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Summary report

Screening and diagnosis of gestational diabetes mellitus

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Synopsis

Title	Screening and diagnosis of gestational diabetes mellitus
Publication date	July 2005
Requested by	*Société de nutrition et de diététique de langue française (SNDLF)*
Produced by	HAS (Guidelines Department)
Intended for	Physicians and midwives
Objective	- To report and summarise the literature on screening and diagnosis methods for gestational diabetes mellitus (GDM) - To provide clinical information useful in assessing screening methods
Assessment method	- Systematic review of the literature - Discussion among members of an *ad hoc* working group - External validation by peer reviewers
Literature search	Period: 1990-2004 (Literature search performed by Emmanuelle Blondet under the supervision of Rabia Bazi and Frédérique Pages)
HAS project leader	Sandrine Danet MD, MPH (Head of Dept: Patrice Dosquet MD)
Report author	Nathalie Roudaut MD, MPH, endocrinologist, Brest
	- Steering committee - Working group (Chair: Professor Alain Fournié, gynaecologist/obstetrician, Angers) - Peer reviewers
Internal validation	Validated by the Committee for Practice guidelines and Practice Improvement (HAS Board) in July 2005
Related HAS publications	- Strategy for the management of type 2 diabetes (excluding management of complications), ANAES, March 2000 - Monitoring of patients with type 2 diabetes (excluding monitoring of complications), ANAES, March 2002 Available on the HAS website (www.has-sante.fr).

1. Definition of gestational diabetes mellitus (GDM)

The following World Health Organisation (WHO) definition has been used by all learned societies which have produced guidelines for GDM screening and diagnosis.

Gestational diabetes mellitus is carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy. The definition applies irrespective of whether or not insulin is used for treatment or the condition persists after pregnancy.

There are 2 problems with this definition:
(i) it is a qualitative rather than an operational definition,
(ii) it covers two populations of women in whom the prognosis for mother and fœtus is unlikely to be the same:
- women who have impaired glucose tolerance prior to pregnancy which has been overlooked,
- women who develop glucose intolerance during pregnancy.

To what extent each of these populations contributes to the global prevalence of the disease is unknown, but the higher the prevalence of type 2 diabetes in the population, the higher that of GDM (1-14% according to population).

2. Guidelines on GDM screening and diagnosis

2.1 Diagnostic strategies

Oral glucose tolerance tests (OGTT) are used to diagnose gestational diabetes mellitus according to most existing guidelines.

- *a 1-step strategy* consists of an OGTT in the target population with a 75 g glucose load.
- *a 2-step strategy* consists of firstly, a screening test (50 g glucose challenge test (GCT) derived from the work of O'Sullivan and Mahan) on the target population, secondly, a diagnostic test (100 g or 75 g OGTT) to confirm or eliminate a diagnosis of GDM in women with screen-positive results.

The 1-step diagnostic strategy might reduce the unpleasant side effects (mainly nausea and vomiting) of a 100 g OGTT and/or reduce the number of women with screen-positive results not undergoing the second test.

Alternative methods: Measuring either fasting or non-fasting blood glucose levels, glycosuria, or glycated haemoglobin are not recommended for GDM diagnosis.

2.2 Who should be screened?

The target population consists of all pregnant women between 24 and 28 weeks' gestation. Women with risk factors for GDM should be screened early in pregnancy.

Risk factors for GDM are:
- Age (threshold between 25 and 40 years according to study and/or international guideline);
- body mass index (BMI) before pregnancy (overweight or obesity) (threshold 25-30 kg/m²);
- ethnic origin (Caucasian women are at lower risk);
- a family history of diabetes;
- a personal history of GDM, fetal death *in utero* or macrosomia.

The prevalence of risk factors for GDM in the population is very high. In certain populations, according to the factors and thresholds used, only 10% of women have no risk factors. On the other hand, the proportion of women with GDM not identified by targeted risk-based screening could be as high as 50%.

Compared to targeted screening, systematic screening gives a lower false negative rate but a higher false positive rate. The positive predictive value of the screening test (50 g GCT) is low. Fewer than 20% of women with screen-positive results are true positives when the cut-off level is 7.8 mmol/L (1.40 g/L). The sensitivity of the test can be increased by reducing the blood glucose cut-off level but this reduces its specificity and increases the false positivity rate.

2.3 Diagnostic cut-off values

The 11 international guidelines identified proposed 7 cut-off levels for the 75 g OGTT and 2 cut-off levels for the 100 g OGTT, namely 7.2 mmol/L (1.30 g/L) and 7.8 mmol/L (1.40 g/L), with some guidelines suggesting that a diagnosis of diabetes should be made when blood glucose at 1 hour is ≥11.1 mmol/L (2 g/L) (see Appendix 1).

- *WHO* advises using the cut-off levels which define glucose intolerance or diabetes outside of pregnancy. These have been defined in the general population and are based on the risk of micro- and macrovascular complications.
- *Other international guidelines* propose several cut-off levels, all derived from the initial study performed by O'Sullivan and Mahan (1964). The methodology used in this study is open to criticism, in particular as the cut-offs were defined:
  - by the risk of diabetes after pregnancy rather than by the risk of perinatal complications,
  - on selected populations of women.
- The *US Preventive Task Force* does not recommend any cut-offs because of the lack of adequate and relevant published findings.

There is no international consensus on screening strategy nor on which diagnostic tools or cut-off values to use (see *Appendix 1*). Cut-off values should ideally be the thresholds at which care significantly reduces perinatal complications.

3. Assessment of screening and diagnosis methods

The benefits of GDM screening and diagnosis should be given by:

- the reduction in risks for mother and fetus during pregnancy and at the time of delivery (in particular, perinatal mortality and events related to macrosomia and pregnancy-induced hypertension). Reducing short-term risk should be the main endpoint.
- the reduction in long-term risks to mother and baby.

3.1 Perinatal mortality

The natural history of GDM is poorly understood. Under current conditions of obstetric care for pregnant women it is impossible to estimate the risk of perinatal death associated with untreated GDM on the basis of the findings in the literature.

3.2 Macrosomia-related complications

- **Link between macrosomia and GDM**

Macrosomia is defined as a birth weight >4 000 g or 4 500 g or > 90th percentile at gestational age, depending upon the study, and concerns 15-30% of pregnancies with GDM. It is associated with complications (Caesarean section, shoulder dystocia and/or brachial plexus injuries) in 4-11% of deliveries. The risk of complications increases with birth weight.

Most macrosomic infants are born to women unaffected by GDM. Fewer than 10% of macrosomic infants can be attributed to GDM.

Maternal obesity, excess weight, and weight gain during pregnancy, together with the mother's ethnic origin, are the main risk factors for macrosomia. These risk factors are more important factors than blood glucose level and are also risk factors for GDM. Their interrelationships are poorly understood.

There is a continuum between maternal blood glucose (fasting blood glucose and/or blood glucose after oral glucose load) and a macrosomic infant, which makes it difficult to select a risk threshold if the endpoint is macrosomia. Macrosomia is an intermediate endpoint for assessing GDM-related morbidity. However, more relevant endpoints would be its complications.

- **Does GDM treatment reduce rates of macrosomia and its complications?**

It is not clear whether insulin reduces rates of macrosomia and its complications effectively. The efficacy of insulin treatment would seem to depend on the severity of maternal hyperglycaemia. Insulin would be effective only in women with "severe" and not "lesser degrees" of hyperglycaemia. No cut-off level can currently be proposed.

It is not clear whether dietary management alone is effective. However, the results of a recent, slightly biased trial suggest that a combination of diet, glycaemic control ± insulin may reduce perinatal morbidity and mortality in women with "moderate" GDM. This needs to be confirmed.

3. 3 Pregnancy-induced hypertension and pre-eclampsia

Pregnancy-induced hypertension and pre-eclampsia are more common in women with GDM but there is no definitive evidence for a causal relationship. An analysis of controlled studies suggests a common terrain which might explain the statistical relationship. When risk factors common to pregnancy-induced hypertension (or pre-eclampsia) and to GDM, in particular age and BMI, are taken into account:

- the relationship between pregnancy-induced hypertension and GDM becomes weaker;
- age and BMI are found to have a greater impact than maternal glycaemia levels on blood pressure levels during pregnancy.

No study has established whether treating GDM reduces pregnancy-related hypertension and its complications, and vice-versa.

There is no direct evidence that systematic or targeted screening for GDM from the 24th week of pregnancy is effective in reducing perinatal mortality and mobidity.

Rates of macrosomia and its complications increase with maternal glycaemia levels. Diagnostic and intervention thresholds, as well as the effectiveness of care, are still a matter of controversy, in particular for "moderate hyperglycaemics".

The diagnosis and care of GDM are not without adverse effects such as anxiety and an increase in the numbers of antenatal appointments, tests, Caesarean sections (even in the absence of fetal macrosomia), inductions and newborns referred to neonatal intensive care.

3.4 Post-gestational diabetes

In women with GDM, the risk of diabetes after pregnancy varies between 2% and 70% according to study population and duration of follow-up. However, the real-world incidence of post-gestational diabetes is unknown. The main predictive factor is elevated fasting blood glucose levels during pregnancy, but the role played by the mother's BMI in this excess risk has yet to be defined. There is no evidence that GDM screening and diagnosis using glucose loading tests is of any benefit in preventing diabetes type 2 outside of pregnancy. These would require cost-benefit studies.

3.5 Obesity in offspring

There is no evidence of any risk of obesity or excessive weight gain in offspring. No properly conducted study provides any support for this hypothesis.

4. Conclusion

Systematic or targeted screening for GDM is controversial, as revealed by discrepancies in international guidelines and professional practice.

On the basis of the findings in the scientific literature, no conclusions can be drawn on:

- the best strategies for screening and diagnosis of GDM
- the methods for implementing such strategies.

The degree of controversy and uncertainty means that guidelines cannot be produced until the results of further studies are available.

Further findings on at-risk populations, screening date, and effective diagnostic and interventional thresholds are necessary. Two studies are ongoing on:
(i) relevant diagnostic thresholds in relation to short-term risk to mother and baby
(ii) efficacy of care for "moderate" forms of GDM.
These should help provide the information urgently needed to clarify the best course of action.

Appendix 1. International guidelines on screening and diagnosis of GDM

Guideline	Screening			Diagnosis	
	Recommended Systematic or targeted	**Method (when to screen)**	**Cut-off value (blood glucose measured on venous plasma)**	**Method**	**Recommended criteria**
ADA, 2004 (United States)	Yes Targeted	50 g GCT (24-28th week)	≥ 7.2 mmol/L (1.30 g/L) **OR** ≥ 7.8 mmol/L (1.40 g/L) at 1 hour	100 g OGTT	Carpenter and Coustan*
		OR 75 g OGTT (24-28th week)	see diagnostic criteria	**OR** 75 g OGTT	ADA**
US Preventive Task force, 2003 (United States)	No recommendations			No recommendations	
ACOG, 2001 (United States)	Yes Targeted	50 g GCT (24-28th week)	≥ 7.2 mmol/L (1.30 g/L) **OR** ≥ 7.8 mmol/L (1.40 g/L) at 1 hour	100 g OGTT	NDDG* **OR** Carpenter and Constant*
SIGN, 2001 (Scotland)	Yes Systematic	Glycosuria (at each appointment) **AND** blood glucose, fasting or non-fasting (at the 1st appointment and 28th week or if glycosuria is positive)	≥ 5.5 mmol/L (1.00 g/L)§ **OR** ≥ 7.0 mmol/L (1.26 g/L)§§	75 g OGTT	SIGN 2001**
WHO, 1999 (International)	Yes Systematic	75 g OGTT (24-28th week)	≥ 7.0 mmol/L (1.26 g/L) fasting **AND** ≥ 7.8 mmol/L (1.40 g/L) at 2 hours **OR** ≥ 11.1 mmol/L (2.00 g/L) at 2 hours	75 g OGTT	WHO 1999** (as for screening)

*see *Table 1*, ** see *Table 2*, § blood glucose in the fasting state or more than 2 hours after food intake, §§ postprandial blood glucose (within 2 hours of food intake).

Appendix 1 (contd). International guidelines on screening and diagnosis of GDM

Guideline	Screening			Diagnosis	
	Recommended Systematic or targeted	**Method (when to screen)**	**Cut-off value (blood glucose measured on venous plasma)**	**Method**	**Recommended criteria**
ADIPS, 1998 (Australia)	Yes Systematic	50 g GCT **OR** 75 g OGTT (26-28th week)	≥ 7.8 mmol/L (1.40 g/L) at 1 hour ≥ 8.1 mmol/L (1.46 g/L) at 1 hour	75 g OGTT	ADIPS 1998**
CMA, 1998 (Canada)	Yes Targeted	50 g GCT (24-28th week)	≥ 7.8 mmol/L (1.40 g/L †) at 1 hour	100 g OGTT **OR** 75 g OGTT	Carpenter and Coustan* CMA 1998**
4th international conference, 1998	Yes Targeted	50 g GCT (24-28th week) **OR** 75 g GCT (24-28th week)	≥ 7.2 mmol/L (1.30 g/L) **OR** ≥ 7.8 mmol/L (1.40 g/L‡) at 1hour see diagnostic criteria	100 g OGTT **OR** 75 g OGTT	Carpenter and Coustan* ADA**
Alfediam, 1996 (France)	Yes Systematic	50 g GCT (24-28th week)	≥ 7.2 mmol/L# (1.30 g/L) At 1 hour	100 g OGTT	Carpenter and Coustan*
CNGOF, 1996 (France)	Yes Systematic	50 g GCT	≥ 7.2 mmol/L (1.30 g/L) **OR** ≥ 7.8 mmol/L# (1.40 g/L) at 1 hour	100 g OGTT	Carpenter and Coustan*
PNCG, 1996 (United Kingdom)	Yes Systematic	glycosuria (at each appointment) **AND** blood glucose, fasting or non-fasting (at 1st appointment and at 28th week or if glycosuria is positive)	≥ 5.5 mmol/L§ **(**1.00 g/L) **OR** ≥ 7.0 mmol/L§§ **(**1.26 g/L)	75 g OGTT	PNCG**

*see Table 1, ** see Table 2, † GDM diagnosed straightaway if blood glucose at 1 hour ≥ 10.3 mmol/L (1.85 g/L), ‡ GDM diagnosed straightaway if fasting blood glucose ≥ 7 mmol/L (1.26 g/L) or if blood glucose at 1 hour ≥ 11.1 mmol/L (2.00 g/L), # GDM diagnosed straightaway if blood glucose at 1 hour ≥ 11.1 mmol/L (2.00 g/L), § blood glucose in the fasting state or more than 2 hours after food intake, §§ postprandial blood glucose (within 2 hours of food intake).

Table 1. Glycaemic thresholds for diagnosing GDM from an oral glucose tolerance test using 100 grams glucose (at least 2 abnormal values are needed to make the diagnosis)

Blood glucose (units)		O'Sullivan and Mahan (1964) Total blood	Conversion NDDG (1979) (rounded up) Plasma	Carpenter and Coustan (1982) (rounded up) Plasma
Fasting	mmol/L g/L	5.0 0.9	5.8 1.05	5.3 0.95
At 1 hour	mmol/L g/L	9.2 1.65	10.6 1.90	10.0 1.80
At 2 hours	mmol/L g/L	8.1 1.43 (*1.45)*[*]	9.2 1.65	8.6 1.55
At 3 hours	mmol/L g/L	6.9 1.27(*1.25)*[*]	8.1 1.45	7.8 1.40

[*] Rounded by O'Sullivan so that the value can be remembered more easily

Table 2. Diagnostic criteria for GDM after 75 g OGTT according to the guidelines: 1 abnormal value out of 2 is needed to make the diagnosis, apart from exceptional cases

Guideline	Blood glucose		
	Fasting [*]	at 1 hour [*]	at 2 hours [*]
ADA [**] (2004)	5.3 mmol/L (0.95 g/L)	10 mmol/L (1.80 g/L)	8.6 mmol/L (1.55 g/L)
SIGN (2001)	5.5 mmol/L (1.0 g/L)	_	9.0 mmol/L (1.64 g/L)
WHO (1999)	7 mmol/L (1.26 g/L)	_	7.8 mmol/L (1.40 g/L)
ADIPS (1998) Australia	5.5 mmol/L (1.0 g/L)	_	8.0 mmol/L (1.46 g/L)
ADIPS (1998) New Zealand	5.5 mmol/L (1.0 g/L)	_	9.0 mmol/L (1.64 g/L)
CMA [**] (1998)	5.3 mmol/L (0.95 g/L)	10.6 mmol/L (1.92 g/L)	8.9 mmol/L (1.61 g/L)
4th international conference on GD [**] (1998)	5.3 mmol/L (0.95 g/L)	10 mmol/L (1.80 g/L)	8.6 mmol/L (1.55 g/L)
PNCG (1996)	6 mmol/L (1.10 g/L)	_	9.0 mmol/L (1.64 g/L)

[*] measured on venous plasma, [**]: 2 abnormal values out of 3 are needed to make the diagnosis.

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