Frequency of Gestational Diabetes Mellitus in Bangladesh
Impact of WHO 2013 Screening Criteria: Efficiency of DIPSI and WHO 1999 Criteria

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Abstract
Objective: To observe the frequency of gestational diabetes mellitus (GDM) and assess the impact of WHO 1999 and 2013 criteria. The study also explored diagnostic efficiency of Diabetes in Pregnancy Study Group India (DIPSI) cut-off for mothers doing 75g oral glucose tolerance test (OGTT) in fasting state.

Methods: 320 pregnant subjects (age: 26.36±4.81 yrs, BMI: 25.39±4.15 kg/m2; mean ± SD) were screened for GDM by 75g OGTT. Among those with normal glucose tolerance (NGT, n=100) before 24 weeks of gestation, 57 repeated the test between 24 to 28 weeks, others failed to respond. Final status was discriminated on basis of either or both of WHO criteria 1999 and 2013. Glucose assay was done by glucose-oxidase method.

Results: Overall frequency of abnormal glucose tolerance (AGT) was 40.9% (131/320). By WHO 2013 criteria, 30.0% (96/320) were GDM and 5.3% (17/320) were diabetes (DM) in pregnancy, while 31.9% (102/320) GDM by WHO 1999 criteria (including repeat test). Of mothers undergoing (57/100) repeat test, 17.6% (10/57) by WHO 2013 and 19.3% (11/57) by WHO 1999 criteria showed AGT. On extrapolation of data (all attended in fasting state), frequency of AGT was 31.3% (100/320; GDM-26.3%, 84/320 and DM-5.0%, 16/320) by DIPSI cut-off which was exactly similar to WHO 1999 criteria (GDM-31.3%; 100/320), but differs from WHO 2013 criteria (GDM 27.2%; 87/320 and DM in pregnancy 5.0%; 16/320). Despite good agreement, some 13.3% (29/218) of NGT by 1999 had intolerance by 2013 criteria; conversely, 8.7% (18/207) of NGT by 2013 had intolerance by 1999 criteria (κ=0.671; p<0.0001). Likewise, 22.6% (19/84) of GDM by DIPSI were NGT by WHO 2013; and 25.3% (22/87) of GDM by WHO 2013 were NGT by DIPSI (κ=0.721; p<0.0001). However, AGT and NGT for DIPSI and WHO 1999 on individual basis was exactly same (McNemar’s test). 32 having 02h glucose between 7.8-8.5 mmol/L were GDM by WHO 1999/DIPSI cut-offs; but only 13 among them could be detected by WHO 2013 criteria (04 by fasting and 09 by 01h value). Out of 60 having 01h value≥10.0 mmol/L, 12 were diagnosed solely by 01h value by WHO 2013 criteria; of these 12, DIPSI could pick 09 GDM by 02h value.

Conclusion: Frequency of GDM seems alarming in Bangladesh. Despite near similar overall frequency, judged on individual basis, efficiency of DIPSI/WHO 1999 criteria for GDM screening of mothers doing 75g OGTT in fasting state appears more feasible and convenient. Disparity of WHO 2013 criteria with DIPSI/WHO 1999 is attributable to low cut-offs for fasting and relaxation of 02h value in WHO 2013 criteria that might be liquefied by reduction of 02h value of the WHO 2013 criteria instead of putting emphasis on fasting and 01h value.

Keywords: GDM, WHO 1999 and 2013 criteria, DIPSI cut-off value
Introduction

Prevalence of GDM ultimately reflects the background rate of type 2 DM in the respective population (1,2). Along with the current epidemic of diabetes mellitus, the prevalence of GDM has increased worldwide over the last generation and occurs in 1% to 28% of all pregnancies, varying substantially between populations and the diagnostic criteria used (1,3). There has been much confusion internationally regarding the optimal method of diagnosing GDM. The consequent variability with regards to the optimal screening and diagnostic criteria has limited the probability of comparison between different studies conducted (4, 5). In Bangladesh, a cross-sectional institution-based study completed in 2012 showed that the prevalence of GDM was 13.2% in the rural population as per the WHO 1999 criteria which is quite high (6). In contrast, a recent study in Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University (BSMMU) has observed far higher frequency (over 40%) of GDM among pregnant women who were done OGTT irrespective of gestational age (7-9). Till date, though not based on studies with maternal and fetal outcomes, to standardize the diagnosis of GDM, the WHO in 1999 recommended 2-hour 75g OGTT with 2h cut-off value of ≥7.8 mmol/l for simplicity and acceptability which was later found to predict the neonatal outcomes in a fairly robust manner (7-9). WHO criteria need two samples (fasting and 2h), although in practice, only the 2h cut-off is used (10).

In 2010, the International Association of Diabetes and Pregnancy Study Group (IADPSG) proposed a new set of diagnostic criteria for GDM, in light of the results of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study in an attempt to unify the GDM criteria throughout the world which was adapted by the American Diabetes Association (ADA) in 2013 (4,11,12). Taking into consideration the ambiguity with regards to fasting plasma glucose values in the WHO 1999 guideline and in an attempt to unify the diagnostic procedure and cut-offs worldwide, the diagnostic criteria and classification of hyperglycemia first detected during pregnancy recommended by the WHO in 2013 decided to accept a new set of diagnostic criteria as proposed by the IADPSG and also the need for distinguishing between diabetes in pregnancy and GDM, which was first brought into light by IADPSG but proposed a slightly different terminology – (diabetes rather than overt diabetes proposed by IADPSG). The WHO 2013 recommendation therefore proposed a distinction between the two entities (i.e. GDM and Diabetes in Pregnancy) based upon the severity of hyperglycemia detected during a standard 75g OGTT at any time during pregnancy (13). The IADPSG criteria require three samples (fasting, 1h and 2h after 75g glucose). Despite the findings of HAPO and the consequent IADPSG criteria, the dream of universally acceptable diagnostic criteria in terms of both efficacy and acceptability remains elusive. Meanwhile, different authorities have continued to constantly pursue the search for an ideal criterion. Diabetes in Pregnancy Study Group India (DIPSI) has proposed a simplified one step screening approach for GDM in this regard, which may be very useful at community level particularly in a low resource-high prevalence setting (14).

In this paper, we have applied the WHO 1999 and WHO 2013 (IADPSG) cut-off values, and compared the two criteria with respect to their impact on diagnosing GDM among pregnant women seen at the ‘GDM Clinic’ in BSMMU. We also explored diagnostic efficiency of DIPSI cut-off for mothers doing 75g oral glucose tolerance test (OGTT) in fasting state.

Methods

Study subjects

This study encompassed 320 pregnant women irrespective of gestational age and risk factors who were screened for GDM by 03 sample 75g OGTT. Informed written consent for participation in the study was taken from each subject. Those with known pre-existing diabetes and history of GDM in previous pregnancy were excluded from the study. Characters of study subjects are shown in Table-I. Subjects performing OGTT before 24 weeks of gestation and found to have normal glucose tolerance (NGT) as per the WHO 2013 criteria were asked for a repeat OGTT between 24 – 28 weeks of gestation. Out of 100 subjects with NGT before 24 weeks of gestation, 57 repeated the test between 24 to 28 weeks, others failed to respond. Final status was discriminated on the basis of fulfillment of either/both the WHO 2013 and 1999 criteria.

Study design and analytic method

It was a cross-sectional study carried out at the ‘GDM Clinic’ in the Department of Endocrinology, BSMMU, Dhaka from January to December 2014. Pregnant women irrespective of gestational age were recruited on consecutive basis for the study. No preparatory diet was given and each eligible candidate was advised to attend
the ‘GDM Clinic’ between 8am - 9am in the morning after an overnight fasting of at least 8 hours, but not exceeding 14 hours to be challenged by 75g OGTT. Any subject falling at the 24th week of gestation or later, but found NGT was not done repeat OGTT.

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. Comparison between the frequencies detected by two criteria was done by Kappa-test or McNemar’s test and for parametric variables by one way ANOVA. P values ≤ 0.05 was considered statistically significant.

Results
As shown in Table-I, following WHO 2013 criteria, out of 320 subjects 96 were found GDM, 17 diabetes in pregnancy and 207 NGT. Mean (±SD, yr.) age of the subjects fell into third decade (26.4±4.8); highest in the group of DM in pregnancy (30.0±5.2) followed by GDM (27.0±4.8) and NGT (25.8±4.6) respectively (p<0.001). Overall BMI (kg/m2, mean±SD) was higher (all subjects: 25.4±4.2; GDM: 26.8±4.1; DM in pregnancy: 26.5±3.3 and NGT: 24.6±4.0 respectively; p<0.001). Unlike history of abortion (p=NS among groups), overall 40% of subjects had family history of diabetes; however, highest frequency was observed in DM in pregnancy followed by GDM and NGT (62.5% vs. 48.5% vs. 33.6%; p<0.006).

Overall frequency (including repeat test) of abnormal glucose tolerance (AGT) was 40.9% (131/320) when results considered in light of both WHO criteria. By WHO 2013 criteria 30% (96/320) were GDM and 5.3% (17/320) were diabetes (DM) in pregnancy; but GDM by WHO 1999 criteria was 31.9% (102/320) that included repeat test (Fig-1). Among mothers responding (57/100) for repeat test, 17.6% (10/57) by WHO 2013 criteria and 19.3% (11/57) by WHO 1999 showed AGT. Frequency of AGT on initial screening by extrapolation of data for DIPSI was 31.3% (GDM 26.3%; 84/320 and DM 5.0%; 16/320), exactly same as WHO 1999 criteria (31.3%, 100/320); but differed from that of WHO 2013 criteria (GDM 27.2%; 87/320 and DM in pregnancy 5.0%; 16/320) (Fig-2).

Comparison between WHO 1999 and 2013 criteria for...
AGT in pregnancy revealed that 13.3% (29/218) of NGT by 1999 had intolerance by 2013 criteria; conversely, 8.7% (18/207) of NGT by 2013 had intolerance by 1999 criteria ($\chi^2=0.671; p<0.0001$). 32 having 02h glucose between 7.8-8.5 mmol/L were GDM by WHO 1999/DIPSI cut-off; but only 13 among them could be detected by WHO 2013 criteria (04 by fasting and 09 by 01h value). Out of 60 having 01h value $\geq$10.0 mmol/L, 12 were diagnosed solely by 01h value by WHO 2013 criteria; of these 12, DIPSI could pick 09 GDM by 02h glucose value (Table-II). Similarly, 22.6% (19/84) of GDM by DIPSI were NGT by WHO 2013; and 25.3% (22/87) of GDM by WHO 2013 were NGT by DIPSI ($\chi^2=0.721; p<0.0001$; Table-III). However, AGT and NGT for DIPSI and WHO 1999 on individual basis was exactly same (Table-IV).

**Discussion**

Frequency of GDM in Bangladesh seems alarming, far higher than that as reported in previously carried out pilot studies wherein prevalence rates of around 10% and 13% were reported in the rural population of Bangladesh using WHO 1999 criteria (6,15). DIPSI criterion is equally effective as WHO 1999 criterion at least in the fasting state and differs very little from the WHO 2013 in terms of overall frequency in picking up abnormal glucose status. The minor disparity of WHO 2013 criteria from that of WHO 1999 and DIPSI is attributable to low cut-offs for fasting and relaxation of 02h PG by WHO 2013 criteria which might be liquefied by reduction of 02h value of the criteria. Moreover, pick up of abnormal status solely by 01h PG value of WHO 2013 criteria are mostly encompassed by the 02h PG value of DIPSI/WHO 1999 criteria diluting the importance the 01h PG estimation of WHO 2013 criteria.

In 1999, WHO published the diagnostic criteria for GDM wherein pregnant women fulfilling the WHO criteria for DM or IGT in non-pregnant adults were classified as
having GDM (16). Because of the inherent contradiction in the diagnostic criteria that recommended the IGT cut-off in non-pregnant adults but completely ignored the IGF entity in the diagnosis of GDM, which appeared more overtly discrepant when the ADA lowered its fasting cut-off from 110mg/dl to 100mg/dl, although there has been some studies encompassing both cut-offs (17), majority of the subsequent studies chose to ignore the fasting cut-off ($\geq 7.0 \text{ mmol/L}$) and use only the 02h cut-off of $\geq 7.8 \text{ mmol/L}$ of the WHO 1999 criteria for diagnosis of GDM although there was never any official recommendation from WHO to drop the FPG cut-off and use only 02h cut-off of 7.8 mmol/L for diagnosis of GDM (10,18). Thus, similar to the findings observed in previous studies, our study observed absolutely no discrepancy at all in the frequencies of GDM detected solely by 02h cut-off of WHO 1999 and the one observed encompassing the fasting cut-off together with 02h value. The IADPSG advocated method and cut-offs for the screening and diagnosis of GDM based upon findings of HAPO which has been accepted by WHO in 2013 expected to generate widespread acceptance and universality in terms of the much debated issue of ideal screening method and diagnostic cut-offs (13). However, despite substantial HAPO-based evidential backup which demonstrated a contiguous increase in adverse pregnancy outcomes at plasma glucose cut-offs at values even below the diagnostic cut-offs proposed (19), concerns have been expressed over the possibility of an overwhelming increase in prevalence of GDM that could result from the low-set cut-off for fasting plasma glucose in the IADPSG criteria that could endure a substantial economic burden on the health system likely to be unbearable for the low economy nations (4). Furthermore, citing the possibility of the likely overwhelming increase in prevalence, certain national authorities who constituted a part of IADPSG in the beginning have withdrawn at the point of acceptance of the finally proposed criteria even expressing concerns on the validity of HAPO findings and the possible future need of more cut-off based outcome studies for final validation (5). Additionally, the rationale behind the inclusion of 01hr. plasma glucose value in the IADPSG criteria that could endure a substantial economic burden on the health system likely to be unbearable for the low economy nations (4).

### Table IV: Frequency of AGT and NGT by DIPSI and WHO 1999 criteria

<table>
<thead>
<tr>
<th></th>
<th>WHO 1999 criteria</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AGT</td>
<td>NGT</td>
</tr>
<tr>
<td>DIPSI cut-off</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDM</td>
<td>65</td>
<td>19 (22.6)</td>
</tr>
<tr>
<td>NGT</td>
<td>22 (25.3)</td>
<td>198</td>
</tr>
<tr>
<td>Total</td>
<td>87</td>
<td>217</td>
</tr>
</tbody>
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(Within parenthesis are percentages over group total) by McNemar’s test

$\kappa = 0.721; p<0.0001$

16 subjects were DM in pregnancy by WHO 2013 and DIPSI

GDM: gestational diabetes mellitus
NGT: normal glucose tolerance
DIPSI: Diabetes in Pregnancy Study group India
number of subjects and ultimately depriving therapeutic intervention. In terms of adverse pregnancy outcomes, review of previous outcome based studies have revealed that though both WHO 1999 and IADPSG criteria detect adverse outcomes with minor discrepancies, the quality of evidence is higher for WHO 1999 criteria based results as the few IADPSG based outcome studies till date revealed inconsistent results. Furthermore, it is noteworthy that though IADPSG criteria classifies as having GDM a larger number of true positives, it appears that they classify as having GDM a larger proportion of women who will not develop adverse outcomes. Most strikingly, it has also been observed that most of the adverse events occurred in women not classified as GDM (13). This has raised a serious question that whether the cases labeled as GDM were actually true positives and those labeled NGT and later developed adverse outcomes true negatives raising serious questions with regards to the low fasting cut-off which probably is the principle contributor of false positive percentage and undue relaxation of 02hr. value that must be responsible for false negatives/missed diagnosis ultimately being deprived of treatment culminating into adverse outcome (13). These findings has provided a strong foundation for implementation of a single cut-off (02h PG≥7.8 mmol/L) screening and diagnostic criteria for GDM which could well be the DIPSI proposed criteria (14).

Though it seems a bit away from the main focus of discussion in this paper, it was observed that higher age, increased weight and family history of DM but not history of miscarriage may be attributable to AGT in pregnancy. As a matter of fact, there are lot many evidences supporting these findings (20-22). There had been differences of opinion regarding the optimum time of OGTT during pregnancy for detection of glucose intolerance. Certain authorities support for testing at 24-28 weeks of gestation in women with risk factors for GDM in view of the maximum likelihood of glucose intolerance attributed to pregnancy induced insulin resistance to occur at this time frame provided pre-existing glucose intolerance has been excluded. Compared with the risk factor based selective screening, universal screening for GDM detects more cases and is associated with a better perinatal outcome but at the cost of increased number of screening tests and therefore increased expenditure (1,3,4,23,24). There are additional data demonstrating that women without risk factors for GDM but ultimately diagnosed to have GDM are no less prone to the complications of GDM, compared to those with risk factors (1). It has also been predicted that over the next two to three decades, approximately 80 million women of the reproductive age group worldwide would have diabetes and of these over 25% would be confined to the south east Asian belt alone, creating a potential for extremely high rates of maternal and infant morbidity (25). So, in a high risk population like ours where timely and effective antenatal evaluation is still a distant dream, pregnant women not known to have pre-existing glucose abnormalities should directly be subjected to a 75gm OGTT at the first antenatal visit and undergo a repeat testing at 24-28 weeks of gestation if initial test result is within normal limits on a universal basis.

We have observed that a good number of subjects with NGT before 24 weeks were found to have AGT in the repeat test after 24 weeks of gestation. In a study carried out in Nigerian women (high risk ethnicity), the crude prevalence of GDM was 13.9% of which 17.4% were detected to have GDM during the first trimester of pregnancy (26). Furthermore, a study carried out in India showed that pregnant women irrespective of the glycemic levels in the early weeks of pregnancy progressed to GDM in the subsequent visit indicating that no glycemic levels in the early weeks of pregnancy predicts GDM, therefore, emphasizing the importance of rescreening in the subsequent visits in women who were initially tested negative for GDM (27). Our group has also observed similar findings in other pilot studies (28). Therefore, it may be wise to do the test as early as possible during pregnancy in order to reduce AGT related adverse pregnancy outcomes which might precede the detection of AGT at later part.

In the present study, frequency of AGT following WHO 2013 and 1999 criteria were not too differing, rather were significantly similar statistically (by Kappa test) in regards to overall assessment. However, it is worth mentioning that, on the basis of individual assessment of each mother in light of these diagnostic criteria, WHO 1999 and DIPSI cut-off were exactly similar and both of them differ from WHO 2013 criteria in discriminating individual mother’s glycemic status. Moreover, subjects with 2h glucose value falling between 7.8-8.5 mmol/L are diagnosed as GDM by WHO 1999/DIPSI criteria but not by WHO 2013 criteria; furthermore important is the fact, as we have observed, more than 50-60% of them are missed by WHO 2013 despite the low-set fasting
Conclusions
It is concluded that frequency of GDM appears alarmingly high in Bangladesh. 75g OGTT in fasting state for GDM screening by DIPSI/WHO 1999 criteria appears more feasible, convenient and efficient compared to WHO 2013 criteria of 03 sample 75g OGTT. Disparity of WHO 2013 criteria with that of DIPSI/WHO 1999 is attributable to low cut-offs for fasting and relaxation of 02h value in WHO 2013 criteria. The disparity might be liquefied by reduction of 02h value of the WHO 2013 criteria instead of putting emphasis on fasting and 01h value of the criteria. Thus, one-step approach of DIPSI criteria appears very convenient for screening of GDM at community level.

References
10. Seshiah V, Balaji V, Balaji M, S, Sanjeevi CB, Green A. Gestational diabetes mellitus in India. JAPI 2004; 52: 707-11
20. Makgoba M, Savvidou MD, Steer PJ. An analysis of interrelationship between maternal age, body mass index and racial origin in the development of gestational diabetes mellitus. BJOG 2011: 278-82
27. Seshiah V, Balaji V, Balaji MS, Panneerselvam A, Thamizharasi M, Arthi T. Glycemic level at the first visit and prediction of GDM. JAPI 2007; 55:630-32

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The only true wisdom is in knowing you know nothing.
— SOCRATES