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

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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,

resources and competing priorities. WHO will provide technical advice in this process.

1.6. Update

It is likely that a substantial body of new data will emerge in the near future, providing currently scarce health and economic evaluation of the recommended criteria applied to various populations and with different approaches (universal screening, screening only women at high risk, diagnostic testing only). The guideline will be updated in 3-5 years, or earlier if new evidence becomes available which could substantially impact the recommendations.

1.7. Format and dissemination

The guideline will be available as a free download on the WHO website.

1.8. Impact and quality of the guideline

Member states will be provided with technical advice on monitoring relevant short-term pregnancy outcomes.

2. Background

2.1. History of diagnostic criteria for Gestational Diabetes Mellitus (GDM)

The first evidence that screening, diagnosis and treatment of hyperglycaemia in women not previously known to have diabetes improve outcomes was provided by O´Sullivan et al. in the 1960s. After investigating the distribution of plasma glucose values of pregnant women, these authors proposed diagnostic criteria for gestational diabetes based on a 3-h 100g OGTT. They then validated these criteria against the development of future diabetes in the mother[11]. Further, they tested whether treatment of gestational diabetes improves pregnancy outcomes. To that end, they randomized 613 women with gestational diabetes to receive a specific diet and insulin (307 women) or only a routine diet (306 women)[12]. The rate of macrosomia was 4.3% in the intervention group compared with 13.1% in the control group. In further support of the importance of detecting and treating gestational diabetes, they reported increased perinatal mortality in offspring of women with gestational diabetes, compared with offspring of women not meeting the diagnostic criteria[13]. Although the authors recognized that hyperglycaemia per se was perhaps not the only factor causing perinatal mortality, their diagnostic criteria for gestational diabetes gained wide acceptance.

When the 2-h 75g OGTT was established in 1979-1980 by international panels as the diagnostic test for diabetes and glucose intolerance[14], the WHO extended this recommendation to pregnant women[15]. The U.S. National Diabetes Data Group (NDDG) continued to use the 3-h 100g OGTT because the 2-h 75g OGTT had been little investigated during pregnancy[14]. The American Diabetes Association (ADA) and many other medical associations around the world followed the NDDG recommendation, although often choosing different cut points for detecting glucose abnormalities in pregnancy. This variability was in large part due to difficulties related to converting glucose values from O´Sullivan´s studies to their equivalents when glucose was analysed using modern analytic methods in plasma. Over the last 3 decades these procedures and criteria were frequently adopted as a two-step procedure: a 50g 1-h challenge test and then a 100g 3-h OGTT for those positive at screening.

Over the years various definitions of GDM have been proposed by WHO committees[15-17]. The 1999 report Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications is the most recent WHO report addressing the classification and diagnosis of gestational diabetes[3]. This report stated:

- Gestational diabetes is a carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy.
- In the early part of pregnancy (e.g. first trimester and first half of second trimester) fasting and postprandial glucose concentrations are normally lower than in normal, non–pregnant women. Elevated fasting or postprandial plasma glucose levels at this time in pregnancy may well reflect the presence of diabetes which has antedated pregnancy, but criteria for designating abnormally high glucose concentrations at this time have not yet been established.
- Formal systematic testing for gestational diabetes is usually done between 24 and 28 weeks of gestation.
- To determine if gestational diabetes is present in pregnant women, a standard OGTT should be performed after overnight fasting (8–14 hours) by giving 75 g anhydrous glucose in 250–300 ml water. Plasma glucose is measured fasting and after 2 hours. Pregnant women who meet WHO criteria for diabetes mellitus or impaired glucose tolerance (IGT) are classified as having GDM. After the pregnancy ends, the woman should be re–classified as having either diabetes mellitus, or IGT, or normal glucose tolerance based on the results of a 75 g OGTT six weeks or more after delivery. The significance of impaired fasting glycaemia (IFG) in pregnancy remains to be established. Any woman with IFG, however, should have a 75 g OGTT.

The HAPO study[18], an international multicentre study of a cohort of 25,505 pregnant women tested with a 2-h 75g OGTT and followed through pregnancy, generated an expectation of universal convergence for the adoption of a 75g OGTT for the diagnosis of gestational diabetes, as well as for the formulation of diagnostic criteria for GDM.

In 2008, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) sponsored an International Workshop-Conference on Gestational Diabetes

Diagnosis and Classification, to review results of the HAPO and other studies which examined associations of maternal glycaemia and perinatal and long-term outcomes in offspring. Subsequently, the IADPSG Consensus Panel recommended the diagnostic criteria for GDM presented in Table 1[19]. These cut offs represent the average glucose values at which the odds for birth weight > 90th percentile, cord C-peptide > 90th percentile, and neonatal percent body fat >90th percentile reached 1.75 times the odds of these outcomes at the mean glucose values, based on fully adjusted logistic regression models.

These cut points were also recommended by the ADA for a 2-h 75g OGTT in its 2011 position statement.[20]

2.2. Most commonly used diagnostic criteria for GDM

The most commonly used guidelines for the diagnosis of GDM recommend the following diagnostic criteria (Table 1):

Table 1. Most commonly used guidelines for the diagnosis of GDM

Organisation	**Fasting Plasma glucose**	**Glucose Challenge**	**1-h plasma glucose**	**2-h plasma glucose**	**3-h plasma glucose**
WHO 1999[3]*	≥ 7.0	75g OGTT	Not required	≥ 7.8	Not required
American Congress of Obstetricians and Gynecologists[21]**	≥5.3	100g OGTT	≥10.0	≥8.6	≥7.8
Canadian Diabetes Association[22]***	≥5.3	75g OGTT	≥10.6	≥8.9	Not required
IADPSG[19]****	≥5.1	75g OGTT	≥10.0	≥8.5	Not required

*one value is sufficient for diagnosis

** two or more values are required for diagnosis

*** two or more values required for diagnosis

**** one value is sufficient for diagnosis

2.3. The need to update the 1999 WHO criteria

The diagnostic criteria for hyperglycaemia in pregnancy recommended by WHO in 1999 were not evidence-based, are over 10 years old and needed to be updated in light of new data. An ongoing issue which has been problematic with the 1999 WHO criteria relates to the fasting plasma glucose (FPG) criterion. The diagnostic level of ≥7.0 mmol/l is universally considered to be too high. This has led to some groups using only the 2-h plasma glucose (PG) measurement without measuring FPG while others have used both FPG and 2-h PG measurement. In the latter case, cut points of ≥7.0 mmol/l or ≥6.1mmol/l (levels diagnostic of impaired fasting glucose) have been used.

3. Questions addressed in systematic reviews to inform guideline development

3.1. Is the association between gestational diabetes and adverse pregnancy outcomes, independent of other risk factors such as age, body mass index and weight gain during pregnancy?

While there is a clear relationship between increased plasma glucose levels during pregnancy and adverse fetal and maternal outcomes, it is important to establish that these are not due to other well-known confounding risk factors, which is why this particular question was asked and reviewed.

Various cohort studies have addressed this question, utilizing different GDM diagnostic procedures and criteria [23-26]. The most comprehensive study is the HAPO study, an international multicentre cohort of 25,505 pregnant women tested with a 2-h 75g OGTT and then followed through pregnancy to detect primary and secondary outcomes [26]. After adjustment for multiple potential confounders, the study demonstrated associations between plasma glucose levels and adverse pregnancy outcomes and that these associations were independent of other known risk factors for these outcomes. Similar to an earlier study by Moses et al[27] that examined the relationship between adverse pregnancy outcomes and glycaemia below diagnostic values for GDM, the HAPO study also showed a continuum of risk across maternal glucose levels for the various adverse pregnancy outcomes. As such, the study reiterated the fact that specific glycaemic cut offs for the diagnosis of gestational diabetes cannot be recommended, but rather that criteria must be developed through evidence-informed consensus.

3.1.1. Quality of evidence

Although GRADE does not provide a formal framework for assessing the quality of evidence for questions related to etiology, the GRADE domains can be used to provide a descriptive assessment of the quality of the evidence.[28]

Direct evidence is available from several well designed prospective population-based cohort studies assessing the association of glycemic levels and important adverse

maternal and perinatal outcomes utilizing different GDM diagnostic criteria. More than 50,000 pregnancies were assessed, positive and associations being found consistently across studies.[24 29 6;25;26;30-33;6;34 31] The most comprehensive study is the HAPO study, an international multicentre cohort of 25,505 pregnant women tested with a 2-hour 75g OGTT and then followed through pregnancy to detect primary and secondary outcomes[26]. Similar to an earlier study by Moses et al[27], the HAPO study showed a dose-response gradient across maternal glucose levels for the various adverse pregnancy outcomes.

The overall risk of bias is low, studies having adequate selection of participants and measurement of outcomes. Although residual confounding cannot be excluded, adjustment for most important confounding factors (maternal race, age, parity, body mass index, and gestational weight gain) was performed, association remaining statistically significant. More importantly, as discussed regarding Question 3.3, RCTs evaluating GDM treatment consistently demonstrate important decreases in adverse outcomes such as macrosomia (high quality), LGA births (high quality), pre-eclampsia (moderate quality) and shoulder dystocia (low quality).[9]
Thus, we conclude that gestational diabetes is independently associated with important adverse perinatal and maternal outcomes, particularly with regard to pre-eclampsia and large for gestational age births.

3.2. What is the increased risk of adverse pregnancy outcomes conferred by a diagnosis of gestational diabetes defined by a 75g OGTT?

Having established that GDM is an independent risk factor for adverse outcomes, this question and review seeks to quantify this relationship and compare risk with the two most frequently used criteria based on a 75 g OGTT – the 1999 WHO and the IADPSG diagnostic criteria.

With the aim of defining the magnitude of the associations for the main GDM diagnostic criteria based on a 75g OGTT (the WHO and the IADPSG criteria) and their related adverse pregnancy outcomes, Wendland et al [6] conducted a systematic review and identified 8 studies which met the selection criteria. One study was performed in Asia[35] , one in North America[30] , two in the Middle East [31;36], one in

Europe [29], two in Latin America [25;37] and one was a multi-country study [2;26].Taken together, the 8 studies provided information on 44,829 women. Only results on untreated women were extracted from these studies, which, in some cases, resulted in a very narrow glucose range. When no published data were available, whenever possible, information was obtained from the database of one of the included studies (the Brazilian Study of Gestational Diabetes – EBDG).[33]

Five studies allowed assessment of the association between untreated GDM according to the WHO criteria and macrosomia [25;29;31;36;37]. The pooled relative risk (RR) was 1.81 (95% CI 1.47-2.22; p<0.001), with very homogenous results across studies (I^2= 0%). No study was available to examine this association using the IADPSG diagnostic criteria but analysis using the EBDG data base showed a RR of 1.38 and 95% CI 1.14 – 1.68; p=0.001. When using large for gestational age (LGA) as the outcome, the magnitude of the association for the WHO criteria[25;26] was slightly lower (RR=1.53, 95% CI 1.39-1.69; p<0.001; I^2 = 0%). For the IADPSG criteria, findings from three studies[25 26;30] produced a higher RR but with very heterogeneous results (RR=1.73, 95% 1.28-2.35; p<0.001, I^2= 93%).

Only two studies[25;29] provided sufficient data on perinatal mortality and both used the WHO criteria. Associations were of clinically relevant size, but lacked statistical significance (RR=1.55, 95% CI 0.88-2.73; p=0.13). For IADPSG criteria, analysis of the EBDG data also showed a non-significant association (RR = 1.40, 95% CI 0.91-2.14; p=0.12).

Three studies [25;26;35] allowed assessment of the association between untreated GDM according to the WHO criteria and pre-eclampsia and showed a RR of 1.69 (95% CI 1.31-2.18; p<0.001; I^2 = 38%). When analysed using the IADPSG criteria [25;26;30], the pooled RR was of similar magnitude (RR= 1.71, 95% CI 1.38-2.13; p<0.001), but the results were very heterogeneous (I^2=73%).

Both the WHO and IADPSG GDM diagnostic criteria detected women at increased risk for caesarean delivery, with a RR of 1.37 (95% CI 1.24-1.51; p< 0.001) for the WHO criteria, and 1.23 (95% CI 1.01-1.51; p=0.04) for the IADPSG criteria. The associations were homogeneous across the four studies[25;26;29;35] analysed according to

the WHO criteria (I^2 = 29%), but there was an important variation across the three studies [25;26;30] that used the IADPSG criteria (I^2=93%).
Results for the WHO criteria were generally more similar than for IADPSG criteria before and after the exclusion of both studies.

3.2.1. Quality of evidence

Since there is no reference standard test for GDM, prognostic properties for future adverse pregnancy outcomes were used. To assess the quality of the evidence, the GRADE framework for diagnostic test accuracy[38] was adapted, using the same domains, but considering longitudinal studies as a source of evidence, instead of cross-sectional studies. The results of applying the diagnostic criteria in the population are presented as the rates of true positives, false positives, false negatives and true negatives per 1,000 women.

Overall, both criteria identify women at higher risk of developing adverse pregnancy outcomes. The quality of the evidence ranged from low to high for the evaluated outcomes (Tables 2-7). A higher quality of evidence was observed for the WHO criteria, since studies evaluating the IADPSG showed inconsistent results. The IADPSG criteria identify a larger number of true positives, however they classify as having GDM a larger proportion of women who will not develop an adverse outcome. Of note also, most of the events occur in women without GDM.

3.2.2. Comments and conclusions

Although many of these associations are significant, they are relatively small within a diagnostic context. Two reasons may explain this. First, both criteria, but especially the IADPSG one, include a milder degree of hyperglycaemia when compared with other diagnostic criteria. Second, as all analysed studies excluded women receiving specific treatments for GDM, the range of glucose tolerance classified as GDM in included women represented a milder degree of hyperglycemia. Given the continuum of risk in the association between plasma glucose and pregnancy outcomes [26], if these criteria were applied to a broader spectrum of glucose intolerance such as seen in the usual clinical setting which includes women at greater risk given their higher glucose

level, the association would be expected to be stronger. Nevertheless, even if glucose-based GDM diagnostic criteria were to reach relative risks close to 3 for these adverse outcomes, magnitudes such as these are unlikely to generate major diagnostic discrimination in terms of post-test probabilities [39]. This suggests the need for further refinement in diagnostic criteria and the possible inclusion of markers other than glucose.

Meta-analysis of studies examining the WHO and IADPSG criteria demonstrate increased risk of adverse pregnancy outcomes, of small but similar magnitudes for both criteria. For the WHO criteria, associations were consistent across studies. For the IADPSG criteria, adequate estimation of the magnitude of associations when applied to non-HAPO settings will require additional studies from different settings.

Based on the findings of the systematic review of cohort studies, both the WHO and IADPSG diagnostic criteria for GDM, clearly identify women at greater risk for adverse pregnancy outcomes, notably, macrosomia and pre-eclampsia, even after excluding the more severe cases who required treatment. Although these diagnostic criteria also identified increased risk for perinatal death, this association was not statistically significant. A recent publication that performed subgroup analyses of the EBDG data base reported a larger and statistically significant association between untreated GDM, diagnosed according to the WHO criteria, and late perinatal death i.e. death occurring after the 34th week of pregnancy[33].

3.3. Can treatment for gestational diabetes reduce adverse pregnancy outcomes?

Having established and quantified a relationship between GDM and adverse outcomes, this question addresses the issue of whether treatment of elevated plasma glucose levels reduced risk of adverse outcomes.

To estimate the magnitude of the effect of treating GDM in a variety of settings and over a broad range of adverse outcomes, Falavigna et al conducted a systematic review[9]. A total of 8 publications pertaining to 7 studies met the selection criteria and were included in the systematic review, totaling 3,157 randomised women [40-47]. Studies were conducted in United States[40;42;43;46], Hong Kong[44], Canada[45] , Australia[41]

and the United Kingdom[41]. The spectrum of hyperglycaemia among women randomized varied across studies, and the interventions offered generally consisted of a stepped approach of lifestyle changes (nutritional counseling and exercise) followed by insulin use if necessary. Random allocation of treatment was performed in four [41;45-47] and quasi-random allocation in three [40;43;44] of the seven studies. Allocation concealment was clearly specified in only two trials [41;46]. None of the trials were double-blinded. One trial provided incomplete information of outcome data [44] because it did not specify to which groups the dropouts belonged and the reasons for these withdrawals.

Treatment for GDM resulted in a statistically significant decrease in the relative risks of macrosomia (0.47; 95% CI 0.34-0.65), large for gestational age (0.57; 95%; CI 0.47-0.71) and shoulder dystocia (0.41; 95% CI 0.22-0.76). Additionally the risks for, perinatal mortality, neonatal intensive care admission and birth trauma were reduced in treated women, but the magnitude of these effects did not reach statistical significance. Only three trials provided information on perinatal mortality while the remaining four reported no cases of perinatal deaths. Most of the 46 perinatal deaths analysed came from the two older, quasi-randomized studies[40;42]. The remaining perinatal outcomes did not differ between GDM patients receiving specified treatment versus conventional obstetric management The consistency across studies was generally high, except for macrosomia (I^2=48%) and respiratory distress syndrome (I^2=58%). The exclusion of the study by Garner et al [45] eliminated the heterogeneity for macrosomia (I^2 = 0) without major change in the magnitude of the effect (0.41; 95% CI 0.33-0.52). In sensitivity analyses, exclusion of the three studies with systematic allocation of treatment produced minimal change in the pooled RRs for the perinatal and maternal outcomes for which data from these studies were available. Treatment of GDM produced statistically significant relative risk reductions for pre-eclampsia (0.61; 95% CI 0.46-0.81) and hypertensive disorders (0.64; 95% CI 0.51-0.81). The risk of caesarean section in treated women decreased by 10%, but this did not reach statistical significance. Only one GDM treatment trial examined the incidence of diabetes after pregnancy[47] and no association was found up to 16 years after GDM. High consistency was seen across studies.

3.3.1. Quality of evidence

GRADE Tables 8 and 9 present information on the quality of the evidence for perinatal and maternal outcomes, respectively. The review concluded that there is high quality evidence indicating that treatment of GDM reduces macrosomia and large for gestational age births, with a number needed to treat (NNT) of 11.4 (9.1-17.3) and 12.2 (9.9-18.1), respectively. Due to the small number of events (Table 8), there is low quality evidence indicating that treatment of GDM reduces the risk for shoulder dystocia, with a NNT of 48.8 (39.9-120) to prevent one event. Regarding maternal outcomes, there was moderate quality evidence that treatment of GDM which reduces the risk for hypertensive disorders in pregnancy and pre-eclampsia (Table 9). The NNTs for these outcomes were 18.1 (13.4 -34.2) and 21.0 (15.1-43), respectively. For all other outcomes, there was moderate to very low quality evidence indicating benefits of treatment, basically due to the small number of events reported.

3.3.2. Comments and conclusions

All studies evaluated high risk women, recruited from two-steps screening programs. Additionally, as the diagnostic criteria used across studies were very heterogeneous, we were unable to summarize results separately for the individual diagnostic criteria. Of note, however, the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial [41], which used the WHO definition of GDM (75g OGTT; 2-h plasma glucose ≥7.8mmol/l [140 mg/dl]), provides evidence that treatment based on this definition reduces the risk of unfavorable outcomes, including perinatal mortality, shoulder dystocia or birth trauma. In addition, the occurrence of macrosomia, large for gestational age birth and hypertensive disorders was reduced. For the remaining studies, diagnostic criteria were generally based on a 100g OGTT, usually requiring two out of four abnormal values (fasting, 1-h, 2-h, 3-h), and using variable cut points. The recently proposed IADPSG criteria are based on a 75g OGTT and require only one abnormal value out of three (fasting, 1-h, 2-h) and therefore define a group of women with milder degrees of fasting hyperglycaemia than in most trials included in this review. In terms of the IADPSG fasting value, the study which enrolled women closest to this cut-point was that of Landon et al [46] which randomized only women with fasting plasma glucose < 95 mg/dl (5.3 mmol/l). This study, however, required

demonstration of greater post-load hyperglycaemia, in that two out of three abnormal values (1-h ≥10mmol/l [180 mg/dl]; 2-h ≥8.6mmol/l [155 mg/dl] ; 3-h ≥7.8mmol/l [140 mg/dl]) were required. Treatment based on these criteria reduced macrosomia, large for gestational age birth, shoulder dystocia, pre-eclampsia, hypertensive disorders in pregnancy and caesarean section.

The clinical significance of the adverse outcomes for which efficacy was demonstrated in this review merits discussion. Macrosomia may lead to obstetric and neonatal complications directly related to the size of the infant, including shoulder dystocia, for which a benefit from GDM treatment was observed. Although treatment effects on additional complications were not demonstrated, a macrosomic or large for gestational age infant may be at increased risk of short term complications, including perinatal death, which may require obstetric intervention (induction of labour, caesarean section) or admission to the neonatal intensive care unit. More importantly, the presence of these conditions may increase the risk of future chronic complications of potentially greater relevance such as childhood obesity, diabetes and hypertension or be markers of underlying pathophysiological processes such as fetal programming which lead to these diseases[48]. It is however unclear whether treatment of GDM, which reduces the risk of macrosomia, also reduces the risk of consequences in later life. A follow-up of the offspring of women included in the ACHOIS trial showed that treatment of mild GDM did not affect BMI at age 4-5 years[49].

The clinical significance of improving maternal outcomes by reducing pre-eclampsia or gestation related hypertension, may also be expressed in terms of short and long term benefit. In the short term, avoiding pre-eclampsia minimizes the risk of eclampsia, a life threatening condition to both mother and newborn. Additionally, over the long term, pre-eclampsia may predispose to future maternal cardiovascular disease [50] and, through altered placental perfusion, may contribute to the development of long term adverse outcomes in the offspring[51]. Similar to lack of data on long-term effects of GDM treatment on offspring morbidity, there is no evidence that treatment of GDM improves maternal outcomes in later life.

These results apply to the general treatment of GDM compared with conventional obstetric care and implications for specific diagnostic criteria are limited. Most

studies included in this review used diagnostic criteria identifying severe hyperglycaemia, and as such, the generalizability of these findings to the treatment of milder hyperglycaemia detected according to the currently used diagnostic criteria, is less clear. However, one recent high quality study utilizing the WHO diagnostic criteria found benefit for the treatment of GDM [41]. Another recent high quality study which used diagnostic cutoffs similar to the IADPSG criteria, also concluded that treatment of GDM was of benefit [46].

Treatment of 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, thus justifying treatment of GDM (Tables 1 and 2). The extent to which these benefits accrue from pharmacologic interventions to reduce hyperglycaemia or from lifestyle interventions which also affect other risk factors for these outcomes, cannot be determined from these data.

3.4. What is the population impact of using the WHO 1999 and IADPSG diagnostic criteria for GDM if applied to all asymptomatic pregnant women followed by treatment for those identified with GDM?

This question and review compare the population impact of using either the WHO 1999 or the IADPSG diagnostic criteria for GDM and treating women diagnosed with GDM. Because direct data from clinical trials was lacking, a simulation study was performed to examine the impact.

Based on data derived from the two systematic reviews presented in sections 3.2. and 3.3., a simulation study was performed by Falavigna et al[52] to evaluate the impact of universal testing (i.e., submitting all pregnant women to a 75g OGTT in the late 2nd trimester) based on the WHO and the IADPSG criteria, compared with notesting. By evaluating the diagnostic criteria in the context of screening (an intervention) it was possible to evaluate their impact on important clinical outcomes (LGA, pre-eclampsia and caesarean section), as recommended by GRADE. Theoretically, the simulation model could have been used to assess the impact of using the criteria within different

screening approaches (e.g. screening only selected groups), but suitable model parameters were not available in the literature. Therefore the simulation study compared universal screening to no-screening.

The simulation assumed a GDM prevalence of 10% according to the WHO criteria, and a 50% higher prevalence (i.e., a 15% prevalence of GDM) for the IADPSG criteria. Such estimates are similar to those observed in the HAPO study, composed of centers from around the world. To further enhance this assessment, given reported variability in GDM prevalence and in the size of the increase in prevalence with the application of the IADPSG criteria, sensitivity analyses were performed , considering settings with 5 to 15% prevalence of GDM and 25 to 100% increase in prevalence with the application of the IADPSG criteria. Additional sensitivity analyses were conducted considering the uncertainty of the model parameters. Effectiveness of treatment was estimated according to the systematic review presented in section 3.3. and assuming that 90% of those diagnosed actually received treatment.

Universal testing using either diagnostic criteria reduced the incidence of LGA and hypertensive disorders. Number needed to screen (NNS) and their respective 95% credibility intervals (CI) to prevent one adverse outcome were 189 (134 - 268) and 117 (77 - 185) for LGA and 376 (223-1010) and 257 (154-679) for pre-eclampsia, according to the WHO and the IADPSG criteria, respectively. For caesarean section, NNS were large and not statistically significant.

When the two diagnostic criteria were compared, the IADPSG criteria performed better than the WHO criteria in 99.97% of the simulations done for LGA births, in 99.93% of those for pre-eclampsia and in 91.07% of those for caesarean section. The adoption of the IADPSG criteria instead of the WHO criteria would reduce the incidence of LGA births by 0.32% (0.09% – 0.63%; NNS = 309; $p<0.001$), of pre-eclampsia by 0.12% (0.01% – 0.25; NNS = 808; $p=0.007$) but not of caesarean section (0.09%; -0.05 to 0.26; NNS = 1141; $p=0.089$).

Tables 10, 11 and 12 summarize these findings for the WHO and the IADPSG criteria and provide the GRADE quality of the evidence to support diagnostic testing based on these two criteria.

4. Recommendations

4.1. Classification of hyperglycaemia first detected during pregnancy

Recommendation 1

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

- **diabetes mellitus in pregnancy**
- **gestational diabetes mellitus**

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

The classification of abnormalities of glucose intolerance first detected during pregnancy continues to be debated. In non-pregnant adults the distinction is made between diabetes and intermediate hyperglycaemia – impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). The WHO 1999 report defines GDM as either diabetes or IGT first recognized in pregnancy. Concern has been expressed about the inclusion of such a wide range of glucose abnormalities in the 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 this level of hyperglycaemia. The large multinational HAPO study which examined the association between maternal glycaemia and maternal and infant outcomes[26] excluded women with fasting glucose levels above 5.8mmol/l (104 mg/dl) and 2-h post load glucose levels above 11.1mmol/l (200 mg/dl). Similarly, the two recent high quality randomised studies on treatment of GDM also excluded these types of patients. The ACHOIS study [41] excluded women with a fasting plasma glucose of 7.0 mmol/l (126 mg/dl) or more and 2-h post-load glucose above 11.0 mmol/l (200 mg/dl) while the study by Landon et al[46] excluded women with a fasting glucose of 5.3 mmol/l (95 mg/dl) or more.

In recent times consensus has moved back in favour of distinguishing between diabetes and lesser degree of glucose intolerance in pregnancy. This position has been adopted based on the following:

- consensus that diabetes during pregnancy, whether symptomatic or not, is associated with significant risk of adverse perinatal outcome[53-55]
- pregnant women with more severe hyperglycaemia have been excluded from epidemiological[26] and intervention studies[41;46]
- management of women with this level of hyperglycaemia is approached differently, especially when detected earlier in the pregnancy

4.1.1. What is new in the classification of hyperglycaemia in pregnancy

Distinguishing between diabetes in pregnancy and GDM was first proposed by IADPSG and the GDG updating the WHO recommendations accepted this distinction, but proposes slightly different terminology – "diabetes", rather than "overt diabetes" proposed by IADPSG. This distinction between diabetes and GDM is a new recommendation and there is lack of published data on the implications of using this classification.

The principles of management of diabetes in pregnancy and GDM are similar. However, there are some differences in the approach to management of women with diabetes in pregnancy compared with GDM, as outlined in existing evidence-based guidelines, such as those of NICE[56] :

- a detailed assessment for the presence of diabetes related complications is recommended at diagnosis of diabetes, especially complications which can affect pregnancy or be aggravated by it, such as retinopathy and renal impairment
- during pregnancy a more intensive monitoring and treatment of hyperglycaemia is recommended and pharmacotherapy is much more likely to be required to control the hyperglycaemia
- following the pregnancy there is need for closer follow-up and ongoing monitoring and treatment of women with diabetes.

4.2. Diagnosis of diabetes mellitus in pregnancy

Recommendation 2

Diabetes mellitus 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-hplasma 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

This label should be used for asymptomatic women first diagnosed at any time during the pregnancy who meet the WHO diagnostic criteria for diabetes [57] . Alternatively the diagnosis can be made in a pregnant woman with classical diabetes symptoms (excessive thirst, frequent urination, unintentional weight loss) who has a random plasma glucose ≥ 11.1 mmol/l (200mg/dl).

GRADE was not used for this recommendation. Current WHO diagnostic criteria for diabetes are based on the risk of developing microvascular complications, predominantly retinopathy. There are no data available to assess diagnostic accuracy of current diabetes diagnostic criteria if used in pregnancy in untreated women. Because numerous studies have shown the high risk of serious adverse pregnancy outcomes in women with plasma glucose values in the diabetic range , all subsequent studies on the relationship between plasma glucose and pregnancy outcomes have treated women with such diabetic values. Therefore, there are no studies, and it is unlikely there will be any, that will not treat any hyperglycaemia (especially the high end of the spectrum) in pregnancy in order to examine whether the relationship between glucose values and specific diabetic complications is the same as in non-pregnant individuals.

4.2.1. What is new in these diagnostic criteria for diabetes in pregnancy

These diagnostic criteria for diabetes are universally accepted in non-pregnant individuals, but pregnant women with these cut-off values were classified as having GDM when first detected during pregnancy.

4.3. Diagnosis of gestational diabetes mellitus

Recommendation 3

The diagnosis of gestational diabetes mellitus at any time during pregnancy should be based on any one of the following values:

- **Fasting plasma glucose = 5.1-6.9 mmol/l (92 -125 mg/dl)**
- **1-h post 75g oral glucose load >=10.0 mmol/l (180 mg/dl)***
- **2-h post 75g oral glucose load 8.5 – 11.0 mmol/l (153-199 mg/dl)**

  ***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 neonatal outcomes and are derived from the HAPO study[26]. 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 (OR) for adverse outcomes compared with mean values for fasting plasma glucose, 1-h, and 2-h OGTT plasma glucose concentrations (4.5mmol/l or 81 mg/dl, 7.4mmol or 133mg/dl, and 6.2 mmol/l or 112mg/dl, respectively), and selected an OR relative to the mean glucose of 1.75. The recommended diagnostic thresholds for fasting plasma glucose, 1-h, and 2-h plasma glucose concentration are the average glucose values at which odds for birth weight >90th percentile, cord C-peptide >90th percentile, and neonatal percent body fat >90th percentile reached 1.75 times the estimated odds of these outcomes at mean glucose values, based on fully adjusted logistic regression models. Adjustment was made for race or ethnic group,

centre, parity, age, body-mass index (BMI), smoking status, alcohol use, presence or absence of a family history of diabetes, gestational age at the oral glucose-tolerance test, sex of the infant, mean arterial pressure and presence or absence of hospitalization before delivery (except for pre-eclampsia), presence or absence of a family history of hypertension and maternal urinary tract infection (for analysis of pre-eclampsia only). Height was also included as a potential confounder, on the basis of post hoc findings of an association with birth weight greater than the 90th percentile.

Since the HAPO and other studies have shown that the association of risk of adverse outcomes is continuous with increasing glucose level, methods for determining diagnostic criteria are based on somewhat arbitrary risk levels of adverse outcomes. The GDG considered that the method proposed by IADPSG (risk level of 1.75) was appropriate and rather than further complicate the current situation by proposing another new set of criteria, it was advisable to adopt the same methodology for setting diagnostic cut-points.

At the time of writing there are no published cohort or intervention studies which compared the IADSPG criteria to the previous WHO criteria, hence the weak recommendation. However, the WHO guideline development group decided to accept the general principles behind how these new criteria were derived, in the interest of moving towards a universal standard recommendation for the diagnosis of GDM.

These diagnostic criteria for GDM are not based on diagnostic accuracy because there is no reference test (“gold standard”) to define the disease status. The diagnostic criteria are based on prognostic accuracy, meaning the risk of individuals developing an adverse outcome in a certain period of time. GRADE methodology has been developed for the evaluation of diagnostic accuracy, but not for prognostic accuracy. Therefore, the GDG decided to use GRADE to evaluate the proposed criteria through their hypothetical implementation in a universal screening programme, applying the GRADE framework for interventions, as described in Section 3.4. Using the GRADE framework, this was considered to be an observational study (as it started with data from cohorts assessing risk); therefore the confidence in the estimates was downgraded by two levels due to indirectness.

The simulation study described in Section 3.4. demonstrated some advantages of these criteria compared with the previous WHO criteria, with lower numbers needed to screen to prevent adverse neonatal and maternal outcomes. On the other hand, these new criteria are expected to increase the number of women identified with GDM and consequently increase the burden on the health system. Possible harms include more intensive surveillance during pregnancy and a higher rate of primary caesarean deliveries ; labeling or treatment of gestational glucose intolerance [58], maternal anxiety and health perception [59;60], although scant available data indicate no increased anxiety[61]. 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 blood sampling outweigh the benefits of diagnostic testing.

In addition, there are economic implications related to the implementation of these diagnostic criteria (use in diagnosis only, use in screening). Thus, cost effectiveness analyses of different implementation strategies in different settings are highly needed.

This definition of GDM applies at any time during pregnancy. However, it should be noted that in non-obese pregnant women, FPG declines during pregnancy by about 0.5 mmol/l (9mg/dl) by the end of the first trimester or early in the second[62]. Consequently, testing early in the first trimester using an FPG cut-point of 5.1 mmol/l (92 mg/dl) might overdiagnose GDM in non-obese women who have values close to the cut-point. On the other hand, higher first trimester FPG levels (but lower than those diagnostic of diabetes) are associated with increased risks of later diagnosis of GDM and adverse pregnancy outcomes[63;64] . Currently it is not known whether there is benefit of diagnosing and treating GDM before the usual window of 24 –28 weeks gestation. Nevertheless, similar to the conclusion reached by the IADPSG Consensus Panel[19] , it is recommended that an FPG value in early pregnancy ≥5.1 mmol/l (92 mg/dl) should be classified as GDM.

4.3.1. What is new in the diagnostic criteria for GDM?

The recommended glucose cut-off values for GDM correspond to those proposed by IADPSG and are lower than those recommended by earlier guidelines. Unlike earlier guidelines, they are based on the association of plasma glucose and adverse maternal

and neonatal outcomes during pregnancy, at birth and immediately following it. The difference from IADPSG guidelines is that these new WHO guidelines set a range of plasma glucose levels to distinguish diabetes in pregnancy and GDM.

5.0 Implications and recommendations for future research

The implications of these recommendations should be considered in the context of each health setting. While international consensus about the diagnostic criteria for hyperglycaemia detected during pregnancy is growing, implementation may be difficult in some countries. Thus, consideration will need to be given to efficient detection strategies. In addition, adaptation for some ethnic groups or geographical regions might be required as the HAPO study did not include participants from all regions. In some ethnic groups fasting plasma glucose values may not be adequate to diagnose GDM.[65]

Recommendations for research:

- Prevalence of GDM and diabetes according to the new criteria.
- Evaluation of the new diagnostic criteria in diverse settings and ethnic groups: costs, acceptability.
- Randomized trials (e.g. country or region specific) comparing different strategies for the detection of GDM.
- Evaluation of a "single step procedure" in diagnosing GDM
- Cost-effectiveness studies with different detection strategies
- Long term risks related to GDM in mother and child and impact of GDM treatment on long-term outcomes in mother and child

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Annex 1. Importance of outcomes for the assessment of GDM treatment effects (GRADE method)[4]

Score	Relative importance
1-3	Low importance for decision making
4-6	Important, but not critical for decision making
7-9	Critical for decision making

Relative importance of perinatal and maternal outcomes in decision making concerning GDM screening and treatment.

Outcome	**Relative Importance**	
Perinatal Mortality	Critical	9
Macrosomia	Critical	7
LGA births	Important	6
Shoulder dystocia	Critical	8
Neonatal ICU admission	Critical	8
Congenital abnormalities	Critical	8
Birth trauma	Critical	8
Hyperbilirubinemia	Important	5
Respiratory distress syndrome	Critical	8
SGA births	Important	6
Neonatal hypoglycaemia	Important	6
Pre-term births	Important	6
Hypertensive disorders in pregnancy	Important	6
Pre-eclampsia	Critical	7
Caesarean section	Critical	7
Diabetes later in life (maternal)	Critical	8

Annex 2. Sensitivity analysis of the impact of screening strategies on the incidence of large for gestational age (LGA) birth and pre-eclampsia, considering different prevalences (WHO criteria) of gestational diabetes (GDM) and assuming different increases in the prevalence with the use of the IADPSG criteria instead of those of WHO. Results of the baseline case (WHO prevalence 10%; increase in prevalence with use of the IADPSG criteria of 50%) are shown in bold.

GDM (WHO) %	Screening based on WHO criteria				Screening based on IADPSG criteria, assuming a 25% increase in prevalence				Screening based on IADPSG criteria, assuming a 50% increase in prevalence				Screening based on IADPSG criteria, assuming a 75% increase in prevalence				Screening based on IADPSG criteria, assuming a 100% increase in prevalence			
	LGA births		Pre-eclampsia		LGA births		Pre-eclampsia		LGA births		Pre-eclampsia		LGA births		Pre-eclampsia		LGA births		Pre-eclampsia	
	ARR (%)	NNS	ARR (%)	NNS	ARR (%)	NNS	ARR (%)	NNS	ARR (%)	NNS	ARR (%)	NNS	ARR (%)	NNS	ARR (%)	NNS	ARR (%)	NNS	ARR (%)	NNS
5%	0.26	378	0.13	753	0.37	272	0.17	601	0.43	229	0.20	505	0.51	198	0.23	437	0.57	174	0.26	385
6%	0.32	315	0.16	627	0.44	228	0.20	502	0.52	192	0.24	423	0.60	166	0.27	366	0.68	146	0.31	323
7%	0.37	270	0.19	538	0.51	196	0.23	431	0.61	165	0.28	363	0.70	143	0.32	315	0.79	127	0.36	279
8%	0.42	237	0.21	471	0.58	172	0.26	378	0.69	145	0.31	319	0.79	126	0.36	277	0.89	112	0.41	246
9%	0.48	210	0.24	418	0.65	153	0.30	336	0.77	130	0.35	284	0.89	113	0.40	247	1.00	100	0.46	220
10%	**0.53**	**189**	**0.27**	**376**	0.72	139	0.33	303	**0.85**	**117**	**0.39**	**257**	0.98	102	0.45	224	1.10	91	0.50	199
11%	0.58	172	0.29	342	0.79	126	0.36	276	0.93	107	0.43	234	1.07	94	0.49	204	1.20	83	0.55	182
12%	0.63	158	0.32	314	0.86	116	0.39	253	1.01	99	0.47	215	1.16	86	0.53	188	1.30	77	0.60	168
13%	0.68	146	0.34	290	0.93	108	0.43	234	1.09	92	0.50	199	1.25	80	0.57	174	1.40	72	0.64	156
14%	0.74	135	0.37	267	1.00	100	0.46	218	1.18	85	0.54	186	1.34	75	0.61	163	1.49	67	0.69	145
15%	0.79	126	0.40	251	1.07	94	0.49	204	1.25	80	0.57	174	1.42	70	0.66	152	1.59	63	0.73	136

Table 2.Prognostic properties of 1999 WHO diagnostic criteria for gestational diabetes mellitus (GDM) in predicting large for gestational age (LGA) births
Population / Setting: pregnant women from the general population submitted to universal screening for GDM at 24-28 weeks
Test : 75g-OGTT applying the 1999 WHO cut-offs
Clinical outcome: LGA births

Test outcome	**Studies**	**Quality criteria**					**Quality of evidence**	**Prognostic properties (95%CI) [1]**	**Result per 1000 tested (95%CI)[2]**
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
True positives	4 cohort studies (28755 pregnancies)	None	Not Serious	Not Serious	Not Serious	None	⊕⊕⊕⊕ High	RR = 1.53 (1.39 - 1.69)	15 (13 – 18)
False negatives	4 cohort studies (28755 pregnancies)	None	Not Serious	Not Serious	Not Serious	None	⊕⊕⊕⊕ High	Sensitivity :15.3% (12.7% – 18%)	85 (82 – 87)
True negatives	4 cohort studies (28755 pregnancies)	None	Not Serious	Not Serious	Not Serious	None	⊕⊕⊕⊕ High	Specificity: 89.9% (87.8% – 92%)	809 (790 – 828)
False positives	4 cohort studies (28755 pregnancies)	None	Not Serious	Not Serious	Not Serious	None	⊕⊕⊕⊕ High		91 (72 – 110)
Complications	Not reported	-	-	-	-	-	-	-	-
Costs	Not reported	-	-	-	-	-	-	-	-

[1] Data abstracted from Wendland[6]. For sensitivity and specificity, data were reanalyzed using a meta-analytical approach, computed with Meta-Disc version 1.4, using random-effects model and over-dispersion correction.
[2] Assuming overall incidence of LGA births = 10%. Results based on sensitivity and specificity of the diagnostic test.

Table 3. Prognostic properties of the IADPSG diagnostic criteria for gestational diabetes mellitus (GDM) in predicting large for gestational age (LGA) births
Population / Setting: pregnant women from the general population submitted to universal screening for GDM at 24-28 weeks
Test : 75g-OGTT applying the IADPSG cut-offs
Clinical outcome: LGA births

Test outcome	**Studies**	**Quality criteria**					**Quality of evidence**	**Prognostic properties (95%CI)** [1]	**Result per 1000 tested (95%CI)**[2]
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
True positives	3 cohort studies (35902 pregnancies)	None	Serious inconsistency[3]	Not Serious	Not Serious	None	⊕⊕⊕○ Moderate	RR = 1.73 (1.28 - 2.35)	28 (24 – 33)
False negatives	3 cohort studies (35902 pregnancies)	None	Serious inconsistency[3]	Not Serious	Not Serious	None	⊕⊕⊕○ Moderate		72 (67 – 76)
True negatives	3 cohort studies (35902 pregnancies)	None	Serious inconsistency[3]	Not Serious	Not Serious	None	⊕⊕⊕○ Moderate	Sensitivity:28.2% (23.8% – 32.5%) Specificity: 83.9% (81.6% – 86.2%)	755 (734 – 776)
False positives	3 cohort studies (35902 pregnancies)	None	Serious inconsistency[3]	Not Serious	Not Serious	None	⊕⊕⊕○ Moderate		145 (124 – 166)
Complications	Not reported	-	-	-	-	-	-	-	-
Costs	Not reported	-	-	-	-	-	-	-	

[1] Data abstracted from Wendland[6]. For sensitivity and specificity, data were reanalyzed using a meta-analytical approach, computed with Meta-Disc version 1.4, using random-
effects model and over-dispersion correction.
[2] Assuming overall incidence of LGA births = 10%. Results based on sensitivity and specificity of the diagnostic test.
[3] Important heterogeneity was seen across studies. Better results were found for the HAPO study, where the IADPSG criteria were generated.

Table 4. Prognostic properties of 1999 WHO diagnostic criteria for gestational diabetes mellitus (GDM) in predicting pre-eclampsia
Population / Setting: pregnant women from the general population submitted to universal screening for GDM at 24-28 weeks
Test : 75g-OGTT applying the 1999 WHO cut-offs
Clinical outcome: development of pre-eclampsia during pregnancy

Test outcome	**Studies**	**Quality criteria**					**Quality of evidence**	**Prognostic properties (95%CI)** [1]	**Result per 1000 tested (95%CI)**[2]
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
True positives	3 cohort studies (26677 pregnancies)	None	Not Serious	Not Serious	Not Serious	None	⊕⊕⊕⊕ High	RR = 1.69 (1.31 - 2.18) Sensitivity: 16.4% (14.3% – 18.4%) Specificity: 90% (87.8% – 92.1%)	7 (6 – 8)
False negatives	3 cohort studies (26677 pregnancies)	None	Not Serious	Not Serious	Not Serious	None	⊕⊕⊕⊕ High		38 (37 – 39)
True negatives	3 cohort studies (26677 pregnancies)	None	Not Serious	Not Serious	Not Serious	None	⊕⊕⊕⊕ High		860 (838 – 880)
False positives	3 cohort studies (26677 pregnancies)	None	Not Serious	Not Serious	Not Serious	None	⊕⊕⊕⊕ High		95 (75 – 117)
Complications	Not reported	-	-	-	-	-	-	-	-
Costs	Not reported	-	-	-	-	-	-	-	-

[1] Data abstracted from Wendland[6]. For sensitivity and specificity, data were reanalyzed using a meta-analytical approach, computed with Meta-Disc version 1.4, using random-effects model and over-dispersion correction.
[2] Assuming overall incidence of pre-eclampsia = 4.5%.

Table 5. Prognostic properties of the IADPSG diagnostic criteria for gestational diabetes mellitus (GDM) in predicting pre-eclampsia
Population / Setting: pregnant women from the general population submitted to universal screening for GDM at 24-28 weeks
Test : 75g-OGTT applying the IADPSG cut-offs
Clinical outcome: development of pre-eclampsia during pregnancy

Test outcome	**Studies**	**Quality criteria**					**Quality of evidence**	**Prognostic properties (95%CI)** [1]	**Result per 1000 tested (95%CI)**[2]
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
True positives	3 cohort studies (35052 pregnancies)	None	Serious inconsistency[3]	Not Serious	Not Serious	None	⊕⊕⊕○ Moderate	RR = 1.71 (1.37 - 2.14) Sensitivity: 27.4% (26% – 28.9%) Specificity: 83.4% (81.4% – 85.4%)	12 (11 – 13)
False negatives	3 cohort studies (35052 pregnancies)	None	Serious inconsistency[3]	Not Serious	Not Serious	None	⊕⊕⊕○ Moderate		33 (32 – 34)
True negatives	3 cohort studies (35052 pregnancies)	None	Serious inconsistency[3]	Not Serious	Not Serious	None	⊕⊕⊕○ Moderate		796 (777 – 816)
False positives	3 cohort studies (35052 pregnancies)	None	Serious inconsistency[3]	Not Serious	Not Serious	None	⊕⊕⊕○ Moderate		159 (139 - 178)
Complications	Not reported	-	-	-	-	-	-	-	-
Costs	Not reported	-	-	-	-	-	-	-	-

[1] Data abstracted from Wendland[6]. For sensitivity and specificity, data were reanalyzed using a meta-analytical approach, computed with Meta-Disc version 1.4, using random-
effects model and over-dispersion correction.
[2] Assuming overall incidence of pre-eclampsia =4.5 %. Results based on sensitivity and specificity of the diagnostic test.
[3] Important heterogeneity was seen across studies. Better results were found for the HAPO study, where the IADPSG criteria were generated

Table 6. Prognostic properties of 1999 WHO diagnostic criteria for gestational diabetes mellitus (GDM) in predicting caesarean section
Population / Setting: pregnant women from the general population submitted to universal screening for GDM at 24-28 weeks
Test : 75g-OGTT applying the 1999 WHO cut-offs
Clinical outcome: caesarean section

Test outcome	**Studies**	**Quality criteria**					**Quality of evidence**	**Prognostic properties (95%CI)** [1]	**Result per 1000 tested (95%CI)**[2]
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
True positives	4 cohort studies (30045 pregnancies)	Serious[3]	Not Serious	Not Serious	Not Serious	None	⊕⊕⊕◯ Moderate	RR = 1.37 (1.24 - 1.51)	26 (18 – 33)
False negatives	4 cohort studies (30045 pregnancies)	Serious[3]	Not Serious	Not Serious	Not Serious	None	⊕⊕⊕◯ Moderate	Sensitivity: 12.8% (8.9% – 16.7%)	174 (167 – 182)
True negatives	4 cohort studies (30045 pregnancies)	Serious[3]	Not Serious	Not Serious	Not Serious	None	⊕⊕⊕◯ Moderate	Specificity: 89.4% (84.6% – 94.2%)	715 (677 – 754)
False positives	4 cohort studies (30045 pregnancies)	Serious[3]	Not Serious	Not Serious	Not Serious	None	⊕⊕⊕◯ Moderate		85 (46 – 123)
Complications	Not reported	-	-	-	-	-	-	-	-
Costs	Not reported	-	-	-	-	-	-	-	-

[1] Data abstracted from Wendland[6]. For sensitivity and specificity, data were reanalyzed using a meta-analytical approach, computed with Meta-Disc version 1.4, using random-
effects model and over-dispersion correction.
[2] Assuming overall incidence of caesarean section =20 %. Results based on sensitivity and specificity of the diagnostic test.
[3] Most of studies without blinding for medical staff

Table 7. Prognostic properties of the IADPSG diagnostic criteria for gestational diabetes mellitus (GDM) in predicting caesarean section
Population / Setting: pregnant women from the general population submitted to universal screening for GDM at 24-28 weeks
Test : 75g-OGTT applying the IADPSG cut-offs
Clinical outcome: caesaraean section

Test outcome	**Studies**	**Quality criteria**					**Quality of evidence**	**Prognostic properties (95%CI)** [1]	**Result per 1000 tested (95%CI)**[2]
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other			
True positives	3 cohort studies (33788 pregnancies)	Serious[3]	Serious inconsistency[4]	Not Serious	Not Serious	None	⊕⊕◯◯ Low	RR = 1.23 (1.01 - 1.51) Sensitivity: 21.4% (19.2% – 23.5%) Specificity: 83.8% (81.3% – 86.3%)	43 (38 – 47)
False negatives	3 cohort studies (33788 pregnancies)	Serious[3]	Serious inconsistency[4]	Not Serious	Not Serious	None	⊕⊕◯◯ Low		157 (153 – 162)
True negatives	3 cohort studies (33788 pregnancies)	Serious[3]	Serious inconsistency[4]	Not Serious	Not Serious	None	⊕⊕◯◯ Low		670 (650 – 690)
False positives	3 cohort studies (33788 pregnancies)	Serious[3]	Serious inconsistency[4]	Not Serious	Not Serious	None	⊕⊕◯◯ Low		130 (110 – 150)
Complications	Not reported	-	-	-	-	-	-	-	-
Costs	Not reported	-	-	-	-	-	-	-	-

[1] Data abstracted from Wendland[6]. For sensitivity and specificity, data were reanalyzed using a meta-analytical approach, computed with Meta-Disc version 1.4, using random-effects model and over-dispersion correction.
[2] Assuming overall incidence of caesarean section =20 %. Results based on sensitivity and specificity of the diagnostic test.
[3] Most of studies without blinding for medical staff
[4] Important heterogeneity was seen across studies. Better results were found for the HAPO study, where the IADPSG criteria were generated

Table 8. GRADE Evaluation of specific treatment for gestational diabetes based on adverse perinatal outcomes
Specific treatment for GDM compared to usual care for preventing adverse perinatal outcomes in women with GDM
Population: women with GDM
Intervention: any kind of specific GDM treatment
Comparison: usual antenatal care
Outcome: adverse perinatal outcomes

Quality assessment						Summary of findings				
Design/ no of studies (patients; events)	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**RR (95% CI)**	**NNT (95% CI) [1]**	**ARR (95% CI) [1]**	**Quality**	**Importance**
Macrosomia										
CCT 6 (3315 ; 480)	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Large effect size [2]	0.47 (0.34 – 0.65)	11.4 (9.1 – 17.3)	88 fewer per 1,000 (58 -110)	High + + + +	Critical
Large for gestational age birth										
CCT 4 (2245; 333)	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	0.57 (0.47 – 0.71)	12.2 (9.9 – 18,1)	82 fewer per 1,000 (55 -101)	High + + + +	Important
Shoulder dystocia										
CCT 2 (1961; 58)	No serious limitations	No serious inconsistency	No serious indirectness	Very serious[3]	None	0.41 (0.22 – 0.76)	48.8 (36,9 – 120)	21 fewer per 1,000 (8 - 27)	Low + + ○ ○	Critical

Table 8 . Cont'd.

Perinatal mortality										
CCT 7 (3396; 46)	Serious[4]	No serious inconsistency	Serious[5]	Very serious[3]	None	0.62 (0.31 – 1.24)	Not significant	Not significant	Very Low + ○ ○ ○	Critical
Neonatal ICU admission										
CCT 2 (1058; 98)	No serious limitations	No serious inconsistency	No serious indirectness	Very serious[3]	None	0.75 (0.52 – 1.08)	Not significant	Not significant	Low + + ○ ○	Critical
Congenital abnormalities										
CCT 3 (1068; 94)	Serious[4]	No serious inconsistency	Serious[6]	Very serious[3]	None	0.81 (0.55 – 1.18)	Not significant	Not significant	Very Low + ○ ○ ○	Critical
Birth trauma										
CCT 2 (1961; 12)	No serious limitations	No serious inconsistency	No serious indirectness	Very serious[3]	None	0.39 (0.11 – 1.35)	Not significant	Not significant	Low + + ○ ○	Critical
Hyperbilirubinaemia										
CCT 4 (2323; 220)	No serious limitations	No serious limitations	Serious[7]	Serious[8]	None	0.81 (0.63 – 1.04)	Not significant	Not significant	Low + + ○ ○	Important

Table 8 . Cont'd.

Quality assessment						Summary of findings				
Design/ no of studies (patients; events)	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**RR (95% CI)**	**NNT (95% CI) [1]**	**ARR (95% CI) [1]**	**Quality**	**Importance**
Respiratory distress syndrome										
CCT 2 (1962; 68)	No serious limitations	Serious[9]	No serious indirectness	Very serious[3]	None	1.05 (0.48 – 2.28)	Not significant	Not significant	Very Low + ○ ○ ○	Critical
Small for gestational age births										
CCT 3 (2088; 145)	No serious limitations	No serious inconsistency	No serious indirectness	Serious[8]	None	1.05 (0.77 – 1.44)	Not significant	Not significant	Moderate + + + ○	Important
Neonatal hypoglycemia										
CCT 4 (2193; 222)	No serious limitations	Serious[10]	Serious[7]	Serious[8]	None	1.16 (0.90 – 1.49)	Not significant	Not significant	Very Low + ○ ○ ○	Important

Table 8 . Cont'd.

Quality assessment						Summary of findings				
Design/ no of studies (patients; events)	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**RR (95% CI)**	**NNT (95% CI) [1]**	**ARR (95% CI) [1]**	**Quality**	**Importance**
Pre-term birth										
CCT 3 (1669; 156)	No serious limitations	No serious inconsistency	Serious[7]	Serious[8]	None	0.90 (0.67 – 1.21)	Not significant	Not significant	Low + + o ○	Important

RR: relative risk; CI: confidence interval; NNT: number needed to treat; ARR: absolute risk reduction; CCT: Clinical controlled trials;

[1] Baseline risk according to the findings of the clinical controlled trials
[2] Presence of relative risk reduction of more than 50%, with adequate precision, quality upgraded for high-effect size
[3] Optimum information size not reached in trial sequential analysis; very small number of events
[4] Most events from studies with inadequate allocation method (based on alternation)
[5] Most events from old studies, when the mortality rate was higher
[6] Lack of standardization for congenital abnormalities
[7] Diverse outcome definition
[8] Optimum information size not reached in trial sequential analysis
[9] Heterogeneity between studies
[10] Inconsistency dependent on the choice of the of the variance estimator in the random-effects model

Table 9 . GRADE Evaluation of specific treatment for gestational diabetes based on adverse maternal outcomes

Specific treatment for GDM compared to usual care for preventing adverse maternal outcomes in women with GDM
Population: women with GDM
Intervention: any kind of specific GDM treatment
Comparison: usual antenatal care
Outcome: adverse maternal outcomes

Quality assessment						Summary of findings				
Design/ no of studies (patients; events)	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**RR (95% CI)**	**NNT (95% CI) [1]**	**ARR (95% CI) [1]**	**Quality**	**Importance**
Pre-eclampsia										
CCT 2 (1931 ; 188)	No serious limitations	No serious inconsistency	No serious indirectness	Serious[2]	None	0.61 (0.46 – 0.81)	21 (15.1 – 43)	48 fewer per 1,000 (23 - 66)	Moderate + + + ○	Critical
Hypertensive disorders in pregnancy										
CCT 4 (2245; 333)	No serious limitations	No serious inconsistency	Serious[3]	No serious imprecision	None	0.64 (0.51 – 0.81)	18.1 (13.4 – 34.2)	55 fewer per 1,000 (29 - 75)	Moderate + + + ○	Important
Caesarean section										
CCT 2 (1961; 58)	Serious[4]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0.90 (0.78 – 1.05)	Not significant	Not significant	Moderate + + + ○	Important

Table 9 . Cont'd.

Quality assessment						Summary of findings				
Design/ no of studies (patients; events)	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**RR (95% CI)**	**NNT (95% CI) [1]**	**ARR (95% CI) [1]**	**Quality**	**Importance**
Diabetes mellitus later in life										
CCT 1 (711; 217)	Serious[5]	No serious inconsistency	No serious indirectness	Serious[2]	None	0.98 (0.79 – 1.21)	Not significant	Not significant	Low + + ○ ○	Critical

RR: relative risk; CI: confidence interval; NNT: number needed to treat; ARR: absolute risk reduction; CCT: Clinical controlled trials;

[1] Baseline risk according to the findings of the clinical controlled trials
[2] Optimum information size not reached in trial sequential analysis
[3] Diverse outcome definition
[4] Unblinded trials or selective blinding for control group
[5] Study with inadequate allocation method (based on alternation)

Table 10. GRADE Evaluation of GDM screening based on the universal application of the WHO criteria
Universal screening for GDM according to WHO criteria compared to no screening in pregnancy
Population: pregnant women from the general population
Intervention: OGGT, with specific treatment for women diagnosed with GDM according to WHO criteria
Comparison: no screening
Outcome: adverse perinatal and maternal outcomes

Quality assessment						Summary of findings			
Study design	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**NNS (95% CI)**	**ARR (95% CI)**	**Quality**	**Importance**
Large for gestational age birth									
Simulation model based on observational and experimental studies	No serious limitations	No serious inconsistency	Very Serious[1]	No serious imprecision	None	189 (134 – 268)	5 fewer per 1,000 (4 - 7)	Very Low + ○ ○ ○	Important
Pre-eclampsia									
Simulation model based on observational and experimental studies	No serious limitations	No serious inconsistency	Very Serious[1]	Serious[2]	None	376 (232 – 1010)	3 fewer per 1,000 (1 -5)	Very Low + ○ ○ ○	Critical

RR: relative risk; CI: confidence interval; NNS: number needed to screen; ARR: absolute risk reduction

[1] Evidence generated from simulation model once no direct evidence was available; absolute effect very dependent from GDM prevalence in model's sensitivity analysis.
[2] Optimum information size not reached in trial sequential analysis for the assessment of the effect of GDM treatment on pre-eclampsia.

Table 11. GRADE Evaluation of GDM screening based on the universal application of the IADPSG criteria

Universal screening for GDM according to IADPSG criteria compared to no screening in pregnancy
Population: pregnant women from the general population
Intervention: OGGT, with specific treatment for women diagnosed with GDM according to IADPSG criteria
Comparison: no screening
Outcome: adverse perinatal and maternal outcomes

Quality assessment						**Summary of findings**			
Study design	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**NNS (95% CI)**	**ARR (95% CI)**	**Quality**	**Importance**
Large for gestational age birth									
Simulation model based on observational and experimental studies	No serious limitations	Serious[1]	Very serious[2]	No serious imprecision	None	117 (77 – 185)	9 fewer per 1,000 (5 -13)	Very Low + ○ ○ ○	Important
Pre-eclampsia									
Simulation model based on observational and experimental studies	No serious limitations	Serious[1]	Very serious[2]	Serious[3]	None	257 (154 – 697)	4 fewer per 1,000 (2 -7)	Very Low + ○ ○ ○	Critical

RR: relative risk; CI: credibility interval; NNS: number needed to screen; ARR: absolute risk reduction

[1] Important heterogeneity among observational studies; better results in the HAPO study population, which generated the IADPSG criteria.
[2] Evidence generated from simulation model once no direct evidence was available; absolute effect very dependent from GDM prevalence in model's sensitivity analysis.
[3] Optimum information size not reached in trial sequential analysis for the assessment of the effect of GDM treatment on pre-eclampsia.

Table 12. GRADE Evaluation of GDM screening comparing the universal application of the IADPSG and the WHO criteria

Universal creening for GDM according to IADPSG criteria compared to screening according to WHO criteria
Population: pregnant women from general population
Intervention: OGGT, with specific treatment for women diagnosed with GDM according to IADPSG criteria
Comparison: OGGT, with specific treatment for women diagnosed with GDM according to WHO criteria
Outcome: adverse perinatal and maternal outcomes

Quality assessment						**Summary of findings**			
Study design	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**NNS (95% CI)**	**ARR (95% CI)**	**Quality**	**Importance**
Large for gestational age birth									
Simulation model based on observational and experimental studies	No serious limitations	No serious inconsistency	Very Serious[1]	No serious imprecision	None	189 (134 – 268)	5 fewer per 1,000 (4 - 7)	Very Low + ○ ○ ○	Important
Pre-eclampsia									
Simulation model based on observational and experimental studies	No serious limitations	No serious inconsistency	Very Serious[1]	Serious[2]	None	376 (232 – 1010)	3 fewer per 1,000 (1 -5)	Very Low + ○ ○ ○	Critical

RR: relative risk; CI: credibility interval; NNS: number needed to screen; ARR: absolute risk reduction

[1] Evidence generated from simulation model since no direct evidence was available; absolute effect very dependent on GDM prevalence in model's sensitivity analysis.
[2] Optimum information size not reached in trial sequential analysis for the assessment of the effect of GDM treatment on preeclampsia.