Diagnostic criteria For gestational diabetes mellitus

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Received: 2nd, 2010; Accepted: November 5th, 2010

Abstract

Aim: To answer two questions: is there a threshold for pathological hyperglycaemia after 24 weeks of gestation? What are the diagnostic criteria for gestational diabetes mellitus?

Materials and methods: Review of the literature considering the relationships between glucose values and complications during pregnancy in women without specific care for this condition. Only the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study meets sufficient quality criteria.

Results: Increasing glucose values during pregnancy, either at fasting and after a 75-g oral glucose tolerance test, are independently associated according to a continuum with an increased risk of maternal-foetal complications, especially birth weight above the 90th percentile for gestational age, Caesarean delivery and foetal hyperinsulinemia. There is no obvious threshold at which risks increase. The International Association of Diabetes Pregnancy Study Group has proposed the following criteria, considering the glycemic values associated with a 1.75-fold increased risk of macrosomia, foetal hyperinsulinemia and adiposity in the HAPO study: fasting plasma glucose ≥ 0.92 g/L (5.1 mmol/L) and/or 1-hour plasma glucose value ≥ 1.80 g/L (10.0 mmol/L) and/or 2-hour plasma glucose value ≥ 1.53 g/L (8.5 mmol/L).

Conclusion: The choice of glycemic thresholds for defining gestational diabetes mellitus is necessarily arbitrary because of a continuum (NP2). Only experts may propose definition criteria.

Keywords: gestational diabetes mellitus, diagnostic criteria, review

Résumé

Critères diagnostiques du diabète gestationnel

Objectif : Répondre à deux questions : y a-t-il, après 24 semaines d’aménorrhée, un seuil d’hyperglycémie pathologique? Quels sont les critères diagnostiques du diabète gestationnel?

Matériels et méthodes : Revue de la littérature étudiant les relations entre glycémies et complications de la grossesse chez des femmes non prises en charge dans ce cadre. Seule l’étude Hyperglycemia and Adverse Pregnancy Outcome (HAPO) répond à des critères exigeants de qualité.

Résultats : L’élévation des glycémies pendant la grossesse, à jeun et après une charge en glucose, s’associe de façon indépendante et selon un continuum à un sur-risque de complications materno-fœtales, notamment poids de naissance élevé pour l’âge gestationnel, césarienne et hyperinsulinisme fœtal. L’International Association of Diabetes Pregnancy Study Group a proposé, en considérant les valeurs glycémiques associées à un sur-risque de 75% de macrosomie, d’hyperinsulinisme et d’adiposité fœtaux dans l’étude HAPO, comme critères diagnostiques : glycémie à jeun ≥ 0,92 g/L (5,1 mmol/L) et/ou glycémie 1 heure après une charge orale de 75 g de glucose ≥ 1,80 g/L (10,0 mmol/L) et/ou glycémie 2 heures après la charge ≥ 1,53 g/L (8,5 mmol/L).

Conclusion : Le choix de seuils glycémiques pour définir le diabète gestationnel est arbitraire du fait d’un continuum (NP2). La définition ne peut être déterminée que sur avis d’experts (NP5).

Mots clés : diabète gestationnel, critères diagnostiques, revue de la littérature

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1. Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy [1]. The diagnostic criteria were initially established over 40 years ago [2] and have been progressively modified (Table 1). The original criteria were designed to identify pregnant women who were at risk of developing diabetes after pregnancy [2, 3] and not to identify an increased risk of perinatal complications. The criteria of the World Health Organization (WHO) are those used in the general population [4]. The currently recommended criteria in France are those of Carpenter and Coustan [5] and have not changed since 1996 [6].

GDM defined by the current criteria is associated with maternal, foetal and neonatal complications (cf. chapter by G. Beucher). Lower levels of glucose tolerance seem to be associated with these types of complications, although with non-homogenous results (Table 2). The studies have limitations however. On one hand, the lack of a uniform international definition makes them difficult to interpret [7-19] (Table 2). Furthermore, the complications associated with the different levels of glucose intolerance could be explained by confounding factors, such as obesity, age of the mother or associated medical complications, which are not always taken into account in multivariate analysis [7, 10, 18, 19]. Intervention bias can be observed: an increase in Caesarean births was noted by some healthcare providers based only on the existence of high plasma glucose levels [20, 21]. Finally, the control group is sometimes poorly defined [22].

In 2005, the French group of experts brought together under the auspices of the High Authority for Health (HAS) therefore concluded its summary report on GDM screening in these terms: “the data in the scientific literature does not enable a conclusion to be drawn as to the best screening and diagnostic strategies for GDM. The extent of controversy and uncertainty is such that no recommendations will be given while awaiting additional studies” [23]. New data, in particular the results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [24], the benefits of the treatment for women presenting with an intermediate hyperglycaemic state [25, 26] and the international will to create uniform diagnostic criteria justified an updated study.

The aim of this review is to answer two questions:

1 – During the third trimester of pregnancy, is there a glycaemic threshold, either fasting (per fasting plasma glucose – FPG) or after an oral glucose tolerance test (75 or 100 g), that is associated with complications of GDM, established according to current definitions? And if so, what?

2 – Which diagnostic criteria should be recommended in France today?

2. Materials and methods

We performed a literature review using referenced studies in the PubMed search engine. We also considered supplementary articles identified in these publications, literature reviews or recommendations originating from consensus conferences. Women without diagnosed GDM were considered in the articles since their medical management would have constituted a bias. Along the same lines, studies were excluded in which the women with intermediate plasma glucose levels were recipients of specific medical management [27-32]. Only the HAPO study responded to the quality criteria, as it was multicentre, international, prospective, using standardised glucose measurements which were not revealed to the women or to the caregivers (except for significant abnormalities which would justify treatment), and with multivariate analyses of the correlations between glucose values and predefined events [24].

3. Results

3.1. During the third trimester of pregnancy, is there a glycaemic threshold, either fasting (per fasting plasma glucose – FPG) or after an oral glucose tolerance test (75 or 100 g), that is associated with a significant increase in complications?

To answer this question, two types of studies can be used. The first type analyses the prevalence of complications according to predefined categories of glucose values (fasting or after a glucose load) (Table 3). The second analyses the determinants, including the continuous glucose values, of events that are considered characteristic of plasma glucose anomalies during pregnancy (Table 4). In the event of an association between an event and a continuous glucose value, an attempt was made to determine a possible threshold. In all of these studies, women with GDM who were therefore receiving treatment were not considered.

Before the initiation of the HAPO study in 2002 [33], the published data using plasma glucose categories (Table 3) were retrospective, performed in single centres, and most of them used the result of the 2-hour oral glucose tolerance test (G2h) using 100 g of glucose [34-36]. One study also used the fasting plasma glucose (FPG), measurements at 1 and 3 hours following a glucose load (G1h, G3h) and the glucose value one hour after an oral 50 g glucose load at any hour (G50, screening glucose challenge test) [36]. The increasing categories of G2h are associated with an increased risk of macrosomia, preeclampsia and Caesarean delivery in two studies [34], independent of potential confounding factors [36], but no neonatal hypoglycaemia risk [35, 36]. The data for the G50, FPG, G1h and G3h [36] show a linear relationship between increasing categories of G50, FPG and G1h and macrosomia; between the G50, G1h and G3h categories and Caesarean deliveries; and between the G50 and G1h categories and preeclampsia; but there was no relationship between glycaemic categories and neonatal hypoglycaemia (Table 3).
Table 1
Diagnostic criteria of gestational diabetes mellitus.

**Criteria after a 75-gram oral glucose tolerance test**
World Health Organization (WHO) criteria [4]

<table>
<thead>
<tr>
<th>Whole venous blood</th>
<th>Whole capillary blood</th>
<th>Venous plasma</th>
<th>Capillary plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>≥ 1.10 g/L</td>
<td>≥ 1.10 g/L</td>
<td>≥ 1.26 g/L</td>
</tr>
<tr>
<td>2-hour glucose</td>
<td>≥ 1.20 g/L</td>
<td>≥ 1.40 g/L</td>
<td>≥ 1.40 g/L</td>
</tr>
</tbody>
</table>

Criteria after a 100-gram oral glucose tolerance test
Gestational diabetes mellitus is defined by at least 2 measurements above the indicated threshold

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose ≥ 0.90 g/L</td>
<td>≥ 1.05 g/L</td>
<td>≥ 0.95 g/L</td>
</tr>
<tr>
<td>1-hour glucose ≥ 1.64 g/L</td>
<td>≥ 1.80 g/L</td>
<td>≥ 1.80 g/L</td>
</tr>
<tr>
<td>2-hour glucose ≥ 1.41 g/L</td>
<td>≥ 1.65 g/L</td>
<td>≥ 1.55 g/L</td>
</tr>
<tr>
<td>3-hour glucose ≥ 1.24 g/L</td>
<td>≥ 1.45 g/L</td>
<td>≥ 1.40 g/L</td>
</tr>
</tbody>
</table>

Table 2
Maternal-foetal complications associated with intermediate glycaemic abnormalities (after exclusion of women with gestational diabetes mellitus).

<table>
<thead>
<tr>
<th>Author Year (Reference)</th>
<th>Type of study</th>
<th>Diagnostic criteria used</th>
<th>Increased risk</th>
<th>Similar risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langer 1987 [7]</td>
<td>Case (n = 42)/controls (n = 42) OGGT performed if G50 ≥ 1.35 g/L</td>
<td>1/4 NDDG criteria positive versus 0/4 positive</td>
<td>Macrosomia Large for gestational age</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neonatal metabolic anomaly (hypoglycaemia/ jaundice/polycythaemia)</td>
<td></td>
</tr>
<tr>
<td>Leikin 1987 [8]</td>
<td>Case (n = 176)/controls (n = 1854) OGGT performed if G50 ≥ 1.35 g/L</td>
<td>0-1/4 CC criteria positive versus G50 normal</td>
<td>Macrosomia*</td>
<td>Hypertension Preeclampsia Hydramnios Low Apgar Shoulder dystocia Congenital malformation Perinatal mortality</td>
</tr>
<tr>
<td>Lindsay 1989 [9]</td>
<td>Case (n = 725)/control (n = 139) OGGT performed if G50 ≥ 1.35 g/L</td>
<td>1/4 CC criteria positive versus G50 normal</td>
<td>Macrosomia* Preeclampsia-eclampsia*</td>
<td>Chronic hypertension Caesarean delivery* Low Apgar Prematurity Shoulder dystocia Congenital malformation Perinatal mortality</td>
</tr>
<tr>
<td>Hod 1991 [10]</td>
<td>Case (n = 132)/controls (n = 380)</td>
<td>1/4 NDDG criteria positive versus 0/4 positive</td>
<td>Macrosomia Hypoglycaemia Jaundice Hypocalcaemia</td>
<td>Hyaline membrane disease Polycythaemia Thrombocytosis</td>
</tr>
<tr>
<td>Author Year (Reference)</td>
<td>Type of study</td>
<td>Number of women considered</td>
<td>Diagnostic criteria used</td>
<td>Increased risk</td>
</tr>
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</tr>
<tr>
<td>Vambergue 2000 [12]</td>
<td>Case (n = 131)/controls (n = 108)</td>
<td>OGTT performed if G50 ≥ 1.30 g/L</td>
<td>1/4 CC criteria positive versus G50 normal</td>
<td>Large for gestational age* Maternal or foetal complications*</td>
</tr>
<tr>
<td>Saldana 2003 [13]</td>
<td>Case (n = 53)/controls (n = 1900)</td>
<td>OGTT performed if G50 ≥ 1.30 or 1.40 g/L according to the centres</td>
<td>1/4 CC criteria positive versus G50 normal</td>
<td>Large for gestational age (black race)* Macrosomia (black race)*</td>
</tr>
<tr>
<td>Ferrara 2007 [11]</td>
<td>Case (n = 600)/controls (n = 1000)</td>
<td>OGTT performed if G50 ≥ 1.40 g/L, Retrospective study</td>
<td>FPG 0.95-1.05 versus G50 normal</td>
<td>Macrosomia* Hypoglycaemia* Jaundice*</td>
</tr>
</tbody>
</table>

**Screening with a 100-gram oral glucose tolerance test**

CC: Carpenter and Coustan adapted criteria [5]; NDDG: National Diabetes Data Group criteria [53]

| Retnakaran 2008 [14]    | Case (n = 91) /controls (n = 166 + 93) | Screening glucose challenge test and OGTT performed in all women Prospective cohort | G50 ≥ 1.40 + NDDG 1/4 versus G50 ≥ 1.40 + NDDG 0/4 versus G50 < 1.40 g/L + NDDG 0/4 positive | Pre-diabetes and diabetes 3 months after pregnancy* | Diabetes at 6 years* |
| Vambergue 2008 [15]     | Case (n = 322)/controls (n = 221) | OGTT performed if G50 ≥1.30 g/L Prospective cohort | 1/4 CC criteria positive versus G50 normal | Glycaemic abnormality at 6 months* | Diabetes at 6 years* |

**Screening per a 75-gram oral glucose tolerance test**

| Aberg 2001 [16]        | Case (n = 131)/controls (n = 470) | G2h 1.40-1.62 versus < 1.40 g/L | Pregnancy duration Small for gestational age Perinatal mortality |
| Yang 2002 [17]         | Case (n = 154) /controls (n = 302) | OGTT performed if G50 ≥ 1.40 g/L | FPG < 1.40 g/L + G2h 1.40-2.00 g/L versus FPG < 1.40 g/L + G2h < 1.40 g/L | Caesarean delivery Perinatal mortality |
| Jensen 2003 [18]       | Case (n = 298) /controls (n = 2596) | G2h (capillary) 1.40-1.60 g/L versus < 1.40 g/L | Preeclampsia Shoulder dystocia Caesarean delivery Hypoglycaemia Jaundice Respiratory distress syndrome |
| Ostlund 2003 [19]      | Case (n = 213)/controls (n = 812) | OGTT performed if random blood glucose ≥ 1.45 g/L | FPG < 1.20 g/L + G2h 1.60-2.00 g/L versus FPG < 1.20 g/L + G2h < 1.40 g/L | Hypertension Preeclampsia Forceps Small for gestational age Low Apgar Jaundice |

*confirmed in multivariate model

G50: plasma glucose concentration 1 hour after oral 50-gram glucose load (screening glucose challenge test); FPG: fasting plasma glucose; G1h, G2h, G3h: plasma glucose 1, 2 and 3 hours after oral glucose tolerance test; OGTT: oral glucose tolerance test
### Table 3
Maternal-foetal complications by glycemic ranges (after exclusion of women with gestational diabetes mellitus).

<table>
<thead>
<tr>
<th>Author Year (Reference)</th>
<th>Type of study (diagnostic criteria)</th>
<th>Sample size</th>
<th>Glycaemic categories</th>
<th>Increased risk</th>
<th>Similar risk</th>
</tr>
</thead>
</table>
| **Screening per a 100-gram oral glucose tolerance test**  
| Tallarigo 1986 [34] | Retrospective study (O’Sul)  
n = 249 | G2h ≤ 1.00; 1.00-1.19; 1.20-1.64 g/L | Macrosomia  
Congenital anomalies  
Preeclampsia or Caesarean delivery | Perinatal mortality  
Prematurity | |
| Warner 1988 [35] | Retrospective study (CC)  
N = 245 | G2h < 1.00; 1.00-1.19; 1.20-1.39; 1.40-1.59; 1.60-1.80 g/L | Low Apgar at 1 minute  
Respiratory distress syndrome | Preeclampsia  
Prematurity  
Large for gestational age  
Neonatal hypoglycaemia  
Low Apgar at 5 minutes | |
| Sermer 1998 [36] | Retrospective study (NDDG, G50 tested on all women)  
n = 3637 | G50 (quartile) | Preeclampsia*  
Macrosomia*  
Caesarean delivery*  
Phototherapy*  
Neonatal hospitalisation period* | Maternal hospitalisation period  
Neonatal trauma  
Congenital anomalies  
Respiratory distress syndrome  
Neonatal hypoglycaemia | |
| | | G1h (quartile) | Preeclampsia*  
Macrosomia*  
Caesarean delivery*  
Phototherapy*  
Maternal hospitalisation period*  
Neonatal hospitalisation period* | Neonatal trauma  
Congenital anomalies  
Respiratory distress syndrome  
Neonatal hypoglycaemia | |
| | | G2h (quartile) | Preeclampsia*  
Macrosomia*  
Caesarean delivery*  
Phototherapy*  
Maternal hospitalisation period*  
Neonatal hospitalisation period* | Neonatal trauma  
Congenital anomalies  
Respiratory distress syndrome  
Neonatal hypoglycaemia | |
| | | G3h (quartile) | Caesarean delivery*  
Phototherapy*  
Maternal hospitalisation period*  
Neonatal hospitalisation period* | Preeclampsia  
Macrosomia  
Neonatal trauma  
Congenital anomalies  
Respiratory distress syndrome  
Neonatal hypoglycaemia | |
| **Screening per a 75-gram oral glucose tolerance test**  
FPG: fasting plasma glucose; G1h, G2h, G3h: plasma glucose 1, 2 and 3 hours after oral glucose tolerance test. | | | | | |
| HAPO 2008 [24] | Prospective study  
n = 23,317  
Women excluded:  
FPG < 0.50 g/L;  
FPG > 1.05 g/L;  
G2h > 2.0 g/L | FPG (7 classes) | Large for gestational age*  
Caesarean delivery*  
Foetal hyperinsulinaemia* | Neonatal hypoglycaemia | |
| | | G1h (7 classes) | Large for gestational age*  
Caesarean delivery*  
Foetal hyperinsulinaemia* | Neonatal hypoglycaemia | |
| | | G2h (7 classes) | Large for gestational age*  
Caesarean delivery*  
Foetal hyperinsulinaemia* | Neonatal hypoglycaemia | |

*confirmed in multivariate model

G50: plasma glucose concentration 1 hour after oral 50-gram glucose load (screening glucose challenge test); FPG: fasting plasma glucose; G1h, G2h, G3h: plasma glucose 1, 2 and 3 hours after oral glucose tolerance test.
Another method is to look for the determinants of events that are potentially associated with dysglycaemia during pregnancy (Table 4), such as macrosomia [24, 36-38] and Caesarean deliveries [24, 36, 37]. All of the studies showed an independent and linear association between these endpoints and FPG or glucose values following a 100 gram [36] or 75 gram glucose load [24, 37, 38]. Most of the studies reported above had small sample sizes, which limited the impact of their results. A multinational, multicenter study with a large sample size providing further data on neonatal hypoglycaemia, foetal hyperinsulinemia and other secondary endpoints might therefore be necessary.

The HAPO study was implemented in 2002 to respond specifically to the question of a possible glycaemic threshold associated with the characteristic complications of GDM [33]. It was a multicentre, international study (15 centres in 9 countries).

Table 4
Independent factors, including continuous glycemic values, associated with maternal-foetal complications (after exclusion of women with gestational diabetes mellitus).

<table>
<thead>
<tr>
<th>Author Year (Reference)</th>
<th>Type of study</th>
<th>N. of women considered</th>
<th>Exclusion criteria</th>
<th>Complications</th>
<th>Predictive factors in multivariate analysis</th>
<th>Research of a threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening per a 100-gram oral glucose tolerance test</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sermer 1998 [36] Prospective study n = 3637</td>
<td></td>
<td></td>
<td>Gestational diabetes (NDDG)</td>
<td>Caesarean delivery</td>
<td>Body mass index, G1h, G3h</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Macrosomia</td>
<td>Body mass index, FPG</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Preeclampsia</td>
<td>Body mass index, G2h</td>
<td></td>
</tr>
<tr>
<td>Screening per a 75-gram oral glucose tolerance test.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sacks 1995 [37] Prospective study n = 3390</td>
<td></td>
<td></td>
<td>FPG ≥ 1.05g/l and/or G2h ≥ 2.0 g/L</td>
<td>Macrosomia</td>
<td>Ethnicity, parity, preconception body mass index, FPG, G2h, weight gain during pregnancy, gestational age at screening</td>
<td>Linear increase without threshold for FPG, G1h and G2h</td>
</tr>
<tr>
<td>Mello 2003 [38] Prospective study N = 829</td>
<td></td>
<td></td>
<td>G1h after 75 g ≥ 1.35 g/L and/or gestational diabetes (CC)</td>
<td>Head circumference/abdominal circumference ratio ≤ 10th percentile</td>
<td>Screening 16-20 weeks LMP, age &gt; 35 years, macrosomia, FPG, G1h, G2h Screening 26-30 weeks LMP, age &gt; 35 years, FPG, G1h, G2h</td>
<td>Linear increase without threshold for FPG, G1h and G2h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ponderal index ≥ 90th percentile</td>
<td>Screening 16-20 weeks LMP, age &gt; 35 years, G1h, G2h Screening 26-30 weeks LMP, age &gt; 35 years, FBS, G1h, G2h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Macrosomia</td>
<td>Screening 16-20 weeks LMP, age &gt; 35 years, FPG, G1h, G2h Screening 26-30 weeks LMP, age &gt; 35 years, FPG, G1h, G2h</td>
</tr>
<tr>
<td>HAPO 2008 [24] Prospective study N = 23,316</td>
<td></td>
<td></td>
<td>FPG &lt; 0.50 g/L, FPG &gt; 1.05 g/L, G2h &gt; 2.0 g/L</td>
<td>Large for gestational age</td>
<td>FPG, G1h, G2h</td>
<td>Linear increase without threshold for FPG, G1h and G2h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Caesarean delivery</td>
<td>FPG, G1h, G2h</td>
<td>Linear increase without threshold for FPG, G1h and G2h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neonatal hypoglycaemia</td>
<td>G1h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Foetal hyperinsulinaemia</td>
<td>FPG, G1h, G2h</td>
</tr>
</tbody>
</table>

FPG: fasting plasma glucose; G1h, G2h, G3h: plasma glucose 1, 2 and 3 hours after oral glucose tolerance test.; CC: Carpenter and Coustan adapted criteria [5]; NDDG: National Diabetes Data Group criteria [53]; weeks LMP: weeks since last menstrual period.
which recruited 28,562 women between July 2000 and April 2006. The included women were over the age of 18 years, with a single pregnancy resulting from natural procreation (without the use of medical assistance) and without known diabetes. They underwent screening using a 75-gram glucose load at the date closest to 28 (24-32) weeks since the last menstrual period. The glucose measurement was done before administration of the glucose load and then 1 and 2 hours afterward. Out of the 28,562 women that signed the consent, 25,505 underwent the screening. In the end, 23,316 pregnancies were available for analysis: 1,412 women were excluded due to a break in the protocol and 7,046 (2.9%) due to unblinding for frank plasma glucose anomalies. In fact, women in whom the FPG exceeded 1.05 g/L (5.8 mmol/L) or in whom the G2h exceeded 2.00 g/L (11.1 mmol/L) were considered to have GDM and were treated. Women presenting with plasma glucose < 0.5 g/L (2.5 mmol/L) were not included in the final analysis. Finally, as a measure of caution, the women participating in the study underwent random glucose testing between 34 and 37 weeks of pregnancy. Glucose values ≥ 1.60 g/L (8.9 mmol/L) or ≤ 0.5 g/L (2.5 mmol/L) was reported to the doctor and the woman was removed from the study [33].

The primary endpoints of the study were Caesarean delivery, macrosomia (birth weight greater than the 90th percentile for gestational age), neonatal morbidity (clinical hypoglycaemia) and foetal hyperinsulinaemia (cord blood C-peptide concentration greater than 90th percentile) [24]. The secondary endpoints were premature delivery (before 37 weeks of pregnancy), shoulder dystocia or trauma at birth, the need for neonatal intensive care, hyperbilirubinaemia and preeclampsia [24]. The statistical analysis studied the correlation between the FPG, G1h and G2h variables (considered continuously and in 7 classes) and the primary and secondary endpoints. The results were adjusted for age, body mass index, tobacco use, alcohol consumption, family history of diabetes, gestational age at the glucose load, sex of the child, parity, mean blood pressure, whether or not hospitalisation occurred before the delivery, and whether or not there was a family history of hypertension or maternal urine infection during pregnancy.

After adjustment, an association was demonstrated between FPG and all the primary endpoints, except for neonatal hypoglycaemia, and all the secondary endpoints, except for the need for neonatal intensive care and hyperbilirubinaemia. The G1h and G2h were independently correlated with all the primary (Tables 3 and 4) and secondary endpoints [24, 39]. A linear relationship was also demonstrated between the FPG, G1h and G2h and the sum of skin folds greater than the 90th percentile [40]. The secondary analysis of independent factors associated with preeclampsia confirmed the predictive character of high C-peptide, body mass index and FPG, G1h and G2h [41].

As the rate of complications increased regularly with the glucose level, both for the continuous analyses and the per class analyses, it was not possible to define the glycaemia thresholds for GDM as had been initially planned.

**In summary, there is therefore no glycaemic threshold, either fasting or following an oral glucose tolerance test, (50, 75 or 100 g) associated with the complications of gestational diabetes mellitus as defined according to the current criteria (NP2).**

### 3.2. Which diagnostic criteria for gestational diabetes mellitus should be recommended today?

The consensus panel of the International Association of Diabetes Pregnancy Study Group (IADPSG) has offered recommendations. This study group was created in 1998 and met in June 2008; 225 doctors from 40 countries studied the results, both published and unpublished, of the HAPO study and studied these results in relation to those of known studies. These recommendations were essentially based on the results of the HAPO study.

The decision to choose the HAPO study analysis of results was founded on the efforts done to standardise procedures in the recruitment of participants, laboratory analyses and data collection. Furthermore, it was a very large, multinational, heterogeneous, multicultural and multiethnic cohort. The summary of the recommendations published in March 2010 in Diabetes Care is presented here [42].

The criteria selected to determine the diagnostic thresholds of GDM are the following: birth weight for gestational age > 90th percentile, cord blood C-peptide concentration at birth > 90th percentile and a percentage of neonatal fat mass > 90th percentile. The IADPSG consensus panel concluded that the predefined value for the odds ratio (OR) had to correspond to a relative increased risk threshold of 75% (OR = 1.75) compared to the reference. The analyses were performed in the adjusted models, taking into account the continuous plasma glucose level and using the mean value of plasma glucose levels in the study population as the limit of the reference group: FPG < 0.81 g/L (4.5 mmol/L); G1h < 1.34 g/L (7.4 mmol/L) and G2h < 1.12 g/L (6.2 mmol/L).

These recommendations are summarised in Table 5. One abnormal value of the three measurements was sufficient grounds for the diagnosis of GDM. These diagnostic criteria made the impaired fasting glucose or impaired glucose tolerance category disappear during the pregnancy. Measuring the FPG alone in the HAPO cohort identified 8.3% of the cohort with GDM. The addition of the G1h measurement identified 5.7% of additional women with GDM. In all, the FPG threshold was removed from the study [33].

<table>
<thead>
<tr>
<th>Glycaemic threshold before and after a 75-gram oral glucose tolerance test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose ≥ 0.92 g/L ≥ 5.1 mmol/L</td>
</tr>
<tr>
<td>and/or 1-hour glucose (g/L) ≥ 1.80 g/L ≥ 10.0 mmol/L</td>
</tr>
<tr>
<td>and/or 2-hour glucose (g/L) ≥ 1.53 g/L ≥ 8.5 mmol/L</td>
</tr>
</tbody>
</table>
11.1% had a single high value, 3.9% had two high values and 1.1% had three high values. Furthermore, 1.7% of the initial cohort had had an initial unblinding due to a high FPG or G2h. With these new criteria, the total prevalence of GDM was therefore 17.8%.

In summary, the definition of GDM can only be determined based on expert opinion.

The answer to the question regarding the new GDM diagnostic criteria to be used in France can only be provided after discussion of this proposition.

4. Discussion

The studies show therefore that plasma glucose levels lower than the GDM threshold based on current definitions (Table 1) are associated with an increased risk of complications. However, this risk is continuous with the plasma glucose values. The determination of new thresholds therefore must be subject to a consensus. The need to determine homogenous criteria worldwide brings us to first take a look at the criteria proposed by the IADPSG.

4.1. Choice of complications defining morbidity relative to hyperglycaemia during pregnancy

With regard to complications for defining the GDM criteria, the IADPSG selected birth weight, cord blood C-peptide concentration and the percentage of fat mass at birth. Foetal macrosomia is considered an essential indicator in the trials on hyperglycaemia complications during pregnancy [36-38]. The associations between high birth weight for gestational age or excess foetal adiposity and hyperinsulinemia are extremely strong and independent of confounding factors [40, 43]. Finally, macrosomia is associated with risks of difficult delivery and maternal and neonatal complications [44, 45]. Foetal macrosomia is also associated with childhood obesity [46, 47] and metabolic disturbances which could increase the subsequent risk of cardiovascular disease [48].

The fact that the experts did not select the “Caesarean delivery” primary endpoint used in the HAPO study deserves attention. It seems that it was because of the significant correlation between percentage of fat mass and this complication. It was justified that neonatal hypoglycaemia was not taken into account, since it was statistically not correlated with glucose values. Some other complications also seem significant in clinical practice and were not considered for evaluating the new diagnostic criteria. These complications, which are listed in Table 6, are about two times more frequent in cases of GDM as defined according to the new criteria.

4.2. Choice of a 75% increased risk of complications for defining gestational diabetes mellitus

The choice of an OR at 1.75 for defining GDM is arbitrary and results in a very high prevalence of GDM (17.8%). If an OR of 2.0 is used, the FPG (0.95 g/L; 5.3 mmol/L), G1h (1.91 g/L; 10.6 mmol/L) and G2h (1.62 g/L; 9.0 mmol/L) thresholds [39] are higher and the prevalence of GDM decreases to 8.8%. However, the group of 7.3% of women who then would have been considered to not have GDM had a complications rate very close to that of the women with GDM (Table 7) [39]. The group of experts therefore did not consider it legitimate to exclude them from the GDM diagnosis.

4.3. Can the proposed thresholds be simplified?

Can fewer measurements be made after the glucose load?

Simplifying the thresholds for the purpose of better memorisation is difficult since countries use values either in mmol/L or in g/L, and the rounded off values do not correspond in both units. Furthermore, reducing the FPG by even a small amount results in a large increased prevalence of GDM. For

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>No gestational diabetes mellitus</th>
<th>Gestational diabetes mellitus</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight ≥ 90th percentile (%)</td>
<td>8.3</td>
<td>16.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cord blood C-peptide ≥ 90th percentile (%)</td>
<td>6.7</td>
<td>17.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Percentage of fat mass ≥ 90th percentile (%)</td>
<td>8.5</td>
<td>16.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Preeclampsia (%)</td>
<td>4.5</td>
<td>9.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Preterm delivery (%)</td>
<td>6.4</td>
<td>9.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Caesarean section (%)</td>
<td>16.8</td>
<td>24.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Shoulder dystocia or birth injury (%)</td>
<td>1.3</td>
<td>1.8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Neonatal hypoglycaemia (%)</td>
<td>1.9</td>
<td>2.7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Hyperbilirubinaemia (%)</td>
<td>8.0</td>
<td>10.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hospitalisation in neonatal intensive care unit (%)</td>
<td>7.8</td>
<td>9.1</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Table 6

Prevalence of complications associated with gestational diabetes mellitus in the HAPO study (International Association of Diabetes Pregnancy Study Group criteria [42]).

example, lowering the threshold from 0.92 g/L (5.1 mmol/L) to 0.90 g/L (5.0 mmol/L) brings the number of women above the threshold from 8% to 12%.

It has been suggested that the G2h need not be performed, since only 2.1% of additional women are diagnosed with GDM after considering the FPG and G1h. This would also make for a shorter diagnostic test. One other possibility would be to retain only 2 times, FPG and G2h, corresponding with those used outside of pregnancy [49]. Unfortunately there is no data available in the IADSPG recommendations for considering this alternative.

### 4.4. Are the proposed thresholds consistent with the data in the literature?

Some thresholds come nearest to those of the IADPSG (FPG 0.90 g/L or 5.0 mmol/L, G1h 1.85 g/L or 10.3 mmol/L and G2h 1.50 g/L or 8.3 mmol/L), resulting in a 7.2% GDM prevalence, with a 23% prevalence of macrosomia (OR 3.2) in the GDM group versus 8.0% in the group without GDM [37]. A further study has suggested that a G1h ≥ 1.60 g/L (8.9 mmol/L) predicted foetal hyperinsulinaemia with a 95% sensitivity [43]. The FPG threshold (0.92 g/L, 5.1 mmol/L) of the new recommendations is much lower than that usually considered as diagnostic criteria (Table 1). Table 8 shows the thresholds proposed in the consensus recommendations relative to the mean glucose levels in several studies. For example, the mean FPG after exclusion of women with confirmed GDM ranged from 0.81 g/L (4.5 mmol/L) [24] to 0.85 g/L (4.7 mmol/L) [38].

### 4.5. Are these criteria universal?

The authors of the recommendations report no differences according to the investigators’ centres or ethnic groups. It therefore seems that these criteria can be used anywhere worldwide. All the statistical analyses were done after adjustment for potential confounding factors, which limits the bias. It should be remembered that the criteria were determined in a selected population with an FPG < 1.05 g/L (5.8 mmol/L) and a G2h < 2 g/L (11.1 mmol/L).

### 4.6. What would the practical consequences be of these new recommendations?

The increased prevalence of GDM would require restructuring the medical teams managing this disease and the capacity to provide for many patients. Financial recognition for therapeutic patient education could help to manage them on an outpatient basis.

The diagnosis of more women with GDM could have harmful psychological and physical consequences. In women with GDM, the first weeks after the screening are followed by an increase in anxiety, increased psychological distress and a poorer perception of their health status. These feelings seem to resolve however by the end of the third trimester of pregnancy and in the post-partum period [50-52]. The Australian Carbohydrate Intolerance Study (ACHOIS) reported better satisfaction scores in women with treated GDM than in those who were not treated or who were uniformed of their GDM [25].

Table 7

<table>
<thead>
<tr>
<th>Glycaemic thresholds FPG, G1h, G2h (g/L)</th>
<th>Subjects ≥ thresholds (%)</th>
<th>Positive predictive value of the exceeded thresholds (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>For large for gestational age*</td>
</tr>
<tr>
<td>0.92/1.80/1.53</td>
<td>16.1</td>
<td>16.2</td>
</tr>
<tr>
<td>0.95/1.91/1.62</td>
<td>8.8</td>
<td>17.6</td>
</tr>
</tbody>
</table>

In the total population, the prevalence of increased weight for gestational age was 9.6%; the value for increased C-peptide was 8.4%; and that for the percentage of fat mass at birth was 9.8%.

FPG: fasting plasma glucose; G1h and G2h: plasma glucose 1 and 2 hours after a 75-gram oral glucose tolerance test. * above the 90th percentile.

Table 8

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG 0.50-1.04 g/L, G2h &lt; 2.0 g/L</td>
<td>FPG &lt; 1.05 g/L</td>
<td>G1h &lt; 1.35 g/L and/or absence of gestational diabetes (CC)</td>
<td></td>
</tr>
</tbody>
</table>

| Fasting plasma glucose (FPG) (g/L) | 0.81 ± 0.69 | 0.84 ± 0.92 | 0.85 ± 0.07 |
| 1-hour glucose (G1h) (g/L)       | 1.34 ± 0.31 | 1.30 ± 0.33 | 1.21 ± 0.30 |
| 2-hour glucose (G2h) (g/L)       | 1.11 ± 0.23 | 1.09 ± 0.25 | 1.03 ± 0.21 |

CC: Carpenter and Coustan adapted criteria [5].
5. Conclusion

Independent of confounding factors, increased plasma glucose levels during pregnancy are associated with an increased risk of maternal-fetal complications, particularly increased neonatal weight for gestational age. Caesarean delivery and foetal hyperinsulinemia. The relationship between glucose levels and complications is however linear, and no threshold can be determined either with fasting or after a glucose load (EL2). The IADPSG proposed new diagnostic criteria for GDM based on the results of the HAPO study (expert opinion). Using these criteria, the prevalence of GDM with systematic screening was close to 18% in the HAPO cohort, which is a higher prevalence than that reported by French teams using the current criteria. If these criteria were to be adopted in France, there may need to be restructuring of the multidisciplinary teams that manage this disease.

6. Conflict of interests

No conflict of interests related to the article.

References


