When should screening be performed for gestational diabetes?

A.-M. Guedj

Service maladies métaboliques et endocriniennes, Hôpital Caremeau, CHU Nîmes, Place Pr Debré, 30900 Nîmes, France

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Abstract

Aim: To consider the arguments for screening outside the standard screening period of 24 to 28 weeks of gestation.

Materials and Methods: A search of the literature between 1990 and 2010 was performed using the PubMed® and Cochrane® databases. Recommendations from learned societies in diabetology and obstetrics & gynaecology were consulted.

Results: Gestational diabetes mellitus screening is classically recommended between weeks 24 and 28 of pregnancy, the period during which glucose tolerance deteriorates. However, the increasing prevalence of type 2 diabetes in women of childbearing age with risk factors requires earlier screening. Fasting blood glucose should be measured at the first visit during early pregnancy for these patients. The diagnostic threshold is the same as for patients who are not pregnant, i.e. blood glucose > 1.26 g/L. However, the benefit of screening for gestational diabetes during early pregnancy for women with risk factors has not been supported by prospective studies. Therefore oral glucose tolerance testing during early pregnancy is not currently recommended for the detection of gestational diabetes.

Screening for gestational diabetes, regardless of the recommended screening policy, must be performed between weeks 24 and 28 of pregnancy. There are no reasons to consider subsequent screening for gestational diabetes at a later stage.

Keywords: Gestational diabetes mellitus; Early pregnancy; Type 2 diabetes; Hyperglycaemia; Review

Résumé

But. Étudier les arguments pour un dépistage en dehors de la période classique de 24 à 28 SA.

Matériel et méthodes. – Recherche bibliographique entre 1990 et 2010 à partir de la base de données Medline et de la Cochrane Database Library. Consultation des recommandations des sociétés savantes de diabétologie et de gynécologie-obstétrique étrangères.

Résultats. – Le dépistage du diabète gestationnel est classiquement recommandé entre 24 et 28 SA, date à laquelle la tolérance au glucose se détériore au cours de la grossesse.

Cependant l’augmentation de la prévalence du diabète de type 2 chez les femmes en âge de procréer nécessite, en cas de facteurs de risque, la recherche d’un diabète de type 2 méconnu par le dosage d’une glycémie à jeun dès le début de la grossesse, à la première visite, le seuil diagnostique étant identique à celui en dehors de la grossesse, soit > 1,26 g/L. En revanche, l’intérêt du dépistage du diabète gestationnel, dès le début de la grossesse en cas de facteurs de risque, n’est pas étayé par des études prospectives. Il n’est donc pas recommandé de pratiquer une HGPO en début de grossesse à la recherche d’un diabète gestationnel.

La recherche d’un diabète gestationnel, indépendamment de la politique de dépistage recommandée, doit être pratiquée entre 24 et 28 SA. Aucun argument n’est apporté pour envisager une nouvelle recherche de diabète gestationnel plus tardivement.

Mots-clés : Diabète gestationnel ; Début de grossesse ; Diabète de type 2 ; Hyperglycémie ; Dépistage ; Revue

* Correspondence
E-mail address: anne.marie.guedj@chu-nimes.fr (A.-M. Guedj).
Gestational diabetes mellitus (GDM) classically occurs in the third trimester of pregnancy, and screening must be performed at 24-28 weeks of gestation (WG). It is caused by physiopathological changes in glucose metabolism during pregnancy [1], and the pivotal study by O’Sullivan [2] demonstrated a correlation between maternal risk of subsequent diabetes and abnormal values in the oral glucose tolerance test (OGTT) at 24-28 WG.

GDM is defined as “a carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy irrespective of whether or not insulin is used for treatment or the condition persists after pregnancy”[3]. This definition includes two different entities: pre-existing undiagnosed type 2 diabetes (T2D) and purely gestational diabetes. (Ref Q1 F Galtier article).

The existence of T2D raises the question as to whether or not screening in the first trimester is beneficial. However, in order to ascertain when to screen, the usefulness of screening beyond 28 weeks needs to be investigated. Screening at 24-28 WG was the subject of an article by Virally (Q6 M. Virally), and will therefore not be dealt with here.

1. Screening before 24 WG

The increase in pregnancy complications in women with T2D, and in particular, the increased risk of malformations, means that screening and treatment are recommended very early on during pregnancy, ideally during the preconception period. In the absence of any prospective comparative studies of the effectiveness of screening for GDM in early pregnancy to reduce perinatal complications, the arguments in favour of this screening can be taken from two types of study:

• studies estimating the prevalence of diagnosed and undiagnosed T2D in women who are either pregnant or of a childbearing age;
• studies involving screening both at an early stage and at 24-28 WG.

1.1. Prevalence of T2D in women of a childbearing age and estimated proportion of undiagnosed cases

NHANES, an epidemiological study conducted in the USA in 2005-2006 [4], included 7,267 subjects aged 12 and above who had completed a household interview. A subgroup (n = 3,178) selected randomly from those without diagnosed diabetes underwent a fasting blood glucose (FBG) test, complemented for some (n = 2,806) by a 75-g OGTT. The diagnostic criteria used in this study for diagnosing diabetes were a FBG ≥ 1.26 g/l (7.0 mmol/l) or ≥ 2.0 g/l (11.1 mmol/l) at 2 hours. Prediabetes was defined by an abnormal FBG (≥ 1.0 g/l [5.6 mmol/l] and < 1.26 g/l [7.0 mmol/l]) and/or glucose intolerance (GI) diagnosed by blood glucose at 2 hours (≥ 1.40 g/l [7.8 mmol/l] and < 2 g/l [11.1 mmol/l]). In the 20-39 age bracket, abnormal glucose levels were found in 20.9% of cases (CI 95%: 17.1–25.0), which represented prediabetes in 17.8% (CI 95%: 13.9–21.7) (13.1% abnormal and 7.3% GI), diagnosed diabetes in 2.1% (IC 95%: 1.5–2.8) and undiagnosed diabetes in 1.0% (CI 95%: 0.4–1.6) of cases.

Diabetes was undiagnosed in a total of 32% of subjects. The prevalence of diabetes was significantly higher compared to the 1.1% (IC 95%: 0.8-1.4) recorded in the period from 1988 to 1994.

There are no comparable studies in France. A study using patients’ data from the national medical insurance database demonstrated an increased prevalence of diabetes (defined as reimbursement for oral antidiabetic drugs at least twice within one calendar year) between 2000 and 2005 in women aged 20-29 (from 0.1 to 0.4%), and aged 30-39 (from 0.6 to 0.7%) [5].

The increased prevalence of diabetes is partly due to the rise in obesity, particularly in women, at an increasingly young age. In the epidemiological study OBEPi, which has been evaluating the prevalence of obesity in France every 3 years since 1997, the most significant increase observed between 2006 and 2009 was in the 25-34 age group (+19.5%); in other age brackets, there was a more modest increase (from +5.3% to +8.5%) [6]. However, factors other than weight have contributed to this development. Indeed, the French epidemiological study DESIR, which carried out an annual follow up over 9 years of 1,962 women and 1,865 men, recorded the onset of diabetes in 92 subjects among the 2,947 patients with a BMI < 27 kg/m² and in 111 subjects among the 879 with a BMI > 27kg/m². Thus, 45% of the diabetic patients had a BMI < 27 kg/m² and 26% had a BMI < 25 kg/m² [7].

In a study carried out in California [8], 2,784 cases of pre-existing diabetes (1.3%) were found among the 209,287 pregnancies monitored between 1999 and 2005. Prevalence adjusted for age, parity and ethnicity increased from 0.81% in 1999 to 1.82% in 2005 (P < 0.001). However, the prevalence of GDM (diagnosed by 100-g OGTT at 24-28 WG, with at least 2 abnormal values: fasting > 0.95 g/l, 1hr > 1.80 g/l, 2hr > 1.55 g/l and 3hr > 1.40 g/l) remained stable (7.4 vs. 7.5%). Thus diagnosed T2D accounted for 10% of pregnancies with diabetes in 1999 and 21% in 2005.
1.2. Estimated proportion of undiagnosed T2D among cases of GDM

The proportion of undiagnosed T2D during pregnancy can be estimated a posteriori by performing an OGTT in the immediate postpartum period. Several studies have performed this evaluation.

In 2009, Ogonowski et al. [9] carried out a prospective study of the early incidence of T2D 6 weeks postpartum. An OGTT was offered to 855 Caucasian Polish women; 318 (31%) underwent the test. Abnormal values were found in 13.5% of cases: diabetes was found in 1.3% of subjects, GI in 7.5% and moderate fasting hyperglycaemia in 2.5%.

A retrospective Australian study [10] of 82,025 children, carried out from 1985 to 1997, revealed that 160 of the children’s mothers had diagnosed T1D, 256 had diagnosed T2D and 1110 had GDM. Among the GDM patients, an OGTT performed 6 weeks after childbirth revealed 178 cases of undiagnosed T2D, which represented 41% of cases of T2D and 16% of GDM.

In a study conducted in the USA of 4,041 pregnancies with GDM [11], a 75-g control OGTT was performed between 1 and 4 months postpartum. Of the 1,636 patients tested, 230 (14%) had T2D.

In another study carried out in the USA [12], a postpartum control test (75-g OGTT at T0 and T120min) was arranged for 344 women with GDM diagnosed at 24 WG. However, only 156 of the women (45%) actually had the test, which was performed at a mean of 7.5 weeks postpartum. Twelve patients (8%) had diabetes.

The estimated proportion of GDM cases corresponding to undiagnosed T2D is between 8 and 15%.

1.3. Comparison of GDM rates according to time of screening

Several studies (table 1) have carried out screening from as early as the first prenatal visit, with repeat screening at 24-28 WG for women considered not to have GDM at the initial examination. In most of these studies, early screening was performed for all women, whereas in some other studies, it was reserved for women with risk factors.

In an older study [13] involving a small cohort of 255 women, 25 cases of GDM were detected, 24 (96%) of which at 16 WG. This led the authors to recommend that screening for GDM be carried out in the first trimester. However, this is the only study to report such high rates.

In a short retrospective study [14] of 329 patients tested in early pregnancy and systematically monitored after 28 WG in the event of negative results in the first trimester, 20 cases of GDM were diagnosed (prevalence = 6.1%), 40% of which (n = 8) during early pregnancy.

In a Spanish study [15] carried out between 1996 and 1998, screening was systematically performed at the first visit, then

Table 1
Prevalence of gestational diabetes according to gestational age

<table>
<thead>
<tr>
<th>Study/Country</th>
<th>Type</th>
<th>Number</th>
<th>GDM prevalence</th>
<th>GDM criteria (OGTT type: thresholds)</th>
<th>According to term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartha (2003) Spain [15]</td>
<td>Prospective</td>
<td>3,986</td>
<td>5.9%</td>
<td>100-g (at least 2 abnormal values) Fasting 1.00 g/l - 1h 1.90 g/l - 2h 1.65 - 3h 1.45 g/l</td>
<td>28% &lt; 24 WG</td>
</tr>
<tr>
<td>Sack (2003) USA [16]</td>
<td>Prospective</td>
<td>4,507</td>
<td>6.7%</td>
<td>75-g (at least 2 abnormal values) Fasting 1.00 g/l - 1h 1.95 g/l - 2h 1.60 g/l</td>
<td>15.2% &lt; 24 WG</td>
</tr>
<tr>
<td>Barahona (2005) Spain [18]</td>
<td>Retrospective</td>
<td>1,708 GDM NA</td>
<td>100-g (at least 2 abnormal values) Fasting 0.95 g/l - 1h 1.80 g/l - 2h 1.55 g/l - 3h 1.40 g/l</td>
<td>17.7% &lt; 24 WG</td>
<td></td>
</tr>
<tr>
<td>Hawkins (2008) USA [19]</td>
<td>Prospective</td>
<td>87,057</td>
<td>3.8%</td>
<td>100-g (at least 2 abnormal values) Fasting 1.05 g/l - 1h 1.90 g/l - 2h 1.65 g/l - 3h 1.45 g/l</td>
<td>22% &lt; 24 WG</td>
</tr>
<tr>
<td>Meyer (1996) [14]</td>
<td>Prospective</td>
<td>329</td>
<td>6.1%</td>
<td>100-g (at least 2 abnormal values) Fasting 0.95 g/l - 1h 1.80 g/l - 2h 1.55 g/l - 3h 1.40 g/l</td>
<td>40% &lt; 24 WG</td>
</tr>
<tr>
<td>Nahum (1990) USA [16]</td>
<td>Prospective</td>
<td>255</td>
<td>9.8%</td>
<td>100-g (at least 2 abnormal values) Fasting 0.95 g/l - 1h 1.80 g/l - 2h 1.55 g/l - 3h 1.40 g/l</td>
<td>96% &lt; 24 WG</td>
</tr>
<tr>
<td>Bito (2005) Hungary [21]</td>
<td>Prospective</td>
<td>163 women with risk factors</td>
<td>54%</td>
<td>75-g (1 abnormal value) Fasting 1.26 g/l and 2h 1.40 g/l</td>
<td>9% &lt; 16 WG</td>
</tr>
<tr>
<td>Maegawa (2003) Japan [17]</td>
<td>Prospective</td>
<td>749</td>
<td>2.9%</td>
<td>75-g (at least 2 abnormal values) Fasting 1.00 g/l - 1h 1.80 g/l - 2h 1.50 g/l</td>
<td>63.6% &lt; 15 WG</td>
</tr>
<tr>
<td>Virally (2007) [34].</td>
<td>Prospective</td>
<td>191 women with risk factors tested at 24-28 WG and later</td>
<td>72%</td>
<td>24-28 WG: 75-g (fasting &gt; 95 g/l or 2h &gt; 1.55 g/l) After 28 WG: FCG &gt; 0.95 g/l or 2h postprandial &gt; 1.20 g/l over 7 days</td>
<td>No test before 24 WG</td>
</tr>
</tbody>
</table>

FCG: Fasting capillary blood glucose
NA: Non applicable
WG: Weeks of gestation
GDM: Gestational diabetes mellitus
at 24-28 WG in the absence of abnormal values. The screening involved 2 stages (50-g test and if > 140 mg/dl, 100-g OGTT, or more abnormal values confirming GDM diagnosis: $T_0 \geq 105$, $T_60 \geq 190$, $T_{120} \geq 165$ and $T_{180\text{min}} \geq 145$ mg/dl). A total of 235 cases of GDM were diagnosed (prevalence = 5.9%). The proportion of GDM diagnosed before 24 WG was 27.7% ($n = 65$). Forty of the 65 women diagnosed early were diagnosed in the first trimester (6-13 WG).

In a study carried out in California between 1998 and 1999 [16], 4,507 women underwent a fasting glucose test during early pregnancy. Patients with a FBG > 1.26 g/l were considered to have GDM. Patients with a FBG between 1.0 and 1.26 g/l underwent immediate diagnostic testing. Patients with a FBG < 1.00 g/l underwent diagnostic testing between 24 and 28 WG. The diagnostic criteria were the same for the different periods (75-g OGTT, positive if at least 2 abnormal values: $T_0 > 1.00$ g/l, $T_60 > 1.95$ g/l, $T_{120\text{min}} > 1.60$ g/l). GDM was detected in a total of 302 women (prevalence = 6.7%). An early diagnosis was performed in 12 cases based on FBG > 1.26 g/l and in 34 cases from OGTT, which corresponded to early GDM diagnosis in a total of 15.2% of cases.

A study conducted in Japan [17] of 749 women detected 22 cases of GDM (prevalence = 2.9%), of which 14 (63.6%) occurred in the first trimester.

A retrospective study carried out in Spain of 2,049 children of women with GDM (screening by 50-g test, 100-g OGTT if blood glucose > 1.40 g/l, OGTT if at least 2 raised values: $T_0 \geq 0.95$, $T_60 \geq 1.80$, $T_{120} \geq 1.55$ and $T_{180\text{min}} \geq 1.40$ g/l) revealed the onset of GDM before 24 WG in 17.7% of cases [18].

In a study carried out in Dallas [19] of 85,057 pregnant women, those with risk factors underwent screening at the first visit and repeated screening at 24-28 WG in the absence of abnormal values. Those with no risk factors underwent screening at 24-28 WG. 3,334 cases of GDM were identified (prevalence = 3.8%), of which 22% ($n = 737$) were diagnosed at the first consultation.

Bartha et al. [20] compared two screening strategies over two successive periods. Systematic screening was performed at 24-28 WG in both periods, whereas early screening was performed in the presence of risk factors in the first period and systematically in the second period. (NB. The second period was the subject of the article cited above [15]). Although the prevalence of GDM did not differ in the two periods (189/3,504 [5.4%] and 235/3,986 [5.9%]), the proportion of cases detected early on was 6% for initial targeted screening and 28% for universal screening.

While all the populations in the above studies consisted of pregnant women, at least for screening at 24-28 WG, a study carried out in Hungary [21] only included women with risk factors ($n = 163$). Eighty-eight (54%) of these women had GDM, only 9% of which were diagnosed before 16 WG. It should be noted that, during this study, the women without abnormal values were systematically screened at 32-34 WG, and 55% of cases of GDM were diagnosed during this period. If this final screening had not been performed, the prevalence of GDM in this population would have been 25% and the proportion of GDM cases detected at 16 WG would have been 20%.

Most of the studies reported above compared the characteristics of women with GDM according to whether or not the condition had been detected early on. According to these studies, women with early GDM have more risk factors in their medical history [15, 18, 19] and are a mean age of 1 year older [18, 19] compared to women diagnosed at 24-28 WG. Furthermore, they have higher rates of perinatal complications [15, 18], gestational hypertension [15] and pre-eclampsia [19], and are more often treated with insulin [16, 18]. These differences are probably due to the fact that there is a high proportion of undiagnosed T2D among cases of early GDM.

**Early GDM accounts for between 15 and 20% of GDM cases.**

### 1.4. Advantage of early treatment

There are no prospective studies demonstrating a reduction in maternal-foetal complications through the early diagnosis and treatment of GDM [22, 23].

In the study by Bartha et al. cited above [20], the authors compared pregnancy complications associated with GDM in both periods. They reported that the group which had been screened early on the basis of risk factors had higher rates of hydramnios (12.7% vs. 2.1%; $P < 0.001$) and premature delivery (11.8% vs. 5.5%; $P = 0.03$), and that all cases of premature membrane rupture ($P = 0.03$) and foetal abnormality ($P = 0.007$) were found in this group.

### 1.5. Diagnostic criteria for screening before 24 WG

Screening before 24 WG raises two questions: firstly, what are the screening criteria for undiagnosed T2D? Secondly, should GDM screening be performed during this early period?

#### 1.5.1. T2D screening

**Glycosuria** is not a reliable test because of its low sensitivity and low specificity [24, 25].

**FBG** varies very little in pregnant women [26, 27]. It decreases considerably during the first weeks of pregnancy, and then remains stable until the end of pregnancy. A study carried out on 361 women without GDM (50-g screening test negative at 24-28 WG) measured FBG at 6, 8, 10, 12, 20, 28 and 36 WG. The median FBG value at 6 weeks was 0.83 g/l. This value lowered to 0.81 g/l at 10 WG, and then to 0.80 g/l at 36 WG. The decrease was significant between 6 and 36 WG ($P < 0.001$), but not between 10 and 36 WG ($P = 0.16$) [28].

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FGB testing as a diagnostic criterion for T2D is generally recommended during early pregnancy. In the absence of prospective studies on the normal FGB threshold during this period, the criteria used outside of pregnancy are adopted. Thus, a T2D diagnosis can generally be performed based on a FGB ≥ 1.26 g/l (7 mmol/l). The diagnostic criteria for abnormal FGB values vary slightly from one learned society to another: > 1.00 g/l (5.6 mmol/l) and < 1.26 g/l (7 mmol/l) according to the American Diabetes Association (ADA) [29], and > 1.10 g/l (6.1 mmol/l) and < 1.26 g/l (7 mmol/l) according to the European Association for the Study of Diabetes (EASD) [30].

In January 2010, the ADA proposed the use of the Hba1c test for the diagnosis of diabetes outside of pregnancy in order to simplify diagnosis, with a fixed threshold of 6.5% [31]. There is a dearth of data on normal Hba1c levels during pregnancy, but it appears that the levels change during early pregnancy [32]. Out of 100 women without GDM, low levels were detected during the first trimester (5.1% +/- 0.3) and late pregnancy (5.0% +/- 0.3) compared to a control group of 145 non pregnant women (normal OGTT) (5.5% +/- 0.4; P < 0.001 [control vs. early pregnancy], P < 0.001 [control vs. late pregnancy]).

Although the IADPSG proposes Hba1c testing with the same threshold (6.5%) in addition to FGB or random blood glucose testing [23], this practice is not yet recommended in France.

OGTT during early pregnancy for the diagnosis of T2D is not recommended by any learned societies.

1.5.2. GDM screening

Glucose tolerance progressively deteriorates whereas FGB remains relatively stable. In a Swedish study of 588 consecutive pregnant women, 288 agreed to undergo FGB testing (75-g glucose and samples obtained at T0, T60, T90 and T120min) on 2 occasions at 17 WG and 32 WG. There was no difference between FGB values, but post-load blood glucose values were significantly higher at 32 WG than 17 WG: this is highlighted by the areas under the curve, 622 ± 112 mmol x mn L-1 at 17 WG versus 809±139 mmol x mn L-1 at 32 WG (P < 0.001). According to WHO criteria, 10 patients (3%) had GDM at 17 WG versus 809±139 mmol x mn L-1 at 32 WG (P < 0.001). Macrosomia and birth weight were considerably higher in group DG2 compared to DG1 and women without GDM. There was no difference in foetal and neonatal outcome other than macrosomia. There was also no difference in maternal outcome (weight gain, AHT, caesarean).

2. Screening after 28 WG

Few studies have examined late screening beyond 28 or 30 GW. The small number of available studies reveals a relatively high prevalence of GDM during this period.

In the study by Barahona [18], 41% of GDM cases were diagnosed after 31 WG, but the study was carried out retrospectively on 1,708 subjects with GDM (50-g test and if > 140 mg/dl, 100-g OGTT, 2 or more abnormal values confirming GDM diagnosis: T0 ≥ 105, T60 ≥ 190, T120 ≥ 165 and T180min ≥ 145 mg/dl) having undergone screening before 24 WG, repeated between 24 and 31 WG, and after 31 WG if results were negative. In the study by Bito et al. [21] cited above, 55% of GDM cases were diagnosed after 31 WG. In the French study by Virally et al. [34] GDM screening was performed at 24-28 WG (75-g, GDM if FGB > 0.95 g/l or 2h > 1.55 g/l), and women without GDM were followed up by capillary glucose testing. They diagnosed GDM if FGB > 0.95 g/l or 2h postprandial > 1.20 g/l over 7 days. The study thus found 104 cases of GDM between 24 and 28 WG (GDM1), and 34 cases of GDM after 28 WG (DG2) (table 1). GDM was therefore found in 72% of cases, 25% of which were late onset. This is the only prospective study evaluating the course of pregnancy according to whether GDM was diagnosed at 24-28 WG or later. Weight had a significantly greater impact in group DG2 compared to group DG1 (P = 0.04). Macrosomia and birth weight were considerably higher in group DG2 compared to DG1 and women without GDM. There was no difference in foetal and neonatal outcome other than macrosomia. There was also no difference in maternal outcome (weight gain, AHT, caesarean).  

3. Conflicts of interest

We have no conflicts of interest to declare.

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