Sensitivity, specificity, and diagnostic accuracy of WHO 2013 criteria for diagnosis of gestational diabetes mellitus in low risk early pregnancies: international, prospective, multicentre cohort study

Huhn, Evelyn A ; Göbl, Christian S ; Fischer, Thorsten ; Todesco Bernasconi, Monya ; Kreft, Martina ; Kunze, Mirjam ; Vogt, Deborah R ; Dölzlmüller, Eva ; Jaksch-Bogensperger, Heidi ; Heldstab, Sandra ; Eppel, Wolfgang ; Husslein, Peter ; Ochsenbein Kölble, Nicole ; Richter, Anne ; Bäz, Elke ; Winzeler, Bettina ; Hoesli, Irene

Abstract: Objective: To evaluate the predictability of gestational diabetes mellitus wth a 75 g oral glucose tolerance test (OGTT) in early pregnancy, based on the 2013 criteria of the World Health Organization, and to test newly proposed cut-off values. Design: International, prospective, multicentre cohort study.SettingSix university or cantonal departments in Austria, Germany, and Switzerland, from 1 May 2016 to 31 January 2019.ParticipantsLow risk cohort of 829 participants aged 18-45 years with singleton pregnancies attending first trimester screening and consenting to have an early 75 g OGTT at 12-15 weeks of gestation. Participants and healthcare providers were blinded to the results. Main outcome measures: Fasting, one hour, and two hour plasma glucose concentrations after an early 75 g OGTT (12-15 weeks of gestation) and a late 75 g OGTT (24-28 weeks of gestation). Results: Of 636 participants, 74 (12%) developed gestational diabetes mellitus, according to World Health Organization 2013 criteria, at 24-28 weeks of gestation. Applying WHO 2013 criteria to the early OGTT with at least one abnormal value gave a low sensitivity of 0.35 (95% confidence interval 0.24 to 0.47), high specificity of 0.96 (0.95 to 0.98), positive predictive value of 0.57 (0.41 to 0.71), negative predictive value of 0.92 (0.89 to 0.94), positive likelihood ratio of 10.46 (6.21 to 17.63), negative likelihood ratio of 0.65 (0.55 to 0.78), and diagnostic odds ratio of 15.98 (8.38 to 30.47). Lowering the postload glucose values (75 g OGTT cut-off values of 5.1, 8.9, and 7.8 mmol/L) improved the detection rate (53%, 95% confidence interval 41% to 64%) and negative predictive value (0.94, 0.91 to 0.95), but decreased the specificity (0.91, 0.88 to 0.93) and positive predictive value (0.42, 0.32 to 0.53) at a false positive rate of 9% (positive likelihood ratio 5.59, 4.0 to 7.81; negative likelihood ratio 0.64, 0.52 to 0.77; and diagnostic odds ratio 10.07, 6.26 to 18.31). Conclusions: The results of this prospective low risk cohort study indicated that the 75 g OGTT as a screening tool in early pregnancy is not sensitive enough when applying WHO 2013 criteria. Postload glucose values were higher in early pregnancy complicated by diabetes in pregnancy. Lowering the postload cut-off values identified a high risk group for later development of gestational diabetes mellitus or those who might benefit from earlier treatment. Results from randomised controlled trials showing a beneficial effect of early intervention are unclear. Trial registrationClinicalTrials.govNCT02035059.

DOI: https://doi.org/10.1136/bmjmed-2022-000330

Originally published at:
Huhn, Evelyn A; Göbl, Christian S; Fischer, Thorsten; Todesco Bernasconi, Monya; Kreft, Martina; Kunze, Mirjam; Vogt, Deborah R; Dölzlmüller, Eva; Jaksch-Bogensperger, Heidi; Heldstab, Sandra; Eppel, Wolfgang; Husslein, Peter; Ochsenbein Kölble, Nicole; Richter, Anne; Bäz, Elke; Winzeler, Bettina; Hoesli, Irene (2023). Sensitivity, specificity, and diagnostic accuracy of WHO 2013 criteria for diagnosis of gestational diabetes mellitus in low risk early pregnancies: international, prospective, multicentre cohort study. BMJ medicine, 2(1):e000330.
DOI: https://doi.org/10.1136/bmjmed-2022-000330

bmjmedicine

Check for updates

Sensitivity, specificity, and diagnostic accuracy of WHO 2013 criteria for diagnosis of gestational diabetes mellitus in low risk early pregnancies: international, prospective, multicentre cohort study

Evelyn A Huhn [1,2] Christian S Göbl,[3] Thorsten Fischer,[4] Monya Todesco Bernasconi,[5] Martina Kreft,[6] Mirjam Kunze,[7] Deborah R Vogt [8,9] Eva Dölzlmüller,[4] Heidi Jaksch-Bogensperger,[4] Sandra Heldstab,[5] Wolfgang Eppel,[3] Peter Husslein,[3] Nicole Ochsenbein Kölble,[6] Anne Richter,[6] Elke Bäz,[7] Bettina Winzeler,[10] Irene Hoesli[11]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjmed-2022-000330).

For numbered affiliations see end of article.
Correspondence to: Dr Evelyn A Huhn, Department of Feto-Maternal Medicine and Obstetrics, University Hospital Basel, Basel, Basel-Stadt, Switzerland; evelyn.huhn@googlemail.com

Cite this as: *BMJMED* 2023;2:e000330. doi:10.1136/bmjmed-2022-000330

Received: 31 July 2022
Accepted: 17 July 2023

ABSTRACT

OBJECTIVE To evaluate the predictability of gestational diabetes mellitus wth a 75 g oral glucose tolerance test (OGTT) in early pregnancy, based on the 2013 criteria of the World Health Organization, and to test newly proposed cut-off values.

DESIGN International, prospective, multicentre cohort study.

SETTING Six university or cantonal departments in Austria, Germany, and Switzerland, from 1 May 2016 to 31 January 2019.

PARTICIPANTS Low risk cohort of 829 participants aged 18-45 years with singleton pregnancies attending first trimester screening and consenting to have an early 75 g OGTT at 12-15 weeks of gestation. Participants and healthcare providers were blinded to the results.

MAIN OUTCOME MEASURES Fasting, one hour, and two hour plasma glucose concentrations after an early 75 g OGTT (12-15 weeks of gestation) and a late 75 g OGTT (24-28 weeks of gestation).

RESULTS Of 636 participants, 74 (12%) developed gestational diabetes mellitus, according to World Health Organization 2013 criteria, at 24-28 weeks of gestation. Applying WHO 2013 criteria to the early OGTT with at least one abnormal value gave a low sensitivity of 0.35 (95% confidence interval 0.24 to 0.47), high specificity of 0.96 (0.95 to 0.98), positive predictive value of 0.57 (0.41 to 0.71), negative predictive value of 0.92 (0.89 to 0.94), positive likelihood ratio of 10.46 (6.21 to 17.63), negative likelihood ratio of 0.65 (0.55 to 0.78), and diagnostic odds ratio of 15.98 (8.38 to 30.47). Lowering the postload glucose values (75 g OGTT cut-off values of 5.1, 8.9, and 7.8 mmol/L) improved the detection rate (53%, 95% confidence interval 41% to 64%) and negative predictive value (0.94, 0.91 to 0.95), but decreased the specificity (0.91, 0.88 to 0.93) and positive predictive value (0.42, 0.32 to 0.53) at a false positive rate of 9% (positive likelihood ratio 5.59, 4.0 to 7.81; negative likelihood ratio 0.64, 0.52 to 0.77; and diagnostic odds ratio 10.07, 6.26 to 18.31).

CONCLUSIONS The results of this prospective low risk cohort study indicated that the 75 g OGTT as a screening tool in early pregnancy is not sensitive enough when applying WHO 2013 criteria. Postload glucose values were higher in early pregnancy complicated by diabetes in pregnancy. Lowering the postload cut-off values identified a high risk group for later development of gestational diabetes mellitus or those who might benefit from earlier treatment. Results from randomised controlled trials showing a beneficial effect of early intervention are unclear.

TRIAL REGISTRATION ClinicalTrials.gov NCT02035059.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The 2013 criteria of the World Health Organization are usually applied at 24-28 weeks of gestation as the reference standard for a diagnosis of gestational diabetes mellitus
⇒ Earlier detection and intervention could potentially improve short and long term neonatal and maternal outcomes
⇒ The 2013 WHO cut-off values have not been assessed prospectively in pregnancy before 24 weeks of gestation, especially in a low risk setting

WHAT THIS STUDY ADDS

⇒ This prospective multicentre study investigated the WHO 2013 criteria in a low risk setting for early screening of gestational diabetes mellitus
⇒ Participants, staff, and initiators were blinded to the early results
⇒ An overview of the diagnostic accuracies and odds ratios of the standard WHO 2013 criteria and newly proposed cut-off glucose values is presented

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ By adaptating the WHO 2013 criteria in a low risk population, half of pregnant individuals with later hyperglycaemia could receive a diagnosis of gestational diabetes mellitus in early pregnancy with an acceptable false positive rate of 9% to detect a high risk group for early intervention
⇒ Results of the 75 g oral glucose tolerance test in early pregnancy could be used to implement early glucose measurements, or life style, dietary, or drug treatment interventions

Introduction

The global prevalence of gestational diabetes mellitus complicating pregnancy is increasing and is currently estimated to be 2-30% worldwide because of older maternal age, higher body mass index, inactive life styles, and changes in screening thresholds.[1]

Diagnostic criteria are based on the risk of adverse neonatal outcomes (odds ratio of 1.75 of neonatal birth weight >90th centile, levels of C peptide in cord blood >90th centile, and neonatal percentage body fat >90th centile).[2] The risk of adverse neonatal outcomes increases depending on the extent of maternal hyperglycaemia, defined by the results of a universally applied 75 g oral glucose tolerance test (OGTT) at 24-28 weeks of gestation. Diagnostic cut-off values (derived from the Hyperglycaemia in Pregnancy Outcome (HAPO) study in 2008[3 4]) are 5.1-6.9 mmol/L (92-125 mg/dL) for fasting concentrations of glucose, and ≥10.0 mmol/L (≥180 mg/dL) for one hour and ≥8.5 mmol/L (≥153 mg/dL) for two hour postload plasma glucose concentrations, where one abnormal value in three is needed for a diagnosis of gestational diabetes mellitus.

The World Health Organization adopted the criteria in 2013 and recommended these cut-off values as a reference standard for the diagnosis of gestational diabetes mellitus at any time in pregnancy.[5] Earlier detection of gestational diabetes mellitus could potentially improve short term neonatal outcomes (eg, infants born large for gestational age, defined as birth weight >90th centile)[6] or maternal complications (eg, caesarean section,[7] shoulder dystocia,[8] and haemorrhage[9]). The International Federation of Gynaecology and Obstetrics (FIGO) recommends universal screening for diabetes and gestational diabetes mellitus.[10] The WHO 2013 criteria have not been assessed for use in pregnancy before 24 weeks of gestation, especially in a low risk population that might benefit from early screening for gestational diabetes mellitus by lowering the rates of infants born large for gestational age.[11] No equivalent of the WHO 2013 criteria for universal screening in early pregnancy exists so far. Recent evidence indicates that a fasting glucose concentration of ≥5.1 mmol/L seems to be poorly predictive of later development of gestational diabetes,[12 13] and that postload glucose levels seem to be lower in early pregnancy than in later gestational ages.[14]

Cut-off values for an association between abnormally high glucose values and gestational diabetes mellitus later in pregnancy, which lie below the diagnostic criteria for pre-existing diabetes mellitus in early pregnancy, have not yet been established. Currently, insufficient data exist to recommend alternative fasting, one hour, or two hour glucose values to diagnose gestational diabetes mellitus in early pregnancy. The aim of this study was to evaluate the WHO 2013 criteria in early pregnancy and to assess the diagnostic accuracy and odds ratio for later development of gestational diabetes mellitus.

Methods

The protocol of the multicentre cohort was previously published.[15] Briefly, the objective of the study was to examine the predictability of gestational diabetes mellitus in early pregnancy by defining a new screening approach for the development of gestational diabetes mellitus based on the early OGTT with or without new biomarkers, such as adiponectin, lipocalin, and glycosylated fibronectin, measured in early pregnancy. We present the first part of the objective, the external validation of the diagnostic performance of the early OGTT to detect gestational diabetes based on the WHO 2013 criteria and other recently proposed cut-offs.

Participants

In this multicentre prospective study on diagnostic accuracy, we included participants aged 18-45 years presenting in early pregnancy to six university or cantonal departments in Austria, Germany, and Switzerland. All participants with singleton pregnancies who wished to undergo first trimester screening received an information leaflet about the study and those interested were recruited. The first trimester scan confirmed or corrected gestational age. Participants were excluded if they had pre-existing diabetes, chronic infectious diseases, such as hepatitis or HIV infection, chronic liver, kidney, or heart disease, if they had previous bariatric surgery, or were receiving metformin or acetylsalicylic acid because of a history of hypertensive disease in a previous pregnancy. Further exclusion criteria were fetal genetic, chromosomal, or morphological abnormalities which required further clarification.

Sample collection

A sampling protocol was distributed to all participating centres. The main focus of the protocol was on the type of tubes for the OGTT, and the aliquots, times, and details of centrifugation for aliquoting the serum and plasma samples.

Test methods: oral glucose tolerance test

Participants were universally screened with the 75 g OGTT at 12-15 weeks of gestation. Participants were advised to eat and drink normally for the two days before the test but not to eat, drink (only a few sips of water), or smoke on the morning of the test. No physical activity was allowed during the test. The first measurement of serum glucose levels was performed after an overnight fasting period of at least 10 hours, between 8 am and 12 pm. Then, after intake of the 75 g glucose load in 250-300 mL of water, blood samples were taken one hour and two hours postload for determination of glucose levels. To minimise the effects of glycolysis in vivo, all centres were asked to send the samples to the laboratory

directly. Only natriumfluorid tubes with citrate buffer were used for the study.

Plasma levels of glucose were measured by an automated colorimetric enzymatic method with the hexokinase-glucose-6-phosphate-dehydrogenase method (GLUC3 test by Roche or the Dimension Vista Hexokinase test) and analysed by the Hitachi-Roche cobas modular analyser (Roche Diagnostics, Rotkreuz, Switzerland) or Siemens Dimension Vista analyser (Siemens Healthcare, Aarau, Switzerland). Both tests have a imprecision value of <1.25% and bias value of <1.23%. The tests are ISO17025 accredited and include the need for external quality control (inter-laboratory comparisons). All participting laboratories were ISO 17025:2017 or ISO15189 accredited.

Participants and healthcare providers were blinded to the results of the early 75 g OGTT. Values were unblinded by hospital laboratories if the fasting plasma glucose concentration was ≥7.0 mmol/L (≥126 mg/dL) or the random or two hour value was ≥11.1 mmol/L (≥200 mg/dL), defined as pre-existing diabetes by the American Diabetes Association.[16] The diagnosis of pre-existing diabetes mellitus had to be confirmed by raised levels of glycated haemoglobin A_{1c} of ≥6.5%. Participants with plasma concentrations of glucose <2.5 mmol/L (≤45 mg/dL) were unblinded for further clarification and underwent a second reference standard 75 g OGTT at 24-28 weeks of gestation.

The WHO 2013 criteria (fasting plasma glucose concentration ≥5.1 mmol/L (≥92 mg/dL), and ≥10.0 mmol/L (≥180 mg/dL) for one hour and >8.5 mmol/L (≥153 mg/dL) for two hour postload plasma glucose concentrations) were used to diagnose gestational diabetes mellitus if at least one value was abnormal.[4] Participants with a diagnosis of gestational diabetes mellitus were treated according to the recommendations of the American Diabetes Association[17] and, if targets could not be reached in 1-2 weeks after changes in lifestyle, insulin was started to control hyperglycaemia.

Prenatal data recording

Personal and family history, height, weight, gravidity, parity, blood pressure, urine dipstick, and medical complications were recorded for each study participant. Also, prenatal care visits, inpatient stays, delivery details, and postpartum visits were recorded in a clinical data management application (secuTrial) maintained by the Clinical Trial Unit, Basel.

Study outcome

We determined the predictability of gestational diabetes mellitus with a 75 g OGTT in early pregnancy based on the WHO 2013 criteria. We tested several proposed cut-off values according to previously published data for fasting (≥5.1 mmol/L (≥92 mg/dL), ≥5.3 mmol/L (≥95 mg/dL), ≥5.7 mmol/L (≥103 mg/dL), and ≥6.1 mmol/L (≥110 mg/dL)) and for postprandial glucose values at one hour (≥8.9 mmol/L (≥160 mg/dL) and ≥10.0 mmol/L (≥180 mg/dL)) and at two hours (≥7.1 mmol/L (≥128 mg/dL), ≥7.5 mmol/L (≥135 mg/dL), ≥7.8 mmol/L (≥140 mg/dL), and ≥8.5 mmol/L (≥153 mg/dL)).[14 18 19] We chose a sample size of 748 participants (assuming a prevalence of 10.9% (n=65) for gestational diabetes mellitus) with a dropout rate of 15% to predict the development of gestational diabetes mellitus with an early 75 g OGTT with or without additional biomarkers. The published study protocol provides full details.[15]

Sample size considerations

We calculated sample size based on the area under the curve of a newly proposed screening method combining the 75 g OGTT with new biomarkers, such as glycosylated fibronectin. The power calculation was performed with a proposed true area under the curve of 0.9 with a lower boundary of 0.8 (95% confidence interval >0.8) which gave a power of 90% and an α level of 5%. Offsetting a dropout rate of 15%, the sample size was 748.[15] The study was not powered to determine the diagnostic accuracy of specific cut-off values.

Statistical analysis

Summary statistics of patient characteristics are reported as mean (standard deviation) or median (interquartile range) for continuous variables, and as frequencies and percentages for categorical variables. The analysis set included only participants with complete early and late OGTTs (n=636) and hence there were no missing values in the six variables relevant for this analysis. For each diagnostic test we reported sensitivity, specificity, overall diagnostic accuracy (percentage of correct diagnoses), and positive and negative predictive values (with 95% confidence intervals). Positive and negative predictive values were derived from the observed prevalence in the analysis set. Positive and negative likelihood ratios, and diagnostic odds ratios, were estimated as prevalence independent measures. We also reported summary statistics for early and late OGTTs dependent on the development of gestational diabetes mellitus. Correlations between early and late OGTTs were assessed by Spearman's rank correlation coefficient.

We made no adjustment for multiplicity, unless otherwise indicated in the manuscript. Heterogeneity between centres was evaluated with a meta-analysis for the WHO 2013 criteria, and forest plots for the diagnostic measures were derived. Models were fitted with centre

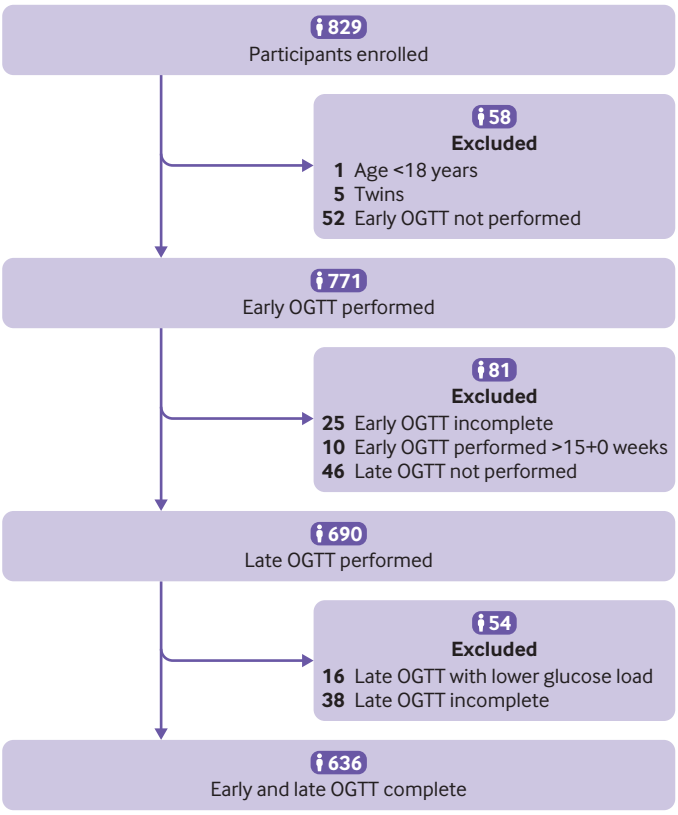

Figure 1 | Flowchart of study population selection. OGTT=oral glucose tolerance test

as a random effect (random intercept); logistic regression was used for proportions (sensitivity, specificity, accuracy, and positive and negative predictive values), and the Mantel-Haenszel method was used for positive and negative likelihood ratios. For the generalised linear mixed models, no weights for centres are provided with this approach. Statistical analyses were performed with R (version 4.0.3, 2020) and related packages.[20]

Patient and public involvement

Patients or the public were not involved in the design of the study, interpretation of the results, or writing of the manuscript. A lay summary of the results will be published on the funders' websites. The main findings of the cohort study will be distributed to our study participants in a research newsletter.

Results

Characteristics of participants

Among 829 eligible pregnant individuals recruited for the study, 636 were included in the analysis with a complete early and late OGTT data set (figure 1) between 1 May 2016 and 31 January 2019. Seventy four (12%) of the 636 participants developed gestational diabetes mellitus diagnosed by a late OGTT. The prevalence of gestational diabetes mellitus in the six university or cantonal centres varied depending on sample size (online supplemental table S4). Table 1 summarises the characteristics of the study cohort.

Individuals with gestational diabetes mellitus tended to have a higher median pre-gravid body mass index (25.41, interquartile range 22.04-30.5) than those with no gestational diabetes mellitus (22.68, 20.52-25.66), and a higher body mass index at the study visit (26.17, 23.1-30.97 *v* 23.61, 21.23-26.36). The two groups were comparable for maternal age, gravidity, parity, and gestational age at study visit.

Diagnostic performance of early oral glucose tolerance test

Table 2 summarises glucose concentrations from the early and late OGTTs. Forty six of 636 (7.3%) OGTT results were abnormal based on the WHO 2013 criteria in early pregnancy. Participants who had a diagnosis of gestational diabetes mellitus later, at 24-28 weeks of gestation, tended to have higher glucose levels in the early OGTT and markedly higher values in the late OGTT than those with no gestational diabetes mellitus. Fasting plasma glucose concentrations did not differ in the early OGTT (median 4.4, interquartile range 4.2-4.6 mmol/L) versus the late OGTT (4.4, 4.1-4.6 mmol/L) in the non-gestational diabetes mellitus group. Only 2.5% of participants (14/562) showed glucose concentrations ≥5.1 mmol/L (≥92 mg/dL) in early pregnancy in the non-gestational diabetes

Table 1 | Baseline characteristics of study cohort

	No gestational diabetes mellitus (n=562)	Gestational diabetes mellitus (n=74)	Summarised mean difference
Mean (SD) age (years)	32.1 (5.2)	32.8 (4.6)	0.15
Ethnic group (No (%))			0.419
White	479 (85)	53 (72)	0.315
South Asian	35 (6)	6 (8)	0.371
East Asian	16 (3)	6 (8)	—
Black	11 (2)	5 (7)	—
Mixed	5 (1)	0	—
Other	6 (1)	1 (1)	—
Unknown	10 (2)	3 (4)	—
Median (IQR) height (cm)	166.1 (6.6)	164.1 (6)	—
Median (IQR) weight before pregnancy (kg)	63.0 (57.0-71.0)	67.0 (58.0-81.9)	—
Median (IQR) weight at study visit (kg)	65.0 (58.6-73.0)	69.0 (60.0-84.3)	—
Median (IQR) pre-gravid body mass index	22.7 (20.5-25.7)	25.4 (22.0-30.5)	0.493
Median (IQR) body mass index at study visit	23.6 (21.2-26.4)	26.2 (23.1-31.0)	0.311
Mean (SD) systolic blood pressure (mm Hg)	116.2 (11.5)	119.5 (10.7)	0.317
Mean (SD) diastolic blood pressure (mm Hg)	70.1 (9.9)	72.8 (10.1)	0.215
Median (IQR) parity ≥1	239 (43)	31 (42)	0.013
Median (IQR) gravidity	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.0108
No (%) of deliveries with assisted reproduction (ie, in vitro fertilisation)	49 (9)	8 (11)	0.087
Median (IQR) gestational age (weeks) at study visit	13.4 (12.6-14.1)	13.6 (12.9-14.1)	0.154

IQR=interquartile range; SD=standard deviation.

mellitus group compared with 20.3% (15/74) in the gestational diabetes mellitus group.

Diagnostic values in the late OGTT in the gestational diabetes mellitus group were low (median fasting plasma glucose 5.1, interquartile range 4.7-5.3 mmol/L; one hour postload 10.0, 8.1-10.7 mmol/L; two hour postload 7.4, 6.0-8.3 mmol/L), in the range of milder degrees of gestational diabetes mellitus. Glucose levels from the early and late OGTTs largely overlapped between the non-gestational diabetes mellitus and gestational diabetes mellitus groups, and the overlap was more pronounced for fasting plasma glucose concentrations than for the one and two hour postload glucose values (figure 2).

Correlation of early versus late OGTT was moderate (figure 3; Spearman's rank correlation: r=0.51 for fasting plasma glucose concentions, r=0.55 for one hour postload, and r=0.55 for two hour postload glucose concentrations). Twenty six of 74 participants had a diagnosis of gestational diabetes mellitus (35.1%) by an early OGTT with the WHO 2013 criteria (n=15 by fasting value of 5.1 mmol/L and n=11 by postprandial levels of 10.0 (n=9) and 8.5 mmol/L (n=9)). Twenty participants without the later diagnosis of gestational diabetes mellitus had abnormal values in early pregnancy (n=14 with fasting values >5.1 mmolL/L). Online supplemental table S3 shows the cross tables and diagnostic statistics.

The WHO 2013 criteria (the standard for screening for gestational diabetes mellitus at 24-28 weeks of gestation) showed low sensitivity (0.35, 95% confidence interval 0.24 to 0.47) and high specificity (0.96, 0.95 to 0.98) in early pregnancy. These results

Table 2 | Summary of fasting and postload (one and two hour) plasma glucose concentrations measured by early (12-15 weeks of gestation) and late (24-28 weeks of gestation) oral glucose tolerance tests

	No gestational diabetes mellitus (n=562)	Gestational diabetes mellitus (n=74)
Early oral glucose tolerance test		
Glucose concentration (mmol/L, mg/dL)		
Fasting	4.4 (4.2-4.6), 79 (76-83)	4.7 (4.4-4.9), 85 (79-88)
1 hour	5.7 (4.7-7.2), 103 (85-130)	7.6 (6.1-9.2), 137 (108-166)
2 hour	4.8 (4.2-5.7), 86 (76-103)	6.1 (4.9-7.4), 108 (88-133)
Late oral glucose tolerance test		
Glucose concentration (mmol/L, mg/dL)		
Fasting	4.4 (4.1-4.6), 79 (74-83)	5.1 (4.7-5.3), 92 (85-96)
1 hour	6.8 (5.7-7.9), 123 (103-142)	10.0 (8.1-10.7), 180 (146-193)
2 hour	5.4 (4.7-6.2), 97 (85-112)	7.4 (6.0-8.3), 133 (108-150)

Values are median (interquartile range).

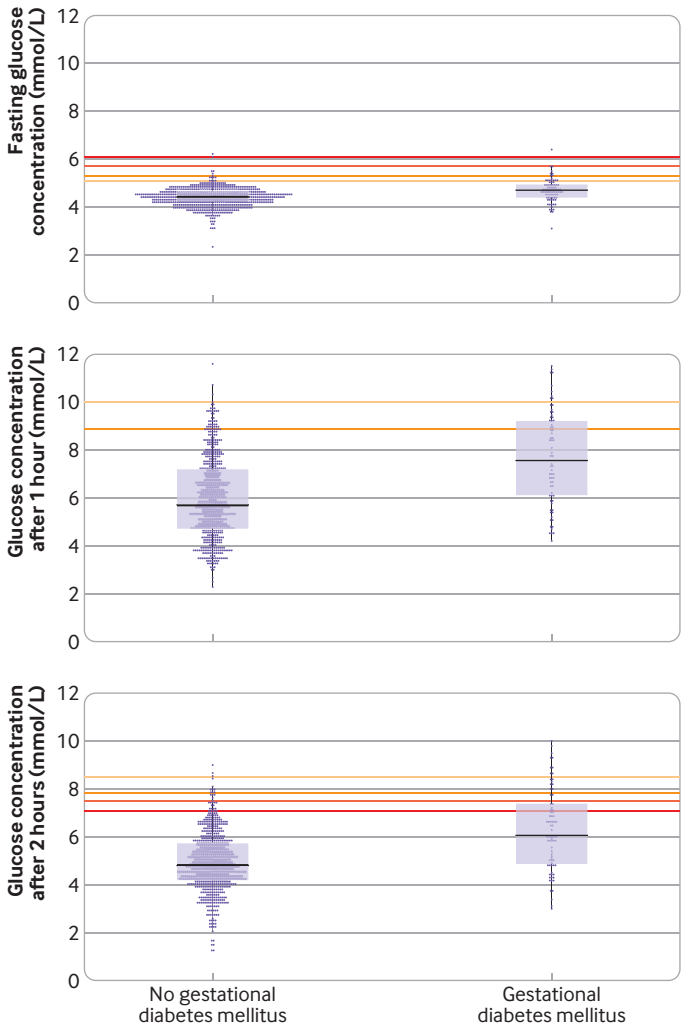

Figure 2 | Box plots overlaid on dot plots of fasting and postload (one and two hour) plasma glucose concentrations after early oral glucose tolerance test (12-15 weeks of gestation) for participants with and without gestational diabetes mellitus. Proposed cut-off values are indicated by horizontal lines: fasting glucose cut-off values=5.1, 5.3, 5.7, and 6.1 mmol/L; one hour glucose cut-off values=8.9 and 10.0 mmol/L; and two hour glucose cut-off values=7.1, 7.5, 7.8, and 8.5 mmol/L

gave a high overall accuracy of 0.89 (0.87 to 0.92), with a positive predictive value of 0.57 (0.41 to 0.71), negative predictive value of 0.92 (0.89 to 0.94), positive likelihood ratio of 9.97 (5.81 to 16.78), negative likelihood ratio of 0.67 (0.57 to 0.80), and diagnostic odds ratio of 14.68 (7.64 to 28.21).

Online supplemental figure S4 shows the receiver operator characteristic curves with corresponding area under the curves for glucose concentrations. Based on only fasting glucose values and increasing the cut-off to 5.3 mmol/L and 5.7 mmol/L resulted in higher positive predictive values. Because only one of the three participants with a fasting glucose concentration ≥6.1 mmol/L developed gestational diabetes mellitus later in pregnancy, however, increasing the cut-off for the fasting glucose value to 6.1 mmol/L gave a low positive predictive value of 0.33. Based on all three values and lowering only the postload levels (cut-off values of 5.1, 8.9, and 7.8 mmol/L) increased sensitivity (0.53, 95% confidence interval 0.41 to 0.64) and negative predictive value (0.94, 0.91 to 0.95) but decreased specificity (0.91, 0.88 to 0.93) and positive predictive value (0.42, 0.32 to 0.53), with a false positive rate of 9%. Online supplemental figure S5A-C shows the box plots of the OGTTs for the six university or cantonal centres. To deal with potential heterogenity between centres, we performed meta-analyses and produced forest plots for the diagnostic measures derived from the WHO 2013 criteria (online supplemental figure S6).

Missing values and incomplete oral glucose tolerance tests

Thirty eight participants had an incomplete late OGTT and therefore a final diagnosis could not be made. Online supplemental table S5 provides summary statistics of the available glucose measurements for these 38 participants. A sensitivity analysis (adding all participants with missing values or incomplete OGTTs to the full analysis set with complete late

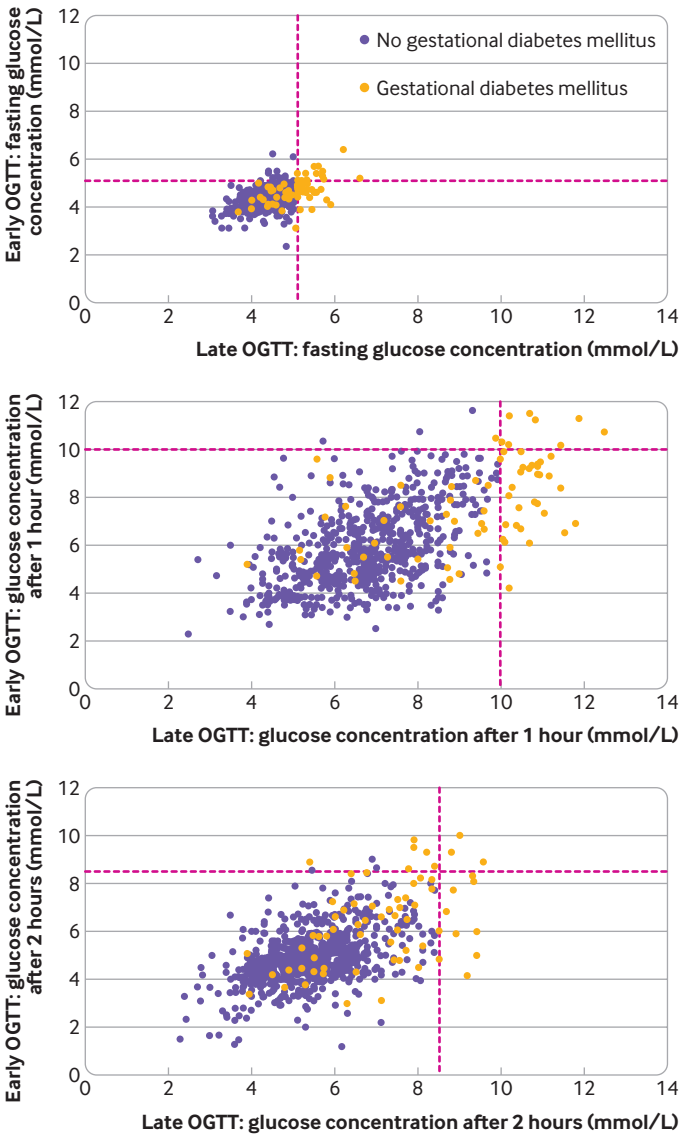

Figure 3 | Fasting and postload (one and two hour) plasma glucose concentrations for early (12-15 weeks of gestation) versus late (24-28 weeks of gestation) oral glucose tolerance test (OGTT) in participants with and without gestational diabetes mellitus. The cut-off values of the World Health Organization's 2013 criteria indicated by horizontal lines

OGTTs) was performed to derive a final diagnosis. This approach resulted in an additional 27 participants in the sensitivity analysis (663 compared with 636 in the full analysis set) and two more participants with gestational diabetes mellitus (76 *v* 74 in the full analysis set). Diagnostic performance measures were estimated based on the respective available data for each measurement time (totals differ because of varying patterns of missingness; online supplemental tables S5-S7). The results of the sensitivity analysis were consistent with the full analysis set.

Discussion

Principal findings

In our observational multicentre study, we tested the WHO 2013 criteria prospectively during screening in the first trimester, at 12-15 weeks of gestation, in a low risk population. In the cohort with a prevalence of gestational diabetes mellitus of 12%, the WHO criteria had low sensitivity (0.35, 95% confidence interval 0.24 to 0.47) and high specificity (0.96, 0.95 to 0.98), giving high overall accuracy (0.89, 0.87 to 0.92). In a previous study, the WHO 2013 criteria were tested at a mean of 15.2±3 weeks of gestation retrospectively in a high risk cohort with obesity (body mass index ≥29) for the DALI (Vitamin D and Lifestyle Intervention for Gestational Diabetes Mellitus Prevention) study, and interventions of healthy eating or physical activity, or both, were implemented afterwards.[21] In the DALI cohort of 1035 participants, gestational diabetes mellitus was diagnosed by a 75 g OGTT in early pregnancy in 22.9% of participants. Of these early abnormal OGTTs, 78.5% had abnormal fasting plasma glucose concentrations of ≥5.1 mmol/L. The researchers did

not compare the results of both OGTTs, however, and the results of the first OGTT were not blinded to participants and healthcare providers. Therefore, the late OGTTs might have been influenced by the interventions implemented after the early OGTT. Early and late OGTTs were compared prospectively in 146 individuals with a diagnosis of early onset gestational diabetes mellitus in Japan; 47% (69/146) had normal OGTTs at 24-28 weeks of gestation, indicating a high false positive rate.[22] An early 75 g OGTT based on the WHO 2013 criteria was performed in 378/1401 early pregnancies (29.6%) and 170 (12.1%) had pathological results.[23] In those with a diagnosis of gestational diabetes mellitus, early treatment was started immediately and hence the OGTT results in early and late pregnancy could not be compared.

Setting the cut-off value for fasting plasma glucose concentrations at ≥5.1 mmol/L might raise concerns of potential overdiagnosis, because fasting plasma glucose levels decrease until 20 weeks of gestation.[12] We showed that the results of early and late OGTTs, especially in the non-gestational diabetes mellitus group, were comparable and only 2.5% of participants had a fasting plasma glucose level above this threshold in the non-gestational diabetes mellitus group versus 20.3% in the gestational diabetes mellitus group. Increasing the cut-off value for fasting glucose slightly improved test performance (positive predictive value was increased although the negative predictive value was only slightly reduced) and effectiveness (diagnostic odds ratio). The best approach in our cohort was to lower the one hour postload cut-off values to ≥8.9 mmol/L and the two hour postload cut-off values to ≥7.8 mmol/L, which gave a detection rate of 53% at a false positive rate of 10%. We are not aware of any study comparing the results of the 75 g OGTT in early and late pregnancy in a setting without increased risks. Studies reporting screening in the first trimester were usually in individuals with a high risk of developing gestational diabetes and were based on fasting plasma glucose and postprandial glucose concentrations as a screening method,[24] thereby potentially missing a substantial proportion of gestational diabetes mellitus in the general population.

The 2013 WHO cut-off values were derived from the HAPO study published in 2008.[3] The HAPO study reported a linear relation between maternal fasting and postload glucose values and perinatal adverse outcomes, such as birth weight >90th centile, levels of C peptide in cord blood >90th centile, and neonatal body fat >90th centile. No one glucose value was strongly correlated with the outccomes and no one value was superior to others in predicting a diagnosis of gestational diabetes mellitus. The defined cut-off values represent the average glucose values at which the odds of developing these perinatal adverse outcomes were increased by 1.75-fold, based on fully adjusted logistic regression models. Only one cut-off value was needed for a positive result on screening and to diagnose gestational diabetes mellitus. The no threshold effect of the 75 g OGTT lowers reproducibility, however, which could lead to missclassification by the reference test. Also, many factors can influence the reproducibility and accuracy of tests before, during, and after analysis (eg, time of fasting maternal diet, smoking, excercise or stress, type of sample, collection tube, storage, and transportation).[25 26] A Chinese study showed overall reproducibility of only 65.6% in men and non-pregnant women between two OGTTs performed in a six week interval.[27] Reproducibility could not be improved even in the high risk group with increased levels of glycated haemoglobin A_{1c}, high body mass index, or high waist-to-hip ratio. Only one small study reported low overall reproducibility (74.2%) with a 75 g OGTT in pregnancy in a sub-Saharan African population.[28] These results are important for the interpretation of our results, and the reported low reproducibility of the 75 g OGTT could result in misclassification of the diagnosis of gestational diabetes mellitus in the predefined period of screening (24-28 weeks of gestation) and might also have an effect on the results of the 75 g OGTT in early pregnancy. Because the 75 g OGTT is the reference standard in pregnancy, these difficulties cannot be overcome at the moment, but biomarkers of glucose metabolism or continuous glycaemic monitoring might improve diagnostic reproducibility and accuracy, and are under evaluation.[15 29 30]

Strengths and weaknesses of the study

The strengths of our study were the prospective design, multicentre approach, and low risk setting, showing the real effect of universal early screening in a general population. Also, participants, study midwives, doctors, and investigators were blinded to the early test results and therefore the significance and efficacy of the therapeutic interventions were unclear, but we consider this blinding to be a strength. Ongoing randomised controlled studies need to clarify these questions, which were not the focus of this study. For conciseness, we did not further investigate maternal characteristics and comorbidities between participants with early or late gestational diabetes mellitus and therefore we cannot describe an early onset phenotype for gestational diabetes mellitus. We also did not perform prediction models and did not analyse the WHO 2013 criteria in terms of maternal and neonatal outcomes. These topics will be analysed separately. Finally, the study population of mainly white participants might limit the generalisability of the findings to more diverse populations.

Comparisons with other studies

Individuals with abnormal glucose values in early to mid-pregnancy seem to have a higher risk of adverse pregnancy outcomes. A study showed that

participants with an abnormal OGTT at 18-20 weeks of gestation and confirmed gestational diabetes mellitus at 24-28 weeks of gestation were more likely to have metabolic disorders, deliver infants that were large for gestational age, and have a higher risk of fetal hyperinsulinaemia.[31] In a retrospective high risk cohort, higher maternal and neonatal adverse outcomes, including a larger proportion of preterm births, caesarean sections, and neonates large for gestational age, were identified.[32] Children born to participants having an early diagnosis of gestational diabetes mellitus were more likely to develop metabolic disorders and obesity.[33] Another study also showed that glucose targets and weight gain could be more easily met if the diagnosis was made by a standard late OGTT rather than during early pregnancy, which hindered the reduction of complications in early diagnosed gestational diabetes mellitus.[32] Milder degrees of hyperglycaemia, lower than the threshold for pre-exisitng diabetes, but diagnosed before 24-28 weeks of gestation, might be a phenotype of gestational diabetes mellitus with higher risks for adverse outcomes, and individuals with a diagnosis of gestational diabetes mellitus after 24 weeks of gestation seem to have a milder phenotype. Therefore, a treatment approach for the early diagnosed, gestational diabetes mellitus phenotype might be justified but more challenging, and the benefits of an early intervention are lacking.[11]

EGGO (Early Gestational Diabetes Screening in the Gravid Obese Woman),[34] a randomised controlled trial published in 2020, investigated early screening (14-20 weeks of gestation) with a two step screening approach (first 50 g glucose challenge test followed by 100 g OGTT based on the criteria of Carpenter and Coustan) in a population with obesity. The study reported no improvement in the primary outcome (macrosomia defined as birth weight >4000 g) in 29 individuals with early diagnosed, gestational diabetes mellitus (<20 weeks of gestation). Group size was low and underpowered for the early intervention group. Obesity in particular is an independent and the most prevalent risk factor for neonatal macrosomia, which might not be improved easily by glycaemic control alone. A Danish study about lifestyle interventions in women with obesity also reported no improvement in primary obstetric and metabolic outcomes.[35]

In the recently published TOBOGM trial (The Treatment of Booking Gestational Diabetes Mellitus),[36] participants with at least one risk factor for hyperglycaemia were tested at 4-20 weeks of gestation (mean 15.6) with a two hour postload 75 g OGTT, with participants randomised to immediate (n=400) or deferred treatment (n=393; dietary advice or drug treatments). The immediate intervention caused a modest improvement in adverse neonatal outcomes (birth at <37 weeks of gestation, birth trauma, birth weight >4500 g, respiratory distress, phototherapy, stillbirth, neonatal death, or shoulder dystocia; 24.9% *v* 30.5%, adjusted relative risk 0.82, 95% confidence interval 0.68 to 0.98) and no substantial differences in pregnancy related hypertension or neonatal lean body fat. A flaw of the study could be that the adverse outcomes of preterm birth, respiratory distress syndrome, or phototherapy were not strongly related to hyperglycaemia. Secondary outcomes, such as infants large for gestational age (16.8% *v* 19.6%) and neonatal hypoglycaemia ≤40 mg/dL within 72 hours (18.9% *v* 22.7%), were improved by a slight increase in small for gestational age infants (12% *v* 9.2%), especially in pregnant individuals with lower glycaemic ranges. The higher rate of infants small for gestational age might be a possitble harm, but neonatal pH or Apgar status, or the possible increased admissions to the neonatal intensive care unit in the pilot study in this group of neonates was not further evaluated in the main study.[37]

Implications for clinicians and policy makers

Early diagnosis of gestational diabetes mellitus is important and treatment is challenging. Few studies have shown a sufficient effect of early diagnosis and intervention in those most at risk of later complications or have explored the cost effectiveness of early diagnosis and treatment. Our study indicated that the 75 g OGTT as a screening tool in early pregnancy is not sensitive enough when applying the WHO 2013 criteria, and the phenotype of early gestational diabetes mellitus cannot easily be described. Ongoing randomised controlled trials on the efficacy of early interventions to prevent maternal, and fetal and neonatal, adverse outcomes might clarify the importance of early screening for gestational diabetes mellitus.

Conclusions

The results of our prospective low risk cohort study indicated that the WHO 2013 criteria need to be modified to detect at least half of pregnant individuals with a later diagnosis of gestational diabetes mellitus. The early onset gestational diabetes mellitus phenotype seems to be associated with poorer pregnancy and neonatal outcomes and treatment is more challenging. Further research should include validation of our findings in different populations and investigation of the effect of early lifestyle and drug interventions in individuals with an early diagnosis versus a late diagnosis of gestational diabetes mellitus.

AUTHOR AFFILIATIONS

[1]Department of Feto-Maternal Medicine and Obstetrics, University Hospital Basel, Basel, Switzerland

[2]Department of Prenatal Diangosis and Obstetrics, University Hospital Hamburg-Eppendorf, Hamburg, Germany
[3]Department of Obstetrics and Gynaecology, Medical University of Vienna, Vienna, Austria
[4]Department of Obstetrics and Gynaecology, Salzburger Landeskrankenhaus, Paracelsus Medical University, Salzburg, Austria
[5]Department of Obstetrics and Gynaecology, Cantonal Hospital Aarau, Aarau, Switzerland
[6]Department of Obstetrics and Gynaecology, University Hospital Zurich, Zurich, Switzerland
[7]Department of Obstetrics and Gynaecology, University Hospital Freiburg, Freiburg, Germany
[8]Department of Clinical Research, University of Basel, Basel, Switzerland
[9]Department of Clinical Research, University Hospital Basel, Basel, Switzerland
[10]Department of Endocrinology and Diabetology, University Hospital Basel, Basel, Switzerland
[11]Department of Obstetrics and Gynaecology, University Hospital Basel, Basel, Switzerland

Acknowledgements We thank Dorothy Huang for critical proofreading in English. We also thank Cristina Granado, Doris Mueller Borer, and Samira Abraham for assistance in study coordination, study visits locally, and data acquisition in Basel, and Ingo Rosicky and Julia Blaetter for study visits and data acquisition in Vienna. We are grateful to Kurt Hecher, Hamburg, for editing the abstract. Special thanks to all of the families who participated in this study.

Contributors EAH was the principal investigator in Basel and coordinating investigator, author of the study protocol, obtained ethical approval, and drafted the manuscript. IH was the sponsor, assisted with the original study protocol and revised the manuscript. DRV performed the statistical analysis and helped revise the draft. CSG, MKr, AR, MKu, MTB, and TF were local investigators at their sites. HJ-B, ED, SH, WE, PH, NOK, EB, and BW made important contributions and critically reviewed the content. All authors have given final approval of the version to be published. EAH and IH accept full responsibility for the work or conducted the study, or both. EAH had access to the data and controlled the decision to publish. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and accuracy of the data analysis. EAH is guarantor. The corresponding author (EAH) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding This study was supported by the Swiss National Fund (grant No SNF 320030_173061), Switzerland, the Diabetes Society Basel, Switzerland, and the Gottfried and Julia Bangerter-Rhyner-Foundation, Bern, Switzerland. Researchers were independent of funders. The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the Swiss National Fund, Diabetes Society Basel, and Gottfried and Julia Bangerter-Rhyner-Foundation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval This study involves human participants and was approved by each local institutional review board in Basel (EKNZ Basec-No PB_ 2016-00611), Freiburg (EK-No 127/16), Salzburg (EK-No 415-E/2014/11-2016), and Vienna (EK-No 1097/2016). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs

Evelyn A Huhn http://orcid.org/0000-0001-5382-1353
Deborah R Vogt http://orcid.org/0000-0002-0668-5675

REFERENCES

1 International Diabetes Federation. IFD diabetes Altlas. Brussels, Belgium, 9th edn 2019, 2021. Available: https://diabetesatlas.org/en
2 Lowe LP, Metzger BE, Dyer AR, *et al*. Hyperglycemia and adverse pregnancy outcome (HAPO) study: associations of maternal A1C and glucose with pregnancy outcomes. Diabetes Care 2012;35:574–80. 10.2337/dc11-1687
3 Metzger BE, Lowe LP, Dyer AR, *et al*. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991–2002. 10.1056/NEJMoa0707943
4 Metzger BE, Gabbe SG, Persson B, *et al*. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676–82. 10.2337/dc09-1848
5 World Health Organization. Diagnostic criteria and classification of Hyperglycaemia first detected in pregnancy: a world health organization guideline. In: Diabetes research and clinical practice 103. 2013: Available: http://apps.who.int/iris/bitstream/10665/85975/1/WHO_NMH_MND_13.2_eng.pdf
6 Kiserud T, Piaggio G, Carroli G, *et al*. The World Health Organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. PLoS Med 2017;14. 10.1371/journal.pmed.1002284
7 Jaber S, Blanchard CT, Lu MY, *et al*. Contemporary trends in cesarean delivery rates and indications. Am J Perinatol 26, 2023. 10.1055/a-2097-1958
8 Hansen A, Chauhan SP. Shoulder dystocia: definitions and incidence. Semin Perinatol 2014;38:184–8. 10.1053/j.semperi.2014.04.002
9 Bláha J, Bartošová T. Epidemiology and definition of PPH worldwide. Best Pract Res Clin Anaesthesiol 2022;36:325–39. 10.1016/j.bpa.2022.11.001
10 Hod M, Kapur A, Sacks DA, *et al*. The International federation of gynecology and obstetrics (FIGO) initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management, and care. Int J Gynaecol Obstet 2015;131 Suppl 3:S173–211. 10.1016/S0020-7292(15)30033-3
11 McLaren RA, Ruymann KR, Ramos GA, *et al*. Early screening for gestational diabetes mellitus: a meta-analysis of randomized controlled trials. Am J Obstet Gynecol MFM 2022;4:100737. 10.1016/j.ajogmf.2022.100737
12 Zhu W-W, Yang H-X, Wei Y-M, *et al*. Evaluation of the value of fasting plasma glucose in the first prenatal visit to diagnose gestational diabetes mellitus in China. Diabetes Care 2013;36:586–90. 10.2337/dc12-1157
13 Corrado F, D'Anna R, Cannata ML, *et al*. Correspondence between first-trimester fasting glycaemia, and oral glucose tolerance test in gestational diabetes diagnosis. Diabetes Metab 2012;38:458–61. 10.1016/j.diabet.2012.03.006
14 Plasencia W, Garcia R, Pereira S, *et al*. Criteria for screening and diagnosis of gestational diabetes mellitus in the first trimester of pregnancy. Fetal Diagn Ther 2011;30:108–15. 10.1159/000324684
15 Huhn EA, Fischer T, Göbl CS, *et al*. Screening of gestational diabetes mellitus in early pregnancy by oral glucose tolerance test and glycosylated fibronectin: study protocol for an international, prospective, multicentre cohort trial. BMJ Open 2016;6:e012115. 10.1136/bmjopen-2016-012115
16 Classification and diagnosis of diabetes: standards of medical care in diabetes—2020. Diabetes Care 2020;43:S14–31. 10.2337/dc20-S002

17 Management of diabetes in pregnancy: standards of medical care in diabetes—2020. Diabetes Care 2020;43:S183–92. 10.2337/dc20-S014
18 Meek CL, Murphy HR, Simmons D. Random plasma glucose in early pregnancy is a better predictor of gestational diabetes diagnosis than maternal obesity. Diabetologia 2016;59:445–52. 10.1007/s00125-015-3811-5
19 Dashora U, Dashora V, Kennedy L. Two-Hour 75-g oral glucose tolerance test early in pregnancy detects most cases of gestational diabetes. Diabetes Care 2002;25. 10.2337/diacare.25.4.803
20 R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2020.
21 Harreiter J, Simmons D, Desoye G, *et al*. IADPSG and WHO 2013 gestational diabetes mellitus criteria identify obese women with marked insulin resistance in early pregnancy. Diabetes Care 2016;39:e90–2. 10.2337/dc16-0200
22 Nakanishi S, Aoki S, Kasai J, *et al*. High probability of false-positive gestational diabetes mellitus diagnosis during early pregnancy. BMJ Open Diabetes Res Care 2020;8:e001234. 10.1136/bmjdrc-2020-001234
23 Jokelainen M, Stach-Lempinen B, Rönö K, *et al*. Oral glucose tolerance test results in early pregnancy: A Finnish population-based cohort study. Diabetes Res Clin Pract 2020;162:108077. 10.1016/j.diabres.2020.108077
24 Agarwal MM, Dhatt GS, Punnose J, *et al*. Gestational diabetes: fasting and postprandial glucose as first prenatal screening tests in a high-risk population. J Reprod Med 2007;52:299–305.
25 Bogdanet D, O'Shea P, Lyons C, *et al*. The oral glucose tolerance test-is it time for a change? A literature review with an emphasis on pregnancy. J Clin Med 2020;9. 10.3390/jcm9113451
26 Pintaudi B, Di Vieste G, D'Anna R, *et al*. The analytical reliability of the oral glucose tolerance test for the diagnosis of gestational diabetes: an observational, retrospective study in a caucasian population. J Clin Med 2022;11:564. 10.3390/jcm11030564
27 Ko GTC, Chan JCN, Woo J. The reproducibility and usefulness of the oral glucose tolerance test in screening for diabetes and other cardiovascular risk factors. *Ann Clin Biochem*.
28 Munang YN, Noubiap JJ, Danwang C, *et al*. Reproducibility of the 75 G oral glucose tolerance test for the diagnosis of gestational diabetes mellitus in a sub-Saharan African population. BMC Res Notes 2017;10:622. 10.1186/s13104-017-2944-7
29 Bogdanet D, O'Shea PM, Halperin J, *et al*. Plasma glycated CD59 (gCD59), a novel biomarker for the diagnosis, management and follow up of women with gestational diabetes (GDM) - protocol for prospective cohort study. BMC Pregnancy Childbirth 2020;20:412. 10.1186/s12884-020-03090-9
30 Northwestern University. Glycemic observation and metabolic outcomes in mothers and offspring (go Moms). 2021. Available: https:// clinicaltrials .gov/ ct2/ show/ NCT04860
31 Liu B, Cai J, Xu Y, *et al*. Early diagnosed gestational diabetes mellitus is associated with adverse pregnancy outcomes: a prospective cohort study. J Clin Endocrinol Metab 2020;105. 10.1210/clinem/dgaa633
32 Sweeting AN, Ross GP, Hyett J, *et al*. Gestational diabetes mellitus in early pregnancy: evidence for poor pregnancy outcomes despite treatment. Diabetes Care 2016;39:75–81. 10.2337/dc15-0433
33 Page KA, Luo S, Wang X, *et al*. Children exposed to maternal obesity or gestational diabetes mellitus during early fetal development have hypothalamic alterations that predict future weight gain. Diabetes Care 2019;42:1473–80. 10.2337/dc18-2581
34 Harper LM, Jauk V, Longo S, *et al*. Early gestational diabetes screening in obese women: a randomized controlled trial. Am J Obstet Gynecol 2020;222:495. 10.1016/j.ajog.2019.12.021
35 Vinter CA, Tanvig MH, Christensen MH, *et al*. Lifestyle intervention in Danish obese pregnant women with early gestational diabetes mellitus according to WHO 2013 criteria does not change pregnancy outcomes: results from the lip (lifestyle in pregnancy) study. Diabetes Care 2018;41:2079–85. 10.2337/dc18-0808
36 Simmons D, Immanuel J, Hague WM, *et al*. Treatment of gestational diabetes mellitus diagnosed early in pregnancy. N Engl J Med 2023;388:2132–44. 10.1056/NEJMoa2214956
37 Simmons D, Hague WM, Teede HJ, *et al*. Hyperglycaemia in early pregnancy: the treatment of booking gestational diabetes mellitus (TOBOGM) study. A randomised controlled trial. Med J Aust 2018;209:405–6. 10.5694/mja17.01129

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjmed-2022-000330).