Clin Chem Lab Med 2006;44(5):568–573 © 2006 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2006.100

National survey on the execution of the oral glucose tolerance test (OGTT) in a representative cohort of Italian laboratories

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Abstract

Background: Recently revised diagnostic criteria for diabetes mellitus and the lack of universal agreement on the methodology for the screening and diagnosis of gestational diabetes mellitus (GDM) still generate inconsistency in execution of the oral glucose tolerance test (OGTT). The aim of the present survey was to evaluate the adherence of Italian laboratories to the internationally accepted guidelines in carrying out the OGTT for the diagnosis of diabetes in the general population and for the screening of GDM.

Methods: A questionnaire was designed to investigate the following issues related to the OGTT: 1) the relationship between laboratories and diabetes centres for the definition of standard protocols; 2) the amount of glucose administered; 3) the number and timing of blood samples; 4) the procedures used for the screening and diagnosis of GDM; and 5) reference to WHO guidelines for the interpretation of the results. The questionnaire was administered to 400 specialists in laboratory medicine working in public or private laboratories nationwide participating in the ''Italian External Evaluation of Quality in Laboratory Medicine'' Study Group.

Results: The survey was completed in the period from June to September 2003. In the observation period, 241 questionnaires were returned by specialists working in laboratories scattered throughout 15 out of the 20 Italian regions. Only 50% of the laboratories performed the OGTT according to protocols defined in agreement with local reference diabetes centres. OGTT using 75 g of glucose in adults and 1.75 g/kg for children as recommended by WHO was performed by 87.1% of the laboratories. WHO indications to collect samples at baseline and at 120 min were followed by 33.2% of the centres. Higher variability was highlighted with respect to the methodology for GDM screening: 49.8% of the laboratories always adopted the two-step procedure consisting of a glucose challenge test (GCT) and subsequent OGTT in positive cases; 4.9% performed the 100-g OGTT with four blood samples; 1.6% the 75-g OGTT with two blood samples; and 2.7% the 75-g OGTT with four blood samples. More than 30% of the centres referred to different diagnostic schemes, 62% of which used individually chosen procedures amongst those reported above, 19% used only the GCT and no subsequent OGTT in positive cases, and 18.4% used a variety of completely different, arbitrarily chosen methods. Finally, only 25.6% of the laboratories referred to the WHO limits for interpretation of the results.

Conclusions: For the Italian laboratories investigated, relevant variability was highlighted for performance of the OGTT in general and GDM screening in particular. A variable relationship between laboratories and diabetes centres was also detected, which might represent a relevant indicator for the need for rationalisation or standardisation of the method for performing an OGTT. These data highlight the need for greater collaboration between these different bodies. We suggest that other similar investigations should be carried out in other countries within the framework of the IFCC Global Campaign on Diabetes Mellitus.

Keywords: diabetes diagnosis; GDM screening; gestational diabetes mellitus (GDM); oral glucose tolerance test.

Introduction

Newly available evidence on the pathophysiology of diabetes mellitus and its late complications, together with its increasing prevalence worldwide, recently induced a significant revision of the classification of and diagnostic criteria for the disease (1–3).

These revisions were carried out to identify metabolic alterations in the early phase of the progression of the disease and to simplify screening procedures.

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Table 1 1999 WHO criteria for diagnosis of diabetes and other categories of glucose intolerance (16).

		Glucose concentration, mmol/L (mg/dL)		
		Whole blood		Plasma
		Venous	Capillary	Venous
Diabetes	Fasting or 2-h post glucose load	≥6.1 (≥110) ≥10.0 (≥180)	≥6.1 (≥110) ≥11.1 (≥200)	≥7.0 (≥126) ≥11.1(≥110)
IFG	Fasting *and, if measured,* *2-h post glucose load*	≥5.6 (≥100) *and* <6.1 (<110) <6.7 (<120)	≥5.6 (≥100) *and* <6.1 (<110 <7.8 (<140)	≥6.1 (≥110 *and* <7.0 (<126) <7.8 (<140)
IGT	*Fasting (if measured)* 2-h post glucose load	<6.1 (<110) *and* ≥6.7 (≥120) *but* <10.0 (<180)	<6.1 (<110 *and* ≥7.8 (≥140) *but* <11.1 (<200)	<7.0 (<126) *and* ≥7.8 (≥140) *but* <11.1 (<200)

IFG, impaired fasting glycaemia; IGT, impaired glucose tolerance.

In fact, it has been widely demonstrated that supposed less severe changes in blood glucose, such as prolonged asymptomatic fasting hyperglycaemia, impaired fasting glucose or even blood glucose levels at the upper limit of the range considered normal and/or glucose intolerance, increase the risk of chronic complications, particularly macrovascular disease (4–7).

The American Diabetes Association (ADA) proposed new diagnostic criteria in 1997 (8) to replace those recommended by the National Diabetes Data Group in 1979 (9) and partially modified by World Health Organization (WHO) in 1985 (10).

The ADA 1997 criteria reduced the fasting blood glucose threshold for diabetes from 140 mg/dL (7.8 mmol/L) to 126 mg/dL (7.0 mmol/L). This change was suggested on the basis of epidemiological data showing a significant increased risk of micro- and macrovascular complications for blood glucose values above 126 mg/dL (7.0 mmol/L) (11–14).

A new class of altered glucose metabolism was also introduced by ADA, impaired fasting glucose (IFG), which defines the condition characterised by fasting blood glucose values in the range between 110 mg/dL (6.1 mmol/L) and 125 mg/dL (6.9 mmol/L). The IFG definition does not require an oral glucose tolerance test (OGTT). Moreover, in the 2005 Position Statements on Diagnosis and Classification of Diabetes Mellitus, the ADA reduced the glucose threshold for IFG from 110 mg/dL (6.1 mmol/L) to 100 mg/dL (5.6 mmol/L) to identify a greater number of individuals at risk of metabolic syndrome and diabetes (15). However, this limit has not yet been universally accepted.

According to the new ADA criteria, the OGTT, which once represented the gold standard for the diagnosis of diabetes, was no longer recommended for diagnosis in the general population, as it was judged cumbersome, time-consuming and characterised by poor reproducibility.

In 1999 WHO published a report indicating new criteria for the diagnosis and classification of diabetes and its complications (16); the existence of IFG as a specific category of altered glycaemic homeostasis was recognised as defined by ADA, but renewed emphasis was placed on the OGTT for the diagnosis of impaired glucose tolerance (IGT) and diabetes in men and non-pregnant women in the adult population (Table 1).

The OGTT is fundamentally recognised for the screening and diagnosis of GDM in pregnant women without diagnostic fasting hyperglycaemia. However, there is still not unanimous agreement on screening procedures and diagnostic criteria. The Fourth Workshop-Conference on Gestational Diabetes (17) and the ADA (18) recommended two different procedures for GDM screening based on a risk assessment for GDM that should be undertaken at the first prenatal visit. The one-step procedure consists of an OGTT performed in pregnant women considered at high risk of GDM (marked obesity, personal history of GDM, glycosuria or a strong family history of diabetes). The two-step procedure consists of initial screening by measuring the plasma glucose level after a 50-g glucose load (glucose challenge test, GCT) in all pregnant women and subsequent OGTT in those with altered GCT [plasma glucose 1 h after GCT ≥140 mg/dL (7.8 mmol/L)]. With either approach, the definitive diagnosis is based on an OGTT performed with 100 g of glucose and four blood samples (0, 60, 120 and 180 min after the glucose load) and interpreted according to Carpenter and Coustan criteria (Table 2) (19). Alternatively, diagnosis can be made using 75 g of glucose and three blood samples (0, 60 and

Table 2 Carpenter and Coustan Criteria for diagnosis of gestational diabetes mellitus with 100-g OGTT (0-, 60-, 120- and 180-min samples) or 75-g OGTT (0-, 60- and 120-min samples); two or more measurements must meet or exceed threshold values for a positive diagnosis (19).

Timing of samples	Plasma glucose	
	mg/dL	mmol/L
Fasting	65	5.3
60 min	180	10.0
120 min	155	8.6
180 min	140	7.8

Table 3 Template of the questionnaire distributed to laboratories.

(A) Is the OGTT performed by the laboratories according to protocols defined in agreement with local reference diabetes clinic?	Yes	No	No diabetes centre in our geographical reference area
(B) Is the OGTT performed with 75 g of glucose in adults and 1.75 g/kg for children as recommended by WHO?	Yes	No	If No Adults …… g Children ….g/kg
(C) Is the OGTT always performed according to WHO indications to collect samples at baseline and at 120 min?	Yes	No	Yes unless otherwise required
(D) Which methodology is used for GDM screening?			
1) Glucose challenge test and confirmatory OGTT with 100 g of glucose and four samples at 0, 60, 120 and 180 min in positive cases?	Yes	No	Other scheme (specify)
2) OGTT with 100 g of glucose and four samples at 0, 60, 120 and 180 min?	Yes	No	
3) OGTT with 75 g of glucose and two samples at 0 and 120 min?	Yes	No	
4) OGTT with 75 g of glucose and four samples at 0, 60, 120 and 180 min?	Yes	No	
(E) Do you refer to the WHO limits for interpretation of the results?	Yes	No	Other guidelines (specify)

120 min after the glucose load) utilising the same glucose thresholds as for the 100-g glucose load. However, ADA has highlighted that the 75-g OGTT is not yet well validated for detection of at-risk infants or mothers compared to the 100-g OGTT.

In contrast, to simplify screening procedures, WHO recommends that an OGTT be carried out in all pregnant women between the 24th and 28th week of gestation, using 75 g of glucose and taking two blood samples at 0 and 120 min after the glucose load, as in the general adult population; thus, pregnant women who meet the general criteria for IGT or diabetes are classified as having GDM (16).

This controversy has led to major debate on which of the procedures can guarantee better specificity and sensitivity for the screening of GDM (20–24).

Such a debate, however, can negatively influence both clinical practice and laboratory services, creating confusion on procedures and interpretation of results, with a consequent lack of standardisation of the diagnostic procedures and methodologies.

In 2003 the International Federation of Clinical Chemistry and laboratory Medicine (IFCC) launched a Global Campaign on Diabetes and created a task force; among its terms of reference, are the review and study of the current use of laboratory tests (www.ifcc.org).

Within this framework, we decided to perform a survey to verify the methodologies used in different Italian laboratories nationwide for performing the OGGT in the paediatric and general adult populations and in pregnant women.

Materials and methods

A cross-sectional survey was conducted in the period from June to September 2003.

A specific five-point questionnaire was developed by SIBioC (Italian Society of Clinical Biochemistry and Molecular Biology)–SIMEL (Italian Society of Laboratory Medicine) Inter-associative Study Group on Diabetes Mellitus (Table 3).

The questionnaire was administered to specialists in laboratory medicine working in public or private laboratories nationwide and participating in the Italian External Evaluation of Quality in Laboratory Medicine Study Group.

The questionnaires were distributed to 400 Italian laboratories nationwide in June 2003.

Completed questionnaires were returned by fax to the study co-ordination centre located at the Umbria Regional

Table 4 Results for children and general adult population (male and non-pregnant females).

Question	Yes, %	No, %	No answer, %
(A) Is the OGTT performed by the laboratory according to protocols defined in agreement with the local reference diabetes clinic?	50.2	47.7*	2.1
(B) Is the OGTT performed with 75 g of glucose in adults and with 1.75 g/kg for children as recommended by WHO?	87.1	6.7	6.2
(C) Is the OGTT always performed according to WHO indications to collect samples at baseline and 120 min?	33.2	56.0[§]	10.8
(E) Do you refer to the WHO limits for the interpretation of the results?	26.5	63.1	9.6

*In 6.7% of cases, there was no diabetes clinic in the geographical area where the laboratory is located.
[§]In 19.9% of cases the WHO procedure was followed only if not uniquely specified by the prescribing physician.

Table 5 Alternative methodologies used for GDM screening in laboratories that did not follow WHO or ADA criteria.

Methodology	No. of laboratories
• OGTT 75 g and 2 samples (0 and 60 min)	2
• All methods reported in the questionnaire but with 6 samples (0, 30, 60, 90, 120 and 180 min)	4
• OGTT 75 g and urinary stick 60 and 120 min	1
• OGTT 75 or 100 g and 6 samples (0, 30, 60, 90, 120 and 150 min)	2
• Fasting glucose, if altered GCT in the next day with 3 samples (0, 60 and 120 min)	1
• OGTT 75 g and 7 samples (0, 30, 60, 90, 120, 150 and 180 min)	1
• OGTT 100 g and 3 samples (0, 60 and 120 min)	5

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Data are described as absolute values and mean ± SD.

Results

Of the 400 laboratories involved, 241 (60.3%) completed and returned the questionnaire by September 2003.

Results related to questions A, B, C and E regarding OGTT methodologies in children and the general adult population are reported in Table 4.

Regarding laboratories that do not follow WHO recommendations for the amount of glucose used for the OGTT (question B), 57% and 14% of them indicated the use of 1 or 0.75 g of glucose per kg of body weight, respectively, and 29% used 100 g of glucose.

In terms of sample collection, for laboratories that do not follow WHO guidelines (question C), 38% collected five samples (baseline, 30, 60, 90 and 120 min), 37.5% collected four samples (baseline, 60, 120 and 180 min), 12.5% collected three samples (baseline, 60 and 120 min) and 12% collected seven samples (baseline, 30, 60, 90, 120, 150 and 180 min).

Concerning GDM screening procedures (question D), 49.8% of the laboratories performed a GCT followed by an OGTT in positive cases, 4.9% only the OGTT with 100 g of glucose and four blood samples, 1.6% only the OGGT with 75 g of glucose and two blood samples, and 2.7% only the OCCT with 75 g of glucose and four blood samples. A further 35.8% of laboratories used variable methods to carry out screening for GDM. Amongst these, 62% used all the methods indicated in the questionnaire, with the test chosen in each case based on the prescribing specialist's request. Moreover, 19% of laboratories performed only the GCT, which is considered sufficient without a confirmatory OGTT in positive cases, and 18.4% used methodologies that differ completely from those indicated in the questionnaire (Table 5).

Of the 241 participating centres, 116 were public laboratories (48.1%) and 125 were private (51.9%). Differences in the distribution of procedures between public and private laboratories are reported in Figure 1.

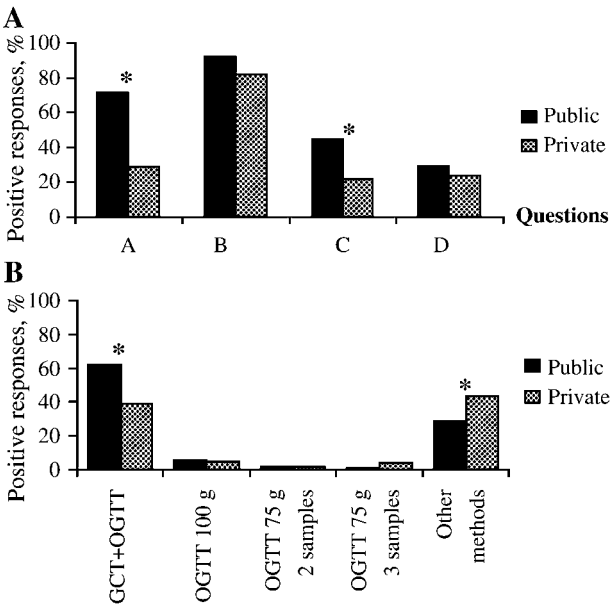

Figure 1 Differences in the distribution of procedures used for the OGTT between public and private laboratories. (A) Percentage of positive (Yes) responses to each questionnaire point related to OGTT methodology in the general adult population (questions A,B,C, E of Table 3). (B) Differences in GDM screening procedures. *$p < 0.05$ between public and private laboratories.

Discussion

New diagnostic criteria for and a new classification of diabetes have been introduced by the ADA and WHO to facilitate screening and early diagnosis of the disease. However, the discrepancies that still exist between these guidelines, in particular with regard to performance of the OGTT, creates confusion, leading to the proliferation of methodologies used in different laboratories.

Our survey provides some evidence of the variability for execution of the OGTT in Italian laboratories. The absence of a specific protocol agreed upon between laboratories and reference diabetes centres was reported by 50% of them, thus indicating little tendency to standardise methodologies.

As a result, the utilisation of 75 g of glucose for the general adult population is accepted by the vast majority of laboratories, while only 33% of laboratories constantly follow the WHO indications with regard to the number of blood samples and their timing; moreover only 26% refer to the WHO criteria for diagnosis.

Wider variability and lack of standardisation was apparent for GDM screening, which can only partially be attributed to differences between the WHO and ADA guidelines in terms of criteria for application, amount of glucose to be administered, number and timing of blood samples, and diagnostic glucose thresholds. The non-homogeneous approach can

mostly be attributed to the poor co-operation between multidisciplinary professionals actively involved in GDM screening, namely, diabetologists, gynaecologists and laboratory medicine specialists. As a result, approximately 50% of centres regularly use ADA criteria for GDM screening, while only a minority follow the WHO recommendations. It is particularly noteworthy that one-third of the laboratories use both criteria, depending on patient characteristics or completely different methodologies (Table 5), increasing the risk of inappropriate interpretation of results. Some of the alternative methodologies reported result in a waste of resources by unnecessarily increasing the number of blood samples, while others are clinically inconsistent.

Of particular concern is the fact that the adoption of such procedures and possible errors in the interpretation of results may negatively affect pregnancy outcome, from both a clinical and a psychological standpoint. A false positive diagnosis of GDM may have a profound psychological impact on a pregnant woman because of concern regarding the outcome of her pregnancy and the risk of future development of overt diabetes (25). On the other hand, a false negative diagnosis of GDM exposes the mother and foetus to higher risk of maternal and neonatal complications and poor pregnancy outcome, which could be avoided by appropriate treatment (26–30).

Some studies seem to suggest a solution for the GDM screening dilemma. Schimdt et al. (31) have shown that a 2-h 75-g glucose OGTT for GDM using both WHO and ADA criteria was equally predictive of poor pregnancy outcome. Owing to the different glucose thresholds, the WHO criteria identify a greater number of women at risk, and thus the authors concluded that this procedure may show higher preventative potential for pregnancy outcome.

De Sereday et al. (32) compared GDM screening according to WHO criteria with the ADA two-step procedure (GCT followed by a 3-h 100-g glucose OGTT). The WHO criteria were able to predict the development of macrosomia with higher sensitivity compared to the ADA criteria, which in turn provided higher specificity and predictive values. However, having demonstrated that the two methods were nearly equivalent, the authors made the suggestion that the WHO single procedure for GDM screening could be preferable and, owing to its simplicity, could be better accepted by pregnant women.

However, these studies had some methodological drawbacks, such as the limited number of women screened and an absence of standardisation for the intervention procedures once GDM was diagnosed. More recently, Nicholson et al. (24) conducted a cost-effectiveness analysis to compare four strategies for universal GDM screening, including the two-step approach, the 100-g and 75-g OGTT alone, and the no-screening strategy. On the basis of their results, the authors concluded that the two-step approach was the most cost-effective strategy and that use of 100-g OGTT alone could be useful in a population where GDM is more prevalent (for example, Hispanics). The 75-g OGTT and the no-screening strategy are not currently viable screening methods.

Clearer guidelines are awaited from a large, ongoing, standardised international trial, the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study (33), which is evaluating 25,000 pregnant women of different racial backgrounds in whom the level of carbohydrate intolerance is being tested with a 75-g OGTT. In addition, data are being collected on maternal and foetal outcome. Hopefully, this study will solve the dilemma on the diagnostic criteria and screening procedures for GDM.

Until these results are available, the major Italian diabetological and obstetrical societies advise that the two-step procedure should be followed. A change in guidelines is expected based on evidence produced by the HAPO Study.

In our survey, analysis of the performance of public and private laboratories highlighted statistically significant differences between them, with the latter showing a lower level of standardisation of the procedures adopted. The lesser penetration of guidelines into private laboratories parallels the absence of a relationship with diabetes centres in more than 70% of cases, in contrast with 30% for public laboratories. The tendency for private laboratories to work in isolation might be considered as one the factors for their poorer performance in screening for GDM.

In conclusion, our survey has highlighted that standardisation of the performance of a basic diagnostic procedure for diabetes mellitus, such as the OGTT in general and in particular in the most important and potentially dangerous area of GDM, is still not satisfactory in Italy. Our results call for significant concerted action between healthcare authorities and the professional societies for diabetologists, obstetricians, laboratory professionals and general practitioners for an effective nationwide educational campaign aimed at standardising procedures for the diagnosis of altered glucose metabolism and diabetes. Strong concerted action at national level is also desirable to prepare the ground for the new standards that are likely to be produced by the international scientific community in the near future based on results of the HAPO study.

We question whether the data collected in our country represent an isolated case, or if similar conclusions could be drawn from surveys in other countries. We suggest that similar surveys could be promoted within the framework of the IFCC Global Campaign of Diabetes.

Acknowledgements

We acknowledge, for their contributions to the design of the questionnaire, its distribution and critical evaluation of the results, the members of the Study Group on Diabetes, in particular the following: M. Carta (Vicenza), F. Ceriotti (Milano), G. Ferrai (Pordenone), M. Graziani (Verona), G. Lippi (Verona), I. Maccaroni (Recanati), M. Marra (Ancona), C. Peirone (Perugia), and M.L. Tomassoni (Terni). Special thanks to M. Borsotti and M. Quercioli (Florence) and to L. Sciaco-

velli (Castelfranco Veneto) for having distributed the questionnaire within the network of Italian laboratories enrolled in the EQAS trials of Azienda Ospedaliera Careggi (Florence), and Centro di Ricerca Biomedica (Castelfranco Veneto).

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Received November 23, 2005, accepted February 6, 2006