Development of a Modified 100-Gram Oral Glucose Tolerance Test for Diagnosis of Gestational Diabetes Mellitus and Its Diagnostic Accuracy

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Objective: *To develop a modified 100-g oral glucose tolerance test (100-g OGTT) for the diagnosis of gestational diabetes mellitus (GDM) in order to reduce the number of values needed for the test.*
Materials and Methods: *Patient charts of pregnant women who completed the 100-g OGTT test at the antenatal clinic, Siriraj Hospital between 2005 and 2006 were reviewed. Cases diagnosed with GDM using standard 100-g OGTT were selected. In non-GDM cases, the last 100-g OGTT test was selected. Diagnostic performances of each glucose value and two or three values in various combinations were determined.*
Results: *One thousand seven hundred sixty three women completed GDM diagnosis throughout their pregnancy. Four hundred three women had GDM while 1,360 subjects were non-GDM. Considering single glucose values, the highest level of accuracy, and the best ROC curve were obtained from the value at 2 hours after glucose ingestion (2-h glucose value) with 93.00% accuracy and the area under the ROC curve of 0.961. The combination of 2-h glucose value with fasting plasma glucose (FPG) showed 93.25% accuracy. FPG combined with 1-h and 2-h glucose values achieved 100% sensitivity with 92% accuracy.*
Conclusion: *FPG in combined with 1-h and 2-h glucose values is an interesting alternative for the diagnosis of GDM.*

Keywords: *Gestational diabetes mellitus, Modified oral glucose tolerance test*

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Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance first recognized during pregnancy. The prevalence varies worldwide among different racial and ethnic groups[1,2]. Such rates may also vary by the testing methods and diagnostic criteria. At Siriraj Hospital, the rate is 2.5%[3]. If untreated, GDM may lead to adverse pregnancy outcomes. Timely detection and management of this condition is therefore crucial.

At Siriraj Hospital, the strategy for GDM detection involves a screening test and a diagnostic test. The screening test is the 50-gram glucose challenge test (50-g GCT) performed on women with one or more risk factors for GDM at the first prenatal visit then subsequently at 24-28 weeks and 32-34 weeks if the prior tests are negative. Once the screening test is positive, the women will be evaluated by a 100-gram oral glucose tolerance test (100-g OGTT) using the NDDG criteria[4]. GDM will be diagnosed when the 100-g OGTT is positive. Therefore, while others may have fewer tests, a number of women may have three screening tests with three sets of 100-g OGTT to achieve the final result.

The 100-g OGTT consists of four plasma glucose measurements, which require a total duration of 3 hours and four blood drawings. Earlier reports demonstrated that the last glucose measurement could be omitted[5,6]. In addition, other modifications

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of 100-g OGTT's such as a summation of the values at 1 and 2 hours[7] or combination of fasting plasma glucose (FPG) and 2-h glucose value[8] have been reported.

The present study employed diagnostic test study as the research methodology to retrospectively evaluate whether an omission of one or two of the four glucose values will yield any significant difference in diagnosis, in an effort to develop a modified 100-g OGTT in order to overcome the drawbacks that accompany the traditional test method in the authors' hospital.

Material and Method

The present study has obtained an approval of the Siriraj Ethics Committee. A retrospective review of pregnant women who attended the antenatal clinic at Siriraj Hospital and were identified as high-risk for GDM using the authors' criteria[3] between 2005 and 2006 was carried out. At booking, they underwent a 50-g GCT and those whose result was positive then underwent the 100-g OGTT one week later. Subsequently the same screening tests were performed between 24 - 28 weeks and between 32 - 34 weeks' of gestation in cases where the previous test came out as negative and also the 100-g OGTT was performed whenever the 50-g GCT was positive until the GDM was diagnosed or until they completed the tests throughout gestation. Diagnosis of GDM was defined using National Diabetes Data Group (NDDG) diagnostic criteria[4].

Eligible candidates included all pregnant women who had an abnormal 50-g GCT, and thus underwent a 100-g OGTT at the authors' institute. The present study excluded pregnant women who did not complete blood tests up to the 3rd trimester.

In GDM cases, all four values in the 100-g OGTT that indicated GDM were obtained while in non-GDM cases the glucose values at the last 100-g OGTT were selected.

Data analysis

Data were analyzed using SPSS version 11.5 for Windows.

To determine which glucose value or combination of which ones from 100-g OGTT is able to diagnose GDM as nearly accurate as the traditional 100-g OGTT with the reduction of number of glucose value determinations, the values of all four glucose levels from 100-g OGTT in women with and without GDM were retrospectively reviewed. Firstly, a receiver operating characteristics curve was constructed and the area under the curve was calculated for each value of the 100-g OGTT. The sensitivity, specificity, positive and negative predictive values (PPV/NPV) and accuracy for different values were determined using standard definitions. Secondly, the best performing glucose value in various pairing with one of the other values were assessed for diagnostic performance. In addition, a trial of three values was carried out to find the best predictor for GDM with minimal loss of diagnostic performance from the standard 100-g OGTT. The result of the test of interest would be considered positive, indicating GDM, when one or more values of the test was/were higher than the cut-off point used in NDDG criteria.

Results

Between January 2005 and December 2006, 6,812 women were at high risk for GDM and underwent the screening test for GDM. One thousand nine hundred ninety six women with a positive 50-g GCT and thus underwent a 100-g OGTT during the study period were identified. Of these, 1,763 women had the GDM detection protocol performed throughout their pregnancy or until GDM was diagnosed. The remaining 233 cases were excluded since they did not complete the GDM detection until the third trimester because it could not be ascertained that they were truly non-GDM. In total, 403 women were classified as GDM (a prevalence of 3.2% of all pregnant women in the study period) while 1,360 subjects were classified as non-GDM.

Performance of each glucose value or various combinations for GDM diagnosis

The ability of a single glucose value to predict GDM was compared using the ROC curves. The AUC for FPG, 1-h, 2-h, and 3-h were, respectively, 0.774, 0.931, 0.961, and 0.837 (Fig. 1). The value at 2-h was considered the best performance value and was assigned to be the value to pair with one of the other values in the next assessment.

Table 1 shows the diagnostic performance of each glucose value in the 100-g OGTT separately and in various combinations. When considered separately, the 2-h glucose value gave the highest accuracy rate with 92.06% sensitivity and 93.31% specificity. The FPG had the highest specificity of 99.78% but its sensitivity was only 31.53%. The values at 1-h and 3-h had a slightly higher specificity than the value at 2-h but the sensitivity was markedly lower. The value

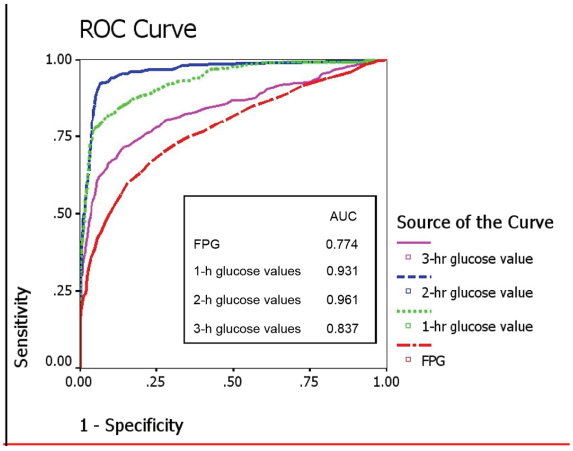

Fig. 1 Area under receiver-operating characteristic curve of each glucose value in 100-g OGTT. The value at 2 hours after glucose value gave the best diagnostic performance for diagnosis of gestational diabetes mellitus
FPG = fasting plasma glucose

at 2-h was therefore considered to be the one retained in the next assessment. However, the pairs without the value at 2-h were still assessed just to be complete as shown in Table 1. Various paring of the glucose values in the 100-g OGTT revealed the highest accuracy in diagnosis of GDM in the pair of FPG and 2-h glucose value. False negative results were observed, however, in both 2-h glucose value alone or in combination with FPG. In order to increase the sensitivity of the pair, the value at 1-h was added and this 3-value combination yielded 100% sensitivity albeit a decrease specificity.

Using the combination of FPG and 2-h glucose value as a modified 100-g OGTT in the presented population resulted in the diagram of the diagnostic accuracy study shown in Fig. 2. Twenty-five GDM cases would have been missed out of 1,763 tested cases and out of 403 cases of GDM diagnosed by the standard method. In addition, 84 cases would be over-diagnosed as GDM.

Using combination of FPG, 1-h and 2-h glucose values as a modified 100-g OGTT in the presented population resulted in the diagram of the diagnostic accuracy study shown in Fig. 3. Thus, no GDM cases have been missed. However, 151 cases would have been over-diagnosed as GDM out of 1,763 tested cases.

Discussion

Owing to the shortcomings associated with the diagnostic method of 100-g OGTT (amongst which are time-consuming, high costs and number of blood drawings and glucose value determinations), the method has limitations in certain situations including patient acceptance[9,10,11]. A number of women have to go through the three courses of 50 g 1-h followed by 100-g OGTT. There is thus the need to develop an effective diagnostic method of GDM with more patient acceptance.

To date, many studies modified 100-g OGTT and yielded variable results. Beginning with Atilano et al who found that high FPG was highly predictive of GDM and omission of the 3-h glucose value decreased the sensitivity by 13%, indicating that this is not an acceptable test[12]. On the other hand, Jakobi et al demonstrated that the omission of the third hour

Table 1. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), false positive rate, false negative rate and accuracy for each 100-g oral glucose tolerance test value separately, in pairs, and the combination of FPG, 1-h and 2-h glucose values

Diagnostic Performance	FPG	1-h	2-h	3-h	FPG or 1-h	FPG or 2-h	FPG or 3-h	1-h or 2-h	1-h or 3-h	2-h or 3-h	FPG or 1-h or 2-h
Sensitivity (%)	31.53	76.43	92.06	61.04	79.16	93.80	64.27	99.90	99.50	99.01	100.00
Specificity (%)	99.78	95.66	93.31	94.19	95.44	93.09	93.97	89.12	89.85	87.94	88.90
Positive predictive value (%)	95.52	83.92	80.30	75.69	83.73	80.08	75.95	72.94	74.40	70.87	72.74
Negative predictive value (%)	80.01	93.19	97.54	89.08	93.92	98.06	89.87	99.67	99.84	99.67	100.00
False positive rate (%)	0.22	4.34	6.69	5.81	4.56	6.91	6.03	10.88	10.15	12.06	11.10
False negative rate (%)	68.47	23.57	7.94	38.96	20.84	6.20	35.73	0.10	0.50	0.99	0.00
Accuracy (%)	80.60	91.26	93.02	86.61	91.72	93.25	87.18	91.38	92.06	90.47	91.44

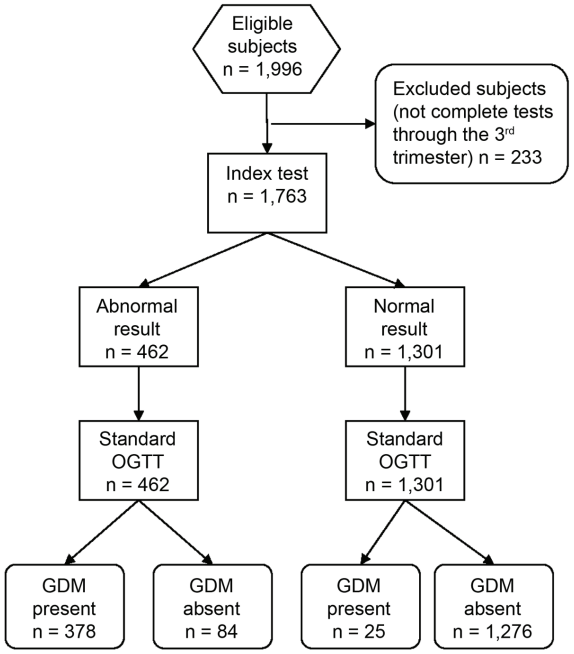

Fig.2 Flow of the study using FPG and 2-h glucose value as the index test
GDM = gestational diabetes mellitus

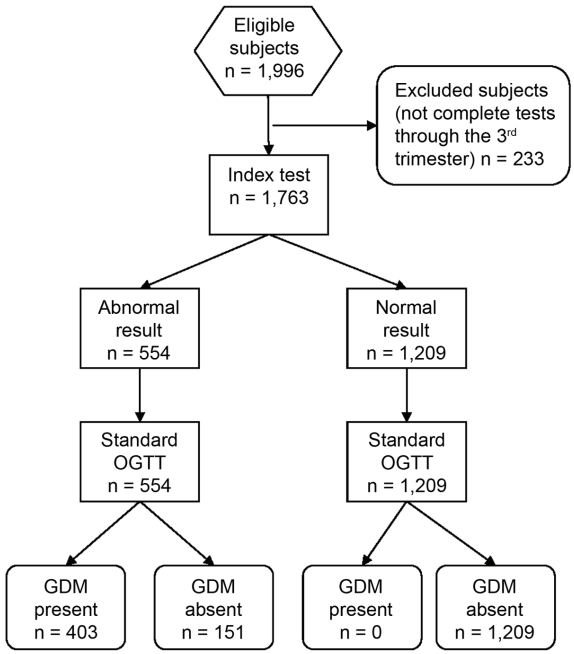

Fig. 3 Flow of the study using FPG in combination with the 1-h and 2-h glucose values as the index test
GDM = gestational diabetes mellitus

glucose measurement failed to diagnose only 18 out of 249 GDM cases and did not alter the perinatal outcome[5]. The same results were obtained in a study of Rodacki et al[6]. This discrepancy may be explained by the different cut-off values of glucose levels and different population. Agarwal et al showed that using only the FPG and 2-h glucose value might be a useful alternative method in high-risk populations with the sensitivity and specificity of 98.5% and 84.7%[8]. Alternatively, Phaloprakarn et al [7] proposed a modified 100-g OGTT using the summation of 1- and 2-h to be used as a diagnostic test as it yielded the sensitivity, specificity, and AUC of 93.5%, 95.2%, and 0.94 respectively.

In the current study, the non-GDM cases were included in a stringent fashion. The women had to complete the GDM detection tests throughout their gestation with negative results to ascertain that they did not develop GDM in the late gestation. Hence, they were truly negative cases. When each glucose value was considered separately, the 2-h glucose value demonstrated the best ROC and accuracy in GDM diagnosis. Indeed, the 2-h glucose value alone was able to diagnose GDM with 92% sensitivity, 93% specificity, and 93% accuracy.

When combinations of two values were studied with the condition that at least one abnormal value was needed to diagnose GDM, the combination of FPG and 2-h glucose value was the best pair in the diagnosis with the accuracy of 93.25%, the sensitivity of 93.8% and the specificity of 93.09%. The benefit of the marginal increased accuracy compared with 2-h glucose value alone was accompanied by the benefit of both values already being used in the follow-up scheme in the authors' hospital because this combination can predict the insulin usage and the severity of DM[13,14]. Therefore, FPG and 2-h glucose value may be an alternative to the standard 4-value determination in 100-g OGTT with the advantage of less time, less number of venepunctures and lower cost. This opinion is in agreement with the study of Agarwal et al[8]. However, concern may be raised about the loss of sensitivity compared with the standard 100-g OGTT. With this regard, cases that would have been false negative were reviewed and no adverse pregnancy outcomes were found. It must be borne in mind though, that they had already been treated. However, it was found that the treatment they needed was only diet control and no insulin was needed. This was reassuring especially in cases with a normal FPG

level. The authors previously found that GDM cases with a normal level of FPG in 100-g OGTT only needed diet therapy for controlling of DM. None of them needed insulin therapy[15].

Still, a concern may be raised that without diet therapy, GDM cases missed by the FPG and 2-h strategy may result in some adverse pregnancy outcomes. Therefore, an attempt to increase the sensitivity with a third value added was assessed. The 1-h value was chosen because it had a better diagnostic performance than the 3-h value (Table 1). In addition, the time needed to complete the test is the same. It would take more time if the 3-h glucose value was selected. The combination of FPG, 1-h and 2-h values with the condition that at least one abnormal value is needed to diagnose GDM yielded 100% sensitivity. The high sensitivity of this combination found in the present study is in contrast with the study of Atilano et al[12] who found that the sensitivity with this method was only 87%. The difference may be caused by the different cut-off values and the different ethnic population. However, the authors' finding of high sensitivity is in line with the study of Rodacki et al and Jacobi et al[5,6]. Nevertheless, this came with a decrease in specificity, which was 89%, and led to a positive predictive value of only 73%. Therefore, while the three values did not miss a GDM case, over-diagnosis was encountered. Of 100 cases diagnosed with GDM by this method, only 73 cases will be truly GDM. On the other hand, from 100 true non-GDM cases diagnosed by the standard method, 89 cases will be tested as non-GDM by this method and 11 cases will be falsely diagnosed as GDM. Whether this magnitude of over-diagnosis will outweigh the benefit of reducing the number of glucose value determination needs to be evaluated in the future research. It can be preliminarily speculated that over-diagnosis will lead to unnecessary diet control and further monitoring of blood sugar levels only. Indeed, the blood sugar monitoring will be within normal limits after initial diet control as the over-diagnosed cases are in fact non-diabetics. Therefore, neither insulin nor meticulous diet control will be needed. The expected intervention would remain only minimal diet control and blood sugar monitoring which should do no harm to pregnancy. Only concern may be economic points of view and some drawback issues of blood tests. Presently, this method may be used with the awareness of the aforementioned limitations. It may also be used in cases where the fourth glucose value determination could not be performed from any reasons with the woman being informed of the test limitations.

Another point to consider is that in the present study, a number of subjects had been excluded due to their inability to complete the test throughout their gestation. Whether this fact would affect the study result needs to be considered. However, the reason for them not meeting the complete test was that they either missed the appointment or declined the test. The authors speculated that this had nothing to do with the prevalence of GDM and the proportion that they would give a positive or negative result to the studied test. Therefore, their exclusion would not significantly affect the outcome of the present study. In addition, from sample size determination, only 385 GDM cases would be adequate for the sensitivity and specificity of the studied test of $\geq$ 90% with margin error of 3% or 95% CI = 90 $\pm$ 3%.

Conclusion

A good diagnostic performance for GDM can be obtained with the use of the FPG in combination with 1-h and 2-h glucose values. In addition, FPG and 2-h pair may be considered as another alternative with a slightly lower sensitivity. At present, both modifications of 100-g OGTT might be applied in some situations where the patient could not complete the fourth glucose value determination with the awareness of the test limits.

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การปรับวิธีการทดสอบความทนต่อการรับประทานน้ำตาลกลูโคส 100-กรัม เพื่อการวินิจฉัยภาวะเบาหวานในระหว่างตั้งครรภ์และความถูกต้องในการวินิจฉัย

พรพิมล เรืองวุฒิเลิศ, ปิยา แช่มสายทอง, เกษม เรืองรองมรกต, สุจินต์ กนกพงศ์ศักดิ์, ประเสริฐ ศันสนียวิทยกุล

วัตถุประสงค์: *เพื่อปรับวิธีการทดสอบความทนต่อการรับประทานน้ำตาลกลูโคส 100 กรัม (100-g OGTT) ในการวินิจฉัยภาวะเบาหวานระหว่างการตั้งครรภ์ (GDM) เพื่อลดจำนวนการตรวจเลือดในการทดสอบ*

วัสดุและวิธีการ: *ทำการทบทวนประวัติสตรีตั้งครรภ์ที่ตรวจ 100-g OGTT ได้ครบถ้วน ที่หน่วยฝากครรภ์ โรงพยาบาลศิริราช ตั้งแต่ พ.ศ. 2548-2549 สำหรับรายที่ได้รับการวินิจฉัยว่ามีภาวะเบาหวานระหว่างตั้งครรภ์ โดยการตรวจ 100-g OGTT ตามมาตรฐาน ค่าของผลการตรวจในครั้งที่วินิจฉัยนั้น จะเป็นค่าที่ นำมาใช้ในการศึกษา ส่วนรายที่ตรวจครบถ้วนตลอดการตั้งครรภ์แล้วไม่พบว่ามีภาวะเบาหวานระหว่างตั้งครรภ์ ค่าของผลการตรวจครั้งสุดท้าย จะเป็นค่าที่นำมาใช้ในการศึกษา ค่าระดับน้ำตาลแต่ละค่า หรือ การรวมกัน 2 ค่า หรือ 3 ค่า จะได้รับการศึกษาถึงความถูกต้องในการวินิจฉัย*

ผลการศึกษา: *สตรีตั้งครรภ์ 1,763 รายได้รับการตรวจวินิจฉัยภาวะเบาหวานระหว่างการตั้งครรภ์ได้ครบถ้วน พบมีภาวะเบาหวานระหว่างการตั้งครรภ์ 403 ราย และไม่พบภาวะดังกล่าว 1360 ราย เมื่อพิจารณาค่าน้ำตาลในเลือดแต่ละค่า ค่าที่ให้ผลถูกต้องสูงสุด และมีพื้นที่ใต้กราฟมากที่สุดเป็นค่าระดับน้ำตาลที่ 2 ชั่วโมงหลังรับประทานน้ำตาล โดยมีความถูกต้อง ร้อยละ 93.00 และ มีพื้นที่ใต้กราฟ 0.961 เมื่อพิจารณาการใช้ระดับน้ำตาล 2 ค่า ค่าระดับน้ำตาลที่ 2 ชั่วโมงหลังรับประทานน้ำตาล ร่วมกับระดับน้ำตาลตอนเช้าหลังงดน้ำงดอาหาร จะ ให้ความถูกต้อง ร้อยละ 93.25 ถ้าใช้ค่าระดับน้ำตาลที่ 1 และ 2 ชั่วโมงหลังรับประทานน้ำตาล ร่วมกับระดับน้ำตาลตอน เช้าหลังงดน้ำงดอาหาร จะได้ความไว ร้อยละ 100 และมีความถูกต้อง ร้อยละ 92*

สรุป: *การใช้ค่าระดับน้ำตาลตอนเช้าหลังงดน้ำงดอาหาร ร่วมกับการใช้ค่าระดับน้ำตาลที่ 1 และ 2 ชั่วโมงหลังรับประทานน้ำตาล เป็นทางเลือกที่น่าสนใจในการวินิจฉัยภาวะเบาหวานระหว่าง การตั้งครรภ์*