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One step procedure for screening and diagnosis of gestational diabetes mellitus

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OBJECTIVE(S) : To study the merits and demerits of different screening and diagnostic procedures that are used at present and to find a one step procedure which serves both as a screening as well as a diagnostic tool.

METHOD(S) : This study was performed in Government Raja Sir Ramaswamy Mudhaliar lying in hospital, Chennai. Consecutive 1251 pregnant women in the 2nd or 3rd trimester were given 50 g oral glucose load for glucose challenge test, (GCT) and blood sample was collected after 1 hour. All of them, irrespective of the glucose value after the GCT, were instructed to come back after 3 days for the subsequent 75 g oral glucose tolerance test (OGTT) recommended by WHO. For stastical analysis EPI 6 was employed using independent chi-square test, chi-squre test for linear trend, Mantel – Haenzel odds ratio, and binomial proportion and corresponding exact binominal 95% confidence limits.

RESULT(S) : A total of 891 pregnant women underwent both 50 g GCT and a subsequent 75 g OGTT. Among them 144 (16.2%) were diagnosed as gestational diabetes mellitus (GDM) as per the WHO criteria of 2 hour postplasma glucose (PPG) ≥ 140 mg/dL). Analysis of these GDM cases revealed that 113 (78.5%) had the initial 50 g value > 130 mg/dL whereas a potential 31 cases (21.5% of the total GDM cases) had the 50 g 1 hour value below the cut off level of 130 mg /dL. Normally the GTT is not done in women with negative GCT. Since in this study we performed GTT for those negative for GCT, we found that GCT lacks specificity (41.8%).

CONCLUSION(S) : Diagnosis of GDM by OGTT based on initial GCT screening leaves 21.5% undiagnosed. The two step procedure of screening with GCT and then diagnosing GDM based on the cut off values with 100 g or 75 g OGTT is not practical as the pregnant women have to visit the clinic at least twice and the number of blood samples drawn vary from 3 to 5. Hence, we suggest a single glucose challenge test with 75 g of oral glucose load and diagnosing GDM if 2 hour PPG is ≥ 140 mg/dL as recommended by WHO. This method serves both as a one step screening and a diagnostic procedure, and is easy to perform besides being economical.

Key words : gestational diabetes mellitus, glucose challenge test, oral glucose tolerance test, fasting plasma glucose, post plasma glucose

Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance with recognition or onset during pregnancy, irrespective of the treatment with diet or insulin. The importance of GDM is that two generations are at risk of developing diabetes in the future. Women with a history of GDM are at increased risk of future diabetes, predominately type 2 diabetes, as are their children [1]. Besides, any abnormal glucose intolerance during pregnancy also has adverse fetal outcome. Increasing maternal carbohydrate intolerance in pregnant women without GDM is associated with a graded increase in adverse maternal and fetal outcomes [2]. However, for the detection and diagnosis of GDM, controversy concerning optimal strategy still continues. The American

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Diabetes Association (ADA) recommends two step procedures for screening and diagnosis of diabetes in selective population. Compared with selective screening, universal screening for GDM detects more cases and improves maternal and offspring prognosis [3]. In the Indian context, screening is essential in all pregnant women as the Indian women have an eleven fold increased risk of developing glucose intolerance during pregnancy compared to Caucasian women [4]. Another area of concern is that among ethnic groups in South Asian countries, the Indian women have the highest frequency of GDM [5]. The recent data shows 16.55% prevalence of GDM in our country [6]. Hence, universal screening during pregnancy has become important in our country. For this, we need a simple procedure which is economical and feasible. Hence, a study was undertaken to find out a one step procedure which serves both as a screening and a diagnostic tool at the same time, and which is acceptable, economical and feasible to perform in the Indian context.

Methods

This study was carried out in the Goverrntment Raja Sir Ramaswamy Mudhaliar lying in Hospital attached to the Government Stanley Medical College and Hospital, Chennai. This hospital was chosen to evaluate the unbiased data of the pregnant women with glucose intolerance as the pregnant women belonging to different socio-economic status attend a government hospital of this type for antenatal checkup and confinement in our country. Consecutive 1251 pregnant women in the 2nd or 3rd trimester who checked into the antenatal clinic were given 50 g oral glucose load for glucose challenge test (GCT) and the venous blood samples were collected after 1 hour [7]. Details of family history of diabetes, history of previous pregnancies, and the socio-economic status were obtained, and the blood pressure measurement and the body mass index were recorded. They were all requested to come after 72 hours on an empty stomach for the 75 g oral glucose toterance test (OGTT) recommended by WHO [8]. Of the 1251 women, 891 responded. Venous blood was drawn in the fasting state and they were given 75 g oral glucose and the venous blood was drawn again after 2 hours. The plasma glucose was estimated by glucose oxidation and peroxidation (GOD-POD) method by using Bayer's kit.

The results were analyzed taking into consideration the screening procedure recommended by ADA (Table – 1) in comparison with WHO (Table – 2). ADA recommends a two step procedure, an initial screening by measuring plasma glucose 1 hour after 50 g oral glucose load (GCT). A glucose threshold value > 140 mg / dL (7.8 mmol/L) identifies approximately 80% of women with GDM, and the yield is further increased to 90% by using a cut off of > 130 mg/dL (7.2 mmol/L). Hence, this latter value was chosen as cut off for screening in our study. Those found positive at the screening test are given 100 g OGTT or 75 g OGTT and a positive diagnosis confirmed if two or more of the venous plasma concentrations met or exeeded the glucose levels given in Table – 1. The ADA criteria given in Table 1, lack the third hour value for the 75 g OGTT.

Table – 1 Diagnosis of GDM.

	100 g OGTT	75 g OGTT
Fasting	95 mg/dL (5.3 mmol/L)	93 mg/dL
1 hour	180 mg / dL (10mmol/L)	180 mg/dL
2 hour	155 mg / dL (8.6 mmol/L)	155 mg/dL
3 hour	140 mg / dL (7.8 mmol/L)	-

Two or more of the venous plasma concentrations must be met or must exceed the above values for a positive diagnosis.

WHO recommendes performing 2 hour 75 g OGTT and diagnosing GDM with a threshold plasma glucose concentration greater than 140 mg/dL (7.8 mmol/L) at 2 hours similar to that of impaired glucose tolerance test (IGT) in the non-pregnant [8].

Table 2. WHO criteria.

	Fasting plasma glucose (mg/dL)	2 hours postplasma glucose (mg/dL)
Impaired glucose tolerance	< 126	140 – 200
Diabetes	≥ 126	≥ 200

Pregnant women who meet WHO criteria for impaired glucose tolerance (IGT) or diabetes with 75 g glucose challenge are classified as having GDM. IGT is diagnosed if 2 hour post glucose is > 140 mg/dL and is ≤ 200 mg/dL with a fasting plasma glucose (FPG) value of < 126 mg/dL. The importance is given to the 2 hour plasma glucose for the diagnosis of IGT. Hene GDM is diagnosed if the plasma glucose is within the IGT range which is 2 hour post plasma glucose (PPG) ≥ 140 mg/dL. If the woman has fasting plasma glucose more than 126 mg/dL and / or 2 hour post glucose more than 200 mg/mL probably she has been having undetected diabetes prior to conception (pre-gestational diabetes).

Results

The mean age of the pregnant women in the study was 23 ± 4 years. The prevalene proportion increased with age from 14.5% (95% confidence limits: 7.7%-23.9%) in the age group

of 15-19 years to 25% (95% confidence limits: 14.4% - 38.4%) in the age group ≥ 30 years (Figure 1). With regard to the age effect, a model of linear trend was statistically significant (P<0.05). Data on body mass index (BMI) was available for 664 women (74.5%) and the prevalence proportion of GDM increased with increasing BMI (Figure 2). The prevalence proportion of GDM increased with gravidity, from 16.3% (95% confidence limits: 12.7% - 20.3%) in the primigravidas to 25.8% (95% confidence limits: 11.9% - 44.6%) in gravidas ≥ 4 (Figure 3).

Figure 1. Prevalence percentage of gestational diabetes by age group.

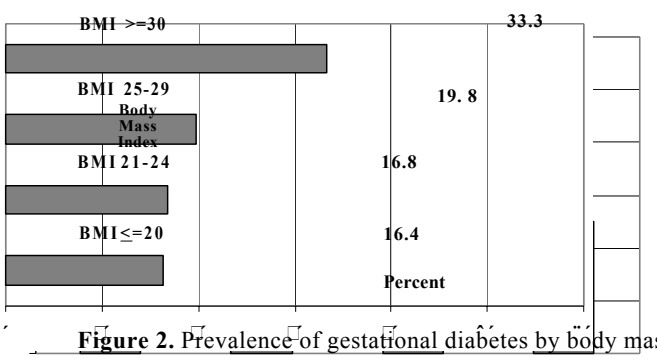

Figure 2. Prevalence of gestational diabetes by body mass index.

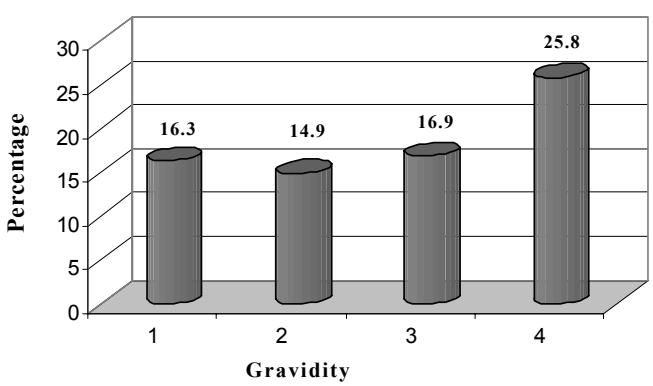

Figure 3. Prevalence of gestational diabetes by gravidity.

A total of 891 pregnant women underwent both the 50 g GCT and a subsequent 75 g OGTT. Among them, 548 (61.5%) were positive for the 50 g GCT and 343 (38.5%) were negative for the 50 g GCT (Table 3). The positive association between a positive outcome of the 50 g 1 hour test and taking part in the subsequent 75 g 2 hour test was statistically significant (Mantel-Heenszel odds ratio after stratification for age : 3.14 [χ^2 (df=1) = 78.067, P<0.0001], and there was no evidence of heterogeneity across age groups [χ^2 (df=4) = 1.770, P=0.778].

In our study population, 144 women (16.2%) were diagnosed as GDM as per the WHO diagnostic criteria (2 hour PPG ≥ 140 mg/dL) [8]. Out of these 144 identified as GDM women, 113 (78.5%) were GCT positive and 31 (21.5%) were GCT negative with the 50 g 1 hour value below 130 mg/dL. Since we had in this study FPG as well as 2 hour PPG performed, we analyzed the values taking into consideration the ADA and WHO criteria for diagnosis of GDM. Among the 891 pregnant women, 294 (32.99%) had FPG ≥ 95 mg/dL; 70 (7.86%) had 2 hour PPG ≥ 155 mg/dL, and 144 (16.2%) had 2 hour PPG ≥ 140 mg/dL. Thirty-five (3.93%) of them had both FPG ≥ 95 mg/dL and 2 hour PPG ≥ 155 mg/dL as per the ADA diagnostic criteria of GDM, whereas applying the WHO diagnostic criteria of 2 hour PPG ≥ 140 mg /dL 144 (16.2%) were identified as GDM.

Discussion

Increasing maternal hyperglycemia is associated with increasing pregnancy morbidity and increased likelihood of subsequent diabetes in the mother. In addition, maternal hyperglycemia has a direct effect on the development of fetal pancreas and is associated with increased susceptibility to future diabetes in the infant, an effect which is independent of genetic factors [9,10]. Over the next two to three decades there will be 80 million reproductive age women with diabetes in the world. Of these 20 million will live in India alone creating a potential for extremely high rates of maternal and infant morbidity. A recent national survey reported the prevalence of IGT in the age groups of 20-29 and 30-39 years as 12.2% and 15.3% respectively in the general population [11]. No gender difference was seen in the prevalene of IGT [11]. With a huge population in the reproductive age in India, a significant segment developing abnormal glucose tolerance is a matter concern. The selective screening recommended by ADA is not suitable for our country and we need universal screening.

FPG as a screening procedure : Sacks et al [12] and Daniele et al [13] have observed that measuring FPG is an easier screening procedure and suggested a cut off value of 95 mg/dL for GDM. However, such level is insufficient as the sole marker of GDM since most cases have FPG values below the putative threshold [14]. Very few women are diagnosed with

GDM on the basis of elevated fasting plasma glucose alone. When the fasting glucose is elevated and the 2 hour glucose is normal, there is a suspicion that the subject has not fasted [15]. We also observed in our study that 32.99% of pregnant women had FPG ≥ 95 mg/dL. If we had followed FPG as a screening procedure, we would have diagnosed a higher number of pregnant women having GDM. For these reasons, the fasting glucose is not favored by the WHO for diagnosing GDM [8].

50 g GCT : The screening test with 50 g glucose challenge [7] was performed on 1251 pregnant women. Out of them, 360 (28.7%) did not return for 75 g OGTT. Magee et al [16] reported that in their follow up 91 of the 457 positive screen individuals failed to undergo diagnostic test. de Aguiar et al [17] also observed in their study that 23% of their screen positive women did not return for OGTT. This phenomenon of no show occurs because the women have to come to antenatal clinic on two occasions for the blood test by two step procedure. Also the requirement of a number of blood samples for diagnosis of GDM is not feasible and conducive especially in the Indian context. The most important observation in the study was the identification of 31 (21.5%) potential GDM women who were negative as per GCT criteria and were not even required to go in for the subsequent OGTT confirmation. Generally OGTT is performed only for those who are GCT positive.

Table 3. Glucose challenge test (GCT) and oral glucose tolerance test (OGTT)

	OGTT +VE n=144	OGTT –VE n=747	Total
GCT +VE	113/144 (78.5%)	435	548
GCT – VE	31/144 (21.5%)	312	343
Total	144	747	891

Estimation of FPG or 50 g 1 hour glucose challenge test recommended byADA needs confirmatory OGTT and hence is not suitable for one step procedure for screening as well as diagnosis which we are looking for.

ADA criteria were originally validated against the future risk of maternal diabetes and not based on the likelihood of adverse perinatal outcome. Though the criteria are still followed in USA, they are little used elsewhere. Pettitt [18], in his editorial, favored WHO recommendation. Further, in clinical practice 2 hour glucose level is preferred for diagnosis of GDM [19,20]. In our study the prevalence of GDM was 3.93% by applying ADA criteria of FPG ≥ 95 mg and 2 hour PPG ≥ 155 mg, whereas, by WHO criteria the prevalence was 16.2%. Schmidt et al [21] found that in their pregnant population the prevalence was 2.4% by applying the ADA criteria and 7.2% by WHO criteria. The diagnostic pick up rate in their study was three times more with WHO criteria than with ADA criteria. In our study, the pick up rate was four times more with WHO criteria than with ADA criteria. This is understandable as Indian women are more prone to develop GDM [4]. They documented an important observation that the subjects with GDM by WHO criteria delivered macrosomic infants. They also detected increased rate of morbidity in women diagnosed as GDM by WHO criteria [21]. WHO test for glucose tolerance during pregnancy was abnormal in the greater percentage of women with adverse outcome than the more cumbersome two step NDDG (ADA) test [19]. More importantly, GDM based on 2 hour 75 g OGTT defined by either WHO or ADA criteria predicts adverse pregnancy outcome [21]. Further, assuming that the effective treatment is available, WHO criteria of 2 hour PPG ≥ 140 mg/dL identifying a large number of cases may have a greater potential for prevention [21] which has been recently confirmed by Meltzer et al [22]. The drawback of ADA criteria is that it permits both 100 g and 75 g OGTT. Though the glucose loads are different, the cut off value is the same. Further, the 3 hour value for 75 g OGTT is not given (Table 1). All these factors, and discussed and published evidences clearly establish the robustness of WHO criteria over the ADA criteria.

Ethnically Indian women have high prevalence of diabetes and the relative risk of developing GDM in Indian women is 11.3 times compared to White women [4], necessitating universal screening for glucose intolerance during pregnancy in India. GDM diagnosis is overlooked in about 1/3rd of the women where selective rather than universal screening is performed [23] and when this is applied to the 20 million reproductive age women in India, we are missing a lot of women likely to have glucose intolerance.

The two step procedure of screening with 50 g GCT and then diagnosing GDM based on the cut off values with 100 g or 75 g OGTT is not practical as the pregnant women have to visit the clinic at least twice and the number of blood samples drawn vary from 3 to 5 which women resent. For universal screening, we suggest a single GCT with a 75 g of oral glucose load and diagnosing women with 2 hour PPG ≥ 140 mg/dL as GDM. This method, recommended by WHO serves both as a one step screening and diagnositic procedure and is easy to perform besides being economical.

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