WHO/NMH/MND/13.2

Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy

Executive summary

The high prevalence of diabetes globally and its increasing frequency in women of gestational age have generated new research data on the relationship between glycaemia and pregnancy outcomes. The diagnostic criteria for hyperglycaemia in pregnancy recommended by the World Health Organization (WHO) in 1999 were not evidence-based and needed to be updated in the light of previously unavailable data. The update follows the WHO procedures for guidelines development. Systematic reviews were conducted for key questions, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was applied to assess the quality of the evidence and to determine the strength of the recommendation on the diagnostic cut-off values for gestational diabetes. Where evidence was absent (diagnosis of diabetes in pregnancy) or GRADE was not deemed suitable (classification), recommendations were based on consensus.

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The systematic review of cohort studies showed that women with hyperglycaemia detected during pregnancy are at greater risk for adverse pregnancy outcomes, notably, macrosomia of newborn and pre-eclampsia, even after excluding the more severe cases of hyperglycaemia that required treatment. Treatment of gestational diabetes (GDM) is effective in reducing macrosomia, large for gestational age , shoulder dystocia and pre-eclampsia/hypertensive disorders in pregnancy. The risk reduction for these outcomes is in general large, the number need to treat is low, and the quality of evidence is adequate to justify treatment of GDM.

1. **Hyperglycaemia first detected at any time during pregnancy should be classified as either :**

    - **Diabetes mellitus in pregnancy (see recommendation 2)**
    - **Gestational diabetes mellitus (see recommendation 3)**

Quality of evidence: not graded
Strength of recommendation: not evaluated

Current definitions of gestational diabetes include women with diabetes and women with intermediate hyperglycaemia – impaired glucose tolerance (IGT)

and impaired fasting glycaemia (IFG) as defined in non-pregnant adults. Concern has been expressed about the inclusion of such a wide range of glucose abnormalities in one definition, especially including those with more severe hyperglycaemia which defines diabetes in non-pregnant adults. This concern centres on special considerations about management during pregnancy and post-partum follow-up in women with more severe hyperglycaemia. Drawing conclusions about this group is particularly difficult because of the lack of good quality data at higher levels of hyperglycaemia since these women are excluded from epidemiological studies and randomised trials of GDM treatment.

Recent consensus has moved back in favour of distinguishing between diabetes and lesser degrees of glucose intolerance in pregnancy. Therefore this guideline recommends a distinct category for pregnant women with glucose levels diagnostic of diabetes in non-pregnant adults based on the following:

- consensus that diabetes during pregnancy, whether symptomatic or not, is associated with significant risk of adverse perinatal outcomes
- pregnant women with more severe hyperglycaemia have been excluded from epidemiologic and intervention studies
- management of women with this level of hyperglycaemia requires assessment of chronic complications and is more likely to require pharmacological intervention , especially when detected earlier in the pregnancy

2. Diabetes in pregnancy should be diagnosed by the 2006 WHO criteria for diabetes if one or more of the following criteria are met:

- **fasting plasma glucose ≥ 7.0 mmol/l (126 mg/ dl)**
- **2-hour plasma glucose ≥ 11.1 mmol/l (200 mg/dl) following a 75g oral glucose load**
- **random plasma glucose ≥ 11.1 mmol/l (200 mg/ dl) in the presence of diabetes symptoms.**

Quality of evidence: not graded

Strength of recommendation: not evaluated

Diagnostic criteria for diabetes in non-pregnant individuals are based on the relationship between plasma glucose values and the risk of diabetes-specific microvascular complications. There are no data on this relationship.in untreated pregnant women and such data are unlikely to emerge. Therefore, it was decided to recommend the same diagnostic criteria for diabetes in both pregnant and non-pregnant individuals.

3. **Gestational diabetes mellitus should be diagnosed at any time in pregnancy if one or more of the following criteria are met:**

   - fasting plasma glucose 5.1-6.9 mmol/l (92 -125 mg/dl)
   - 1-hour plasma glucose ≥ 10.0 mmol/l (180 mg/dl) following a 75g oral glucose load*
   - 2-hour plasma glucose 8.5-11.0 mmol/l (153 -199 mg/dl) following a 75g oral glucose load

   ***there are no established criteria for the diagnosis of diabetes based on the 1-hour post-load value

Quality of evidence: very low
Strength of recommendation: weak

Diagnostic criteria for GDM are based on the risk of adverse pregnancy outcomes. However since there is a continuous risk of adverse outcomes with increasing glycaemia, any diagnostic thresholds will be somewhat arbitrary. The IADPSG Consensus Panel decided to define diagnostic values on the basis of an odds ratio of 1.75 for adverse neonatal outcomes (birth weight >90th percentile, cord C-peptide >90th percentile, and neonatal percent body fat >90th percentile) compared with mean values, for fasting plasma glucose, 1-hour, and 2-hour OGTT plasma glucose values.
The simulation study reported in Section 3.4.1. demonstrated some advantages of these criteria compared with the previous WHO criteria, with lower numbers needed to screen to prevent adverse outcomes. In the interest of moving towards a universal standard recommendation for the diagnosis of GDM, the WHO guideline development group decided to accept the general principles behind how the

International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria were derived and adopt these criteria, rather than introduce another set of arbitrary cut-off values. This definition applies for the diagnosis of GDM at any time during pregnancy.

This guideline:

- takes into consideration new evidence from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study

- proposes a new classification for hyperglycaemia first detected in pregnancy

- removes the ambiguity with regard to fasting plasma glucose values in the 1999 WHO guideline

- clarifies ambiguities in the IADPSG criteria related to ranges of plasma glucose values for distinguishing diabetes in pregnancy and GDM.

1. Introduction

Diabetes complicating pregnancy is associated with adverse maternal and perinatal outcomes[1]. Lesser degrees of glucose intolerance have also been shown to be harmful[2]. However, how one defines what constitutes glucose intolerance in pregnancy has been an issue of considerable controversy, complicating clinical practice and research over the last three decades. The main reason for this diagnostic dilemma is the large number of procedures and glucose cutoffs proposed for the diagnosis of glucose intolerance in pregnancy. In 2010, the WHO convened an expert group to reviewed the current WHO recommendations on definition, diagnosis and classification of glucose intolerance in pregnancy[3]

1.1. Objectives and target audience

The objective of this guideline is to update the 1999 WHO recommendations for diagnosing and classifying hyperglycaemia in pregnancy[3]. The target users are health care professionals who care for pregnant women, most frequently primary care physicians and obstetricians/gynaecologists. However, researchers and policy makers will also find it useful.

1.2. Members of the Guideline Development Group

A guideline development group (GDG) was constituted, which included external experts and WHO staff.

External experts

Dr Mukesh M. Agarwal
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Dr Sara Meltzer
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Area of expertise: diagnosis of GDM, economic evaluation of screening strategies, guideline development

Dr Boyd Metzger
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Area of expertise: diagnostic criteria for GDM, principal investigator of HAPO Study

Dr Yasue Omori
Tokyo Women's Medical University
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Area of expertise: GDM in Eastern Europe, pregnancy in diabetes, diabetes management, development of national guidelines

Dr Maria Inês Schmidt
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Area of expertise: epidemiology of diabetes in women of gestational age, development of national guidelines for GDM

Dr Veerasamy Seshiah
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WHO guideline steering group
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Dr Ana Pilar Betran
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1.3. Funding and declarations of interest

This work was funded by the Government of Japan. The donor has had no influence on the guideline development.

All experts who participated in the development of this guideline were required to complete the WHO Declaration of Interests form and declare their interest at the meeting. Out of the 15 participating experts, 8 experts declared an interest in the subject matter of the meeting:

Dr Edward Coetzee has reviewed a technical report on diabetes in pregnancy for the International Diabetes Federation. He has not received payment for this work.

Dr Sara Meltzer has participated, as the chair and representative of the Canadian Diabetes in Pregnancy Interest Group, in the Consensus Panel that developed the 2010 Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy for International Association of Diabetes and Pregnancy Study Groups. As a member of the Expert Review Committee for the IDF Clinical Guidelines Task Force, she participated in the development of the 2009 Global Guideline on Pregnancy and Diabetes. She has received no payment for this work.

Dr Veerasamy Seshiah: His institution, the Dr Balaji Diabetes Care Centre, has received funding, in the amount of USD 5217 per year for a period of 3.5 years, from the World Diabetes Foundation for a study on the screening for gestational diabetes in Tamil Nadu.

Dr David Simmons has received financial support (in the amount of approximately GBP 1000) to cover his attendance at the annual meeting of the American Diabetes Association 2010, from the company Novo Nordisk. In addition, in 2007, the Eli Lilly Foundation has paid Dr Simmons consulting fees in the amount of GBP 2500 for the creation of a patient advisory group.

Dr Eugene Sobngwi has received an honorarium of EUR 1800 from Novo Nordisk for his membership on the advisory board of the Diabetes Attitudes, Wishes and Needs (DAWN-2) Study funded by Novo Nordisk and conducted by questionnaire.

Dr Boyd Metzger chaired the guideline development group of the International Association of Diabetes and Pregnancy Study groups (IADPSG) that has issued recommendations on diagnosing and screening for GDM. He has not received payment for this work.

Dr Maria Inês Schmidt was part of the guideline development group of the International Association of Diabetes and Pregnancy Study groups (IADPSG) that has issued recommendations on diagnosing and screening for GDM. She also participated in the development of the 2009 Global Guideline on Pregnancy and Diabetes for the IDF Clinical Guidelines Task Force. She has not received payment for this work.

Dr Stephen Colagiuri has written a technical report on diabetes in pregnancy for the International Diabetes Federation. He has not received payment for this work.

The experts' participation in the guideline development group was approved by the WHO Office of the Legal Counsel. All external members of the guideline development group participated in the discussions and in the formulation of the recommendations, as there was no objection from GDG members.

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1.4. Methodology and process

1.4.1. Scope of the guideline

The guideline development group used the GRADE methodology (The **Grading of Recommendations Assessment, Development and Evaluation)** to formulate the questions and to assess the quality of the evidence to support the main recommendations[4]. To this end, the importance of GDM outcomes was classified according to the GRADE guidelines (Annex 1). When the assessment of the quality of evidence by GRADE was not possible, we used expert opinion and consensus. This is because GRADE methodology is designed for assessment of interventions and currently does not cover disease classification based on risk or prognosis[5].

1.4.2. Identification and generation of evidence

The following databases were searched for publications on the relationship between glycaemia in pregnancy and various maternal and child outcomes up to March 2011: MEDLINE, EMBASE, LILACS, the Cochrane Library, CINHAL, WHO-AFRO library, IMSEAR, EMCAT, IMEMR and WPRIM) without language, time of publication or country restrictions. No systematic reviews were identified and a systematic review was commissioned from the Universidade Federal do Rio Grande do Sul, Porto Alegre and Universidade Federal de São Paulo, São Paulo, Brazil (Dr MI Schmidt).[6]

For the effect of treating hyperglycaemia in pregnancy compared with usual antenatal care the following databases were searched up to February 2012: African index medicus; CENTRAL; ClinicalTrials.gov register; WHO.int trial search; EMBASE;

IMEMR; IMSEAR; IndMED; ISI Web of Knowledge; KoreaMed; LILACS; Panteleimon; PubMed; WPRIM) without language, country or time of publication restrictions. Two recent systematic reviews were identified [7;8]. However, to gain a more global and broader perspective, and to be able to include the critical outcome of perinatal mortality, not directly addressed in these systematic reviews, a new systematic review, which also included older trials using quasi-randomization, was commissioned from the Universidade Federal do Rio Grande do Sul and the Universidade Federal de São Paulo.[9] The same institution performed a modelling study based on data derived from these two systematic reviews to compare the impact of applying the 1999 WHO criteria and the IADPSG criteria in a universal screening programme.

The researchers of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study provided results of additional analyses of the dataset as requested by the guideline development group.

1.4.3. Formulation of recommendations and decision making

The recommendations were formulated by the co-chairs and discussed at two group meetings and by e-mail communication. The diagnostic cut-off plasma glucose values for GDM are based on GRADE evidence tables. The GRADE process was not used for the recommendations on classification of hyperglycaemia first detected in pregnancy due to limitations of GRADE for this purpose, nor for diagnostic criteria for diabetes first diagnosed in pregnancy, due to lack of data on the relationship between glycaemia and specific chronic diabetic complications throughout the glycaemic range in untreated pregnant women. Consensus was a priori defined as agreement of a large majority of guideline group members, without strong disagreements. If the group members were unable to reach consensus, the recommendation would be put to a vote and would stand if voted for by a simple majority and the dissenting views presented in the report. However, the group reached consensus on every recommendation.

1.4.4. Strength of recommendations

The strength of recommendations is stated only for recommendations arrived at by the GRADE process.

Strong: Moderate or high quality evidence of effectiveness for at least one critical outcome, desirable effects judged to outbalance the undesirable, or very low quality evidence on undesirable effects; can be adopted in most settings.

Weak/conditional: low or very low quality evidence of effectiveness for all critical outcomes, small benefits, or harms judged to dominate over benefits; questionable feasibility in low-resource settings.

1.4.5. Risks and benefits, values and preferences

We considered potential benefits (to mother and child) of adopting the new criteria in the prevention of short-term pregnancy and perinatal outcomes. Potential long-term benefits to the health of the mother and her offspring were not considered given the paucity of the data available.

We did not evaluate potential risks of treating GDM, with the exception of delivering low birth weight and premature delivery. There are no data on the consequences of false positive or false negative test results, nor on whether or not the (arguably minor) inconveniences/harms of an oral glucose load and blood sampling outweigh the benefits of diagnostic testing.

Potential negative effects of adopting the new diagnostic criteria on the personal satisfaction, quality of life or psychological aspects of individual patients were not evaluated as data on this still have to emerge following eventual implementation of the new criteria. The cost-effectiveness of using these diagnostic criteria will depend on underlying population glucose intolerance and whether the test will be used for diagnostic testing only, or for screening of various scope (testing all pregnant women, testing "at high risk" women only). The cost-effectiveness data are yet to emerge.

We estimated the impact of adopting the new criteria on the incidence of adverse outcomes of GDM and on the number needed to screen to prevent one potential adverse outcome.

The values and preferences accounted for in the decision making process were those of the GDG given that several of its members are women and the impracticality of including pregnant women in the lengthy guideline development process. Data on the preference of pregnant women for a particular diagnostic test are unavailable. Based on their clinical experience, the GDG considered that pregnant women were more concerned about the outcome of their pregnancy than by the relatively minor inconveniences of diagnostic testing labelling and possible treatment of limited duration.

1.4.6. Peer review

The draft recommendations were reviewed by 6 experts and suggestions considered by the majority of the guideline development group as relevant were included in the document.

Reviewers:

Dr Anne Karen Jenum
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All peer reviewers of this guideline were required to complete the WHO Declaration of Interests form. Two experts declared an interest:

Dr Anne Karen Jenum has received financial support for research (in the amount of 25000 Euros) and honoraria for lectures (in the amount of 500 Euros) from the Norwegian Diabetes Association. She has received honoraria for lectures (in the amount of 500 Euros per year) from various pharmaceutical companies, and has had her travel to major diabetes congresses paid by pharmaceutical companies in 2008 and 2010.

Dr Gloria Lopez Stewart has reviewed the 2009 IDF Global Guidelines on Diabetes and Pregnancy. She has not received payment for her work.

The experts' participation in the peer review of the guideline was approved by the WHO Office of the Legal Counsel.

1.4.7. Major issues raised by the reviewers

One reviewer proposed to retain the 1999 WHO criteria, or alternatively apply them at the first visit and apply the new criteria at 24-28 weeks because the HAPO Study did not examine the relationship between glycaemia before the 24th week and pregnancy outcome. The reviewer acknowledges that the 1999 WHO criteria were not evidence based, but perceives them as being easy to implement. This reviewer also proposes to recommend universal screening for diabetes at the first antenatal visit and an OGTT at 24-28 weeks, this being standard practice in many countries, and argues that data would be needed to justify the modification of this approach. However, this updated report, like the 1999 WHO recommendations, leaves it to local health authorities to specify the screening coverage according to local burden, resources and priorities.

Another reviewer was concerned over the public health impact of the new criteria, with the likely increase in the prevalence of hyperglycaemia in pregnancy and the implications for resources and psychological effect on pregnant women. The reviewer proposes that instead of a 75% increase in risk of adverse pregnancy outcome, the cut-off glycaemia value at which this risk increases by 100% be used to define GDM, which could better balance the benefits and risks, although there are no data to compare the consequences of applying either of the arbitrarily selected values. The reviewer criticized the presented comparison of the impact of new diagnostic criteria versus 1999 WHO criteria on adverse pregnancy outcomes, arguing that the prevalence assumptions in the model underestimate the likely prevalence by the new criteria and thus led to an inadequate assessment of the IADPSG criteria. We included sensitivity analysis (Annex 2) showing that when the increase in prevalence with the new criteria is greater, the impact of these criteria is also greater. The reviewer is also concerned that many members of the WHO Guideline Development Group were part of the expert panel of the International Association of Diabetes in Pregnancy Study Groups (IADPSG), and would therefore support the earlier recommendations of this particular body. However, although eight members of the WHO Guideline Development Group had been part of the IADPSG panel, these members did not unanimously agree with the IADPSG recommendations, nor could they have, in case of disagreement, outvoted the group members that were not linked to the development of the IADPSG criteria.

1.5. Adaptation and implementation

The diagnostic test is simple and the implementation of diagnostic criteria and classification is conditional on availability of plasma glucose measurement , which could be a problem in low-resource settings. The WHO Action Plan for noncommunicable diseases[10] supports member states in improving access to essential technologies for diagnosis and monitoring of major noncommunicable diseases and their risk factors. Measurement of plasma glucose values can be used for screening as well as diagnosis of any hyperglycaemic state. The design and implementation of programs to screen for and treat women with hyperglycaemia first detected during pregnancy will need to be determined by individual countries and health services taking into consideration prevalence of glucose intolerance in the population,