Screening and diagnosis of gestational diabetes

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SUMMARY
Gestational diabetes mellitus (GDM) is a risk factor for the mother and foetus. The risks increase proportionally to the maternal blood sugar concentration along a glycaemic continuum. However, there is ongoing controversy about the objectives of active screening and diabetic and obstetrical management for GDM. Various screening and diagnostic tests are used. None of them offers the combination of qualities to be expected from a test: simplicity of use, reproducibility, specificity and sensitivity, but each of them provides a basis on which recommendations can be established.
The need to screen GDM as a risk factor in the whole population of pregnant women has led us to propose the use of simple, universally applied test, such as the “practical” test constituted by the assay of fasting and post-prandial blood glucose levels. In addition to screening, a classification which will take into account the results of subsequent as well as initial blood glucose levels could be preferable to evaluate the management and results.

Key-words: Gestational diabetes · Screening · Glucose challenge test.

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RÉSUMÉ
Dépistage et diagnostic du diabète gestationnel
Le diabète gestationnel est un facteur de risque maternel et fœtal. Les risques augmentent selon un continuum proportionnel à l’élévation des glycémies maternelles. Les modalités et les objectifs du dépistage et de la prise en charge sont actuellement controversés. Différents tests de dépistage et de diagnostic sont utilisés sans que l’un d’entre eux offre toutes les qualités attendues d’un test : simplicité, reproductibilité, spécificité et sensibilité, mais chacun d’eux a permis d’établir des seuils glycémiques sur lesquels sont basées les différentes recommandations.
La nécessité de dépister le DG dans toute la population des femmes enceintes nous conduit à proposer un test simple, pouvant être employé de façon universelle, dit test pragmatique constitué par les dosages de la glycémie à jeun et de la glycémie post prandiale. À l’issue du dépistage, pour évaluer la prise en charge du DG et ses conséquences, il apparaît nécessaire d’établir une classification fondée à la fois sur le niveau glycémique au diagnostic et durant le traitement.

Mots-clés : Diabète gestationnel · Dépistage · Test de charge glucosée.

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F rom a superficial point of view, gestational diabetes mellitus is a clearly defined affection which is simple to treat, but the reality is more confusing. Gestational diabetes is defined as carbohydrate intolerance of variable severity, with onset or first recognition during pregnancy [12]. This very general definition covers an heterogeneous scope, including previously undiagnosed type 2 diabetes (more and more frequently), type 1 diabetes beginning during pregnancy, as well as a transient carbohydrate intolerance occurring in the third trimester of pregnancy. Furthermore, the hyperglycaemia of GDM is considered as a dichotomous variable, whereas no clear cutoff can separate pregnant women into those with high risk of adverse perinatal outcomes and those with no risk at all. Gestational diabetes is responsible for 3% to 5% of complications of all births and is one of the most common medical complications of pregnancy [15].

Because gestational hyperglycaemia is associated with adverse outcomes which could be prevented, screening for gestational diabetes is recommended by consensus conferences throughout the industrialised world. The basic principles are selective or universal screening with a plasma glucose challenge test. Since the first guidelines were issued by the American College of Gynaecologists and Obstetricians in 1978, others have followed with slight modifications. Those of the ADA issued in January 2003 are based on the conclusions of the international consensus meeting of March 1997 [14]. In France, testing for glycosuria is mandatory at each prenatal visit, but expert panels have recommended screening based on blood sugar determinations. The French recommendations issued jointly by the CNGOF (National College of Obstetricians and Gynaecologists in France) and the ALFEDIAM (French Language Association for the Study of Diabetes and Metabolic Diseases) in December 1996 (published in December 1997 in a supplement to Diabetes and Metabolism) adopted almost the same strategy as the American panels [1].

How are these recommendations followed? In France, the proportion of pregnancies screened with venous plasma glucose sample is variable, 72% [16], 64% [17] or 46% [18], according to the policies adopted by each maternity. This is far from the universal screening of the recommendations. In Great Britain, screening is universal only in 44% of maternity units and the tests used vary equally from one practitioner or one maternity unit to another [10]. In a study in the United States, 94% of obstetricians stated that they undertook universal screening [6].

Our hypothesis is that practitioners are uneasy with GDM screening for two major reasons: what are the fundamental benefits of testing and what are the best testing methods? [6, 13].

Why undertake the diagnosis?

Since the 1950’s, GDM was found to be related to increased risks of stillbirth, macrosomic infants, perinatal mortality and neonatal biochemical disorders (hypoglycaemia, hypomagnesaemia, hyperbilirubinaemia, polycythaemia, hypercalcaemia) as well as a high incidence of diabetes mellitus in the woman in the years following delivery. This was in the absence of any treatment. The management of GDM, but also obstetrical care in general, have changed fundamentally, and have lead to a marked decline in the rates of perinatal death. Thus, there is no recent data showing a statistically significant relation between GDM and perinatal death. Today, the main outcome measures are short-term “intermediate” risks, of which the predominant criterion is foetal macrosomia.

**Macrosomia: the main justification for GD screening**

Children born of mothers with GDM present with an excess of fat mass, evidenced in an above-average birth weight, and also morphological characteristics such as an increase in the bi-acromial diameter. The proportion of neonates who are large for gestational age (LGA), defined by a birth weight above the 90th centile for gestational age, is twice what it is in the non-hyperglycaemic population, i.e. on the order of 20% instead of 10%. This definition corresponds to a birth weight of about 4000 g in a term neonate. The 97th centile for a term baby is 4500 g. Macrosomia is related to an increased risk of complications during delivery [7], which at the same level of foetal weight are more frequent in case of maternal diabetes. Shoulder dystocia in the baby and lesions of the anal sphincter in the mother are of particular concern because they can lead to irreversible sequellae.

In theory, the detection of GDM can be beneficial if it reduces the maternal blood sugar level, and therefore the degree of macrosomia, and if it leads to better identification of LGA foetuses, which may be delivered by caesarean section.

Although it has been shown that intervention in maternal blood glucose levels reduces the incidence of LGA foetuses, the benefit in terms of health is not proven. For Schwartz, interventions to reduce the level of macrosomic foetuses will remain marginal [2], with a reduction in those over 4000 g from 17.1% to 16.9% and those [2] 4500 g from 2.99% to 2.95%. To try to evaluate the effect of the management of blood glucose on the “hard” risk of elongation of the brachial plexus would require the inclusion of several thousands of pregnancies (this calculation has been attempted [6]. The risk of macrosomia is also related to weight and maternal age and to genetic factors, so that evidence of the impact of blood glucose control alone is fairly difficult to obtain. In a recent study [8], 7% of neonates were LGA and GDM was present in 16.2% of cases, which is consistent with previous literature. Despite 40 cases of shoulder dystocia in 385 macrosomic infants, there was no case of brachial plexus elongation. This study underscores
the poor coverage of GDM screening, since 43% of the mothers of macrosomic foetuses had not been tested during pregnancy.

Antenatal evaluation of macrosomia is a key factor if GDM screening is to translate into decreased perinatal risks. The screening of GDM is best done when macrosomia is suspected before delivery and, conversely, macrosomia is best suspected when the diagnosis of GDM is established. Unfortunately, the antenatal clinical and ultrasound criteria for macrosomia remain disappointing in terms of decision-making. By improving the antenatal evaluation of macrosomia and screening for GD, the need for intensified treatment of GDM might be applied only to at-risk foetuses (30), as well as obstetrical strategies.

What are the maternal risks?

There has been insufficient study of the incidence of pelvic floor lesions following delivery in diabetic women. An entirely different type of maternal risk which has received attention in the literature is that of caesarean section. Women who receive a diagnosis of GDM are clearly at increased risk of caesarean section, 22 to 30% vs 17% in the general population in the literature. In our experience, the rates of caesarean delivery were 35% with GDM, 24% with glucose intolerance, and 19% for women with a normal test at the Port Royal maternity unit. This cannot be considered as an adverse outcome because its purpose is to prevent complications related to the vaginal delivery of a macrosomic baby. However, labelling a woman as “diabetic” has been found to lead to an increase in caesarean sections even in the absence of confirmed macrosomia [4]. What is the iatrogenic effect of the diagnosis of GDM?

The major maternal complications of GDM is a lifetime risk of diabetes mellitus. Since the key study by O’Sullivan and Mahan, women who exhibit hyperglycaemia during a gestational OGTT are known to be at increased risk of type 2 diabetes. The blood glucose thresholds adopted by O’Sullivan and Mahan were defined by this risk [2]. Since then, the thresholds for positive tests have been reduced, but the subsequent maternal diabetes has rarely been evaluated with these new values: for example in a recent study, 13.8% diabetes and 42.4% abnormalities of blood glucose control 11 years after GDM [21].

Reducing the perinatal morbidity associated with GDM: a threshold issue

The basis of managing gestational diabetes is intensified blood glucose control and obstetrical monitoring. The major issue to be considered is the choice of blood glucose levels, for both diagnosis and therapeutic management, in the absence of sufficient data to perform benefit/risk analysis. Arbitrary thresholds have been established along the continuum of risk associated with maternal hyperglycaemia. However, since the initial publications on the obstetrical risks associated with GDM, the blood glucose level for intervention has been repeatedly lowered.

The HAPO (Hyperglycaemic Adverse Pregnancy Outcomes) study, whose results are expected in 2007, should give us the level of blood glucose which place the mother, the fetus and neonate at increase risk of adverse pregnancy outcome. This international multicentre study is evaluating the maternal-foetal risks in pregnant women undergoing the 75 g-2 hours OGTT blindly and who have all been followed up until delivery without treatment, except for overtly diabetic patients with fasting blood glucose levels > 1.05 g/l and/or post-challenge > 2 g/l.

Apart from these risk-related intervention thresholds, a more subtle classification of gestational diabetes is desirable. Few studies have stratified the risk associated with GDM in relation to the degree of hyperglycaemia. As these are intermediate criteria, the intervention and the consequences for health depend considerably on the clinician’s judgement and the results are “biased” [6]. Schwartz [2] in 1999 urged a revision of the classification of gestational diabetes into three groups:

- Diabetes diagnosed during pregnancy, defined as fasting blood glucose > 1.16 g/l
- Abnormal fasting blood glucose in a pregnant woman, between 1 and 1.16 g/l.
- Abnormal carbohydrate tolerance during pregnancy according to the classification of Carpenter and Coustan.

These three groups should be evaluated separately in terms of their consequences and be used to modulate obstetrical management.

Reducing the long term adverse outcomes associated with GDM

Concerning the long-term morbidity, these thresholds may also determine the future risk of maternal diabetes. Actually in current practice, this recognition of the risk is reflected simply in the provision of information to the patient and the follow-up of these women is either not known or only known in a few individual cases. The early postpartum glucose tolerance screening could identify the 10% of women who have diabetes after delivery but also identify a very high risk group of impaired glucose tolerance who need intensive follow up and behavioral intervention. Perhaps in the future the determination of this risk will entail treatment with glitazone, at least if the preliminary results of the Tripod study are confirmed. The screening of GDM as a marker of a subsequent maternal risk of diabetes obeys a public health logic in the more general context of the current “epidemic” of type 2 diabetes.
As regards the hypothesis of a higher risk of diabetes for the child following foetal exposure to hyperglycaemia, this awaits confirmation since only a few studies raise this possibility.

Whether intervention influences the fetal and/or maternal outcomes remains to be proven in large studies of high index pregnancies. These outcomes studies are dependant on first accepting the need for screening.

Establishing the diagnosis of gestational diabetes

While awaiting definitive proof of which level of blood glucose correction improves foetal and maternal outcomes, it is necessary to choose a screening strategy for GDM which is as reliable and practical as possible.

All the tests currently recommended are based on an evaluation of blood glucose levels following a glucose challenge, whether for the screening or diagnosis of GDM. Three challenge levels (50, 75 and 100 g of glucose) and different blood glucose threshold levels are used, depending on the professional society (ADA, EASD, WHO).

The diagnostic procedure most often recommended by a “pragmatical consensus”, as in France [1], involves a three-pronged approach:

Non-selection of the population concerned: since 1998, it has been accepted that all pregnant women should undergo screening. In reality, however, even in the most highly motivated teams 20% of women are not screened. There may be high-risk women among the non-participants, due to their ethnic and socio-economic background.

The O’Sullivan screening test between 24 and 28 weeks of amenorrhoea, with plasma blood glucose levels measured 1 hour after 50 g of glucose, irrespective of the time and conditions.

The diagnostic test: OGTT (oral glucose tolerance test) with 100 g or 75 g depending on the method adopted. The criteria of positivity are summarised in Table I.

Current criticisms

The disparity in the challenge tests and the thresholds adopted result in a disparity in the evaluations: the WHO test diagnoses twice as many women as the NDDG, while the ADA test yields a prevalence of GDM between the two [6]. OGTT with 75 g for 2 hours yields twice as many positive diagnoses as the two-stage method with OGTT 100 g.

The threshold of positivity of the screening test for GDM has been reduced to 1.30 g/l since 1994. This increase in the sensitivity of the test enables more women to be screened who are at increased risk of GDM and who will be positive in the diagnostic test, but results in an OGTT being performed in 10% of the population of pregnant women.

<table>
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<tr>
<th>Table I</th>
<th>Screening and diagnosis of gestational diabetes.</th>
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<td>Diagnosis</td>
<td>Screened</td>
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<tr>
<td>Blood glucose level</td>
<td>100 g</td>
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<tr>
<td>Fasting</td>
<td>1.05</td>
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<td>1 h</td>
<td>5.8</td>
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<td></td>
<td>1.90</td>
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<td>10.6</td>
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<tr>
<td>2 h</td>
<td>1.65</td>
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<td>9.2</td>
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<td>3 h</td>
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**At least two values needed for the diagnosis. *At least one value needed for the diagnosis [14].

Fasting blood glucose determination

The fasting blood glucose (FBG) level contributes to the establishment of the diagnosis of GDM and is, independently of pregnancy, the reference test for the diagnosis of diabetes mellitus. Its systematic control at the early stage of the pregnancy could detect women with already overt diabetes. Might it provide a more extensive contribution to GDM screening?

For Atilano, fasting blood glucose levels ≥ 1.05 g/l are associated with an abnormal OGTT in 23/24 cases (predictive value in 96%) [11]. For Schwartz [2], it is when the FBG is less than 1 g/l that the OGTT should be used.

Fasting blood glucose remains the most discriminative value for stratifying the risk above 1 g/l. Fasting blood glucose is certainly the most sensitive test as long as the threshold is reduced to 0.80 g/l (4.4 mmol/l). However, this

<table>
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<th>Table II</th>
<th>Sensitivity and specificity of the fasting glucose thresholds in screening for GDM compared to the diagnostic test.— Fasting blood glucose (FBG) g/l (mmol/l).</th>
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<tbody>
<tr>
<td>Screening method</td>
<td>Sensitivity (%)</td>
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<tr>
<td>FBG &gt; 0.86 (4.8) (13)</td>
<td>81</td>
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<tr>
<td>FBG &gt; 0.88 (4.9) (3)</td>
<td>88</td>
</tr>
<tr>
<td>FBG &gt; 0.73 (4.1)</td>
<td>92</td>
</tr>
<tr>
<td>Test 1 h/50 g &gt;1.40 (7.8)</td>
<td>59</td>
</tr>
<tr>
<td>Test 1h/50 g &gt;1.35 (7.5)</td>
<td>61</td>
</tr>
<tr>
<td>Test 1 h/50 g &gt;1.26 (7.0)</td>
<td>68</td>
</tr>
<tr>
<td>OGTT</td>
<td>79</td>
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</tbody>
</table>
threshold will reduce its specificity to 27% and will require a glucose challenge test in an additional third of the population. That is not acceptable in terms of feasibility.

Fasting blood glucose alone is certainly insufficient to screen all pregnant women with GDM. As GDM combines insulin resistance and a quantitative defect of insulin secretion to varying degrees, the initial abnormality relates either to fasting or to postprandial blood glucose levels as in IFG and IGT which precede type 2 diabetes. To evaluate the abnormalities of carbohydrate metabolism regulation during pregnancy, the two glucose values are essential.

**Challenge tests**

Glucose challenge tests for GDM have been criticised for years, as being poorly reproducible, unpleasant, time-consuming and expensive. The blood glucose levels for all tests were established in a relatively arbitrary fashion (but can it be otherwise with a continuum of risk which appears linear?), a compromise between sensitivity and specificity.

One of the principal criticisms of the screening test is the lack of reproducibility. The challenge test with 50 g of glucose has a reproducibility of 83% in women with abnormal results (the reproducibility is 90% in women with a normal test). The sensitivity and reproducibility are related to the interval between the test and the previous meal. Subsequent exposure to carbohydrates increases the sensitivity to insulin and the utilisation of glucose and reduces the sensitivity of the test (Staub Traugott effect). However, 73% of the population underwent the test less than 2 hours after a meal [4]. The OGTT with 100 g of glucose is not reproducible one week later in 24% of women [4]. When this test was used for the diagnosis of diabetes outside of pregnancy, the procedure had been defined to enhance its reproducibility: normal diet with 50% carbohydrates for the previous three days, tests conducted at rest, beginning after an overnight fast lasting 8 to 12 hours. These procedures are not required for the diagnosis of GDM. The reliability of all these tests is poor. For Harlass, 23% of women with a positive screening test had contradictory responses in two successive OGTT at one week’s interval [6].

After these poorly reproducible test conducted under non-standardised conditions fewer than one woman in five with positive screening test will have a positive diagnostic test. Would a better standardisation of the test allow a better evaluation of GD? That, however, was already on the agenda in 1987.

Is it possible to shorten the duration of OGTT 100 g, which takes 3 hours? If the 3rd hour is omitted, 13% of the diagnoses of GDM are lost. Is it possible to use only the second hour of the OGTT 75 g/3 hours? Although there is no valid threshold for all the criteria of evaluation, the threshold of 9 mmol/l at 2 hours might be the most acceptable for all criteria [5].

Which threshold should be chosen? There is a continuum of risk of macrosomia associated with blood glucose levels, even for values below the threshold value of 140 mg 2 hours post-challenge [19]. All the abnormal values of these tests are predictive of macrosomia, but often this correlation declines or disappears following adjustment for parity, maternal weight, age and race. As mentioned above, the question of threshold values requires a large study such as HAPO.

**Glucose or carbohydrates?**

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Newer screening methods therefore have to be validated against the OGTT to gain acceptance and hence popularity. This “practical” test, which combines both the screening test and the diagnosis test, has the advantage of being practical, simple, less time-consuming and above all...
uses the same thresholds as those required for therapeutic intervention. The follow-up of the outcome is based on the same parameters: fasting and postprandial blood glucose levels.

Pregnancy is a constantly changing metabolic state: insulin resistance increases as the pregnancy progresses, maternal weight gain is not predetermined, maternal blood glucose levels may change from the normal to the pathological from one month to the next. In this moving metabolic situation, repetition of this pragmatic test in the event of doubt is simpler than the OGTT.

Conclusion

Currently, the recommendations for the screening and management of gestational diabetes obey the principle of precaution rather than that of evidence-based medicine. Insofar as the principle of precaution is applied more or less systematically by clinicians, screening is insufficient.

As the recognition of glucose intolerance and the blood glucose control should be part of the evaluation of all maternal risk factors, which should allow a better assessment of obstetrical risks by the team, to facilitate the practice of screening, we suggest using the following simple measures:

- Measurement of at least the fasting blood glucose following the first antenatal visit, in order to detect women who are already diabetic or likely to develop glucose intolerance: the threshold of 1 g/l might be adopted and all women testing positive followed up regularly.
- Systematic blood glucose testing in the key period of 24-28 weeks of amenorrhoea; the double blood glucose measurement of the practical test [9] with the fasting threshold of 0.90 g/l and 1.20 g/l postprandially after breakfast, which is relatively less constraining than challenge tests and as sensitive, might be more widely used.
- The current definition of GDM should be modulated by classifying the risk according to the type and level of hyperglycaemia at the time of diagnosis, as well as its evolution during follow-up, in order to reduce the overmedicalisation engendered by the term gestational diabetes.
- With the improvement of the screening for GDM, further research to evaluate the maternal and foetal risks by interventional studies needs to be undertaken to manage this risk factor correctly.

References