Impaired glucose tolerance in pregnancy

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Gestational diabetes mellitus is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. It has been shown that the risk of adverse maternal, foetal, and neonatal outcomes in gestational diabetes mellitus is related to the degree of glucose intolerance and/or hyperglycaemia; gestational diabetes mellitus also has long-term sequelae for both the mother and the offspring. As gestational diabetes mellitus is rarely symptomatic, diagnosis of the condition relies on screening. The diagnostic criteria and the management of gestational diabetes mellitus are discussed and areas of controversy and recent advances highlighted.

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Introduction

Pregnancy causes significant changes in carbohydrate tolerance. Fasting plasma glucose falls slightly during pregnancy whereas postprandial values rise and insulin secretion is increased. The diabetogenic effect of pregnancy is partly due to an increase in insulin demand, to the metabolic effects of sex steroids and other hormones whose secretion increases in pregnancy, and to the development of insulin resistance especially during the second half of pregnancy. It is therefore not surprising that some individuals will develop glucose intolerance during pregnancy. Although the adverse effects of carbohydrate intolerance on pregnancy and foetal outcome were first described nearly 100 years ago, it was not until 1979 that gestational diabetes mellitus (GDM), a condition of glucose intolerance that occurs in pregnancy and usually resolves after delivery, was formally recognised as a subgroup of diabetes mellitus (DM) by the National Diabetes Data Group (NDDG).[1] That GDM is a distinctentity and poses an important health risk during pregnancy has now gained widespread acceptance, as evidenced by the position statements issued by the American Diabetes Association (ADA),[2] the World Health Organization (WHO),[3] and the American College of Obstetricians and Gynecologists (ACOG).[4]

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Definition and diagnostic criteria

Gestational diabetes mellitus is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. The definition applies irrespective of whether or not insulin is used for treatment or whether the condition persists after pregnancy. It does not exclude the possibility that the glucose intolerance may have antedated the pregnancy. Two sets of criteria are currently recommended by various national or international organisations for the diagnosis of abnormalities of glucose tolerance during pregnancy. The NDDG criteria divide the pregnant population into two categories, those with normal glucose tolerance and those with gestational diabetes,[1] whereas the WHO approach has an intermediate category of impaired glucose tolerance (IGT).[3] The NDDG criteria are based on an adaptation of the criteria proposed by O'Sullivan and Mahan in 1964.[5] A two-step procedure is recommended in which a 3-hour 100-g oral glucose load is administered to women who have a glucose concentration ≥7.8 mmol/L after an initial screening test using a 1-hour 50-g glucose load (Table). The NDDG criteria are endorsed by the ADA and ACOG and are in general use in North America whereas the WHO criteria are used in most other parts of the world. The WHO criteria are based on a test that uses a 75-g oral glucose load. It is recommended that the glycaemic criteria for diagnosing diabetes and IGT in the nonpregnant adult is also applied in the pregnant adult with the important proviso that the management of IGT during pregnancy should be the same as for DM (Table). Both sets of diagnostic criteria have

Table. Glycaemic criteria for the diagnosis of impaired glucose tolerance and gestational diabetes mellitus

	Venous plasma glucose concentration (mmol/L)			
	Fasting	**1 h**	**2 h**	**3 h**
WHO (75-g OGTT)*				
DM†	≥7.8		≥11.1	
IGT‡	<7.8		≥7.8, <11.1	
NDDG§ (100-g OGTT)‖				
GDM¶	≥5.8	≥10.6	≥9.2	≥8.1

*OGTT oral glucose tolerance test
†DM diabetes mellitus
‡IGT impaired glucose tolerance
§NDDG National Diabetes Data Group
‖Diagnosis of GDM is made when any two values are met or exceeded
¶GDM gestational diabetes mellitus

been criticised for various reasons. The WHO criteria are based on the upper limits of normal glucose values derived from mixed populations and are not specific for pregnancy. Allowances are therefore not made for the normal physiological adaptations that occur during pregnancy. The NDDG criteria for diagnosing GDM are based on the predictive value of the glucose response to the 100 g oral glucose tolerance test (OGTT) that is administered during pregnancy to test for the likelihood of the development of overt DM in the mother. The NDDG diagnostic criteria do not optimally predict critical outcomes such as perinatal mortality.

Despite the fact that three international workshop-conferences on GDM have been convened over the past decade, there is still no universal agreement with regard to the diagnostic criteria of GDM. The lack of a common diagnostic approach and internationally agreed methodology has hampered research in this field and makes comparability of data from different centres difficult. A strong case was made during the Third International Workshop-Conference on GDM for a critical look at the diagnostic methodology and glycaemic criteria used for GDM.[6] Studies that compare the performance of the two major contending diagnostic approaches are required and future diagnostic criteria should take into account both maternal and foetal outcomes.

Maternal and foetal risks associated with gestational diabetes mellitus

The glucose intolerance of GDM is usually mild and most often asymptomatic. Nevertheless, undiagnosed, untreated GDM is associated with a higher incidence of complications during pregnancy and increased perinatal mortality and infant morbidity. For the mother with GDM, there is a higher risk of hypertension, pre-eclampsia, urinary tract infections, caesarean section and future diabetes.[7,8] The predominant acute effects of GDM, however, occur not to the mother but to the foetus. Many of the problems associated with overt diabetic pregnancies such as macrosomia, neonatal hypoglycaemia, hypocalcaemia, hypomagnesaemia, hyperbilirubinaemia, birth trauma, prematurity syndromes, and subsequent childhood and adolescent obesity can be seen in infants of gestational diabetic pregnancies.[9,10] Macrosomia has been the most widely studied of these adverse outcomes and has been shown to be directly associated with increasing maternal glycaemic response to glucose challenge.[11] Excessive foetal growth is observed two to three times more often in women with GDM. Treatment of the mother improves the prognosis for the foetus. Widespread testing and identification of GDM as well as intensive management appear to be associated with a decrease in overall morbidity in the infant and the likelihood of intrauterine foetal death in a patient with appropriately treated GDM is not significantly greater than that for a normal pregnancy.[9]

There is little controversy about the need to detect and treat those women who are pregnant and have unequivocal degrees of glucose intolerance that qualify for the current WHO and NDDG diagnosis of GDM. However, there is much less certainty regarding those individuals with lesser degrees of glucose intolerance who fall into the category demarcated by the WHO as IGT but who are indistinguishably encompassed in the broad NDDG class of GDM. Whether these groups of patients with 'gestational IGT' have the same entity as 'gestational diabetes' is difficult to tell with the existing information. The use of the single NDDG diagnostic class of GDM gives only an estimate of the average risk across the whole range of glucose intolerance, even though the lesser degree of glucose

intolerance might contribute little, if anything, to it. The WHO has claimed that retaining the distinction between diabetes and IGT in pregnancy makes it possible to determine more specifically the effects of lesser degrees of glucose intolerance upon maternal and child health.[3] It is important to define the putative risks, maternal or foetal, in this group of patients and to set them against the cost and risks of diagnosis and intervention.

There is relatively little evidence from adequately controlled studies currently available on the significance of lesser degrees of glucose intolerance in pregnancy. Preliminary data suggests that the glucose intolerance in these patients is usually mild and perinatal complications are rare. No adverse perinatal risk was detected in pregnant women with IGT in the report of the Diabetic Pregnancy Study Group of the European Association for the Study of Diabetes.[12] Li et al[13] reported on the perinatal outcome in 158 Hong Kong Chinese women who were positive by the NDDG OGTT but non-diabetic or with IGT by a subsequent WHO OGTT. The women were randomly assigned to a restricted diet and blood glucose–monitored group or to an untreated control group. The perinatal outcomes in these two groups were very similar except that those who were treated for IGT had smaller babies that were born 1 week earlier than those of the control group.

In a retrospective study of 120 pregnant women with IGT who were treated with dietary therapy in Northern Ireland, no significant difference was found in the incidence of antenatal complications compared with mothers with normal glucose tolerances.[14] There was a higher rate of induced labour and caesarean section in the IGT group but there was no difference in foetal outcome or neonatal morbidity. Likewise, another retrospective study comparing the outcomes of 212 pregnant women with untreated IGT with those who had normal glucose tolerance found no adverse perinatal outcomes.[15] It is difficult to draw clear conclusions from retrospective studies and, particularly in the IGT range, confounding factors such as maternal age, obesity, and parity may play an important role in determining the foetal outcome rather than glucose tolerance per se. A recent prospective cohort study involving more than 3600 patients with various degrees of glucose intolerance but who do not fulfill the current NDDG criteria for the diagnosis of GDM demonstrated a modest graded increase in adverse maternal-foetal outcomes with increasing maternal carbohydrate intolerance, even in the absence of GDM.[16] It is increasingly being recognised that glucose intolerance in pregnancy represents a continuum. A new multicentre, multiracial, and multinational longitudinal study to measure adverse perinatal outcome and to correlate it with various degrees of glucose intolerance is currently being planned.[17] Large, randomised, interventional trials will be required in the future to evaluate the efficacy and cost-effectiveness of treating these patients.

The incidence of gestational diabetes mellitus

The incidence and prevalence of GDM varies worldwide and among different racial and ethnic groups. The variability is partly due to the different screening regimens and diagnostic criteria used to identify GDM,[18] and to the different background prevalence rates of DM among different populations. In the United States, GDM occurs in approximately 3% to 5% of pregnant women annually, but the prevalence of GDM has been reported to be as high as 12.3% in an inner city American population consisting predominantly of Hispanics and African Americans.[19] The overall incidence in the UK and most of Europe is about 1% to 3%. In Australia, the incidence of GDM varies according to country of birth, from 4.3% in Australian women to 15% in women born on the Indian subcontinent.[20] Studies have indicated that the incidence of GDM is increased in Asian and Chinese populations.[20,21] According to the statistics from the Department of Obstetrics and Gynaecology at The University of Hong Kong, the incidence of gestational glucose intolerance in women attending their antenatal unit has risen from 2.1% in 1981 to 6.8% in 1991 (Lao TT, personal communication). This is not surprising as the prevalence of non–insulin-dependent diabetes mellitus (NIDDM) has also been increasing with the adoption of a westernised lifestyle in Hong Kong.

Screening and diagnosis

Gestational diabetes mellitus is rarely symptomatic and can only be detected by screening. Several screening methods for GDM have been proposed but so far no optimal methods have been generally accepted and recommendations vary in both criteria and procedure. Traditionally, obstetricians have relied on historical and clinical risk factors to identify those patients most likely to develop GDM. Potential diabetic features include: (1) a first-degree relative with diabetes; (2) obesity (above 120% ideal body weight); (3) previous overweight baby (greater than 90th percentile); (4) unexplained stillbirth or neonatal death; and (5) a history of latent diabetes (e.g. during previous pregnancy or illness). Selective screening methods based on poten-

tial risk factors in conjunction with the measurement of either fasting or random glucose levels are still favoured in most European centres. Diagnosis is then based on the result of a formal OGTT. Selective screening is also the method used in most centres in Hong Kong. In some populations, however, almost half of all patients with GDM lack specific risk factors and universal screening has therefore been advocated. The ADA has recommended that all pregnant women who have not been identified with glucose intolerance earlier in pregnancy should be screened with a 1-hour 50-g glucose challenge test between 24 and 28 weeks of pregnancy.[2] A plasma glucose value ≥7.8 mmol/L should be used as the threshold level and indicates the need for a 3-hour 100-g OGTT. These recommendations are also supported by the Third International Workshop-Conference on Gestational Diabetes. The ACOG recommends screening of all pregnant women older than 30 years, and younger women only if risk factors are present.[4]

Since there is no universal agreement on the diagnostic criteria for GDM, studies have been performed to evaluate different criteria.[18,22] It was recommended in the Second and Third International Workshop-Conferences on Gestational Diabetes that the 75-g OGTT should eventually be universally used to define GDM after sufficient experience during pregnancy has been secured.[6] Sacks et al evaluated the 75-g OGTT in more than 3000 unselected pregnant women and found that there was no meaningful threshold relationship between glucose tolerance test values and clinical outcome.[23] Consequently, they suggest that the criteria for defining GDM probably need to be established by consensus. The appropriateness of the WHO diagnostic criteria for pregnant Chinese women in Hong Kong has been evaluated by Li et al.[24] An unselected population of 618 pregnant Chinese women underwent a 75-g OGTT between 24 and 28 weeks of gestation. After 2 hours, the glucose levels of this population at two and four standard deviations above the mean came very close to the values suggested by the WHO for the diagnosis of IGT and GDM respectively. The glycaemic values used in the WHO criteria seem to be valid for our local population.

Medical management

Maternal hyperglycaemia leads to foetal hyperglycaemia, which leads to foetal hyperinsulinaemia and overgrowth. The goal of medical management is to reduce the perinatal mortality and morbidity by normalising the level of glycaemia. The foetal insulin response to a hyperglycaemic environment is related to the severity of hyperglycaemia and not to the nature or aetiology of the maternal diabetes. Hence, there is no apparent reason to allow more severe hyperglycaemia in patients with GDM than in those patients with pre-existing diabetes who are pregnant. The degree of hyperglycaemia that would prompt a change in therapy for a mother with pre-existing diabetes should be the same for a mother with GDM.

Dietary therapy

As with all forms of diabetes, diet therapy is the cornerstone of intervention in women with GDM. The optimal dietary prescription should be one that provides the calories and nutrients necessary for maternal and foetal health, results in normoglycaemia, prevents ketosis, and results in appropriate weight gain. There are no specific dietary recommendations or guidelines for pregnant women with GDM. The ADA recommends that women with GDM should follow the dietary guidelines for people with diabetes.[2] The diet should be individualised and the recommended average weight gain during pregnancy is determined by the prepregnancy body weight of the woman, with an inverse relationship between prepregnancy body weight and the recommended average weight gain during pregnancy. The ADA recommendations generally prescribe an isocaloric diet (i.e. 35-38 kcal/kg of prepregnancy ideal body weight). On the other hand, many European centres choose to institute a hypocaloric diet consisting of 1200 to 1500 kcal since GDM frequently occurs in obese women. The use of hypocaloric diets may ameliorate the degree of hyperglycaemia and reduce the weight of the baby at birth, thus lessening the magnitude of any macrosomia. Levels of free fatty acids and ketones may increase, however, and caloric restriction in GDM remains one of the most contentious issues.

One of the major concerns with low-calorie diets during pregnancy is that starvation and subsequent ketonuria might impair the intellectual functioning of the offspring.[25] Rizzo et al[26] studied the intellectual function of offspring from pregnant women with insulin-dependent diabetes mellitus, with GDM, and with normal glucose tolerance. No relationship was found between maternal hypoglycaemia and intellectual function of the offspring. Scores of the Standard-Binet tests, however, correlated inversely with the third trimester β-hydroxybutyrate and free fatty acid plasma concentrations. The women who had elevations of plasma ketones and free fatty acids were those with diabetes out of control and not those who had calorie-restricted diets. Hence, it was suggested that there

might be a difference between starvation ketosis and the ketosis that develops with poorly-controlled diabetes. A review of the literature shows that moderate caloric restriction in obese, pregnant women with GDM is safe and effective in the short term. The long-term effects, however, are unknown and it remains to be ascertained whether caloric restriction might adversely affect the future health of the infant. Whether caloric restriction has long-term benefits for the mother in delaying the onset of IGT or subsequent diabetes is also uncertain.

Insulin therapy and blood glucose monitoring

The majority of patients with gestational IGT by the WHO criteria will have a satisfactory response to dietary treatment as the degree of glucose intolerance is mild in this group. About 10% to 30% of all women with GDM will demonstrate fasting or postprandial hyperglycaemia despite dietary treatment and will need insulin therapy. Target blood glucose levels recommended by the ADA[2] and ACOG[4] are the same as for women with pre-existing DM—fasting plasma glucose should be <5.8 mmol/L and 2-hour postprandial levels <6.7 mmol/L. Insulin can either be given as intermediate-acting insulin or as a mixture of short- and intermediate-acting insulin twice daily. Multiple daily injections are only rarely needed. Insulin treatment should be discontinued after delivery. Since insulin treatment might be required in future pregnancies or during intercurrent illness, human insulin should preferably be prescribed to minimise the likelihood of antibody formation. The use of so-called prophylactic insulin therapy has so far not been proven and there is no convincing evidence supporting the use of insulin therapy in women with GDM who are able to achieve euglycaemic levels with dietary therapy. Oral hypoglycaemic drugs are currently not recommended for use during pregnancy.

Ongoing monitoring of efficacy of intervention in patients with GDM is necessary. Control of plasma glucose is evaluated every 1 to 2 weeks by measuring fasting and postprandial plasma glucose levels until delivery. Although the ADA and ACOG suggest using the 2-hour postprandial measurements, several centres use the 1-hour time point because it reflects the peak glycaemic response to a meal. Either 1- or 2-hour postprandial values are appropriate, but different thresholds for intervention apply to each approach. The availability of accurate and simple monitoring devices for measuring whole blood capillary glucose has made glycaemic control simpler. Because of the cost of the equipment necessary to perform self-monitoring of blood glucose (SMBG) and the human resources required to instruct patients of its appropriate operation, routine use of this technique in women with GDM has not been instituted. Consensus agreement supports the use of SMBG devices only in those individuals with GDM that requires insulin therapy.

The value of exercise in reducing blood glucose levels

Exercise forms an important adjunct to dietary therapy for achieving normoglycaemia in diabetic patients. However, there is a paucity of information on the usefulness of exercise in GDM. Studies in small groups of subjects have shown that exercise may have a beneficial effect. One trial demonstrated a significant improvement in fasting plasma glucose level, the response to a 50-g oral glucose challenge, and glycosylated haemoglobinA_{1c} measurement in a randomised trial of regular arm ergometry exercise plus diet versus diet alone in 19 women with GDM.[27] Further large studies are required to ascertain the effects of cardiovascular fitness training on foetal outcome before exercise as a form of therapy for GDM can be supported. The ACOG recommends that women with GDM who previously had an active lifestyle should be encouraged to continue a programme of exercise approved for pregnancy.[4]

Obstetric management of gestational diabetes mellitus

The goal of obstetric management is to detect foetal compromise, macrosomia, and the optimum time for delivery. The most likely complication of a GDM pregnancy is suboptimal metabolic control and subsequent infant morbidity. Foetal surveillance in the third trimester is one of the most important ways of preventing perinatal morbidity although currently there is no consensus as to the ideal time to commence surveillance in patients with GDM. Some obstetricians recommend weekly biophysical foetal testing as early as 34 weeks of gestation while others do not begin testing until 40 weeks. Most women with GDM proceed to term and have a spontaneous vaginal delivery. If a preterm delivery for a GDM mother is considered for either obstetric or medical reasons, some centres advocate the assessment of foetal pulmonary maturation by testing for the presence of surfactant amniotic fluid.[28] This is because carbohydrate disturbances may delay foetal lung maturation by a mechanism mediated by foetal hyperinsulinism.[29] Others have shown that there are significant differences in foetal lung maturity between hyperglycaemic and non-

diabetic pregnancies.[30] However, if clinical judgement indicates a greater benefit from the early delivery of the foetus, this should be performed regardless of lung testing results. An evaluation of foetuses delivered in spite of immature lung test results has so far suggested that lung morbidity in neonates can be minimised with modern neonatal care.[28] Therefore, assessment of foetal pulmonary maturation is only useful if the timing of delivery can be influenced by the result obtained.

Long-term implications

The evidence that GDM is associated with an increased risk for later overt DM in the mother has been established without doubt. Women with GDM should be evaluated initially at the first postpartum visit by a 2-hour 75-g OGTT and their glucose tolerance status reclassified. Follow-up testing is recommended thereafter on a yearly basis. Metzger et al[31] demonstrated that in their population of women with GDM, the 5-year cumulative incidence rate of diabetes was 50%. The 2-hour glucose and basal insulin values were strongly associated with early postpartum diabetes, whereas maternal obesity and the total integrated insulin response during the 3-hour 100-g OGTT were predictive of later diabetes development. Lam et al[32] found that the following variables were predictive of persistent carbohydrate intolerance in a population of Hong Kong Chinese women with GDM: a high fasting glucose during pregnancy and at the first postnatal visit, a high 2-hour blood glucose antepartum and postpartum, and the requirement of insulin during pregnancy. This information is helpful in the planning of postpartum follow up and in patient counselling. Because women with GDM are a high-risk group for developing overt diabetes after pregnancy, behavioural interventions (e.g. exercise, weight reduction, dietary modifications) after pregnancy might be of benefit and should be encouraged. However, long-term compliance with behavioural changes has not been good. There are attempts to use pharmacological agents as potential interventions to delay or prevent NIDDM in women with prior GDM. Clinical trials using the drug troglitazone, a new class of insulin sensitiser, are currently underway to determine whether amelioration of insulin resistance with this drug can delay or prevent NIDDM in high risk women with prior GDM.

Maternal GDM also has long term sequelae for the offspring. A foetus exposed to a diabetic intrauterine environment exhibits long-term effects on body composition and metabolism after birth. Childhood obesity at 7 years of age has been reported in children who were the macrosomic infants of GDM mothers, and there is a correlation between increased maternal glycaemia during the third trimester and this later obesity.[33] As the offspring of mothers with GDM age, these children have a higher risk of developing obesity, insulin resistance and abnormal glucose tolerance in later life.[34] These risks are not confined to those who were overweight at birth and may be more directly related to changes in foetal islet function during intrauterine development.

Conclusion

The prevalence of DM is increasing worldwide and evidence indicates that the number of cases of GDM is also increasing. There is a need to improve the criteria for screening and diagnosing GDM and to develop more sensitive indices for the prediction of perinatal morbidity. This may require either intensification of glycaemic criteria, or the inclusion of more sophisticated metabolic measurements. In view of the present lack of universally accepted diagnostic criteria, the WHO criteria using a 75-g OGTT seems to be valid for Hong Kong Chinese as it has been evaluated in the local population. Once identified, patients with GDM should start an isocaloric diet (unless they are obese) and insulin therapy should be added if glycaemic control remains unsatisfactory. The role of exercise in the management of GDM is still controversial, as positive effects of exercise have not been established for this population. With current treatment modalities, infant mortality has been reduced to that seen in non-diabetic pregnancies but the reduction in the incidence of perinatal morbidity and macrosomia has been less impressive. It is important to remember that GDM also has long-term sequelae for both the mother and the offspring and the provision of health care extends beyond the pregnancy. The high prevalence of subsequent diabetes in women with previous GDM may serve to make them an ideal group on which interventions designed to prevent the development of diabetes in the future can be studied.

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