SCREENING FOR GESTATIONAL DIABETES IN HIGH-RISK POPULATIONS: THE UNITED ARAB EMIRATES EXPERIENCE

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Gestational diabetes mellitus (GDM) is a controversial condition without a consensus on its definition, diagnosis or management.[1] The spectrum of opinion includes opposing viewpoints,[2,3] with some experts even doubting its existence. The Expert Committee of the American Diabetes Association continues to recognize it as an important clinical diagnosis,[4] with their approach being widely accepted in North America.

There is a high prevalence of GDM in the United Arab Emirates (UAE).[5,6] The Fourth International Workshop/ Conference on GDM[7] recommends universal screening on all high-risk populations, using either a two-step (50 g screen [GCT] followed by a 100 g oral glucose tolerance test [OGTT]), or a single-step approach (100 g or 75 g OGTT) on all patients as early in pregnancy as feasible. According to the American College of Gynecologists (ACOG),[8] all pregnancies in high-risk populations can be considered to be screen positive, and must progress directly to the diagnostic OGTT. However, any of these recommendations using oral glucose is difficult to follow in our setting, and would make unrealistic and excessive demands on the health delivery system.

We report our experience of gestational diabetes screening in the UAE, using practical alternatives in order to reduce all forms of oral glucose testing. The high prevalence of GDM would increase the predictive value of any laboratory test, while the simpler approach without the GCT/OGTT would help in decreasing the laboratory workload, reduce the associated financial healthcare burden and be much easier on patients.

Patients and Methods

The patients in all our prospective studies[5,6,9-11] were the females of our multi-ethnic population attending routine antenatal clinics at the Al Ain Hospital, Al Ain, in the United Arab Emirates. Approximately 5000 women deliver annually in this hospital, i.e., 90-100 per week. Universal screening using non-fasting, 1-hour post-50 g plasma venous glucose over 7.8 mmol/L (140 mg/dL) between 24 and 28 weeks' gestation is not practiced in our hospital but is done routinely by some obstetricians. We included those women referred for an OGTT on the basis of clinical history (previous GDM, family history of diabetes, past macrosomia, and large-for-date pregnancies), as well as the mothers with a positive GCT.

The patients reflected our multiracial population and included nationals from the Indian subcontinent, Chami Arabs from Jordan, Palestine, Lebanon and Syria, Arabs from the UAE and the Arabian Peninsula (Saudi Arabia, Yemen and Oman), Arabs from North Africa (Egypt, Tunisia and Morocco), and East Africa (Sudan and Somalia). A standard OGTT protocol was used. Plasma glucose was estimated by the glucose oxidase method (CX7 Synchron Systems, Beckman-Coulter Instruments, California, USA), and a diagnosis of gestational diabetes was based on Carpenter's modified criteria.[12]

Fructosamine was measured on the fasting blood sample using a second-generation commercial kit (Roche Products Limited, Welwyn Garden City, UK) adapted on the automated CX7 Synchron Systems. The total protein was also by the Biuret method on CX7 Synchron, and the protein-corrected fructosamine (cFRUC) value was calculated as:

$$\text{cFRUC} = \text{fructosamine} * (72/\text{total protein g/L})$$

Hemoglobin A_{1c} (HBA_{1c}) was measured on the fasting sample using the Abbott IMx (Borate affinity method). The laboratory subscribes to an external quality control (United Kingdom–NEQAS). The analysis was done in the following independent cohorts in the various studies in our ongoing work on GDM:

1. Fasting plasma glucose (FPG) estimation, n=682,[10] 430,[11] 1276[5] and 368[5]
2. cFRUC, n=231[10] and 430[6]
3. HBA_{1c}, n= 426[6]
4. GCT, n=1401[9]

Data were logged into a computer database and a data set prepared for analysis using the SPSS 10.0 for Windows statistical analysis program running on a personal computer. The ability to correctly classify a subject with or without GDM was judged by the 100 g 3-hour OGTT, which was the "gold standard." The sensitivity, specificity, positive and negative predictive values for different threshold values in each of the four groups were calculated

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TABLE 1. *Ethnic distribution of pregnant women in two cohorts (%).*

Ethnic group	N=1644	N=430
Indian subcontinent	25.5	29.1
UAE Arabs	22.4	19.1
Other Arabian Peninsula	7.8	5.8
Chami Arabs	17.3	18.8
North African Arabs	11.8	14.2
East African Arabs	7.5	8.4
Other	2.0	4.6

TABLE 2. *Fasting plasma glucose with associated test sensitivity, specificity, positive (PPV+) and negative (NPV–) predictive values at optimal threshold in four cohorts.*

N	Sensitivity (%)	Specificity (%)	PPV+ (%)	NPV– (%)	Reference
Level mmol/L	<4.4	≥5.3	≥5.3	<4.4	
682	66.7	96.9	56.1	88.7	10
430	87.1	97.5	87.5	92.8	11
1276	94.7	93.9	84.6	93.1	5
386	96.6	90.8	80.2	94.6	5

TABLE 3. *Selected threshold values of corrected fructosamine with associated test sensitivity, specificity, positive (PPV+) and negative (NPV–) predictive values.*

N	Level (μmol/L)≥	210	215	220	230
430	Sensitivity (%)	92.2	82.8	79.3	59.5
	Specificity (%)	22.9	33.8	45.2	65.9
	PPV+ (%)	30.7	31.6	34.9	39.2
	NPV– (%)	88.8	84.1	85.5	81.5
231	Sensitivity (%)	86.8	79.4	72.1	60.3
	Specificity (%)	66.9	77.3	83.4	90.8
	PPV+ (%)	52.2	59.3	64.5	73.2
	NPV– (%)	92.4	90	87.8	84.6

using standard definitions.[13] The likelihood ratios of a positive and negative test were also calculated.

Results

Table 1 shows the ethnic distribution of pregnant women in our population in two cohorts.[5,6] Table 2 shows the selected threshold values for fasting glucose with the associated sensitivity, specificity, positive and negative predictive values on four cohorts. Table 3 shows the selected threshold values for cFRUC in two studies,[6,10] with the associated sensitivity, specificity, positive and negative predictive values.

We used the rule-in and rule-out strategy[13] for all the tests used, which is an alternative application of the ROC curve. Basically, this involves considering two cut-off values for each test. The higher cut-off value, which has an increased specificity, is used to rule in the disease under consideration, while the lower threshold cut-off value with its inherent increased sensitivity is used to rule out the disease in question.

Discussion

Accurate data on the prevalence of GDM in this population is not yet available. However, multiple authors have found an increased prevalence of GDM among expatriate Middle Eastern and Indian subcontinent nationals. A prevalence of 11% has been reported in Saudi Arabia and 5.4% in Bahrain.[9] An approximation of 8% has been made for the UAE, but accurate comparison is difficult due to the varying methodology and diagnostic criteria.[6]

Fasting Plasma Glucose (FPG)

Fasting plasma glucose as a screening test is very appealing. It is easy to measure, is inexpensive, reliable and reproducible. It has been advocated as a screening test even for low-risk populations.[14] A need to examine the value of FPG as a screening test[15] in different populations has been expressed.

Using an FPG value ≥5.3 mmol/L (95 mg/dL) as the higher FPG threshold to rule in GDM, four cohorts in our population showed similar results (Table 2). The specificities were 96.9%, 97.5%, 93.9% and 90.8%, respectively. Using the lower FPG of <4.4 mmol/L (80 mg/dL) to rule out GDM, the negative predictive values were 88.7%, 92.8%, 93.1%, and 94.6%, respectively. Combining the data from three studies involving 2092 patients and using FPG≥5.3 mmol/L as the higher value to rule in GDM, the OGTT would not be needed in 627 of 2074 patients (30.2%), with 82 being false-positives (3.9%). Using a lower FPG cut-off of <4.4 mmol/L to rule out GDM, 572 (27.6%) would not need an OGTT, with 40 patients (1.9%) being false-negatives. Thus, the FPG alone would have eliminated the need for 57.8% of the OGTTs, including 5.9% of patients being misclassified. Following the false-positive women for blood glucose control does not present a major problem. Missing 1.9% is potentially more serious and would be the compromise for using FPG as a screening test. Thus, all our studies have validated the consistent and superior performance of fasting glucose as a screening test.

Protein-Corrected Fructosamine

Glycated proteins (fructosamine and HBA_{1c}) are believed to be of limited use in screening for GDM, and that seems to be the consensus of most studies.[16]

In our population, cFRUC was more sensitive than specific. A cut-off of <210 μmol/L attained a sensitivity of 92.2% and 86.8% and a negative predictive value of 88.8% and 92.4%, respectively, in our two studies involving 430 and 231 patients. It is of less value in ruling in disease with low specificity and low positive predictive values (Table 3). Thus, it has potential in our population for ruling out GDM in combination with FPG. If used in combination with FPG, an additional 10.4% (data on 430 patients) would not need the OGTT. The advantage is that both these tests can be done on the same fasting sample.

50 g GCT Screen

For a limited period during one study, we screened 1401 patients with the 50 g GCT.[9] Even during the study period, it became very hard for the phlebotomy department to deal with the numbers involved. Of these, 277 women were screen positive, but only 97 (35%) proceeded to have an OGTT. This study highlights the problems of using the GCT as a screening test in our population. The laboratory would not be able to handle the massive numbers involved. After the positive screen, many patients were lost to follow-up or refused to have the OGTT. This shows that the most popular screening test for GDM, i.e., the GCT, however good its performance, would be a difficult test to use in our setting.

HBA_{1c}

Considerable progress has been made towards the standardization of HBA_{1c} assays. The newer methodologies make it a simpler test technically, so it was worth considering it as a screening test. In one of our previous studies,[6] it was shown that HBA_{1c} has some value in the work-up of patients for GDM. At a level of <5% with a negative predictive value of 90.5%, it would have ruled out GDM in 22.3% of patients. Using a high cut-off of 7% to rule in GDM, only five of the 114 patients (classified as GDM by the OGTT) would have been picked up as GDM. The number of patients identified (4.3%) was too small to be of any practical use. The advantage of using HBA_{1c} in our population would be that a combination of FPG, cFRUC and HBA_{1c} could be analyzed on the same sample, which is convenient for the patient. The performance of HBA_{1c} was slightly better than cFRUC in ruling out GDM. However, considering the cost of the test to its usefulness, the value of HBA_{1c} as a screening test in our population appears to be limited.

The main limitation of our studies has been pre-selection bias, with high prevalence of disease improving the performance of the screening tests. Thus, the conclusions can be valid for only selected high-risk populations and they must find their own prevalence-based cut-offs.

A simple approach to our setting would be to do FPG. Using the cut-offs suggested we would be able to rule in or rule out GDM in over 50% patients. If resources were available, adding the cFRUC would be a useful, easy and cost-effective test and would help to rule out GDM in another 10% of patients. The HbA_{1c} is currently less useful but could become an additional test, if the cost decreased with time. A diagnostic OGTT would be needed on the remaining pregnant women not classified by these simple tests.

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