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REVIEW

An Update on Screening Strategies for Gestational Diabetes Mellitus: A Narrative Review

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Abstract: Gestational diabetes mellitus (GDM) is a frequent medical complication during pregnancy. Screening and diagnostic practices for GDM are inconsistent across the world. This narrative review includes data from 87 observational studies and randomized controlled trials (RCTs), and aims to give an overview of the current evidence on screening strategies and diagnostic criteria for GDM. Screening in early pregnancy remains controversial and studies show conflicting results on the benefit of screening and treatment of GDM in early pregnancy. Implementing the one-step "International Association of Diabetes and Pregnancy Study Groups" (IADPSG) screening strategy at 24–28 weeks often leads to a substantial increase in the prevalence of GDM, without conclusive evidence regarding the benefits on pregnancy outcomes compared to a two-step screening strategy with a glucose challenge test (GCT). In addition, RCTs are needed to investigate the impact of treatment of GDM diagnosed with IADPSG criteria on long-term maternal and childhood outcomes. Selective screening using a risk-factor-based approach could be helpful in simplifying the screening algorithm but carries the risk of missing significant proportions of GDM cases. A two-step screening method with a 50g GCT and subsequently a 75g oral glucose tolerance test (OGTT) with IADPSG could be an alternative to reduce the need for an OGTT. However, to have an acceptable sensitivity to screen for GDM with the IADPSG criteria, the threshold of the GCT should be lowered from 7.8 to 7.2 mmol/L. A pragmatic approach to screen for GDM can be implemented during the COVID-19 pandemic, using fasting plasma glucose (FPG), HbA1c or even random plasma glucose (RPG) to reduce the number of OGTTs needed. However, usual guidelines and care should be resumed as soon as the COVID pandemic is controlled.

Keywords: gestational diabetes mellitus, screening, diabetes, pregnancy

Introduction

Gestational diabetes mellitus (GDM) is defined as diabetes diagnosed in the second or third trimester of pregnancy provided that overt diabetes was excluded before pregnancy or at the latest in early pregnancy.[1] Most international guidelines such as the American Diabetes Association (ADA) and World Health Organization (WHO) recommend to screen for overt diabetes at first prenatal visit, since these women have (untreated) a very high risk for pregnancy complications and need treatment with insulin.[1,2] The prevalence of GDM is rising globally and if left untreated, the condition is associated with an increased risk of fetal and maternal complications such as preeclampsia and large-for-gestational age (LGA) infants.[3,4] Shortly after delivery, the glucose values generally normalize, but women with GDM and their offspring are at increased risk to develop type 2 diabetes (T2DM) later in life.[5–7] Two

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large randomized controlled trials (RCTs) have confirmed that treatment of GDM between 24 and 28 weeks of pregnancy results in a lesser degree of perinatal complications, mainly in the frequency of LGA and preeclampsia.[3,4] However, controversy exists regarding the optimal screening and diagnostic approach for GDM. These controversies are situated in various domains such as the use of different diagnostic criteria for GDM, selective screening based on risk factors versus universal screening, one-step screening or two-step screening, the use of alternate screening methods like fasting plasma glucose (FPG) or HbA1c, the potential benefit of screening for GDM in early pregnancy, screening for GDM in specific populations or circumstances, such as in women who underwent bariatric surgery or in the COVID-19 pandemic setting.

The initial diagnostic criteria of GDM were established by O' Sullivan almost 60 years ago.[8] In the 1980s, Carpenter and Coustan modified these criteria and proposed a two-step screening method, consisting of a 50g glucose challenge test (GCT) and subsequent a 3h 100g oral glucose tolerance test (OGTT) if screening threshold of the GCT was exceeded.[9] However, these criteria were chosen to identify women at high risk for the development of diabetes after pregnancy and not necessarily to identify pregnancies with an increased risk for adverse perinatal outcomes.[10] In 1980, the 2h 75g OGTT was established as the diagnostic test for diabetes and glucose intolerance, and the WHO extended this recommendation to pregnant women. However, the ADA and many other medical associations continued to follow the National Diabetes Data Group (NDDG) recommendation to use the 3h 100g OGTT, because the 2h 75g OGTT had been little investigated during pregnancy. In 2010, the "International Association of Diabetes and Pregnancy Study Groups" (IADPSG) made an attempt to unify the guidelines for screening and diagnosis of GDM by recommending a universal one-step approach with a 75g OGTT and more stringent diagnostic criteria.[11] This recommendation was based on the results of the "Hyperglycemia and Adverse Pregnancy Outcomes" (HAPO) study, which demonstrated a continuous and graded relationship between maternal hyperglycemia and the risk for adverse perinatal outcomes.[12] However, the adoption of the IADPSG criteria remains controversial due to the significant increase in the number of women categorized and treated as GDM. Recently, a review on current screening guidelines for GDM assessed 16 different guidelines across the world and confirmed that there is an ongoing lack of consensus, with inconsistencies mainly focusing on the screening process (one-step vs two-step) and criteria for the OGTT.[13] In addition, a survey in 2015 on screening practices in Europe demonstrated that the majority of European societies still recommended risk-factor-based screening and about one-third recommended a universal one-step approach with a 75g OGTT and IADPSG criteria.[14] This lack of consensus creates problems in addressing and comparing prevalence, outcomes, efficacy of treatment, and follow-up of GDM.

This comprehensive review provides an update on screening strategies and diagnostic criteria for GDM in early and late pregnancy. In addition, evidence on pragmatic approaches to screen for GDM after bariatric surgery and in a pandemic setting such as COVID-19 are discussed.

Methods

A literature search was conducted on PubMed between January 2021 and March 2021. Cross-sectional studies, case–control studies, cohort studies, and RCTs were considered for this narrative review. The populations studied included pregnant women with or without GDM, in which we evaluated the effects of the implementation of different protocols, guidelines or programs for screening for GDM, compared with the absence of screening, or compared with other protocols, guidelines or programs for screening. Screening strategies included universal versus selective screening, one-step versus two-step screening, early versus late screening, screening after bariatric surgery, and screening in times of COVID-19. We excluded animal studies, descriptive designs (case series and case reports), studies with a low quality (no method section, no p-values mentioned), and articles written in a language other than English, French or Dutch. The search was not limited to a certain time period. The following search strategy was used in PubMed: ((("Screening"[Title/Abstract] OR "screening strateg*"[Title/Abstract]) AND ("diabetes, gestational"[MeSH Terms:noexp] OR "Gestational diabetes"[Title/Abstract] OR "Pregnancy-Induced Diabetes"[Title/Abstract] OR "gestational hyperglycemia"[Title/Abstract] OR "hyperglycemic pregnancy"[Title/Abstract] OR "Pregnancy-Induced Diabetes"[Title/Abstract] OR "gestational hyperglycemia"[Title/Abstract] OR "gestational glucose intolerance"[Title/Abstract])) AND ((("Universal"[Title/Abstract] OR "one-step"[Title/Abstract]) AND "Screening"[Title/Abstract]) OR ("risk factor"[Title/

Abstract] AND "Screening"[Title/Abstract]) OR ("two-step"[Title/Abstract] AND "Screening"[Title/Abstract]) OR ("early screening"[Title/Abstract] OR "in early pregnancy"[Title/Abstract]) OR ("Bariatric Surgery"[MeSH Terms] OR "Gastric Bypass"[MeSH Terms] OR "Gastrectomy"[MeSH Terms] OR "Bariatric Surgery"[Title/Abstract] OR "Gastric Bypass"[Title/Abstract] OR "Gastrectomy"[Title/Abstract]) OR ("COVID-19"[MeSH Terms] OR "SARS-CoV-2"[MeSH Terms] OR "COVID-19"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR "Coronavirus Disease-19"[Title/Abstract])).

In addition, the reference lists of all identified articles were examined to identify studies not captured by the electronic search. As this is not a systematic review of the literature, we reported our results in a descriptive manner.

Overview of the Included Publications

We identified 737 articles of which 164 were selected as possibly relevant. After examination of the full-text articles, 87 studies were included in this review (Figure 1).

Screening in Early Pregnancy

The Impact of Screening in Early Pregnancy on Pregnancy Outcomes

The aim of early screening would be to identify women at low or high risk for GDM later in pregnancy. In addition, this might help to identify women who already have GDM to allow earlier treatment and potentially improve maternal and neonatal outcomes.

Early testing in pregnancy for diabetes will lead to the identification of hyperglycemia under the threshold of overt diabetes. These women could be labeled as early GDM. However, the IADPSG criteria have not been validated for use in early pregnancy. Observational studies show conflicting results as to whether screening for early-onset GDM can improve pregnancy outcomes (Table 1). Several studies reported an improvement in maternal and neonatal outcomes.[15–18] A retrospective cohort study by Bartha et al found that early glucose intolerance screening with a GCT could avoid diabetes-related complications such as polyhydramnios, fetal anomalies and preterm birth in women diagnosed with GDM.[16] Ryan et al demonstrated that early screening improved the primary composite outcome [emergency caesarean section, neonatal

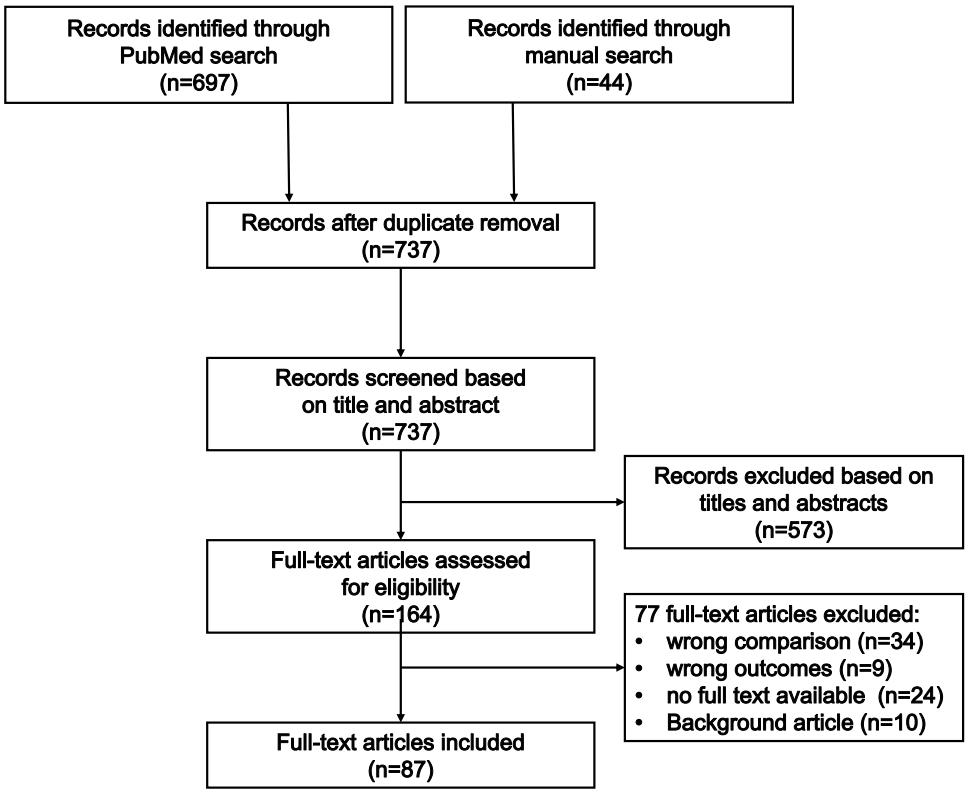

Figure 1 The literature search and selection process.

Table 1 Screening for GDM in Early Pregnancy

Author, Year/Country (Ref.)	Design	Subjects (N)	Study Population	Timeframe Early Testing (Weeks)	GDM Diagnosis Criteria	Comparison	Main Results
Observational studies							
Bartha, 2002/ Spain[16]	Retrospective cohort study	424	Women with GDM	First antenatal visit (early)	50g GCT followed by, if abnormal, a 3h 100g OGTT/ GDM diagnosis if ≥2 values abnormal (≥.5.8, 10.6, 9.2, 8.1 mmol/L)	Earlier vs later (24–28 weeks) screening	Early glucose intolerance screening with a GCT could avoid diabetes-related complications in women diagnosed with GDM
Riskin, 2009/ Israel[32]	Retrospective study	6129	Singleton pregnancies >24 weeks in mothers without ODIP or FTFPG ≥5.8 mmol/L	<13 weeks	50g GCT followed by, if abnormal, 3h 100g OGTT at 24–28 weeks/CC criteria and GCT ≥11.1 mmol/L	FPG categories (<4.2, 4.2–4.4, 4.5–4.7, 4.8–5.0, 5.1–5.2, 5.3–5.5 and 5.6–5.8 mmol/L)	Higher FTFPG in early pregnancy increased the risk of adverse pregnancy outcomes
van Leeuwen, 2010/the Netherlands[40]	Prospective cohort study	995	Singleton pregnancies in women without ODIP <20 weeks	<20 weeks	50g GCT and RPG at 24–28 weeks followed by 2h 75g OGTT if RPG ≥6.8 mmol/L or 1h ≥7.8 mmol/L/ WHO 1999 criteria	50g GCT vs RPG	Use of a clinical prediction model is an accurate method to identify women at increased risk for GDM, and could be used to select women for additional testing for GDM
Teede, 2011/ Australia[41]	Retrospective study	4276	Singleton pregnancies	12–15 weeks	Two-step method: GCT followed by, if abnormal, a 2h 75g OGTT at 28 weeks/ADIPS criteria	Derivation (used to develop a simple predictor scoring tool that specified GDM risk based on identified clinical risk factors) vs validation group	The risk prediction tool, derived from risk factors in early pregnancy, enables simple identification of women at an increased risk of developing GDM
Zhu, 2013/ China[34]	Retrospective cohort study	14,039	All pregnant women without ODIP	First antenatal visit (<24 weeks)	2h 75g OGTT at 24–28 weeks/ MOH China criteria (fasting, ≥5.10 mmol/L; 1 h, ≥10.00 mmol/L; and 2 h, ≥8.50 mmol/L)	6 FPG groups (<4.1, 4.1–4.59, 4.60–5.09, 5.10–5.59, 5.6–6.09, 6.10–6.99 mmol/L)	Only 30.3% of women who had a FPG of ≥5.1 mmol/L still had a FPG of ≥5.1 mmol/L at 24–28 weeks

(*Continued*)

Table 1 (Continued).

Author, Year/Country (Ref.)	Design	Subjects (N)	Study Population	Timeframe Early Testing (Weeks)	GDM Diagnosis Criteria	Comparison	Main Results
Alunni, 2015/ US[20]	Retrospective cohort study	2652	Singleton pregnancies in women without ODIP	≤24 weeks	Early screening: (1) HbA1c 5.7–6.4% or FPG 5.1–6.9 mmol/L at ≤24 weeks, (2) one abnormal value on a 2h 75g OGTT at 24–28 weeks if normal early screening Standard approach: 1h 50g GCT followed by a 3h 100g OGTT/ CC Criteria	Early screening vs standard two-step ACOG approach	Implementing early screening for GDM gave no significant difference in neonatal outcomes
Hong, 2016/ US[21]	Retrospective cohort study	569	Singleton GDM pregnancies with ≥1 indication for early screening (GDM or macrosomia in a prior pregnancy or obesity)	<20 weeks	1h 50g GCT followed by a 3h 100g OGTT if the former was ≥7.5 mmol/L/CC criteria	Early (<20 weeks) vs routine (>24 weeks) screening	Early GDM screening was not associated with a decreased risk of adverse perinatal outcomes
Sweeting, 2017/ Australia[39]	Retrospective cohort study	3098	High risk women	<24 weeks	Universal testing at 24–28 weeks with 2h 75g OGTT or 50g GCT and, if positive, a subsequent OGTT/ADIPS criteria	Early GDM (<24 weeks) vs standard GDM (≥24 weeks)	HbA1c >5.9% early in pregnancy identified an increased risk of LGA, macrosomia, C-section, and hypertensive disorders in standard GDM
Mañe, 2017/ Spain[35]	Prospective multi-ethnic cohort study	1228	Singleton pregnancies in women without ODIP	First trimester	Two-step approach: 50g GCT followed by, if abnormal, a 3h 100g OGTT at 24–28 weeks/ NDDG criteria	HbA1c ≥5.9% vs 5.9–6.4%	Early HbA1c ≥5.9% identified women at high risk of adverse pregnancy outcomes independently of GDM diagnosis later in pregnancy

(*Continued*)

Table 1 (Continued).

Author, Year/Country (Ref.)	Design	Subjects (N)	Study Population	Timeframe Early Testing (Weeks)	GDM Diagnosis Criteria	Comparison	Main Results
Benaiges, 2017/ Spain[36]	Retrospective analysis of a non-randomized prospective cohort	1158	Women with a singleton pregnancy without ODIP	<12 weeks	Two-step method: 50g GCT followed by a 3h 100g OGTT if the former was positive/NDDG criteria	First trimester HbA1c of <4.8% vs 4.8–5.5% vs ≥5.6%	HbA1c in early pregnancy lacks sensitivity/ specificity for use as diagnostic test, but could be useful in simplifying the diagnostic algorithm for GDM
Hosseini, 2018/ Iran[22]	Prospective population-based cohort study	929	Singleton pregnancies	6–14 weeks	Universal screening with FPG for ODIP and early GDM at 6–14 weeks. 2h 75g OGTT at 24–28 weeks/ IADPSG criteria	Normal pregnancy vs early-onset GDM (6–14 weeks) vs late-onset GDM (24–28 weeks)	Early-onset GDM was associated with poorer pregnancy outcomes
Ryan, 2018/ UK[18]	Retrospective clinical audit of a prospectively maintained database	576	High risk singleton pregnancies	11–13 weeks	FPG/ 2h 75g OGTT/SIGN 2010 thresholds	Routine vs early screening	Early screening improved the pregnancy outcomes, such as emergency C-section, macrosomia and neonatal hypoglycemia
Bianchi, 2019/ Italy[19]	Retrospective study	290	High risk women	16–18 weeks	2h 75g OGTT (and FPG)/ IADPSG criteria	Early (16–18 weeks) vs standard (24–28 weeks) screening	Similar short-term maternal-fetal outcomes in both groups
Boe, 2019/US[37]	Retrospective cohort study	4144	Women without multiple gestations and second deliveries	First antenatal visit (<24 weeks)	HbA1c and/or 3h 100g OGTT/ HbA1c ≥ 6.5% (ODIP) vs 5.9–6.4% vs <5.9% and CC criteria	Early HbA1c vs CC testing	Early HbA1c as an isolated test could not replace routine CC testing for GDM because of poor sensitivity
Punnose, 2020/ India[38]	Retrospective cohort study	2275	Singleton pregnancies in women without ODIP	First trimester (before 13 6/7 weeks)	One-step 2h 75g OGTT at <24 weeks (in case of risk factors) or at 24–28 weeks/ IADPSG criteria	HbA1c <5.2% vs 5.2–5.5% vs ≥5.6%	Early HbA1c is an independent GDM predictor in Asian Indian women but lacks sensitivity and specificity for use as a diagnostic test

(*Continued*)

Table 1 (Continued).

Author, Year/Country (Ref.)	Design	Subjects (N)	Study Population	Timeframe Early Testing (Weeks)	GDM Diagnosis Criteria	Comparison	Main Results
Benhalima, 2020/Belgium[42]	Multi-centric prospective cohort study	1843	Singleton pregnancies without ODIP and history of bariatric surgery	6–14 weeks	Non-fasting GCT and 2h 75g OGTT at 24–28 weeks/ IADPSG criteria	Accuracy of the developed prediction model using clinical and biochemical risk factors in early pregnancy vs two validated models (van Leeuwen and Teede)	This prediction model for GDM had a moderate accuracy and could identify women at risk for GDM before or in early pregnancy
Cosson, 2020/ France[15]	Retrospective study	523	Women with singleton pregnancy and without ODIP and bariatric surgery	<22 weeks	FPG or 2h 75g OGTT/ IADPSG criteria	Immediate care vs no immediate care for early fasting hyperglycemia	Treating women with early fasting hyperglycemia, especially when FPG is ≥5.5 mmol/L, may improve pregnancy outcomes
Liu, 2020/ China[17]	Prospective cohort study	522	Singleton pregnancies	18–20 weeks	2h 75g OGTT/ IADPSG-2015 guidelines	4 groups: NGT (no GDM diagnosis), EGDM (GDM in only early OGTT), LGDM (GDM in only standard OGTT) and GDM (GDM diagnosis in both OGTTs)	Early GDM diagnosis at 18–20 weeks is associated with adverse outcomes
Benhalima, 2021/Belgium[33]	Multi-centric prospective cohort study	2006	Singleton Pregnancies without ODIP and history of bariatric surgery	6–14 weeks	Non-fasting GCT and a 2h 75g OGTT at 24–28 weeks/IADPSG criteria	FPG ≥5.1–5.5 mmol/L in early pregnancy vs FPG <5.1 mmol/ L in early pregnancy	Group with increased FPG in early pregnancy had significantly more NICU admissions
RCTs							
Osmundson, 2016/US[27]	RCT	83	Women with singleton pregnancy without ODIP, with HbA1c 5.7–6.4%	<14.0 weeks	2h 75-g OGTT at 26–28 weeks/ IADPSG and California Sweet Success Guidelines	Usual care vs early treatment for GDM with diet, BG monitoring, and insulin as needed	Early treatment did not significantly reduce the risk of GDM except in non-obese women

(*Continued*)

Table 1 (Continued).

Author, Year/Country (Ref.)	Design	Subjects (N)	Study Population	Timeframe Early Testing (Weeks)	GDM Diagnosis Criteria	Comparison	Main Results
Hughes, 2018 (ongoing)/New Zealand[24]	RCT	47	Women with singleton pregnancy without ODIP, with HbA1c ≥5.9–6.4%	<14.0 weeks	2h 75h OGTT/ New-Zealand criteria	Standard care vs early intervention in pregnancies complicated by prediabetes	First results expected in 2021
Simmons, 2018 (ToBOGM pilot study)/ Australia[25]	RCT	79	High risk women with singleton pregnancy	<20.0 weeks (4–19.6 weeks)	2h 75g OGTT/ IADPSG criteria	Women with booking GDM receiving immediate (clinical referral or ongoing treatment) vs deferred (no) treatment vs women without booking GDM ('decoys')	More NICU admission in the early GDM group with a tendency for more SGA but less LGA
Simmons, 2018 (ToBOGM study protocol)/ International[28]	RCT	4000	High-risk women with singleton pregnancy	<20.0 weeks (4–19.6 weeks)	2h 75g OGTT at 24–28 weeks/ 2014 ADIPS criteria	Intervention (immediate treatment) vs control (no treatment) vs decoys (NGT but undergo all procedures) vs non-active (NGT and records reviewed postnatal)	First results expected mid-2021
Vinter, 2018/ Denmark[30]	RCT	90	Obese pregnant women (BMI 30–45 kg/m^2) with singleton pregnancy	12–15 weeks	2h 75g OGTT/ IADPSG Criteria	Lifestyle intervention vs standard care	Lifestyle intervention was not effective in improving obstetric or metabolic outcomes
Roeder, 2019/ US[31]	RCT	157	Women with hyperglycemia (HbA1c 5.7–6.4% and/or FPG 5.1–6.9 mmol/L) and a singleton pregnancy without ODIP	≤15.0 weeks	2h 75g OGTT at 24–28 weeks/ IADPSG criteria	Early pregnancy vs 3rd trimester treatment of hyperglycemia	Treatment in early pregnancy did not improve maternal or neonatal outcomes significantly

(*Continued*)

Table 1 (Continued).

Author, Year/Country (Ref.)	Design	Subjects (N)	Study Population	Timeframe Early Testing (Weeks)	GDM Diagnosis Criteria	Comparison	Main Results
Harper, 2020/ US[29]	RCT	922	Obese women (BMI ≥30 kg/ m^2) without ODIP and history of bariatric surgery	14–20 weeks	Two-step method: 1h 50g GCT followed by a 3h 100g OGTT/CC criteria	Early GDM screening (14–20 weeks) vs routine screening (24–28 weeks)	Early GDM screening in obese women did not reduce the composite perinatal outcomes, such as macrosomia, C-section and shoulder dystocia
NCT03523143 (TESGO study) (ongoing)/ Taiwan[26]	RCT	2068	Singleton pregnancy without ODIP	18–20 weeks	2h 75g OGTT/ IADPSG criteria	Early screening group (18–20 weeks) vs standard screening group (24–28 weeks)	Results expected beginning of 2021

Abbreviations: GDM, gestational diabetes mellitus; GCT, glucose challenge test; OGTT, oral glucose tolerance test; FTFPG, first trimester fasting plasma glucose; CC, Carpenter and Coustan; FPG, fasting plasma glucose; RPG, random plasma glucose; WHO, World Health Organization; ADIPS, Australasian Siabetes in Pregnancy Society; MOH, Ministry of Health; HbA1c, hemoglobin A1C; ACOG, American Congress of Obstetricians and Gynecologists; LGA, large-for-gestational age; C-section, caesarian section; NDDG, National Diabetes Data Group; ODIP, overt diabetes in pregnancy; IADPSG, International Association of the Diabetes and Pregnancy Study Groups; SIGN, Scottish Intercollegiate Guidelines Network; NGT, normal glucose tolerance; EGDM, early-onset gestational diabetes; LGDM, late-onset gestational diabetes; NICU, neonatal intensive care unit; RCT, randomized controlled trial; BG, blood glucose; SGA, small-for-gestational age; BMI, body mass index; TESGO, The Effect of Early Screening and Intervention for Gestational Diabetes Mellitus on Pregnancy Outcomes.

hypoglycemia and macrosomia; 41.2% vs 30.3%, adjusted OR (aOR) 0.62, 95% CI 0.43–0.91] in high-risk pregnant women.[18] More recently, a large French study reported that women with early fasting hyperglycemia who received initial care versus those who did not, were more likely to be insulin-treated during pregnancy (58.0% vs 20.9%, respectively; $p < 0.00001$), gained less gestational weight (8.6 ± 5.4 kg vs 10.8 ± 6.1 kg, respectively; $p < 0.00001$), had a lower rate of preeclampsia [1.2% vs 2.6%, aOR 0.247 (0.082–0.759), $p = 0.01$], and similar rates of LGA infants and shoulder dystocia.[15] On the contrary, no beneficial effect of early diagnosing or treatment of GDM on maternal or neonatal outcomes was found in several other studies.[19–22] These studies showed that early screening for GDM nearly doubled the prevalence of GDM and that women with an early GDM diagnosis were treated to a greater extent with pharmacotherapy. However, no differences were observed in neonatal outcomes such as small-for-gestational age (SGA) and LGA infants, cesarean sections and macrosomia.[19,20] Hong et al reported that women who were screened prior to 20 weeks were more likely to receive insulin and to deliver preterm compared with routinely screened women.[21] They hypothesized that early screening and diagnosis of GDM could result in more aggressive management of the disease due to a presumption of pregestational diabetes. Another prospective cohort study showed that early-onset GDM was associated with an increased risk of Apgar score at 1 min <7, neonatal respiratory distress syndrome and neonatal intensive care unit (NICU) admission compared to the late-onset group.[22] In addition, the DALI (vitamin D And Lifestyle Intervention for GDM prevention) study in obese women showed that women with early GDM had a profile similar to the metabolic syndrome and that pre-pregnancy body mass index (BMI) was a strong predictor of early GDM.[23] These findings support the need for weight control before pregnancy to improve perinatal outcomes.

Few results are yet available from large RCTs comparing treatment of early-onset GDM with standard treatment of GDM between 24 and 28 weeks of pregnancy (Table 1). Several large RCTs are still ongoing, such as the "Prediabetes in pregnancy, can early intervention improve outcomes" (PINTO) study,[24] the "Treatment of Booking Gestational diabetes Mellitus" (ToBOGM) study[25] and the "Effect of Early Screening and Intervention for Gestational

Diabetes Mellitus on Pregnancy Outcomes" (TESGO) study (NCT03523143).[26] A small RCT demonstrated that early treatment of mild hyperglycemia (HbA1c of 5.7–6.4%) did not reduce the risk of GDM, except in non-obese women.[27] A pilot study of the ToBOGM trial showed that early GDM treatment was associated with a reduced LGA rate (0% vs 33% p = 0.030) but an increased NICU admission rate (36% vs 0% p = 0.043), largely driven by a higher rate of SGA infants.[28] SGA can be a consequence of overtreatment or insufficient gestational weight gain. Other smaller RCTs did not show benefits of early screening and treatment of GDM on pregnancy outcomes. The EGGO study, for instance, showed no effect of early screening for GDM on the composite perinatal outcome consisting of macrosomia, primary cesarean delivery, hypertensive disease of pregnancy, shoulder dystocia, neonatal hyperbilirubinemia, and neonatal hypoglycemia in obese women.[29] The LiP study evaluated the impact of lifestyle intervention vs standard care on metabolic and clinical outcomes in obese women with GDM in early pregnancy, classified according to the IADPSG criteria. They found no differences in obstetric or metabolic outcomes except for a higher rate of planned cesarean sections in the early treated group (22.2% vs 5.6%, p = 0.02).[30] In addition, an RCT in 200 women with hyperglycemia in early pregnancy showed that early treatment could not improve maternal or neonatal outcomes significantly.[31]

Different methods have been suggested for the screening of GDM in early pregnancy: direct glycemic markers such as FPG, indirect methods like HbA1c, and more recently biochemical markers (Table 1). Riskin et al demonstrated that higher first-trimester FPG levels in the non-diabetic range increased the risk for adverse pregnancy outcomes, including cesarean sections, LGA infants and macrosomia.[32] Likewise, a multicentric Belgian prospective cohort study showed recently that women with a FPG of 5.1–5.5 mmol/L in early pregnancy had a significantly higher NICU admission rate compared to women with FPG < 5.1 mmol/L (20.4% vs 9.3%, p = 0.009).[33] On the contrary, several studies have shown that a FPG ≥ 5.1 mmol/L in early pregnancy was a poor predictor of GDM.[15,33] A Belgian study demonstrated that only 37% of all women with an FPG ≥ 5.1–5.5 mmol/L in early pregnancy developed GDM based on the IADPSG criteria later in pregnancy.[33] A large Chinese study showed that in their population an FPG 6.1–7.0 mmol/L in early pregnancy was a much stronger predictor for GDM later in pregnancy compared to an FPG ≥ 5.1 mmol/L.[34] A French study recommended to use a threshold of 5.5 mmol/L for starting GDM treatment in early pregnancy, as they demonstrated improved pregnancy outcomes in these women.[15]

Few studies evaluated the use of HbA1c in early pregnancy to diagnose GDM.[35–39] It has been established that an early HbA1c ≥5.9% identified women at high risk of adverse pregnancy outcomes independently of GDM diagnosis later in pregnancy.[35,39] HbA1c can be used to screen for overt diabetes, but most studies demonstrated that HbA1c in early pregnancy has insufficient sensitivity and specificity to use as a diagnostic test for GDM. However, it could still be useful in simplifying the algorithm for GDM screening.[36–38] A retrospective cohort study showed that HbA1c at first prenatal visit allowed an early diagnosis of GDM in 25.8% of women; however, HbA1c could not replace routine testing for GDM later in pregnancy with an OGTT because of poor sensitivity.[37] HbA1c could be used as an adjunct to routine testing, identifying those with values between 5.9% and 6.4% at high risk of GDM early in pregnancy, allowing early intervention to potentially improve perinatal outcomes. However, RCTs are needed to prove that treatment of women with mildly elevated HbA1c in early pregnancy leads to better outcomes.

Prediction Models in Early Pregnancy

Improved prediction of GDM through identification of risk factors might increase the diagnostic accuracy of selective screening strategies and allow lifestyle interventions in early pregnancy to prevent the development of GDM and adverse pregnancy outcomes. Various risk factors for GDM have been identified, but it remains a struggle to accurately predict who is at increased risk to develop GDM. Several studies have proposed prediction models, such as the risk scores of van Leeuwen en Teede[40,41] (Table 1). More recently, Benhalima et al developed a prediction model for GDM based on the IADPSG criteria, using easy available clinical and biochemical risk factors in early pregnancy.[42] In this model, a history of a first degree relative with diabetes, a history of GDM, non-Caucasian origin, age, height, weight, FPG, triglycerides and HbA1c were independent predictors for GDM, with an area under the curve (AUC) of the model of 0.72 [95% confidence interval (CI) 0.66–0.78] after cross-validation, compared to an AUC of 0.67 (95% CI 0.63–0.71) using the van Leeuwen model and an AUC of 0.66

(95% CI 0.62–0.70) using the Teede model.[40–42] In conclusion, prediction models based on variables in early pregnancy seem to have moderate accuracy to predict GDM.

Screening for GDM Between 24 and 28 Weeks of Pregnancy

Introduction of the IAPDSG Criteria: What is the Impact on Prevalence and Outcomes?

Since 2010, the IADPSG recommends a universal one-step approach with a 75g OGTT at 24–28 weeks of pregnancy for screening and diagnosis of GDM. The IADPSG criteria have been adopted by the WHO since 2013, and are therefore now commonly referred to as the 2013 WHO criteria for GDM.[2,11] However, the IADPSG recommendation remains controversial due to the significant increase in GDM prevalence. Moreover, the implementation of the IADPSG screening strategy leads to an increased workload with the need for a fasting test, and this might lead to increased medicalization of care. An overview of the most commonly used guidelines for screening and diagnosis of GDM is shown in Table 2.

Many studies reported a substantial increase in the prevalence of GDM if the more stringent IADPSG criteria are adopted.[43–49] However, conflicting evidence exists regarding the impact of introducing IADPSG criteria on maternal and neonatal outcomes. There are no RCTs that have compared treatment of GDM based on the IADPSG criteria with no treatment. Some observational studies reported no difference or even an increase in adverse perinatal outcomes,[46,47,50–55] whereas others showed a significant improvement in perinatal outcomes associated with the use of the IADPSG criteria[56–58] (Table 3).

A Spanish study reported that the prevalence of GDM doubled following the introduction of the IADPSG screening strategy compared to the previous use of the two-step screening strategy with the Carpenter and Coustan criteria (CC). The adoption of the IADPSG criteria improved pregnancy outcomes such as a reduction in the rate of gestational hypertension (4.1 to 3.5%; −14.6%, p <

Table 2 Current Guidelines for Screening and Diagnosis of GDM

Guideline, Year	Range	One-Step	Two-Step	OGTT Criteria	OGTT Time	Risk Factors List	Screening in Early Pregnancy
IADPSG, 2010	Global	√		≥5.1 (fasting), ≥10.0 (1h) and/or ≥8.5 mmol/L (2h)	24–28 weeks	√	FPG ≥5.1mmol/L in early pregnancy is diagnosed as GDM
WHO, 2013	Global	√		IADPSG	Any time		Criteria apply for the diagnosis of GDM at any time during pregnancy
FIGO, 2015	Global	√		IADPSG	24–28 weeks or any other time	√	Not applicable due to lack of clear evidence
NICE, 2015	UK	√		≥5.6 mmol/L (fasting) or ≥7.8 mmol/L (2h)	24–28 weeks	√	75g 2h OGTT in women with previous GDM as soon as possible after booking
ACOG, 2018	US		√	CC/NDDG	24–28 weeks	√	Consider testing in all women with BMI >25 kg/m^2 (or >23 kg/m^2 in Asian Americans) and with ≥1 additional risk factors
ADA, 2021	US	√	√	IADPSG/CC	24–28 weeks	√	OGTT for high-risk women at the first antenatal visit and classified as T1DM or T2DM

Notes: The OGTT threshold value of IADPSG criteria is 5.1–10.0– 8.5 mmol/L for a 2h 75g OGTT. One or more of these threshold values must be equaled or exceeded for the diagnosis of GDM. The OGTT threshold value of CC criteria is 5.3–10.0–8.6–7.8 mmol/L for a 3h 100g OGTT. The OGTT threshold value of NDDG criteria is 5.8–10.6–9.2–8.0 mmol/L for a 4h 100g OGTT. For CC and NDDG criteria, a diagnosis generally requires that two or more thresholds be met or exceeded, although some clinicians choose to use just one elevated value.

Abbreviations: GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; IADPSG, International Association of Diabetic Pregnancy Study Group; FPG, fasting plasma glucose; WHO, World Health Organization; FIGO, International Federation of Gynecology and Obstetrics; NICE, National Institute for Health and Care Excellence; ACOG, American Congress of Obstetricians and Gynecologists; CC, Carpenter and Coustan; NDDG, National Diabetes Data Group; BMI, body mass index; ADA, American Diabetes Association; T1DM, Type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Table 3 One-Step Screening with IADPSG Criteria versus One- or Two-Step Screening with Other Criteria

Author, Year/ Country (Ref.)	Design	Subjects (N)	Study Population	Comparison	Main Results
Observational Studies					
Agarwal, 2010/ UAE[45]	Retrospective cohort study	10,283	All pregnant women	Impact of IADPSG criteria on GDM diagnosis compared to ADA criteria	The IADPSG criteria caused a 2.9-fold increase in GDM prevalence (37.7% of all pregnant women with IADPSG criteria vs 12.9% with ADA criteria)
Rajput, 2012/ India[49]	Prospective study	607	Pregnant women without ODIP	HbA1c in combination with ADA vs IADPSG criteria for diagnosis of GDM	7.1% were diagnosed as having GDM based on ADA criteria while 23.72% women were diagnosed as having GDM using IADPSG criteria
Benhalima, 2013/ Belgium[59]	Retrospective cohort study	6727	Singleton pregnancies without ODIP and bariatric surgery	CC criteria (old GDM) vs IADPSG criteria (new GDM) for GDM screening	More women were identified as having GDM using the IADPSG criteria and these women carried an increased risk for adverse gestational outcome compared to women without GDM
Duran, 2014/ Spain[56]	Prospective cohort study	3276	Pregnant women without ODIP	One-step IADPSG vs two-step ADA recommended GDM screening	Application of IADPSG screening was associated with a 3.5-fold increase in GDM prevalence as well as significant improvements in pregnancy outcomes
Fuller, 2014/ US[50]	Pre–post comparison study	812	Pregnant women without ODIP and gastric bypass	One-step (2h 75g OGTT, IADPSG criteria) vs two-step (50g GCT followed by 3h 100g OGTT and CC criteria if GCT ≥7.5 mmol/L)	Despite a 4.7% increase in GDM (from 7% to 11.7%), no differences in delivery or neonatal outcomes and no lower rates of compliance with screening were found when using one-step vs two-step screening
Hung, 2015/ Taiwan[58]	Before–after retrospective cohort study	6697	Singleton pregnancies >24 weeks without ODIP	One-step IADPSG screening (P2) vs two-step screening (50g GCT followed by 100g 3h OGTT with CC criteria if the GCT ≥7.8 mmol/L) (P1)	GDM incidence increased from 4.6% in P1 to 12.4% in P2. Adoption of the IADPSG criteria led to a significant reduction in maternal weight gain during pregnancy, birth weight, and the rates of macrosomia and LGA
Meek, 2015/ UK[60]	Retrospective study	25,543	Singleton pregnancies without ODIP	One-step IADPSG criteria vs one-step NICE 2015 criteria for GDM screening	The IADPSG criteria identified women at substantial risk of complications such as LGA who would not be identified by the NICE 2015 criteria
Feldman, 2016/ US[52]	Before–after retrospective cohort study	6066	Singleton pregnancies without ODIP	One-step (IADPSG criteria) vs two-step GDM screening (CC criteria)	The IADPSG screening method was associated with a higher rate of GDM (27% vs 17%) but not with a reduction in LGA newborns or cesarean deliveries

(*Continued*)

Table 3 (Continued).

Author, Year/ Country (Ref.)	Design	Subjects (N)	Study Population	Comparison	Main Results
March, 2016/ US[53]	Retrospective cohort study	235	Singleton pregnancies	One-step (IADPSG) vs two-step (NDDG criteria) GDM screening	The one-step method identified women with at least equally high risk of adverse outcomes as the two-step method
Waters, 2016/ North America[48]	Secondary analysis of prospectively collected data	6159	Singleton pregnancies without ODIP and fertility treatment	GDM based on CC criteria (also GDM based on IADPSG criteria) vs GDM diagnosed with IADPSG criteria but not CC criteria vs no GDM	Women diagnosed with GDM based on IADPSG criteria had higher adverse outcome frequencies compared with women without GDM
Huhn, 2017/ Switzerland[43]	Retrospective cohort study	1367 allocated	Women with singleton pregnancy and without ODIP	Two-step screening with 50 g GCT and 2h 75g OGTT (period 1) vs one-step 75g OGTT with IADPSG criteria (period 2)	Introduction of the IADPSG criteria resulted in an absolute increase of GDM prevalence of 8.5% (3.3% in period 1 to 11.8% in period 2)
Adam, 2017/ South Africa[44]	Prospective cohort study	554	All pregnant women <26 weeks	IADPSG vs NICE vs WHO 1999 vs Western Cape criteria using universal or selective screening	Substantial increase in prevalence of GDM with use of the IADPSG criteria, regardless of universal or selective screening
Luewan, 2018/ Thailand[46]	Prospective descriptive study	648	Singleton pregnancies excluding those with high risk for GDM	One-step (IADPSG) vs two-step GDM screening based on preference	Prevalence of GDM was significantly higher in the one-step group (32.0% vs 10.3%) without clear evidence of better outcomes
Goedegebure, 2018/the Netherlands[55]	Multicenter retrospective cohort study	1386	Singleton pregnancies without ODIP	WHO-2013 (IADPSG) vs WHO-1999 GDM criteria	Using WHO-2013 criteria resulted in earlier GDM diagnosis, less need for insulin treatment and more spontaneous deliveries, but no differences in adverse pregnancy outcomes compared to WHO-1999 criteria
Benhalima, 2018 (Diabetes Care)/ Belgium[89]	Multicentric prospective cohort study	2006	Singleton pregnancies without ODIP and history of bariatric surgery	Sensitivity and specificity of the 50g GCT in a universal two-step screening strategy for GDM using IADPSG criteria vs a universal one-step screening with the 75g OGTT and IADPSG criteria	The GCT has a moderate diagnostic accuracy in a universal two-step screening strategy with IADPSG criteria; lowering the threshold for the GCT from 7.8 to 7.2 mmol/L would increase sensitivity from 60% to 72% and more than 60% of all OGTTs could be avoided
Pocobelli, 2018/US[54]	Before–after cohort study	23,257	Singleton live birth deliveries in women without ODIP	Two-step screening with 50g GCT/ FPG test followed by a 3h 100g OGTT vs one-step IADPSG screening	Adopting the one-step approach was associated with an increase in GDM diagnosis (by 41%), and in rates of labor induction and neonatal hypoglycemia, without association with other outcomes including cesarean delivery or macrosomia

(*Continued*)

Table 3 (Continued).

Author, Year/ Country (Ref.)	Design	Subjects (N)	Study Population	Comparison	Main Results
Costa, 2019/ Belgium[51]	Retrospective cohort study	6051	Singleton pregnancies without ODIP	Two-step (50g GCT and 75g OGTT if GCT ≥7.8 mmol/L; CC criteria) vs one-step screening (IADPSG criteria)	GDM prevalence increased from 3.4% to 16.3%, without having a statistically significant impact on pregnancy outcomes
Cade, 2019/ Australia[57]	Quasi-experimental retrospective study	14,498	Singleton pregnancies without ODIP	1991/1998 ADIPS criteria vs IADPSG criteria	Adoption of IADPSG criteria increased the incidence of GDM by 74% and the overall cost of care without obvious changes in immediate clinical outcomes
Meloncelli, 2020/ Australia[47]	Pre–post comparison study	124,117	All pregnant women giving birth >24 weeks	Two-step process and 1998 ADIPS GDM diagnostic criteria (in 2014) vs one-step process and IADPSG criteria (in 2016)	GDM diagnosis increased from 8.7% to 11.9%, with no observed changes to measured perinatal outcomes, except for a very small decrease in respiratory distress
RCTs					
Mirzamoradi, 2015/Iran[61]	RCT	189	Singleton pregnancies without ODIP, with a disturbed FPG or blood sugar at the OGTT	Interventional (one-step screening with IADPSG criteria) vs control group (two-step GDM screening according to ACOG recommendation and CC/NDDG criteria)	Although the treatment of mild GDM (IADPSG) could not significantly decrease severe gestational outcomes, it did significantly reduce the risk of hyperbilirubinemia (OR 0.25) and its subsequent complications
Abebe, 2017 (ongoing)/US[65]	RCT	921	Pregnant women from 18 to 28 weeks gestation	50g GCT for all participants, then 1:1 randomization in 75g (one-step, IADPSG) or 100g (two-step, CC) OGTT	No results published yet
Satodiya, 2017/India[62]	RCT	1000	Pregnant women without ODIP	Two-step screening (ACOG recommendation, group A) vs one-step screening (IADPSG criteria, group B)	Incidence of GDM using IADPSG criteria was almost doubled (11.8% vs 19.2%), whereas maternal and fetal outcomes were comparable, except in 15.8% women diagnosed as GDM and suffered from hypoglycemia
Fadl, 2019 (ongoing)/ Sweden[64]	RCT	± 65,000	Pregnant women without ODIP	Intervention (WHO 2013 criteria) vs control group (former Swedish diagnostic criteria)	No results published yet (expected in 2020)
Hillier, 2021/ US[63]	RCT	23,792	Singleton pregnancies without history of bariatric surgery	One-step (2h 75g OGTT according to IADPSG criteria) vs two-step GDM screening (1h 50g GCT and a 3h 100g OGTT according to CC criteria)	Despite more diagnoses of GDM with the one-step approach (16.5% vs 8.5%), there were no significant differences in the risks of the primary outcomes relating to perinatal and maternal complications

Abbreviations: UAE, United Arab Emirates; IADPSG, International Association of the Diabetes and Pregnancy Study Groups; GDM, gestational diabetes mellitus; ADA, American Diabetes Association; ODIP, overt diabetes in pregnancy; HbA1c, hemoglobin A1C; CC, Carpenter and Coustan; OGTT, oral glucose tolerance test; GCT, glucose challenge test; LGA, large-for-gestational age; NICE, National Institute for Health and Care Excellence; NDDG, National Diabetes Data Group; WHO, World Health Organization; FPG, fasting plasma glucose; ADIPS, Australasian diabetes in pregnancy society; RCT, randomized controlled trial; ACOG, American Congress of Obstetricians and Gynecologists.

0.021), cesarean section (25.4 to 19.7%; −23.9%, p < 0.002), LGA rate (4.6 to 3.7%; −20%, p < 0.004), SGA rate (7.7 to 7.1%; −6.5%, p < 0.042), and NICU admissions (8.2 to 6.2%; −24.4%, p < 0.001).[56] In contrast, an Australian study showed a 74% increase in annual incidence of GDM by changing from the "Australasian Diabetes in Pregnancy Society" (ADIPS) diagnostic criteria to the universal IADPSG strategy. This was not associated with improvements in primary health outcomes such as caesarean section rates, hypertensive disorder of pregnancy, LGA infant rates and preterm birth.[57] However, babies born to mothers with GDM diagnosed with the IADPSG criteria had lower rates of neonatal hypoglycemia and NICU admissions, suggesting a milder form of the disease.[57] A Belgian retrospective cohort study reported that GDM prevalence increased significantly from 3.4% to 16.2% comparing a two-step screening strategy with one-step IADPSG criteria, but no significant differences in maternal and neonatal complications were observed.[51] A pre-post comparison study in Australia also found that the introduction of the IADPSG criteria increased GDM prevalence from 8.7% to 11.9%, but that it was not associated with lower rates of gestational hypertension, cesarean birth, or LGA or SGA neonates.[47] A multicenter retrospective study demonstrated that introducing the IADPSG criteria resulted in an earlier GDM diagnosis, lower rates of insulin treatment and more spontaneous deliveries compared with a cohort diagnosed with the 1999 WHO criteria. However, no significant differences were found in adverse pregnancy outcomes.[55] Studies that evaluated perinatal outcomes of women diagnosed with GDM by the IADPSG criteria who would not have been identified with other criteria showed in general that these women had higher adverse outcome rates compared with GDM-negative controls.[48,59,60]

These conflicting results highlight the need for long-term, adequately powered, prospective research to establish if applying the IADPSG one-step screening strategy decreases the frequency of adverse outcomes. An overview of the (ongoing) RCTs is given in Table 3. A small Iranian RCT compared pregnancy outcomes in women diagnosed with GDM by the IADPSG one-step screening versus two-step screening using the CC criteria. They demonstrated that the group diagnosed with the IADPSG criteria had only a decreased risk of neonatal hyperbilirubinemia (odds ratio (OR) 0.25, 95% CI 0.68–0.88).[61] Another RCT performed in 1000 pregnant women compared the incidence, maternal and fetal outcomes of GDM diagnosed using the one-step screening with IADPSG criteria versus two-step screening with GCT and diagnosis based on a 100g OGTT with CC criteria.[62] They found that the incidence of GDM using IADPSG criteria almost doubled (19.23% vs 11.81%, p=0.0001), and that maternal and neonatal outcomes were comparable in both groups except for lower rates of preterm delivery (11.6% vs 24.1%, relative risk (RR) 2.08, 95% CI 1.01–4.2, p = 0.046) and neonatal hypoglycemia (7.4% vs 29.31%, RR 3.98, 95% CI 1.75–9.01, p = 0.003) when using IADPSG criteria. Very recently, a large pragmatic RCT in about 23,000 pregnant women from the US evaluated the impact of a one-step screening strategy with IADPSG criteria compared with two-step screening with GCT and 100g OGTT using the CC criteria. They showed that despite a much higher rate of GDM diagnosis in the IADPSG group (16.5% vs 8.5%,), there were no significant differences in perinatal and maternal complications between both groups.[63] The Changing Diagnostic Criteria for Gestational diabetes (CDC4G) in Sweden study is an ongoing RCT (ISRCTN41918550) that also aims to evaluate whether treating women with GDM diagnosed by the IADPSG screening strategy will reduce the risks of adverse pregnancy outcomes.[64] Another ongoing RCT (NCT02309138) involves 921 women to compare diagnosis of GDM and pregnancy outcomes according to the CC criteria compared with the IADPSG criteria.[65]

In conclusion, implementing the IADPSG screening strategy leads to a much higher prevalence of GDM without evidence of improvement pregnancy outcomes compared to a two-step screening strategy using the CC criteria for GDM. However, long-term follow-up studies are needed since women identified as GDM by the IADPSG screening strategy might be a higher risk population for diabetes and obesity postpartum. The HAPO Follow-up Study investigated whether GDM diagnosed with IADPSG criteria was associated with long-term risks for a disorder of glucose metabolism in mothers and greater adiposity in children.[66] They found that GDM diagnosed with IADPSG criteria was significantly associated with maternal development of prediabetes or T2DM (OR 3.44), but not with childhood overweight or obesity at a median follow-up of 11.4 years. However, additional analysis showed that the children of these mothers had increased measures of adiposity and a higher risk of impaired glucose tolerance compared with offspring of mothers without GDM.[67,68] With the increasing prevalence of GDM and potential transgenerational impact on the

offspring, adequately powered interventional trials are needed to investigate the effect of prevention and treatment of GDM diagnosed with IADPSG criteria on long-term maternal and childhood outcomes.

Screening Based on Risk Factors or Universal Screening for GDM

The debate on the best way to screen for GDM continues, with conflicting recommendations for universal and selective screening. Over the past years, different screening tools have been proposed to diminish the need for an OGTT, but large inconsistencies exist regarding the specific screening procedures and outcomes that should necessitate diagnostic testing. The ongoing discussion is also due to the lack of RCTs that have evaluated whether universal screening for GDM leads to better pregnancy outcomes than selective screening for GDM.

In several guidelines, the decision for a diagnostic test is often still based on maternal risk factor assessment,[69–72] but there is no clear consensus on which risk factors should be included in the decision-making process and whether this is an adequate approach to screen for GDM. Comparing the accuracy of different European selective screening guidelines to detect GDM, Benhalima et al showed that about 50% of pregnant women would need an OGTT with the lowest number of missed cases (33%) by the Dutch guidelines.[73] Various studies have confirmed that a risk-factor-based approach misses 5–45% of GDM cases[74–81] (Table 4). An argument for using a selective, risk-factor-based approach would be that women who are only detected as part of universal screening and not by risk-factor-based screening, have a milder form of GDM with similar pregnancy outcomes as the background pregnant population. A French retrospective cohort study found that selective screening based on risk factors would have missed one-sixth of GDM cases diagnosed with IADPSG criteria, but that these cases were milder, characterized by normal FPG, and that LGA was only associated with GDM in the presence of risk factors.[80] A more recent retrospective study in more than 12,000 women confirmed that women with GDM diagnosed according to the IADPSG criteria without risk factors had fewer obstetric and neonatal complications compared with those having risk factors.[82] In contrast, several studies showed that missed GDM cases without risk factors had worse pregnancy outcomes than women without GDM.[77,78] For example, data from the Irish ATLANTIC-DIP study reported that selective screening based on risk factors in a Caucasian population missed 20% (using National Institute for Health and Care Excellence (NICE) criteria), 16% (following Irish guidelines), and 5% (with ADA guidelines) of women diagnosed with GDM using IADPSG criteria.[78] Moreover, outcomes in these pregnancies were worse compared with normal glucose tolerance (NGT) pregnancies, including hypertensive disorders, cesarean sections, polyhydramnios, congenital malformations and NICU admissions.[78] Often, the choice between universal and selective screening depends on the organization of prenatal care and the characteristics of the pregnant population, which differ widely internationally. In general, most guidelines such as the ADA, WHO and the International Federation of Gynecology and Obstetrics (FIGO) recommend universal screening in countries with enough resources, while alternative screening strategies can be used in low resource settings.[1,2,83]

One-Step versus Two-Step Screening

Several professional associations such as the American College of Obstetricians and Gynecologists (ACOG), the National Institute of Health (NIH), German and Flemish guidelines recommend a universal two-step screening strategy, using a non-fasting 50g GCT to limit the number of OGTTs that are needed.[84–87] The GCT has the advantage that it can be performed in the non-fasting state, it is better tolerated and takes less time than the OGTT, and can therefore be easily implemented in primary care. The GCT has been used in combination with the 100g OGTT or the 75g OGTT with various diagnostic criteria such as the CC criteria, the NDDG criteria, the 1999 WHO criteria, or the Canadian Diabetes Association criteria. A systematic review showed in 2013 that the sensitivity and specificity for the OGTT at a GCT threshold of 7.8 mmol/L after 1 hour were 70–88% and 69–89% respectively. At a threshold of 7.2 mmol/L after 1 hour, sensitivity varied between 88% and 99% and specificity between 66% and 77%.[88] More recently, the two-step screening strategy with diagnosis based on the 100g OGTT and CC criteria has been shown to lead to similar pregnancy outcomes compared to the one-step approach with IADPSG criteria, while it has the advantage that the number of OGTTs can be limited and that the prevalence of GDM is much lower[63] (Table 3). A large Belgian multicentric prospective cohort study (BEDIP-N) has demonstrated that a GCT can also be used in a two-step screening strategy with the diagnosis of GDM based on a 75g OGTT with the IADPSG criteria[89] (Table 3). However, to have an

Table 4 Selective Screening Based on Risk-Factors versus Universal Screening

Author, Year/ Country (Ref.)	Design	Subjects (N)	Study Population	GDM Criteria	Comparison	Main Results
Cosson, 2006/ France[77]	Observational study	4020	Singleton pregnancies without ODIP	2h 75g OGTT /FPG >5.3 mmol/L (French guidelines) or 2h >7.8 mmol/L (WHO 1999) or both	Selective (risk-factor based) vs universal screening	Universal rather than selective screening for GDM may improve outcomes as universal screening might reduce delay of diagnosis and care
Dahanayaka, 2012/Sri Lanka[75]	Cross-sectional descriptive study	405	All pregnant women	IADPSG criteria vs WHO 1999 criteria at 24–28 weeks	GDM diagnosis based on IADPSG criteria (75g OGTT) vs risk-factor based approach (WHO 1999 criteria)	The risk-factor based approach missed 38.9% of GDM cases
Arora, 2013/ Thailand[74]	Cross-sectional study	593	All pregnant women	1h 50g GCT followed by, if GCT ≥7.8 mmol/L, a 3h 100g OGTT/ACOG (CC) criteria	Risk vs non-risk factor group	21.8% of GDM cases had no risk factor and only 52.8% of pregnant women would enter the screening process when using risk-based screening
Avalos, 2013/ Ireland[78]	Retrospective cohort study	5500	All pregnant women	2h 75g OGTT at 24–28 weeks/IADPSG criteria	Universal (IADPSG) vs selective GDM screening (Irish vs ADA vs NICE guidelines)	20% (NICE), 16% (Irish), and 5% (ADA) of women with GDM had no risk factor and would have gone undiagnosed
Olagbuji, 2015/Nigeria[81]	Prospective observational study	1059	Singleton pregnancies without T2DM	2h 75g OGTT at 24–32 weeks/IADPSG criteria	Universal one-step (75g OGTT) vs risk factor based GDM screening at 24–32 weeks using WHO 1999, WHO 2013/IADPSG criteria	20% of GDM cases would have been undiagnosed if risk-factor based approach was employed
Miailhe, 2015/ France[80]	Retrospective cohort study	2187	Singleton pregnancies without ODIP	2h 75g OGTT at 24–28 weeks/IADPSG criteria	Universal vs selective (risk factors were those recommended by the IADPSG and French guidelines) GDM screening	Selective screening would have missed 17% of GDM cases diagnosed with IADPSG criteria, but these cases were milder; LGA was associated with GDM in the presence but not in de absence of risk factors
Meththananda Herath, 2016/ Sri Lanka[79]	Clinic-based cross-sectional study	452	Pregnant women without ODIP	2h 75g OGTT at 24–28 weeks/IADPSG criteria and WHO 1999 criteria	Risk factor based vs universal screening using IADPSG and WHO 1999 criteria	Risk-based screening had a lower detection rate of GDM; however, it reduced the necessity of screening by 20%

(*Continued*)

Table 4 (Continued).

Author, Year/ Country (Ref.)	Design	Subjects (N)	Study Population	GDM Criteria	Comparison	Main Results
Agbozo, 2018/ Ghana[76]	Prospective blind comparison with a gold standard study	491	All pregnant women ≥15 years without ODIP	WHO 2013 criteria vs NICE 2015 criteria	Selective screening at 13–20 weeks using reagent-strip glycosuria vs RPG vs presence of ≥1 risk factor(s) vs universal screening at 20–34 weeks following the 'one-step' approach	Use of risk factors is a better screening tool compared to glycosuria/ RPG because risk factors would miss ±50% of the true positive rate, whereas glycosuria and RPG would miss ±90%
Benhalima, 2019/ Belgium[73]	Retrospective analysis of prospectively collected data	1811	Singleton pregnancies without ODIP and history of bariatric surgery	2013 WHO criteria vs NICE 2015 (English) guidelines vs Irish guidelines from 2010 vs French guidelines from 2010 vs Dutch guidelines from 2010	Universal screening (75g OGTT) vs selective screening according to NICE 2015 vs Irish guidelines from 2010 vs French guidelines from 2010 vs Dutch guidelines from 2010	By applying selective screening by most European guidelines, about 50% of women would need an OGTT with the lowest number of missed cases (33%) by Dutch guidelines; GDM women without risk factors had higher rates of neonatal hypoglycemia than NGT women
Matta-Coelho, 2019/ Portugal[82]	Retrospective cohort study	10,443	All pregnant women	2h 75g OGTT at 24–28 weeks/IADPSG criteria	Universal vs risk factor based GDM screening	31.8% would have remained undiagnosed if risk factor based screening was implemented and women with risk factors diagnosed with GDM on universal screening presented worse obstetric and neonatal outcomes

Abbreviations: GDM, gestational diabetes mellitus; IADPSG, International Association of the Diabetes and Pregnancy Study Groups; OGTT, oral glucose tolerance test; WHO, World Health Organization; ADA, American Diabetes Association; NICE, National Institute for Health and Care Excellence; T2DM, type 2 diabetes mellitus; FPG, fasting plasma glucose; LGA, large-for-gestational age; RPG, random plasma glucose; HbA1c, hemoglobin A1C; ODIP, overt diabetes in pregnancy; NGT, normal glucose tolerance.

acceptable sensitivity to screen for GDM with the IADPSG criteria, the threshold of the GCT should be lowered from 7.8 to 7.2 mmol/L after 1 hour. In our center, a modified two-step screening strategy combining the GCT ≥7.2 mmol/L with clinical risk factors is applied.[87] Women with a BMI ≥30 kg/m^2 and/or a previous history of GDM immediately receive a 75g OGTT with the use of IAPDSG criteria at 24 weeks since they are at high risk for GDM, while women without any of these risk factors would be screened with a 50g GCT. This strategy can reduce the workload and the need for an OGTT in nearly 60% of the women while reducing the number of women that would be missed with GDM.

Additional Screening Methods

An overview of studies investigating additional screening methods for GDM to limit the number of OGTTs needed is given in Table 5.

An FPG at the time of screening for GDM between 24 and 26 weeks of pregnancy can be used to decide whether

Table 5 Use of FPG, HbA1c or pGCD59 as a Screening Tool

Author, Year/ Country (Ref.)	Design	Subjects (N)	Study Population	Comparison	Main Results
FPG					
Agarwal, 2010/UAE[45]	Retrospective cohort study	10,283	All pregnant women screened for GDM at 24–28 weeks	GDM diagnosis based on IADPSG vs ADA criteria /FPG ≥4.2 mmol/L vs ≥4.4 mmol/lL vs ≥4.7 mmol/L vs 5.0 mmol/L vs 5.1 mmol/L	Rule-in/rule-out approach for FPG to predict GDM with FPG ≥ 5.1 mmol/L ruling in GDM in 28.9% of women with 100% specificity and FPG < 4.4 mmol/L ruling out GDM in 21.7% women at a sensitivity of 95.4%, eliminating half of the OGTTs needed
Göbl, 2012/ Austria[93]	Secondary analysis of a prospective cohort study	1336	Women without ODIP	Elaboration of a screening algorithm combining (1) FPG and (2) a multivariable risk estimation model focused on individuals with normal FPG levels to decide if a further OGTT is indicated	A risk estimation model in addition to FPG was accurate for detecting GDM in participants with normal FPG
Maesa, 2018/ Spain[92]	Retrospective study	6573	All pregnant women	Three groups: normal glycaemia vs glucose intolerance (1 point in OGTT equal or above established thresholds) vs GDM diagnosis	Women with FPG ≤3.4 mmol/L were at low risk of developing GDM with a sensitivity of 91.3%, thereby avoiding a two-step screening in 10% of their population
Saeedi, 2018/ Sweden[91]	Cross-sectional population-based study	3616	All pregnant women	Risk factors and FPG vs IADPSG criteria for GDM diagnosis	Risk factor screening for GDM was poorly predictive, but FPG of 4.8–5.0 mmol/L high sensitivity and specificity irrespective of diagnostic model and resulted in a low rate of OGTTs
Dickson, 2020/South Africa[90]	Cross-sectional prospective study	589	Pregnant women without ODIP <28 weeks	Selective screening (risk factor based) vs universal application of FPG ≥4.5 mmol/L to identify women with GDM	Universal screening using FPG ≥4.5 mmol/L had greater sensitivity and specificity in identifying GDM and required fewer women to undergo a resource-intensive diagnostic OGTT than selective screening
FPG					
O'Connor, 2012/Ireland[98]	Prospective cohort study	311	Non-diabetic Caucasian pregnant and non-pregnant women	Non-pregnant vs T1 (trimester 1) vs T2 vs T3	HbA1c trimester-specific reference intervals are required to better inform the management of pregnancies complicated by diabetes
Lowe, 2012/ International[96]	Secondary analysis of a prospective cohort study	21,064	Singleton pregnancies without ODIP	Association of HbA1c and model 1 vs model 2 vs model 3	Associations were significantly stronger with glucose measures than with HbA1C for adverse neonatal outcomes, suggesting that measurement of HbA1c is not a useful alternative to an OGTT for diagnosing GDM in pregnant women

(*Continued*)

Table 5 (Continued).

Author, Year/ Country (Ref.)	Design	Subjects (N)	Study Population	Comparison	Main Results
Rajput, 2012/ India[49]	Prospective cohort study	607	Women without ODIP	ADA vs IADPSG criteria/OGTT in combination with HbA1c <5.45% vs 5.45–5.95% vs >5.95%	HbA1c in combination with an OGTT obviated the need of OGTT in 61.8% of GDM cases and HbA1c >5.95% could be used to diagnose GDM in pregnant women with a specificity of 92.7%
Renz, 2015/ Brazil[97]	Diagnostic test accuracy study	262	Pregnant women without ODIP	Reference test (OGTT) vs index test (HbA1c)/sensitivity, specificity and likelihood ratios of different HbA1c cut-off points	Different HbA1c cut-off points in combination with an OGTT may be a useful diagnostic tool for GDM
Khalafallah, 2016/ Australia[99]	Prospective cohort study	480	Singleton pregnancies without early GDM diagnosis (<24 weeks)	HbA1c levels (4.6–10%) vs OGTT results	Pregnant women with an HbA1c of ≥5.4% should proceed with an OGTT, resulting in a significant reduction in the burden of testing
Odsaeter, 2016/ Norway[100]	Retrospective analysis of RCT data	677	Singleton viable pregnancies without high risk	HbA1c levels alone or in combination with patient characteristics and GDM-WHO vs GDM-IADPSG	HbA1c may have a potential for screening for GDM since it is possible to exclude GDM in a significant proportion of women and could therefore reduce the number of OGTTs
pGCD59					
Ghosh, 2017/ US[102]	Case-control study	1000	Women undergoing routine two-step GDM screening	pGCD59 in women with normal GCT (control subjects) vs women with a failed GCT and a subsequent OGTT (case patients)	One pGCD59 measurement during weeks 24–28 identified pregnancy-induced glucose intolerance with high sensitivity and specificity and could potentially identify the risk for LGA
Ma, 2020/ Europe[103]	Ancillary descriptive study	693	Obese women (BMI> 29) undergoing a 75g, 2h OGTT at <20 weeks	pGCD59 in NGT women vs GDM diagnosed <20 weeks vs GDM diagnosed 24–28 weeks	pGCD59 accurately identified GDM in early pregnancy; One-unit increase in maternal pGCD59 level was associated with 36% increased odds of delivering an LGA infant
Bogdanet, 2020 (ongoing)/ Ireland[104]	Prospective cohort study	±2000	Pregnant women without ODIP	pGCD59 at first antenatal visit, 24–28 weeks, in T3 and at 12 weeks postpartum vs 75g OGTT/ sensitivity and specificity of pGCD59 to predict the results of the OGTT, adverse outcomes and/or postpartum glucose intolerance	No results published yet

Abbreviations: UAE, United Arab Emirates; GDM, gestational diabetes mellitus; IADPSG, International Association of the Diabetes and Pregnancy Study Groups; ODIP, overt diabetes in pregnancy; ADA, American Diabetes Association; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; GCT, glucose challenge test; NDDG, National Diabetes Data Group; WHO, World Health Organization; HbA1c, hemoglobin A1C; pGCD59, plasma glycatedCD59; LGA, large for gestational age; BMI, body mass index.

a full OGTT is needed for the diagnosis of GDM. When FPG is ≥ 5.1 mmol/L, GDM can be diagnosed according to the IADPSG criteria and an OGTT can be avoided.[2] Alternatively, an FPG threshold with a high negative predictive value for GDM could be applied (in low resource settings) to reduce the number of women requiring an OGTT and at the same time avoiding missed diagnoses. In 2010, a retrospective cohort study in a South Asian population suggested a rule-in/rule-out approach for the FPG to predict GDM, with a higher FPG threshold of ≥5.1 mmol/L ruling in GDM in 28.9% of women with 100% specificity and a lower FPG threshold of <4.4 mmol/L ruling out GDM in 21.7% women at an acceptable sensitivity of 95.4%.[45] This approach could eliminate half of the OGTTs needed to diagnose GDM, thereby providing relief to health-delivery systems in countries with high-risk populations. More recently, a prospective study in South-African women confirmed that universal screening using FPG ≥ 4.5 mmol/L had greater sensitivity and specificity in identifying GDM-affected women and required fewer women to undergo a resource-intensive diagnostic OGTT than risk-factor-based selective screening.[90] Likewise, a retrospective study found that risk factor screening for GDM alone or in combination with random capillary glucose was poorly predictive of GDM, but FPG 4.8–5.0 mmol/l showed good test characteristics and resulted in a low rate of OGTTs needed.[91] A study evaluating FPG as a screening tool to rule-out GDM in a low-risk population found that women with FPG ≤3.4 mmol/L were at low risk of developing GDM with a sensitivity of 91.3%, thereby avoiding a two-step screening in 10% of their population.[92]

Some authors suggest that sensitivity and specificity for risk-factor based GDM screening could be considerably improved by using clinical risk prediction models that include combinations of several risk indicators in combination with FPG for improved prediction. For example, an estimation model developed by an Austrian research group (including history of GDM, glycosuria, family history of diabetes, age, preconception dyslipidemia and ethnic origin, in addition to FPG) showed that it was accurate for detecting GDM in participants with normal FPG. The ROC AUC of the screening algorithm was 0.90 (95% CI 0.88, 0.91) and a cut-off value of 0.20 was able to differentiate between low and intermediate risk for GDM with a high sensitivity.[93] More recent research is also focused on the use of risk models to connect hyperglycemia in pregnancy (HIP) with adverse pregnancy outcomes. A risk calculator developed by an Australian research group integrated the risks of hyperglycemia, maternal BMI and other basic demographic data available at the OGTT, and had a superior performance on ROC analysis for predicting an individual's absolute risk of adverse pregnancy outcomes compared to the existing GDM diagnostic criteria.[94] The Prediction for Risk-Stratified care for women with GDM (PeRSonal GDM) study is still ongoing and will develop, validate and evaluate the clinical utility of a prediction model for adverse pregnancy outcomes in women with GDM.[95] These models show promise for use in clinical practice, but further research and development is necessary.

Several studies evaluated the usefulness of an HbA1c measurement for the diagnosis of GDM. In the large HAPO study cohort, associations were significantly stronger with glucose measures than with HbA1C for different adverse neonatal outcomes, suggesting that measurement of HbA1c is not a useful alternative to an OGTT for diagnosing GDM in pregnant women.[96] Later studies confirmed that even though HbA1c measurement does not have sufficient sensitivity and specificity to be used as the only diagnostic test for GDM, different HbA1c thresholds in combination with an OGTT could be useful in detecting GDM[49,97–100]. In 2019, a systematic review bundled the results of eight studies that investigated the accuracy of HbA1c in the diagnosis of GDM.[101] The diagnostic accuracy of HbA1c was reported at different thresholds ranging from 5.4% to 6.0%, and the AUC was 0.825 (95% CI 0.751–0.899), indicating a good level of overall accuracy. They concluded that the HbA1c test presented high specificity but low sensitivity regardless of the threshold used to diagnose GDM. Therefore, HbA1c could be useful as a rule-in test in association with standard diagnostic tools such as an OGTT to diagnose GDM.

Globally, researchers are working to identify biomarkers that may have potential future application in diagnosing women with GDM. One such promising biomarker is plasma glycated CD59 (pGCD59), a cell membrane-anchored complement regulatory protein that protects "self" cells from complement-mediated damage. A case–control study evaluated levels of pGCD59 in plasma samples from 1000 women who underwent routine screening and diagnosis of GDM. It was the first study to demonstrate that a single measurement of pGCD59 at 24–28 weeks of gestation could identify women with GDM

with high sensitivity and specificity, and that it could potentially identify the risk for LGA.[102] More recently, these findings were confirmed by Ma et al, showing that pGCD59 in pregnant women before 20 weeks of pregnancy accurately predicts the results of the OGTT and that pGCD59 levels were associated with a higher risk of delivering an LGA infant.[103] However, prospective studies are needed to confirm the clinical utility of pGCD59 as a biomarker for detection and diagnosis of GDM. An ongoing study aims to prospectively examine the validity of pGCD59 as a biomarker for the prediction, diagnosis, management and follow-up of women with GDM diagnosed using IADPSG criteria in a one-step approach in an unselected pregnant population.[104]

Two recent systematic reviews elucidated the potential role of other first-trimester biochemical predictors such as inflammatory markers (C-reactive protein, tumor necrosis factor-alpha), insulin resistance markers (fasting insulin, sex hormone-binding globulin), adipocyte-derived markers (adiponectin, leptin) and placenta-derived markers (follistatin-like-3, placental growth factor, placental exosomes).[105,106] However, to convert the findings from observational studies of these biomarkers to clinical practice, strategies that use first-trimester biomarkers to avoid additional screening for GDM should be examined for effects on outcomes and costs.

Screening After Bariatric Surgery

Bariatric surgery (BS) is an effective way to reduce the risk for GDM in obese women.[107] Nevertheless, women often remain overweight after BS and the risk to develop GDM is generally still higher compared to pregnant women with a normal weight. Therefore, screening for GDM is still required in women with a history of BS. However, the diagnosis of GDM after BS is challenging, since an OGTT can trigger dumping syndromes with serious adverse effects. In addition, wide variations in glucose excursions and reactive hypoglycemia on the OGTT have been reported in pregnant women with a history of BS.[108–110] An OGTT is therefore not recommended to use in pregnant women with BS. Guidelines on screening for GDM in women with BS are lacking and there is no evidence that treatment of GDM diagnosed with an OGTT leads to improved pregnancy outcomes in this population.[109] A recent narrative review[111] summarized the results of studies that tested different screening strategies for GDM after BS, and concluded that capillary blood glucose measurements may currently be the most acceptable alternative to the OGTT for screening in pregnancy after BS. They suggested a pragmatic approach in which all pregnant women with a history of BS are screened at 24–28 weeks of pregnancy by recording capillary blood glucose daily before and after meals during 3–7 days. For the diagnostic and intervention glycemic targets, the same treatment targets as recommended by the ADA were proposed (FPG < 5.3 mmol/L, 1h after the meal <7.8 mmol/L or 2h after the meal <6.7 mmol/L). More research is needed to define optimal glycemic targets in this population. In addition, as an alternative to capillary blood glucose measurements, continuous glucose measurement (CGM) should be evaluated for the diagnosis of GDM. Large studies are needed to evaluate the association between glycemic metrics from the CGM with pregnancy outcomes in this population.

Screening in Times of COVID-19

Due to the COVID-19 pandemic, screening for GDM might lead to an increased risk for exposure to the virus. Temporary changes to diagnostic testing procedures for GDM have been recommended. Several large observational studies described how screening for GDM could be organized in a pragmatic way using blood tests and risk calculators (Table 6).

McIntyre et al described how altered diagnostic processes and criteria for GDM during COVID-19 in Australia, Canada and the United Kingdom (UK) would affect GDM frequency and adverse outcomes.[112,113] They showed that the COVID-19 diagnostic approaches reduced GDM frequency by 81% in the UK, by 82% in Canada and by 25% in Australia. Missed GDM cases in Canada displayed similar rates of pregnancy complications to those with GDM, while using UK and Australian modifications, the missed GDM group was respectively at slightly and substantially lower risk. Meek et al[114] reported that women with hyperglycemia at risk of suboptimal pregnancy outcomes were identified with an RPG ≥ 8.5 mmol/L at 12 weeks, and an FPG ≥ 5.2–5.4 mmol/L or HbA1c ≥5.7% at 28 weeks of pregnancy. They recommended using these easy-to-perform laboratory tests when an OGTT is not possible. Thangaratinam et al suggested to undertake additional tests at booking to detect overt diabetes and identify those at highest risk for GDM.[115] At 24 weeks, they recommended to combine FPG with HbA1c to improve the detection rate, since evidence showed that using FPG alone will only pick up about half of all women with GDM, based on NICE or IADPSG criteria. Furthermore,

Table 6 Screening During the COVID-19 Pandemic

Author, Year/Country (Ref.)	Pragmatic Approach	Main Results
Torlone, 2020/Italy[117]	Screening for overt diabetes: FPG ≥6.9 mmol/L or RPG ≥11.1 mmol/L or HbA1c ≥6.5% A single value can be considered valid during COVID-19 emergency Screening for GDM: risk factors assessment Women at high risk for GDM: FPG ≥5.1 mmol/L at 16–18 weeks → GDM Women at high risk for GDM: FPG ≤5.1 mmol/L at 16–18 weeks → FPG at 24–28 weeks ≥5.1 mmol/L → GDM Women at medium risk for GDM: FPG ≥5.1 mmol/L at 24–28 weeks → GDM	An FPG value can be considered diagnostic for GDM only when it is obtained at the gestational age when the OGTT should have been carried out (16–18 weeks in high-risk pregnant women or 24–28 weeks in medium-risk women)
McIntyre, 2020 (Diagnosis and management of GDM during COVID-19)/UK, Canada and Australia[112]	Early in pregnancy: all guidelines: HbA1c ≥ 5.9% Standard screening (24–28 weeks): *UK*: at risk; GDM if HbA1c ≥ 5.7% and/or FPG ≥ 5.6 mmol/L and/or RPG (not preferred) ≥ 9.0 mmol/L *CAN*: GDM if HbA1c ≥ 5.7% and/or RPG ≥ 11.1 mmol/L *AUS*: FPG <4.7 mmol/L=normal; FPG 4.7–5.0 mmol/L=OGTT (WHO 2013 criteria); FPG ≥5.1 mmol/L=GDM	Detecting only those with marked hyperglycemia
Thangaratinam, 2020[115]	Early GDM screening: additional tests at booking (HbA1c and RPG) to detect overt diabetes and identify those at highest risk for GDM. Suggested thresholds and actions: HbA1c ≥ 6.5% or RPG ≥ 11.1 mmol/L: treat as preexisting diabetes. HbA1c 5.9–6.5% or RPG 9–11 mmol/L: consider managing using the GDM pathway. Avoid OGTT at 24–28 weeks and instead offer HbA1c along with FPG or RPG if fasting values are not available Suggested thresholds and actions: HbA1c ≥ 5.7% or FPG ≥ 5.6 mmol/L or RPG ≥ 9 mmol/L: treat as GDM.	Using FPG alone will only pick up half of all women with GDM, based on NICE or IADPSG criteria. Combining FPG with HbA1c may improve the detection rate. Maintaining existing FPG thresholds may be preferable, and services may consider lower thresholds consistent with the IADPSG diagnostic criteria (FPG ≥ 5.1) if resources allow
Van Gemert, 2020/Australia[119]	ADIPS temporary criteria during the COVID-19 pandemic are based on the Queensland Clinical Guidelines: HbA1c measurement in the first trimester for women with risk factors FPG at 24–28 weeks gestation for women not already diagnosed with GDM → GDM diagnosis if FPG is ≥5.1 mmol/L, no OGTT required if FPG ≤4.6 mmol/L, OGTT recommended if FPG of 4.7–5.0 mmol/L	Using a FPG ≤4.6 mmol/L as cut-off to determine that a 75g 2h OGTT is not necessary will reduce the number of women being potentially exposed, but would miss nearly a third of GDM cases
Meek, 2020/UK, Canada, New Zealand and Australia[114]	To evaluate the diagnostic and prognostic performance of alternative diagnostic strategies to 2h 75g OGTTs: HbA1c, RPG and FPG GDM diagnosis: criteria of the UK National Institute for Health and Care Excellence and IADPSG criteria	RPG at 12 weeks, and FPG or HbA1c at 28 weeks identify women with hyperglycemia at risk of suboptimal pregnancy outcomes

(*Continued*)

Table 6 (Continued).

Author, Year/Country (Ref.)	Pragmatic Approach	Main Results
McIntyre, 2020 (Testing for GDM during COVID-19)/UK, Canada and Australia[113]	*UK*: Risk factor based; no OGTT; GDM if HbA1c ≥ 5.7% and/or FPG ≥ 5.6 mmol/L and/or RPG ≥ 9.0 mmol/L *CAN*: universal testing; no OGTT; GDM if HbA1c ≥ 5.7% and/or random VPG ≥ 11.1 mmol/L *AUS*: FPG < 4.7 mmol/L = normal; FPG 4.7–5.0 mmol/L = OGTT (WHO 2013 criteria); FPG ≥ 5.1 mmol/L = GDM	All post COVID-19 modified pathways reduced GDM frequency. Missed GDMs in Canada gave similar rates of pregnancy complications, while using UK and Australian modifications, the missed GDM group was at slightly and substantially lower risk.
Seshiah, 2020/India[116]	"Single test procedure" for diagnosing GDM: 2h PG ≥ 7.8 mmol/L with 75g oral glucose administered to a pregnant woman in the fasting or non-fasting state, without regard to the time of the last meal (glucose load can also be taken at home and the pregnant woman can visit the hospital 2h after the glucose ingestion to give a single sample for plasma glucose estimation)	The economical and evidence based "single test procedure" of DIPSI is most appropriate for screening during COVID-19 as performing OGTTs is resource intensive, the fasting state is impractical with very high dropout rate.
Van-de-l'Isle, 2020/UK[121]	NICE guidelines methodology (75g 2h OGTT) vs RCOG COVID testing for GDM (two-step testing approach): First, women with risk factors for GDM (according to NICE) are tested with HbA1c and RPG at booking → RPG ≥11.1 mmol/L is diagnostic of T2DM, and HbA1c value of 6.8–7.7% is considered indicative of pre-diabetes (women with a value in this range and a prior history of GDM are managed as GDM) Testing at 28 weeks is recommended and a diagnosis of GDM is made if any of the following criteria were satisfied: FPG ≥5.3 mmol/L or HbA1c ≥ 5.7% or RPG ≥9 mmol/L	The overall rate of women identified as having GDM decreased from 7.7% to 4.2% and the COVID-19 regimen failed to detect 57% women identified as GDM
Nachtergaele, 2021/France[118]	Reference standard testing: OGTT at 22–30 weeks according to IADPSG/WHO criteria applying universal screening Seven tested algorithms (termed as "Options"): OGTT only in women with risk factor for HIP, ie, applying selective screening (Option Sel); OGTT in women with FPG 4.7–5.0 mmol/L at 22–30 weeks, applying universal (Option 1) or selective screening (Option 1-Sel) OGTT in women without history of HIP (previous HIP is considered as GDM) and with FPG 4.7–5.0 mmol/L at 22–30 weeks, applying universal (Option 2) or selective screening (Option 2-Sel) FPG alone measured, applying universal (Option 3) or selective screening (Option 3-Sel)	Consideration of a history of HIP and measuring first FPG can avoid more than 80% of OGTTs and identify women with the highest risk of adverse HIP-related events

(*Continued*)

Table 6 (Continued).

Author, Year/Country (Ref.)	Pragmatic Approach	Main Results
Zhu, 2021 /Australia[120]	Initial division into groups according to FPG results (mmol/L): FPG <4.7, FPG 4.7–5.0 and FPG ≥5.1 Division into groups according to how GDM was managed during pregnancy: diet, metformin (MF), insulin and MF + insulin	HbA1c and FPG are poor screening tests for GDM. During the COVID-19 pandemic, the OGTT should be given clinical priority in high-risk patients, an HbA1c cut-off of 5.7% is proposed if it is used for screening. Elevated FPG is a significant predictor for needing medical management for GDM and could be used to enable individualized treatment

Abbreviations: FPG, fasting plasma glucose; RPG, random plasma glucose; HbA1c, hemoglobin A1c; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; UK, United Kingdom; CAN, Canada; AUS, Australia; WHO, World Health Organization; NICE, National Institute for Health and Care Excellence; IADPSG, International Association of the Diabetes and Pregnancy Study Groups; ADIPS, Australasian diabetes in pregnancy society; RCOG, Royal College of Obstetricians and Gynaecologists; T2DM, type 2 diabetes mellitus; HIP, hyperglycemia in pregnancy; MF, metformin.

they suggest that lower FPG thresholds consistent with the IADPSG criteria (FPG ≥ 5.1) could be considered if resources allow. In India, the use of a "single test procedure", consisting of 2h plasma glucose ≥7.8 mmol/L with 75g oral glucose administered to a pregnant woman in the fasting or non-fasting state, without regard to the time of the last meal, is considered most appropriate for screening during the COVID-19 pandemic.[116] Italian guidelines recommended that screening for GDM based on risk factors and FPG forms an acceptable alternative if screening with an OGGT cannot be safely performed.[117] A French study retrospectively applied in more than 4000 women the seven proposals of the Australian-New Zealand Societies to limit the number of OGTTs during the COVID-19 pandemic.[118] In their cohort, the option in which OGTTs would be performed in women without history of HIP and with FPG 4.7–5.0 mmol/L between 22 and 30 weeks of pregnancy, applying universal screening, was preferred. This approach offered a good compromise because it reduced the rate of women undergoing OGTTs by more than 80%, while identifying around 70% of the women with HIP, especially those with the highest risk of adverse outcomes.

Temporarily modified guidelines for GDM screening to limit the number of OGTTs in the context of the COVID-19 pandemic will inevitably lead to underdiagnosing of GDM. A retrospective analysis in almost 2000 women diagnosed with GDM showed that 29% of them had a FPG <4.7 mmol/L and would have been missed applying the temporary ADIPS criteria.[119] Based on these data, the cut-off for the FPG required to identify at least 95% of GDM cases would be ≥4.0 mmol/L. Likewise, a retrospective Australian study[120] showed that 25.3% of GDM cases would be missed using the COVID-19 guidelines. A study from the UK examined the differences in detection rate for GDM comparing the methodology recommended by NICE with the temporarily guidelines for screening during COVID-19 pandemic.[121] They found that the overall rate of women identified as having GDM decreased from 7.7% to 4.2% and that the COVID-19 regimen failed to detect 57% women identified as GDM.

Considerations

There is an ongoing lack of consensus regarding the screening and diagnostic approaches for GDM, with inconsistencies mainly focusing on the appropriate timing of screening, the screening process (one-step vs two-step), the use of a risk-factor-based approach and the different diagnostic criteria for the OGTT.

Up to date, screening for GDM in early pregnancy remains controversial. Observational studies have shown conflicting results on the effect of screening and treatment of GDM in early pregnancy. Smaller RCTs have also not shown conclusive evidence of the beneficial effect of early screening and treatment of GDM. Evidence from large RCTs is needed to evaluate whether early treatment has a positive effect on maternal and neonatal outcomes, without an increased risk for harm such as a higher rate of SGA infants. Awaiting the results of several large ongoing RCTs, screening and treatment of GDM before 24–28 weeks of gestation is currently not recommended in our center.[87] Instead, a pragmatic approach is proposed for women diagnosed with mild hyperglycemia (FPG 5.5–6.9 mmol/L) in early pregnancy. These women are not labeled as early GDM, but we advise a follow-up with a dietician early in pregnancy and provide screening for GDM with a 75g OGTT and IAPDSG criteria at 24 weeks

of pregnancy.[87] Moreover, there is no clear consensus on which criteria should be used to define GDM in early pregnancy. Several studies have shown that FPG and HbA1c in early pregnancy are a poor predictor for GDM later in pregnancy because of low sensitivity. However, they could still be useful in simplifying the algorithm for GDM screening later in pregnancy.

The debate on the most appropriate screening strategy for GDM at 24–28 weeks of pregnancy is also ongoing. Implementing the one-step IADPSG screening strategy often leads to an important increase in the prevalence of GDM, without conclusive evidence regarding the benefits on pregnancy outcomes compared to a two-step screening strategy with GCT. Adequately powered RCTs are also needed to investigate the impact of prevention and treatment of GDM diagnosed with IADPSG criteria on long-term maternal and childhood outcomes. In several guidelines, selective screening for GDM is still applied, using a risk-factor-based approach or a two-step screening strategy with a GCT to limit the number of required OGTTs. However, most studies reported significant numbers of missed GDM cased when implementing a risk-factor-based approach, with conflicting results regarding the impact on pregnancy outcomes. Another potential selective screening approach is the two-step screening strategy with a GCT. This approach has the potential to reduce the need of an OGTT, but evidence has shown that the threshold of the GCT should be lowered to 7.2 mmol/L to reach an acceptable sensitivity when using the IADPSG criteria. Other additional screening methods such as FPG or HbA1c often lack sensitivity and/or specificity to be used as the only diagnostic test, but could be helpful as screening test in association with diagnostic tests. In conclusion, the choice between universal and selective screening often depends on the organization of prenatal care, the characteristics of the pregnant population, and the resources of the country, which differ widely internationally.

In pregnant women with bariatric surgery, capillary blood glucose measurements may currently be the most acceptable alternative to the OGTT for GDM screening. The lack of specific guidelines regarding the screening and management of GDM in women with bariatric surgery highlights the need for more research for a better understanding of how to define and treat dysglycemia in a pregnancy after bariatric surgery.

Since 2020, the COVID-19 pandemic is having a major impact on health care delivery, including the screening processes for GDM and overt diabetes in pregnancy. OGTTs could often not be performed since they involve high risk of exposure and an increased burden on health services. Several guidelines have proposed a pragmatic approach to screen for GDM with HbA1c, FPG or even RPG as an alternative during the COVID-19 pandemic. However, usual guidelines and care should be resumed as soon as the COVID pandemic is controlled.

We performed an extensive narrative review including data from 87 observational studies and RCTs on screening and diagnosing of GDM. We covered several controversial areas, including screening and diagnostic approaches for GDM in early and late pregnancy, after bariatric surgery and in pandemic times such as COVID-19. However, we did not perform a systematic review and could therefore not perform a meta-analysis. We could therefore also not assess the risk of bias of individual studies and did not contact the authors for obtaining missing and unpublished data.

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