Screening for gestational diabetes – we are still looking for that elusive test

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History and background

The first known mention of diabetes symptoms was in 1552 BC when Hesy-Ra an Egyptian physician documented frequent urination as a symptom of a mysterious disease that also caused emaciation[1]. Also around this time, ancient healers noted that ants seemed to be attracted to the urine of people who had the disease. In 150 AD the Greek physician Arateus described what we now call diabetes as "the melting down of flesh and limbs into urine."

Centuries later people known as "water tasters" diagnosed diabetes by tasting the urine of people suspected to have it. To acknowledge this feature in 1675 the word "mellitus" meaning honey, was added to the name "diabetes". In 1800s scientists developed chemical tests to detect the presence of sugar in the urine and the first demonstrated evidence of the effects of hyperglycaemia in pregnancy was in 1824. Bennetwitz recorded a case of severe fetal macrosomia and stillbirth in a 22-year-old multigravida in Berlin[2]. She had symptoms of severe hyperglycaemia and the symptoms disappeared after delivery. Until the discovery of insulin in 1921 by Banting and Best there was no effective treatment for this condition. By the 1940s it was becoming recognized that lesser degrees of maternal hyperglycaemia were also a risk to pregnancy outcomes.

The first attempt to define the concept of hyperglycaemia in pregnancy was over 50 years ago in Boston, USA. O'Sullivan used a 50 g oral glucose load with a single one hour measurement as a first screening test, followed by a three hour 100 g oral glucose load with four samples[3]. A sub-committee of WHO in 1965 decided that the results of a two hour 75 g oral glucose tolerance test could be used in pregnancy[4]. The term Gestational Diabetes Mellitus (GDM) was popularized by Freinkel in Chicago in 1980[5]. The HAPO (Hyperglycaemia And Pregnancy Outcome) study in 2008 defined the relationship of maternal glucose tolerance to neonatal outcomes in over 23000 women[6]. In this study risk of adverse outcomes were very low when fasting plasma glucose was less than 80g%.

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Screening and diagnosis

Placenta secretes anti-insulin hormones lactogen, glucogen and cortisol. As a result insulin requirements in pregnancy increases. GDM is defined as "any degree of glucose intolerance with onset or first recognition during pregnancy". This definition also includes unrecognized pre-existing diabetes. NICE (National Institute for Health and Clinical Excellence) guidelines in 2008 recommended screening of high-risk women in pregnancy. The risk factors for GDM by NICE were[7].

1. Body mass index more than 30 kg/m^2
2. Previous macrosomic baby weighing 4.5 kg or more
3. Previous gestational diabetes
4. Family history of diabetes (first degree relatives with diabetes)
5. Family origin with a high prevalence of diabetes – South Asia, Black Carribbean and Middle Eastern.

Global prevalence of GDM
America - 3.9%
Europe - 3.6%
China - 2.3%
Asian - 8.7-17.7%

In Sri Lanka the incidence has been identified as 8% in 1987[8]. A study done in Australia found that the prevalence of GDM increased from 2.9% to 8.8% over 24 years[9]. This may well be the case for Sri Lanka as well. As a result of high prevalence of GDM in Sri Lanka all pregnant mothers need to be screened. Diagnostic criteria for GDM for the 75g oral glucose tolerance test in 1999 by NICE and WHO[10].

Fasting > 126g%

2 hour > 140g%

An effective screening test should be

1) Safe
2) Simple
3) Inexpensive
4) Reproducible
5) Should identify a high proportion of affected individuals in the population

In a study by Crowther et al. compared standard care to aggressive management of GDM and analyzed adverse out comes such as neonatal death, fracture, shoulder dystocia and nerve palsies. There were 490 women in active management arm and 510 women in standard care arm. There was a reduction from 4% to 1% in the active management arm[11].

These data suggested that both screening and management of GDM are beneficial to both mother and child.

OGTT as a screening test is not the best. It is a very inconvenient test to be done in a pregnant woman.

The woman has to be fasting. Not tolerable in pregnancy.

Oral glucose load causes vomiting very often.

The patient has to wait for 2 hours. Not the ideal in a time conscious world.

Therefore there is a great need to look at a more realistic test to be used as a screening test.

Urine for sugar – Traditionally this has been the oldest documented screening test. Although this is a very simple test it's accuracy is not acceptable. Renal glycosuria is common in pregnancy due to lowering of the renal threshold for glucose excretion. Our national maternal and child health (MCH) system currently performs the Benedict's test for random glycosuria to screen for GDM at every antenatal visit.

Fasting blood sugar – In pregnancy FBS is lower than in the non-pregnant state as a consequence of increased fetal utilization and therefore it cannot be used as a screening test. It also has the inconvenience of the patient having to come to the laboratory early morning in fasting state[12]. A study has shown that lowering the fasting plasma glucose increases the sensitivity but reduces specificity and positive predictive value[13]. In the same study it was recommended to replace the fasting plasma glucose test of the 75g OGTT with the 1 hour glucose estimation and there by limit hospital based screening in the laboratory setting to only two tests.

Post-prandial blood sugar – This has been suggested as a cost-effective patient friendly method of screening[14]. But the hallmark of diabetes is a chronic elevation of the blood sugar levels and a single level is not sufficient to make a diagnosis.

Oral glucose challenge test – This test consists of taking a blood sample 1 hour after the ingestion of a 50g glucose load. In a previous study sensitivity of a OGCT was found to be 79% and the specificity 87% when used as a screening test for GDM[15]. Further the OGCT is inconvenient to the woman as she needs to spend more time in the laboratory and the glucose drink can cause vomiting.

Research done by the author

Weerasekera and Peiris performed a study to assess the value of glycolysated haemoglobin (HbA1c) as a screening test to detect GDM and published the results in the *Ceylon Journal of Medical Science* in 2000. The life span of haemoglobin is closer to 6-8 weeks, and therefore, glycolysated haemoglobin measurement reflects the average glucose concentration over this period. We studied 244 women attending antenatal clinics at Colombo South Teaching Hospital at 28 weeks of gestation[16]. Venous samples were taken on all 244 women after over night fasting and this was followed by oral intake of 75 g of glucose and a second venous blood sample was collected two hours later. Sensitivity and specificity was calculated to assess the reliability of HbA1c test. The cut off point with regard to glycolysated haemoglobin for diagnosis of gestational diabetes was regarded as a value greater than 7% and the two hour plasma glucose level after 75g OGTT was regarded as greater than 144g.

The OGTT was positive in 100 pregnant women of whom 88 tested positive for HbA_{1c}. Therefore the sensitivity of this test was 88%. Of the 144 pregnant women tested negative by the OGTT, 112 were correctly identified by the HbA1c test giving a specificity of 78%.

In a more recent study done in 2016 and published in the *British Medical Journal* using a cut off value for HbA1c at 5.1% for detecting GDM showed a sensitivity of 61% and a specificity of 68% with a negative predictive value of 93%. When the HbA1c cutoff value was taken as 5.4% the sensitivity dropped to 27% and the specificity increased to 95% with a negative predicting value of 91%. They concluded that pregnant women with an HbA1c of 5.4% or more should proceed with an OGTT. This may result in a significant reduction in the burden of testing on both patients and testing facility staff and resources[17]. But further investigations are required to integrate and optimize the HbA1c as a single, non-fasting, screening tool for GDM.

In another study done by the Weerasekera DS and Peiris H and published in the *Journal of Obstetrics and Gynaecology* the value of serum fructosamine in comparison with oral glucose tolerance test (OGTT) as a screening test for detection of GDM was determined[18]. This was a cross sectional descriptive study on 210 pregnant women attending Ante Natal Clinic at Colombo-South Teaching Hospital. A 75g OGTT and serum fructosamine assay in the fasting state and 2 hours after ingestion of oral glucose was performed.

Fructosamine was discovered about 30 years ago. It is a marker of glucose control reflecting the average glycaemic level over the preceding 2-3 weeks. Fructosamine is measured bichromatically as an end-point reaction based on the ability of glycated proteins to reduce nitro blue tetrazolium in an alkaline solution. The test requires a small sample volume, and results are resistant to the effects of storage and heat on the specimens. Samples for fructosamine assay requires no pretreatment and the fructosamine assay has been found to be less expensive than HbA1c assay.

The effect of ingestion of 75g of glucose on the mean serum fructosamine value.

	Fasting (µmol/l)±SD	2 hours after ingestion of glucose (µmol/l)±SD
Normal (n=138)	220 ± 21	224 ± 19
GDM (n=64)	278 ± 12	281 ± 11

Above results showed that there was no significant difference in the serum fructosamine values in fasting and 2 hours after ingestion of glucose.

The cut off point with regard to fractosamine for diagnosis of non-diabetic subjects was regarded as 265 µmol/l as the upper level. GDM was defined as fasting plasma glucose of more than 126g% and 2-hour plasma glucose level after 75g oral glucose between 144g% to 198g%. The desired sample was selected using systematic sampling techniques. The statistical significance of fructosamine values was assessed by

Student's t-test. Calculating the sensitivity and specificity assessed the reliability of fructosamine test. The OGTT was positive in 64 mothers of whom 56 tested positive for fructosamine demonstrating a sensitivity of 87.5%.

Of the 146 mothers tested negative by the OGTT 138 were correctly identified by the fructosamine test giving a specificity value of 94.5%.

	Sensitivity	Specificity
Glycolysated haemoglobin	88%	78%
Serum fructosamine	88%	94%

In a study published in 1986 in the *American Journal of Obstetrics and Gynecology* also confirmed that serum fructosamine may be a useful screening test for gestational diabetes[19].

In a study done in 2015 and published in the *Journal of Pharmacology and Bioallied Sciences* also showed that serum fructosamine to be a better indicator than Glycolysated Haemoglobin for monitoring of GDM[20].

Discussion and Conclusions

Proper diagnosis of Gestational Diabetes Mellitus and its good glycaemic control during pregnancy cannot be over emphasized. But there is no consensus regarding screening and diagnostic methods for gestational diabetes mellitus.

NICE Guidelines for screening and diagnosis of GDM in 2015 are[21]

1. Assess risk of GDM using risk factors in a healthy population. If woman had GDM in previous pregnancy do 75g OGTT as soon as possible, if negative repeat again at 24-28 weeks. Other women with any other risk factors screen at 24-28 weeks by 2 hour OGTT with 75g glucose load
2. Do not use fasting plasma glucose, random blood glucose, HbA1c, glucose challenge test or urine analysis for glucose to assess risk of developing GDM
3. Glycosuria of 2+ or more on one occasion or 1+ or above on 2 or more occasions by regular strip test on ANC needs further testing to exclude GDM
4. Diagnosis of GDM is made if the woman has either fasting plasma glucose level of 5.6 mmol/l (100g%) or above or a 2-hour plasma glucose level of 7.8 mmol/l (140g%) or above.

These guidelines would lead us to following questions as practicing clinicians

1. Looking at these guidelines where do we stand
2. What would be the ideal in a developing low resource country like Sri Lanka
3. Whatever the method used, it is important to do universal screening in Sri Lanka as our incidence of GDM is high
4. More effective and simpler strategies should be developed in future clinical practice by which the need for performing OGTT can be avoided.
5. Why is serum fructosamine not mentioned in above guidelines?

Research and literature review in this presentation shows that serum fructosamine is an effective test for screening for gestational diabetes mellitus and provide a good index for glycaemic control. In addition to its reliability, it is technically simple to perform, is of low cost, the value does not change depending on the time of last meal and is of short analytical time.

The fructosamine determines the average glucose levels over the past 2 to 3 weeks and the assay is not affected by the food consumed during the day.

Larger studies and more research will see a break-through with regard to finding a simple and an effective test to screen for gestational diabetes mellitus.

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