The Importance of Screening for, and Managing, Gestational Diabetes Mellitus in Malta

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Abstract

The detection and management of gestational diabetes mellitus (GDM) has been a source of controversy for many years. Evidence has now accumulated that dietary and insulin therapy are effective and reduce the risk of macrosomia and Caesarean section. Studies are underway to assess the impact of screening and of the different diagnostic criteria for GDM. However, studies to date have reported only an impact on obstetric, neonatal and fetal outcomes. It is now possible to prevent or at least delay the onset of maternal Type 2 diabetes, and interventions targeting women with a history of GDM are likely to have a substantive impact on the current diabetes epidemic. An even greater impact may result from preventing excessive intra-uterine exposure to hyperglycaemia, increasingly implicated as a cause of obesity and diabetes in the offspring of women with past GDM. Developing and implementing approaches to preventing long term risks to mother and baby across populations will take many years and possibly decades. In the meantime, all women should be screened for GDM so that the need for long term follow up, and, where possible, intervention for mother and baby can be identified. Such action requires knowledge of the diagnosis not only by the health care team but also the woman herself.

Keywords

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Introduction

The high prevalence of diabetes observed among the people of Malta was first reported in 1965 [1] and continues to rise [2] with 57,368 cases predicted by the WHO in 2030.[3] Gestational diabetes mellitus (GDM) is defined as glucose intolerance that begins or is first detected during pregnancy [4] and the presence of GDM reflects the risk of developing Type 2 diabetes later.[5] In spite of being a population at "high risk" of Type 2 diabetes, only 1.9% (236/12260) of pregnancies were diagnosed as gestational diabetes mellitus (GDM) in 1999-2001.[6] This is comparable to Anglo-Celtic populations who are considered a low risk ethnic group.[7,8] The explanation for this apparent dichotomy has been demonstrated by cross sectional studies, where the prevalence of GDM was indeed high, 11.5% using WHO criteria.[9] Clearly, while all Maltese women (as a high risk ethnic group) should be screened for GDM according to the latest guidelines [4], such "universal screening" is not happening. This may simply relate to organizational issues as historically GDM has been a contentious diagnosis and this may be continuing to influence Maltese antenatal care and policy.

Screening for GDM: a historical perspective

The association between maternal glycosuria and fetal macrosomia in GDM was first described in 1823. It subsequently became recognised that intrauterine exposure to hyperglycaemia is a major contributing factor to fetal macrosomia with attendant adverse obstetric outcomes. In 1961, GDM was demonstrated to be a precursor of future maternal diabetes.[10] Subsequent studies demonstrated that up to 62% of women diagnosed as having GDM developed permanent diabetes (largely Type 2 diabetes).[11] Data from the Boston cohort study published in 1973 showed significantly increased fetal morbidity and even perinatal mortality among the offspring of the cohort defined as having GDM.[12] From a clinical viewpoint, screening all pregnancies for GDM using a glucose challenge test ("universal screening") became justifiable in order to predict which deliveries were more likely to have adverse outcomes. Women were also advised on lifestyle changes which might be associated with a reduced risk of Type 2 diabetes.

However, even as the evidence mounted that GDM was associated with significant implications for mother and baby, confusion grew with the introduction of a plethora of different criteria for diagnosing GDM using different glucose loads, different cut off points and other challenges (eg standard meals).[13] In parallel, the risk of perinatal mortality and obstetric morbidity dropped with improved obstetric care whether GDM was diagnosed or not. As the adverse obstetric and perinatal

outcomes used to justify screening for GDM became less frequent, other possible causes of the adverse outcomes were also identified. Macrosomia, initially considered a major hallmark for GDM, also became known to be associated with obesity, another major risk factor for GDM.[13] Indeed, in Malta during 1999-2001, GDM and diabetes in pregnancy overall, were diagnosed in association with only 4.0% of perinatal deaths, 2.2% of malformations, 3.8% of Caesarean sections, 5.0% of babies born >4.0kg and 19.0% of all shoulder dystocia.[6]

As the reasons for screening for GDM from an obstetric point of view receded, the diagnosis of GDM itself was found to lead to increased operative delivery and associated morbidity in some (but not all) centres.[15,16] Other considerations, including the costs of screening for GDM (even though antenatal screening for much rarer conditions such as syphilis continue), a lack of randomized controlled trials showing that screening for GDM made a difference to outcomes and the lack of evidence for interventions to prevent GDM progressing to diabetes, resulted in screening for GDM not being justified.[17] However, recent evidence means that this situation has now changed markedly.

Evidence that the management of GDM improves outcomes

The evidence that treating the hyperglycaemia associated with GDM reduces adverse fetal outcomes has recently been reviewed.[13] There is now considered to be level I evidence (ie from at least one properly randomized controlled trial) regarding the benefits from treating hyperglycaemia with dietary treatment alone [18] and with insulin therapy.[19,20] However, this data relates predominantly to preventing macrosomia (which is a subject of debate over criteria and importance), neonatal hypoglycaemia (which is a subject of debate over criteria and management) and Caesarean section (which is probably more influenced by obstetrician and personal choice). Hard outcomes, such as perinatal mortality and fetal injury, are too uncommon to have been included in the size of studies to date.

Evidence that screening for GDM is associated with reduced adverse fetal outcomes is under active investigation. There is one randomized controlled trial, with the obstetric team blinded from the screening results, comparing screening for GDM and associated intervention with controls (the ACHOIS study) and the results of this are expected soon. A cross sectional multicentre study of 25,000 pregnant women is seeking to identify a clear cut off point for obstetric and fetal complications from GDM (the Hyperglycaemia and Adverse Pregnancy Outcome Study, HAPO) but the results to this study are not expected until 2007.[21]

At this stage, and on the basis that at least some outcomes are improved by the management of GDM, guidelines now recommend that screening for GDM is at least selective.[4] In Malta, as a population at high risk of diabetes, this means that all women should be screened for GDM. Of concern is that having a risk assessment approach (eg only screening the obese or older women), rather than a universal screening approach, adds a level of complexity in the management process which is likely to reduce screening overall.[22] Furthermore, even in populations with a large proportion of women at low risk of GDM (eg Australia), it would still be necessary for 80% of pregnant women to be tested using local criteria.[23]

The world has now changed

While discussion has been raging about the plasma glucose cut off point for diagnosing GDM (always a difficult debate whenever a continuous variable is used to define a dichotomous state) and whether screening for GDM should occur, the world has changed.

Firstly, the world is now experiencing an epidemic of obesity (paralleled by a rise in diabetes).[24] For example, in Malta, between 1970 and 1984, obesity among women increased by 21% and among men by 144%.[25] Being either overweight or obese affects 45% of women aged 25-34 years and 62% of women aged 35-44 years [25] (the later fertile years) and was present in 37% of pregnant primipara aged 20-29 years.[26] Obesity in 10 year old children in 1990-91 was 18.9% in boys and 24.3% in girls [25] and will have increased substantially over the last decade in parallel with international trends.[27] Alongside the pandemic of obesity is the epidemic of Type 2 diabetes [27], which in Malta is expected to be associated with increases in numbers with Type 2 diabetes from 19,700 in 1995 [27] to 39,177 in 2000 and the prevalence is expected to rise to 57,368 by 2030.[3]

Now, not only is the age specific prevalence of Type 2 diabetes increasing [28], but the age at which Type 2 diabetes is diagnosed (and by inference, commences) is decreasing.[29] For example, paediatric endocrinology clinics are now reporting that 33% of their diabetic patients have Type 2 diabetes, while before, this was an uncommon phenomenon.[30] However, not only are there growing numbers of children and adolescents with Type 2 diabetes who will become pregnant in the future, but the numbers of potentially fertile women developing Type 2 diabetes is also growing very rapidly (and disproportionately) in comparison with that in older age groups. In the 30-40 year age group in the USA, the number of women with Type 2 diabetes has increased by 70% between 1990 and 1998 (vs 33% across all ages).[31]

These developments have a number of implications for the treatment of GDM. A proportion of the women with GDM will have their hitherto undiagnosed Type 2 diabetes first detected in pregnancy. This group has perinatal mortality rates at least as high as those with previously known Type 1 or Type 2 diabetes.[32] As GDM and Type 2 diabetes share common risk factors [5], a growth in the numbers with GDM is expected. Surprisingly little data exists monitoring GDM prospectively, possibly due to changing criteria, but in a study across many ethnic groups in Victoria, Australia, a major increase in the prevalence of GDM occurred over a 5 year period.[33] Furthermore, even if a woman does not have GDM, the massive increase in overweight and obese women at a younger age, means that the proportion of women with additional risks and the potential health benefit of screening will increase. However, this is not relevant in Malta as all women are considered at risk.

As if the changing epidemiology of GDM were not sufficient to stimulate increased GDM screening rates, there is now clear evidence from a number of randomized controlled trials that progression from impaired glucose tolerance and from GDM, to Type 2 diabetes can be prevented.[34] The implication of this is that if a woman has GDM diagnosed, then intervention is possible. Even if active treatment is not happening currently, at least the woman will have the information (and hopefully

the services) to act in the future. The health and economic impact of this will be major in a world with an epidemic of Type 2 diabetes and where long term diabetic complications, such as nephropathy, are much more likely to occur in those whose diabetes commenced at a younger age. The re-introduction of screening for GDM for the purposes of preventing future Type 2 diabetes, represents a major shift from a focus on short term obstetric, fetal and neonatal outcomes to considering GDM a major public health problem: a perspective proposed by Norbert Freinkel in 1979.[35]

Long term importance of GDM for the baby

Freinkel's perspective of GDM as a major public health problem included the concept of "fuel mediated teratogenesis", ie that the excess supply of fuels (particularly glucose) to the fetus led to irreversible structural and metabolic changes.[36] This hypothesis in relation to GDM, followed on from the early recognition that following intrauterine exposure to hyperglycaemia, fetal beta cells become hyperplastic and this is associated with excessive fetal fat deposition. Support for this hypothesis is growing with evidence from long term studies of offspring of mothers with diabetes in pregnancy, including Type 1 diabetes and from prospective studies of GDM in different ethnic groups.[37-41] The data suggest that exposure to a "diabetic" intrauterine environment is associated with an increase in risk of future obesity, IGT and diabetes. Among Pima Indians, it has been clearly shown that diabetes is much more common in the offspring of women with maternal diabetes occurring during, rather than after, pregnancy.[40] The excess risk of developing diabetes in this group with exposure to diabetes in utero is 10.4 times with a population attribual risk of 35.4% (ie 35.4% of diabetes in this cohort was due to exposure to diabetes *in utero*).[41]

It is not known if intervention during or before pregnancy will ameliorate this "potential amplifier" for the current epidemics of obesity and diabetes. Obtaining long-term data about the efficacy of treatment will clearly take many decades. In one small, non randomized study, adiposity was less in the offspring of mothers with GDM treated with insulin rather than diet alone, but further evidence is needed as to whether preconceptual and antenatal interventions are of benefit.[42] However, if intrauterine exposure to hyperglycaemia is known, then the offspring can be identified as high risk, followed up and childhood-based interventions implemented as they become practicable. This requires both the screening to take place and for both health care professionals and the women themselves to be aware of the risks – present and future.

Conclusion

In conclusion, the world around GDM has moved on from a debate around short-term obstetric, fetal and neonatal outcomes to preventing obesity and Type 2 diabetes in both the mother and the baby over the long term. In order to manage this risk in Malta, and to be prepared for interventions as they are developed, all pregnant women require proper screening for GDM as recommended by all major guidelines. Based on existing data, this will require a major improvement in current GDM screening practices.

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