cases would have been detected, leaving out 54.4% of cases. FPG is quick and reproducible but it lacks the necessary sensitivity, whereas, OGTT is relatively cumbersome and expensive, yet it is the preferred method as it has got higher sensitivity. As a matter of fact, in the present study, sensitivity of FPG at cut-off 6.1 mmol/L was only 48.48% over persistence of post-partum glucose intolerance. Data presented at 5th International Workshop- Conference on GDM indicated that, at post-partum only 34% of women with IGT or Type-2 DM had impaired fasting glucose and that 44% of those with Type-2 DM had a fasting level 5.5 mmol/L (8). Reinblatt et al. showed in a Canadian study that FPG would miss 39% of women with a post-partum glucose abnormality, whereas a full OGTT would pick up 100% AGT cases (1). Apropos with this, some other investigators observed the poor predictive capacity of FPG (17, 18). Therefore, a complete, full 2hr-75g-OGTT should be used for post-partum screening.

While conducting this study on our post-pregnant population we confronted multiple obstacles, most notably poor adherence to post-partum testing. Though there was a long list of subjects in our recruitment diary, only a few reported for post-partum testing despite repeated reminder over the telephone. A convenient window period of 6-12 week post-delivery was offered for the benefit of the mothers, yet many failed to respond. Probable factors leading to non-adherence to testing were lack of awareness, superstition, and difficulty in time management with a small baby. Other studies also observed similar poor rates of adherence topost-partum

testing (19. 20).Recent reports of low rates of post-partum glucose tolerance testing and of lifestyle modification in women with prior GDM show that a dramatic paradigm shift in clinical practice is necessary to improve the lifelong health of these women.

Conclusions

This study showed that the rate of persistence of glucose intolerance at 6-12 week post-partum was quite high among our post-pregnant population. It also showed that a formal, complete 2hr-75g-OGTT had better sensitivity when compared to FPG in this regards. Continued follow-up over time is required, as because the NGT might convert to AGT thereby increasing the prevalence of persistence. Management of diabetes risk in these mothers should be coupled with appropriate family planning and with efforts to detect and minimize the development of obesity in her children in order to arrest the vicious cycle of trans-generational diabetes.

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If all misfortunes were laid in one common heap whence everyone must take an equal portion, most people would be contented to take their own and depart.

— SOCRATES