Diagnosis of Gestational Diabetes Mellitus

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Chapter 3
Diagnosis of Gestational Diabetes Mellitus

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Highlights

- The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommendations describe a single-step screening strategy using a 75 g oral glucose tolerance test (OGTT), and GDM is diagnosed based on one abnormal value for the fasting, 1-h, or 2-h plasma glucose level.
- The two-step screening strategy consists of an initial non-fasting 50 g glucose challenge test (GCT) and an abnormal test result (i.e., a plasma glucose value after 1 h ≥7.8 mmol/l) is followed by a 100 g OGTT.
- The differences between the various guidelines in terms of cut-off levels indicate the need for large cost–benefit studies of the treatment of GDM diagnosed according to the IADPSG criteria.
- By adopting the IADPSG/WHO diagnostic criteria, the prevalence of GDM has increased, which has a major impact on the costs and the capacity of healthcare systems.
- Universal screening implies that all pregnant women will undergo screening between 24 and 28 weeks of pregnancy, and many countries and societies have adopted such a screening strategy.
- Selective screening based on risk factors is mainly recommended to limit the number of OGTTs performed and limit the risk of somatization/medicalization of pregnancy.

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1 Introduction

Gestational diabetes mellitus (GDM) is defined as hyperglycemia (high blood glucose levels), which is first detected during pregnancy. It was estimated that GDM might affect up to 10–20% of all pregnancies, and the prevalence is expected to keep increasing, among others, as a consequence of an increasing number of pregnant women who are overweight or obese. Untreated GDM is associated with a high risk of obstetric and neonatal complications such as macrosomia (high birth weight), birth trauma, preeclampsia, and cesarean section [1, 2]. Furthermore, women with GDM have an increased long-term risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular diseases in the subsequent years after pregnancy. There is also growing evidence for long-term health consequences for the child (obesity and/or T2DM) [3, 4].

Guidelines around the world describe best practice procedures to screen for the presence of diabetes during pregnancy. The current international discussion focuses on the optimal diagnostic thresholds for GDM and whether it is desirable to screen all pregnant women or only those with specific risk factors for GDM. Earlier studies like the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study have demonstrated an almost linear association between fasting and 2-h post-load glucose levels and the risk of adverse pregnancy outcomes [1]. However, for some pregnancy complications, there is no clear threshold risk found, and therefore, it is unclear at which degree of maternal hyperglycemia any form of glucose-lowering treatment should be provided [5]. This is reflected by the large variation in criteria for GDM diagnosis across countries and guidelines. It must be realized that not all diabetes detected during pregnancy may be GDM. When elevated glucose levels are found in the first trimester of pregnancy, it should be considered that there was preexisting diabetes mellitus before becoming pregnant or a certain form of genetic diabetes, like MODY2.

Tip

Early diagnosis and appropriate treatment of GDM with, for instance, insulin can reduce the risk of pregnancy and neonatal complications [6, 7]. The primary goal of screening for GDM is, therefore, to detect these high-risk pregnancies and subsequently to provide the best possible treatment to achieve optimal glycemic control during pregnancy to prevent these maternal and fetal complications. The first step in treatment is dietary advice by a dietician. Many women achieve adequate glucose levels with such a regimen. If dietary measures fail to achieve and maintain adequate glucose control, starting insulin therapy is the second step, although some guidelines advocate or support the use of oral glucose-lowering agents, especially metformin [8]. Currently, several studies assessing the possible effects of oral agents are ongoing, such as the SUGAR-DIP trial [9] and the Pregnancy Outcomes: Effects of Metformin Study (POEM Study, ClinicalTrials.gov Identifier: NCT02947503). The number of women receiving glucose-lowering therapy in addition to dietary treatment varies considerably between studies. It may amount between 10 and 40% depending on the clinical setting, the population under study, but

also the screening strategy and criteria to diagnose GDM. When a higher cut-off value for fasting plasma glucose is applied, pregnant women are identified who are more severely hyperglycemic, and therefore, relatively more women will need insulin therapy [10].

Finally, it is recommended to do follow-up glucose testing 6–8 weeks after delivery and subsequently once a year for, at least, the next 5 years to detect (early) development into T2DM.

2 Diagnosis: International Diagnostic Thresholds

The original diagnostic criteria for GDM were established in 1964 [11]. The criteria of O'Sullivan and Mahan were based on a 3-h 100 g oral glucose tolerance test (OGTT), and they were specifically chosen to identify women who had a high risk of developing diabetes after pregnancy [11]. Around 1980, the 2-h 75 g OGTT was introduced as a diagnostic test for non-pregnant people. Following, the World Health Organization (WHO) advised that the 75 g OGTT could also be used to diagnose diabetes in pregnancy, initially with similar cut-off values for the diagnosis of GDM as for T2DM, i.e., a fasting plasma glucose (FPG) ≥7.8 mmol/l and a 2-h glucose concentration ≥11.1 mmol/l [12, 13]. In 1997, the American Diabetes Association (ADA) proposed to lower the criterium for fasting plasma glucose from 7.8 to 7.0 mmol/l outside the context of pregnancy [14]. Two years later, the WHO presented its new report on the definition, screening, and diagnosis of GDM, and this was the first step aiming toward a universal guideline [15]. In that report, the same fasting glucose concentrations were recommended for pregnant women as those proposed by the ADA [15]. However, in this period, the diagnostic criteria were not specifically intended to identify those pregnant women with increased risk of adverse maternal and neonatal outcomes.

Background Information
It has been uncertain for a long time to which degree the existence or development of hyperglycemia during pregnancy was responsible for an increased risk of adverse maternal and neonatal outcomes. Several studies have suggested a gradually increasing risk for adverse pregnancy outcomes with increasing blood glucose concentrations in the mother [16–20]. In 2008, a multinational prospective observational study called the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study reported the relationship between fasting and 1- and 2-h plasma glucose concentrations during an OGTT and the subsequent risk of adverse maternal and neonatal outcomes [1]. In this landmark study, over 25,000 women without diabetes with singleton pregnancies

underwent a 75 g OGTT at 24–32 weeks of gestation and were followed for obstetrical and newborn outcomes. The study showed a continuous association between maternal blood glucose concentrations and increased rates of adverse pregnancy outcomes, i.e., birth weight >90th percentile, primary cesarean section, clinical neonatal hypoglycemia, and cord blood serum C-peptide levels >90th percentile, as well as premature delivery, shoulder dystocia or birth injury, admission of the newborn to intensive care, hyperbilirubinemia, and preeclampsia [1]. Already a fasting plasma glucose of 4.8–4.9 mmol/l and 2-h post-OGTT glucose of 7.0–7.7 mmol/l was associated with a doubling of newborns with a birth weight >90th percentile and with a 33% increase in primary cesarean section [1]. As a result of these findings, guidelines for GDM were adapted worldwide. In 2010, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) published their new criteria for the diagnosis of GDM by recommending the following glycemic thresholds for a 75 g OGTT: fasting plasma glucose value ≥5.1 mmol/l (92 mg/dl); 1-h value ≥10.0 mmol/l (180 mg/dl); and 2-h value ≥8.5 mmol/l (153 mg/dl) [5]. These specific cut-off values were chosen because they predict a 75% higher chance of adverse pregnancy outcomes compared to normal blood glucose values [1, 5].

Tip

The IADPSG criteria were adopted by the ADA in 2010 [21] and by the WHO in 2013 [13]. However, the ADA did not follow the one-step diagnostic approach with a 75 g OGTT as recommended by the IADPSG, but also provided the alternative to perform a two-step screening strategy, as described in the National Institutes of Health (NIH) consensus conference report [21, 22]. The IADPSG recommendations describe a single-step screening strategy using a 75 g OGTT, and GDM is diagnosed based on one abnormal value for either the fasting, 1-h or 2-h plasma glucose level. The two-step screening strategy consists of an initial non-fasting 50 g glucose challenge test (GCT), and an abnormal test result (i.e., a plasma glucose value after 1 h ≥7.8 mmol/l) is followed by a 100 g OGTT. GDM is then diagnosed based on two abnormal values in this 100 g OGTT for the fasting, 1-h, 2-h, or 3-h glucose levels, using either the traditional Carpenter and Coustan (CC) criteria [23] or the National Diabetes and Data Group (NDDG) criteria (Table 3.1) [24]. The major reason for supporting a two-step approach was an anticipated twofold to threefold increase of GDM diagnoses with the one-step 75 g OGTT. The major concerns that were expressed were doubts regarding limited benefits, but higher additional direct and indirect healthcare costs associated with diagnosing more women with GDM, as well as fear for higher numbers of cesarean deliveries, more intensive newborn assessments, and psychosocial burdens consequently [22]. This has not been confirmed in additional studies, suggesting that specific application of the NDDG criteria may increase healthcare costs. On the one hand, applying these criteria may decrease the number

of patients diagnosed with GDM; on the other hand, the fear has been expressed that this may increase the costs related to more maternal and neonatal complications [29] (Table 3.1).

Table 3.1 Selection of diagnostic criteria (plasma glucose in mmol/l) for GDM worldwide since 1979

	OGTT	Fasting	1-h	2-h	3-h	Number of abnormal values
NDDG [24]	100 g	≥5.8	≥10.6	≥9.2	≥8.0	≥2
Carpenter/coustan [23]	100 g	≥5.3	≥10.0	≥8.6	≥7.8	≥2
WHO 1999 [15]	75 g	≥7.0		≥7.8		≥1
IADPSG 2010 [5]/WHO 2013 [25]	75 g	≥5.1	≥10.0	≥8.5		≥1
ADIPS [26]	75 g	≥5.1	≥10.0	≥8.5		≥1
ADA 2015 [21]	75 g	≥5.1	≥10.0	≥8.5		≥1
	100 g	≥5.3	≥10.0	≥8.6	≥7.8	≥2
NICE 2015 [8]	75 g	≥5.6		≥7.8		≥1
NVOG 2010 and 18 [27]	75 g	≥7.0		≥7.8		≥1
Flemish consensus 2019 [28]	75 g	≥5.1	≥10.0	≥8.5		≥1

ADA American Diabetes Association, *ADIPS* Australasian Diabetes in Pregnancy Society, *NDDG* National Diabetes and Data Group, *NICE* National Institute for Health and Care Excellence, *NVOG* Nederlandse Vereniging Voor Obstetrie en Gynecology/Dutch Association for Obstetrics and Gynecology, *WHO* World Health Organization

Tip

Not all countries have followed the internationally recognized IADPSG/WHO criteria. In The Netherlands, the 2nd Dutch Society of Obstetrics and Gynecology guideline "Diabetes and Pregnancy" for the screening and treatment of GDM was implemented in 2010. This guideline recommended screening for GDM in high-risk women using a one-step approach with the 75 g OGTT, and for diagnosis of GDM, the older WHO 1999 criteria were advised. In 2018, the guideline was slightly updated, but the cut-off values for diagnosis have not been changed, with a fasting venous plasma glucose ≥7.0 mmol/l or capillary blood glucose ≥6.1 mmol/l, and a 2-h post-OGTT venous plasma or capillary blood glucose level of ≥7.8 mmol/l being diagnostic for GDM. This means that women with fasting plasma levels between 5.2 and 7.0 mmol/l are, in contrast to the IADPSG/WHO criteria, not considered to have GDM. One study, published in 2018, found a limited difference in birth outcomes between the two criteria, GDM/CC and GDM/IADPSG 2010 criteria [30]. However, this study was performed between 2006 and 2010, and data on the treatment of the women were not available. A more recent study from the UK, published in 2015, demonstrated that women with a 2-h post-load level

≥7.5 mmol/l (for Caucasian women) and ≥7.2 mmol/l (South-Asian women) are at increased risk of adverse pregnancy outcomes [31]. This study not only suggested lowering the 2-h post-OGTT threshold but also supported the use of ethnicity-specific diagnostic criteria for GDM.

In summary, there is not a single set of diagnostic criteria for GDM which are accepted worldwide. The most important criteria used by different expert groups are summarized in Table 3.1. The main differences between these guidelines are related to either different cut-off values for fasting plasma higher than those of the IADPSG criteria or differences in post-OGTT glucose concentrations [8, 27]. These differences between the various guidelines in terms of cut-off levels also indicate the need for large cost–benefit studies of the treatment of GDM diagnosed according to the IADPSG criteria. Such studies may help overcome reluctance for a broad implementation of strict diagnostic criteria and perhaps also indicate whether it is appropriate to lower the 2-h post-OGTT glucose to ≥7.8 mmol/l, or even lower, as suggested by Farrar et al. [31]. Arguments that are often brought into the discussion are the limited evidence for the benefit and cost-effectiveness of treatment of GDM when diagnosed according to the IADPSG criteria (mild GDM), and the fact that an OGTT has moderate to poor reproducibility [32, 33]. One of the main reasons for this reluctance is related to the financial consequences for healthcare, especially regarding the burden of obstetric care. Worldwide adoption of the IADSPG criteria would cause a considerable increase in the prevalence of GDM, and as a consequence, a higher burden to obstetric healthcare and higher costs [22, 34–36], and perhaps also a shift in care, with women referred from a midwife to the care by a hospital-based gynecologist. Other reasons include fear of somatization of pregnancy [37, 38]. It should be noted that the increase in the prevalence of GDM is mainly caused by the strict cut-off values for fasting glucose.

Although outside the scope of this chapter, most guidelines advise pregnant women diagnosed with GDM to perform home blood glucose monitoring in the fasting state, and approximately 1 h after each meal, and to maintain fasting blood glucose concentration <5.3 mmol/l (95 mg/dl) and postprandial blood glucose <7.8

Table 3.2 Risk factors for GDM according to the Dutch guideline

• Previous GDM
• Pregestational body mass index (BMI) ≥30 kg/m^2
• Previous infant ≥95th percentile, or ≥4500 g at birth
• First-degree relative with T2DM
• Ethnic origin (South-Asian, Hindu, Afro-Caribbean, Mediterranean, and Middle-Eastern)
• History of intrauterine fetal death
• History of polycystic ovary syndrome
• Signs suggestive of GDM (like fetal macrosomia and/or polyhydramnios)

mmol/l (140 mg/dl) [39]. The ADIPS consensus advised the following glycemic targets: fasting capillary blood glucose ≤5.0 mmol/l, 1 h after commencing meal ≤7.4 mmol/l, and 2 h after commencing meal ≤6.7 mmol/l. Surprisingly, cut-off values for diagnosis and glycemic targets for therapy can differ within the same country-specific guideline.

3 Universal or Risk Factor–Based Screening

There is a lot of controversy in the literature about the screening of GDM, not only about the timing of screening and the diagnostic criteria but also whether selective screening (only high-risk women) or universal screening should be applied. Universal screening implies that all pregnant women will undergo screening between 24 and 28 weeks of pregnancy, and many countries and societies have adopted such a screening strategy. In selective screening, only women who have specific risk factors in developing GDM or who exhibit a possible consequence of hyperglycemia, i.e., macrosomia or polyhydramnios, will undergo an OGTT. The list of risk factors for GDM is long [40]. From a practical point of view, the most important risk factors, as recommended, for instance, in the current Dutch guidelines, are given in Table 3.2.

Selective screening based on risk factors is mainly recommended to limit the number of OGTT's performed and limit the somatization/medicalization of pregnancy. One major issue in the risk factor–based screening is that the number of risk factors varies per country. In addition, some guidelines mention a BMI ≥25 kg/m^2 as a risk factor, while others consider BMI ≥ 30 kg/m^2. There is only limited literature on how many more GDM pregnancies are detected with universal vs. risk factor–based screening. The Atlantic Diabetes in Pregnancy network reported that risk factor–based screening in 5500 pregnant women would have failed to diagnose GDM in 5–20% of women, depending on the set of risk factors applied to selected women [41]. A recent study in France reported 1061 GDM cases in a total cohort of 4518 women [42]. Screening only of women with risk factors would have failed to diagnose 15.4% of those with GDM according to IADPSG/WHO criteria. The risk factors applied in this study were: BMI ≥25 kg/m^2, age ≥35 years, first-degree relative with a history of diabetes, and previous pregnancy with hyperglycemia or a previous macrosomic baby weighing 4.5 kg or more. This was a multi-ethnic cohort of women, with over 60% having an ethnic background, which is considered a risk factor for GDM in other countries [43, 44]. A meta-analysis comprising 29 published studies incorporating over 200,000 pregnant women reported that risk factor–based screening would not detect all women with GDM, and depending on the specific set of risk factors, it will only identify between 65 and 98% [45]. The analyses also suggest that a risk factor combination of age and BMI (age ≥25 years, BMI ≥25 kg/m^2) would identify the majority (>95%) of women with GDM, but this would also mean that an OGTT were to be offered to the majority of women [45].

Benhalima et al. evaluated the differences of risk factor–based screening for GDM based on the predefined sets of risk factors used in various countries like England,

France, and the Netherlands [46]. Compared to universal screening, which yielded a 12.5% prevalence of GDM in 1843 women, risk factor–based screening led to a 50% or higher reduction of OGTT's but also would miss a considerable number of GDM cases. Especially the application of the NICE criteria would reduce the number of OGTT to below 30% but miss almost half of cases with GDM [46]. Applying maternal age ≥30 years or BMI in early pregnancy ≥25 kg/m^2 as risk factors would result that 70% of women were eligible for an OGTT but would only miss 19% of GDM cases. Women with GDM without risk factors had similar pregnancy outcomes but fewer cesarean sections [46]. However, comparing pregnancy outcomes and complications in such studies is difficult, as often information of the specific treatment of GDM (especially the need for insulin treatment) is lacking [45, 47].

Despite the progress in screening and treatment of GDM (the implementation of), current guidelines may not be optimal in reducing the number of large-for-gestational age (LGA) neonates. In an earlier study in The Netherlands, we found that a considerable proportion of women were diagnosed with GDM later than 28 gestational weeks [48]. Consequently, treatment of hyperglycemia started relatively late in pregnancy, which could have resulted in excessive fetal growth.

4 One-Step or Two-Step Approach

Screening for GDM may follow either a one-step or a two-step approach (Table 3.3). In the one-step approach, GDM is diagnosed based on the results of a single 75 g OGTT, whereby GDM is diagnosed based on one abnormal value for the fasting, the 1-h, or the 2-h glucose level based on the IADPSG/WHO criteria. As discussed earlier, the two-step screening strategy is based on the National Institutes of Health (NIH) consensus conference report [21, 22]. This screening strategy makes use of a nonfasting 50 g glucose challenge test (GCT), whereby an abnormal test result (i.e., a 1-h plasma glucose value ≥7.8 mmol/l) is followed by a 100 g OGTT. GDM is then diagnosed based on two abnormal values in this 100 g OGTT for the fasting, 1-h, 2-h, or 3-h glucose levels, using either the Carpenter and Coustan criteria [23] or the NDDG criteria (Table 3.1) [24]. The major reason for supporting a two-step approach has been an anticipated twofold to threefold increase of GDM diagnoses with the one-step approach.

Table 3.3 Differences between the one-step and two-step approaches

Approach	OGTT	Plasma glucose
One-step	75 g OGTT at 24–28 weeks	Fasting, 1 h, 2 h
		Fasting, 2 h
Two-step	Non-fasting 50 g GCT at 24 weeks	1 h
	Followed by a 100 g OGTT	Fasting, 1 h, 2 h, 3 h
Modified two-step [28]	Non-fasting 50 g GCT at 24 weeks	1 h
	Followed by a 75 g OGTT	Fasting, 1 h, 2 h

The approach taken in specific countries sometimes is even more complicated. In 2019, a Belgian consensus was published, in which it was advocated to perform universal screening for overt diabetes when planning a pregnancy or at the latest at first prenatal contact, by measuring fasting plasma glucose and using the same diagnostic criteria as in the nonpregnant situation [28]. In women with impaired fasting glycemia (defined as FPG 100–125 mg/dl), but also women with GDM risk factors, defined as BMI ≥30 kg/m^2 or a previous history of GDM, screening for GDM is to take place between 24 and 28 weeks with a one-step 75 g OGTT. In all other women, so also those with other risk factors like ethnicity or family history of T2DM, a modified universal two-step screening strategy is proposed with a 50 g GCT at 24 weeks followed by a 75 g OGTT, when the glucose level 1 h after the GCT is ≥7.2 mmol/l (130 mg/dl) [28]. Subsequently, GDM is diagnosed according to the IADPSG/WHO criteria. Thus, this Belgian consensus follows an approach in which after an abnormal GCT, a 75 g OGTT, and not a 100 g OGTT is proposed [28].

Several authors have expressed concern about the two-step approach. This appears to be mainly a discussion of underdiagnosis versus overdiagnosis. There is evidence, summarized in a large systematic review, that with this algorithm, 25% of cases with GDM may be missed [49]. A clinical audit performed between 2007 and 2010 in Canada revealed that adherence to the process was not good: overall follow-up was missed in 14.5% of those screened, and only 36% of those who were eligible for the follow-up 75 g OGTT did undergo this test [50]. Additionally, in the usual two-step approach, GDM is diagnosed based on two abnormal values (out of four plasma glucose measurements, i.e., fasting, 1 h, 2 h, and 3 h) in this 100 g OGTT. In this situation, women diagnosed only based on fasting plasma glucose measurement according to the IADPSG/WHO criteria may be labeled “non-GDM” in the two-step screening when the post glucose load values are normal. A recent randomized study compared both approaches and found GDM incidence was 8.1% in the one-step approach and 5.6% in the two-step approach [51]. This difference was not significant, but the groups were relatively small (total n = 249 women). There is a need to identify better which women are diagnosed with the one-step approach versus the two-step approach and whether this would have clinically relevant repercussions on incident maternal and neonatal complications.

5 Prevalence of GDM

Background Information

As mentioned, the prevalence of GDM may vary according to the geographic region and population studied and largely depends on the screening strategy and diagnostic cut-off values for blood glucose. Worldwide, the overall

prevalence of GDM is increasing because of the increase in obesity in the general population and changes in lifestyle, such as an increase in sedentary behavior, as well as advancing maternal age, and excessive weight gain during pregnancy [52]. Several studies have demonstrated that by implementing the IADPSG/WHO criteria, the prevalence of GDM will rise extensively [22, 36]. A study in Ireland reported a major increase in the incidence of GDM rates from 3.1% in 2008 to 14.8% in 2017 after the adoption of the IADPSG 2010 criteria, but also a large variation of GDM incidence between centers, which may indicate differences in implementation of the new criteria [53]. A recent comparison between IADPSG/WHO and NICE 2015 criteria showed a low level of agreement between both, while the IADPSG/WHO identified 25.1% and NICE 2015 identified 11.6% [54]. This difference is mainly caused by the strict fasting glucose criterium of the IADPSG/WHO: the majority (>68%) of the women diagnosed by IADPSG criteria had elevated fasting plasma glucose values alone [54]. This is in accordance with earlier work from our group, reported in 2018 (Table 3.4) [47]. Data on screening was available from 10,642 women who had undergone a 75 g OGTT between January 2011 and September 2016 due to risk factors or signs suggestive of GDM, with measurement of glucose levels at both fasting and 2-h post glucose load. In these women, the prevalence of GDM was 22% if the WHO 1999 criteria were applied and 32% if the WHO 2013 criteria were used (Table 3.4) [47]. By applying the IADPSG/WHO criteria, more women were classified as having GDM, especially based on an elevated fasting glucose concentration. As we did not measure a 1-h post-load glucose concentration, the prevalence of 32% may be underestimated, as in the participants of the HAPO study, 5.7% additional GDMs were identified by the 1-h values when using the IADPSG/WHO criteria [5].

Table 3.4 Differences between WHO 1999 and IADPSG/WHO criteria in 10,642 women for the diagnosis of gestational diabetes

Criteria	WHO 1999	IADPSG/WHO	Mix WHO 1999/2013
Glucose levels (mmol/l)	Fasting ≥7.0 and/or 2 h ≥7.8	Fasting ≥5.1 and/or 2 h ≥8.5	Fasting ≥5.3 and/or 2 h ≥7.8
Total GDM, *n* (%)	2326 (22)	3364 (32)	3153 (30)
Elevated fasting glucose, but 2 h below threshold, *n* (%)	14 (1)	2045 (61)	861 (27)
Elevated 2 h, but fasting glucose below the threshold, *n* (%)	2267 (97)	634 (19)	1570 (50)
Both elevated fasting and 2 h, *n* (%)	45 (2)	685 (20)	742 (23)

Adapted from [47]

Tip
A striking finding of the study was that the women with risk factors for GDM, and who were subsequently found to have normal glucose tolerance, still had a higher incidence of LGA neonates than women in the general obstetric population (18% vs. 11%). This finding suggests that even women eligible for screening but considered not to have GDM are at increased risk of giving birth to an LGA neonate. It is not yet clear whether this is based on the level of obesity of this group, as pregestational BMI>30 kg/m^2 is a prevalent risk factor for GDM, or whether screening may have been carried out too early during pregnancy. Indeed, screening before 24 weeks of gestation may well increase the number of false-negative OGTTs, as insulin resistance gradually increases during the second and third trimesters, and therefore may precede an abnormal OGTT. Therefore, it could be argued to provide an additional screening test after 28 weeks of gestation to identify women who did develop GDM after the second trimester or to identify women who became hyperglycemic after initially testing negative for GDM at the first screening test [55]. Some guidelines indeed offer this [40], while others advocate performing a repeated evaluation with an OGTT in women who initially had a normal test but develop macrosomia and/or hydramnios at 32–34 gestational weeks [39, 56].

In another study, we evaluated specific characteristics of the mother and outcomes of pregnancy in two cohorts in the Netherlands, which applied different diagnostic criteria for GDM, i.e., IADPSG/WHO versus WHO 1999. Women in both cohorts were treated based on the national guideline for GDM, aiming for fasting glucose ≤5.3 mmol/l and 1-h postprandial glucose of ≤7.8 mmol/l. Women in the IADPSG/WHO cohort were more often overweight and were often hypertensive during pregnancy compared with women in the WHO 1999 cohort. In addition, GDM was diagnosed earlier in pregnancy, and these women needed additional insulin therapy less often and had a higher percentage of spontaneous deliveries and a lower percentage of LGA neonates [57].

Finally, we recently assessed what the consequences would be when the diagnostic level of fasting plasma glucose would be increased from ≥5.1 to ≥5.3 mmol/l. Women with fasting plasma glucose of 5.1 and 5.2 mmol/l but post-OGTT<8.5 mmol/l had similar age and prepregnancy BMI compared to those diagnosed according to the IADPSG/WHO criteria. Although only 12.4% of these women were treated (of whom 5.1% with insulin), they had similar rates of gestational hypertension, cesarean section, and LGA neonates, and similar birth weight according to gestational age at delivery (Wolffenbuttel et al., unpublished results). More research into the possibilities to apply less strict fasting plasma glucose levels to diagnose GDM is urgently needed.

6 Specific Thresholds for Fasting and 2-h Glucose Levels

Although many guideline committees have adopted the new IADPSG diagnostic criteria for GDM (75 g OGTT, FG glucose ≥5.1 mmol/l, and/or 1 h ≥10.0 mmol/l, and/or 2 h ≥8.5 mmol/l), evidence that applying these more stringent diagnostic criteria improves short- and long-term pregnancy outcomes has been limited [58]. Therefore, the question remains whether identifying women with mild GDM improves pregnancy outcomes, including reducing the number of LGA neonates.

In an earlier study, we evaluated pregnancy outcomes in a large group of women diagnosed with GDM through a risk factor–based screening [47]. The lower fasting glucose threshold in the IADPSG/WHO criteria identified a group of women who are more likely than those with normal glucose tolerance to be obese and hypertensive [47]. Data on pregnancy outcomes were available for 4431 of these women and were compared between a normal glucose tolerance (NGT) control group and different GDM classification groups. We observed worse outcomes in the women classified as having GDM based only on the IADPSG/WHO criteria for fasting glucose: they were more likely to have gestational hypertension (7.8% vs. 4.9%, $p = 0.003$), to have a planned cesarean section (10.3% vs. 6.5%, $p = 0.001$) and induced labor (34.8% vs. 28.0%, $p = 0.001$) compared with women with normal glucose tolerance. Furthermore, although their babies had similar birth weight, they had a higher likelihood of having macrosomia (22.2% vs. 20.9%, $p = 0.452$) or being born LGA (21.0% vs. 18.0%, $p = 0.077$) and were more likely to have had an Apgar score <7 after 5 min or needing admission to the neonatology department. None of the other neonatal outcomes showed significant differences between these two groups [47]. Thus, we have shown that the lower fasting glucose cut-off value of the WHO 2013 criteria successfully identified a group of women (i.e., women with FG ≥5.1 to ≤6.9 mmol/l) with an increased risk of adverse pregnancy outcomes [47]. Moreover, when compared with the general obstetric population, these women had a twofold higher rate of LGA neonates (21% versus 11%). These findings provide evidence that this category of high-risk women should not be left untreated, and the fasting glucose cut-off level in the guidelines is necessary to improve pregnancy outcomes further. Nevertheless, in our national guidelines, the cut-off for fasting plasma glucose was maintained at ≥7.0 mmol/l during the 2018 revision indicates the different opinions between gynecologists in guideline committees worldwide.

In a recent study in Sweden, a fasting glucose level ≥4.8 mmol/l had a 91% sensitivity and 85% specificity to predict an abnormal OGTT according to the IADPSG/WHO criteria, with a subsequent reduction in the need to perform OGTT [59]. However, the data of the latter study were collected between 1994 and 1996, and the clinical phenotype of GDM has changed much in recent years.

With the evidence that (untreated) mild GDM is associated with an increased risk of adverse pregnancy outcomes, the second question remains whether treating women with mild GDM improves pregnancy outcomes. We already mentioned that women diagnosed with the IADPSG/WHO criteria and treated according to the national guideline had a lower likelihood of having an LGA neonate, a relatively reduced need for insulin treatment and more spontaneous deliveries when compared

with women diagnosed according to the WHO 1999 criteria [57]. It has to be borne in mind that this multicenter study was performed in two different regions in the Netherlands. There might be some differences in the study populations and obstetric management between the hospitals. The women in the WHO 2013 cohort were earlier diagnosed with GDM, which may have influenced the study results. However, as stated before, this last finding could also be a strength of the WHO 2013 criteria.

The implementation of the IADPSG/WHO diagnostic thresholds with the higher 2-h glucose cut-off value of 8.5 mmol/l may exclude a group of women who are otherwise diagnosed and treated for GDM according to the older WHO 1999 criteria (i.e., women with a 2-h glucose level ≥7.8 and ≤8.4 mmol/l). There is not much information on whether women with a 2-h glucose level between 7.8 and 8.5 mmol/l can be safely left untreated. Earlier, we have demonstrated that this category of women had pregnancy outcomes comparable to those of NGT women [47]; however, these women were treated for GDM. Over 20% of them received insulin treatment in addition to dietary therapy to control hyperglycemia [47]. Withholding treatment in these women will increase the proportion of LGA neonates by 10–30%.

Recent data by other investigators demonstrated that even women with a 2-hour post-load glucose level ≥7.5 mmol/l are at increased risk of adverse outcomes [31]. The diagnostic 2-h glucose thresholds (2-h glucose ≥7.5 mmol/l for Caucasian women and 2-h glucose ≥7.2 mmol/l for South Asian women) proposed by these authors are therefore much lower than those of the IADPSG/WHO criteria. Also, in the United Kingdom, the National Institute for Health and Care Excellence (NICE) guideline from 2015 recommended diagnostic criteria different from the IADPSG/WHO thresholds. The NICE guideline recommended using the older WHO 1999 2-h glucose cut-off value of ≥7.8 mmol/l for diagnosis of GDM, because of the limited evidence to increase the threshold value and fears for increased healthcare costs by applying the higher 2-h glucose level [8].

A study by Duran et al. [60] evaluated the healthcare costs of the IADPSG/WHO diagnostic criteria compared with the Carpenter and Coustan criteria (summarized in Table 3.1). The authors showed that the use of IADPSG/WHO criteria is associated with an improvement in pregnancy outcomes and that the new criteria did not increase healthcare costs because of lower rates of cesarean sections and neonate admission to the intensive care unit [60]. A recent systematic review looked at even a broader perspective and suggested that screening is cost-effective or even dominant over non-screening and that both a one-step screening and universal screening are more likely to be cost-effective than the two-step approach or risk factor–based screening [61].

7 The Role of Obesity

As mentioned earlier, the overall prevalence of GDM is also increasing as a consequence of the increasing prevalence of overweight and obesity [36]. Maternal obesity is an important risk factor for GDM and T2DM [62, 63]. Moreover, obesity and

GDM are both associated with insulin resistance and hyperglycemia [64]. In our GDM populations, 60% of the women were overweight or obese and had other metabolic syndrome features, such as chronic hypertension [47]. However, it should be noted that screening for GDM follows a risk factor–based approach, and obesity is one of the important risk factors in this respect. Here there is an important finding regarding the diagnostic criteria, as women classified based on an elevated cut-off for fasting plasma glucose (FG ≥5.1 to ≤6.9 mmol/l) were more frequently obese (BMI ≥30 kg/m^2) and hypertensive than women with normal glucose tolerance [47].

Obesity and maternal weight gain during pregnancy are major risk factors for adverse pregnancy outcomes, including LGA neonates [65–67]. Both the factors are also important confounders in the association between mild hyperglycemia and adverse pregnancy outcomes, as demonstrated in the HAPO study: high maternal BMI was associated, independent of maternal hyperglycemia, with increased risk of pregnancy complications [64]. This study also demonstrated that a combination of GDM pregnancy and obesity had a greater impact on adverse pregnancy outcomes than either of these risk factors alone [64].

8 Testing in Early Pregnancy

8.1 Preexisting or Early-Onset Diabetes

Most guidelines advocate screening for dysglycemia already in the first trimester of pregnancy. Usually, this is done by measuring fasting glucose [5, 28]. Some countries start with measuring random glucose values, diagnose diabetes when this value is ≥11.1, and proceed to recommend a fasting blood glucose measurement when the random value is 6.1–11.0 mmol/l (Fig. 3.1).

A systematic review from 2017 suggested that many women with GDM may have mild hyperglycemia during the first trimester, but the exact diagnostic thresholds are unknown and/or undefined [68]. Often, the glucose cut-off levels are applied which are valid outside pregnancy, i.e., fasting plasma glucose ≥7.0 mmol/l (126 mg/dl), random plasma glucose ≥11.1 mmol/l (200 mg/dl), or HbA_{1c} ≥6.5% (48 mmol/mol). However, several guidelines advocate using more strict criteria, and sometimes the same criteria as applied during 24–28 weeks' screening. The review indicated large heterogeneity between studies: the prevalence of early pregnancy diabetes was reported to range from 0.8 to 22.9%, with considerable differences in criteria for GDM diagnosis and screening strategy [68]. This is also reflected in the large gaps in available medical information from these studies, with only a limited number of studies reporting prepregnancy BMI, family history of diabetes, or gestational weight gain. However, it should be considered that in normal pregnancy, insulin sensitivity increases in the first trimester, and therefore, glucose levels are slightly lower than outside pregnancy. Early pregnancy hyperglycemia is, among others, predictive of the need for insulin treatment and perinatal mortality [68]. Early hyperglycemia is not one single syndrome but may be caused by or associated

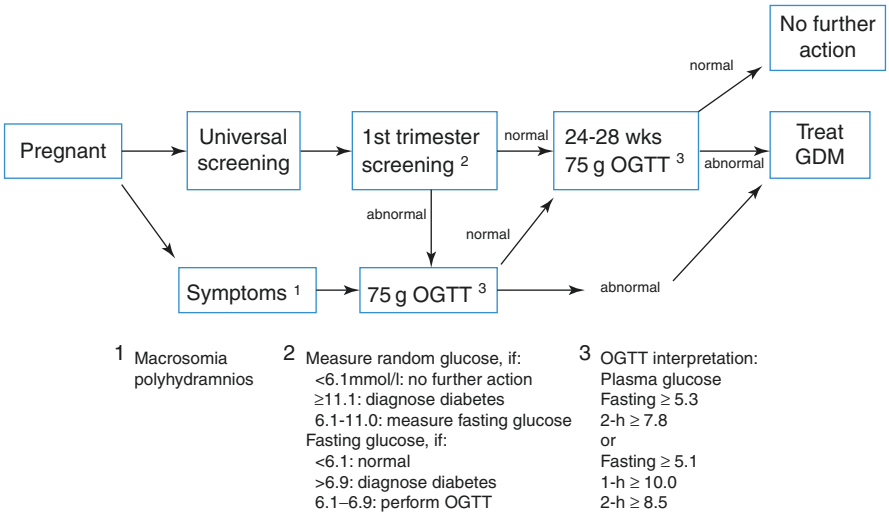

Fig. 3.1 Alternative scenarios for GDM screening. Universal screening (bottom) is more likely to be cost-effective than risk factor–based screening (top). Two scenarios for risk factor–based screening are presented, as well as two sets of diagnostic criteria

with several conditions, including prevalent metabolic syndrome, impairments of beta-cell function [68], but also with certain forms of diabetes like MODY2, or even preexisting, but not yet detected, T2DM.

Participants in the Vitamin D and lifestyle intervention for GDM prevention (DALI) study underwent a 75 g OGTT in early pregnancy. In these women, with a mean prepregnancy BMI of 35 kg/m^2, 23% were diagnosed with GDM according to the IADPSG/WHO criteria, with 78.5% being diagnosed on elevated fasting glucose alone [69]. These women had higher BMI and waist circumference, blood pressure, and triglycerides, compatible with greater insulin resistance/metabolic syndrome [69]. It should be noted that a recent large study in France found no benefit on pregnancy outcomes of early screening in almost 10,000 women, but women detected early were more likely to receive insulin therapy. Unfortunately, data on adherence to self-monitoring and achieved glycemic control were not available [42].

8.2 Early Risk Assessment for Later GDM Development

As classic GDM typically develops after 24 gestational weeks, many investigators have attempted to assess the risk of developing GDM by evaluations in early pregnancy. Several studies have shown the association between fasting plasma glucose levels early in pregnancy and the later development of GDM [70–72]. A recent study showed that higher fasting levels of C-peptide were associated with a higher risk of developing GDM [73], and higher fasting plasma glucose and C-peptide were predictive of future need for glucose-lowering medication. However, the

correlation between fasting parameters in early pregnancy and an abnormal glucose tolerance test (GTT) at a later stage was relatively weak (AUC for the ROC curve 68–71%). In contrast, the quantitative insulin sensitivity check index from C-peptide (QUICKIc) provided a slightly better predictive power (AUC ROC 72.1%) [73].

Other authors have tried to predict the risk for GDM based on specific sets of risk factors collected or evaluated before or early in pregnancy. Although such a risk assessment may guide early intervention by—for instance—lifestyle, yet many of these risk models have not been validated, and their predictive power has been limited. A recent paper showed that a combination of risk factors, including a first degree relative with diabetes, history of GDM, non-Caucasian background, age, height and weight, and fasting levels of glucose, triglycerides, and HbA_{1c} showed a moderate predictive power (AUC ROC 72% after calibration) to predict later GDM [74]. In a recent congress presentation, it was shown that of 15 prediction models evaluated, only four had sufficient predictive power, although based on the ROC AUC, the predictive accuracy of these models remains moderate [75].

In addition, early prediction to improve lifestyle sounds promising, but the effects of early lifestyle intervention have been limited. The UPBEAT, a dietary and physical activity intervention in obese pregnant women, did not reduce the risk of developing GDM or the number of babies born LGA [76]. The DALI [vitamin D and lifestyle intervention in the prevention of gestational diabetes mellitus (GDM)] study intended to evaluate the possible prevention of GDM with lifestyle interventions or vitamin D supplementation and reported limited gestational weight gain, although GDM risk was unchanged [77].

Higher HbA_{1c} levels early in the second trimester of pregnancy were associated with impairment of β-cell function (assessed with OGTT), the need for glucose-lowering medication later during pregnancy, and a higher risk for having an LGA baby, although overall predictive accuracy was moderate to fair [78]. On theoretical grounds, it can be expected that HbA_{1c} is only a moderate predictor of future GDM, as both genetic factors and the presence of anemia may influence the robustness of the HbA_{1c} measurement [79, 80].

The specific "case-mix" of women referred for GDM evaluation and treatment allows to recognize a more "complex-care" group of insulin-treated women with GDM, but on the other hand, a potential "low-risk" group of women treated with diet alone and likely to have good obstetric and/or neonatal outcomes. There are several predictors of need for additional insulin therapy: previous diagnosis of GDM; family history of diabetes; a previous infant weighing ≥4500 g at birth; Middle Eastern/North-African descent; multiparity; pre-gestational body mass index (BMI) ≥30 kg/m^2; and as expected, higher concentrations of fasting and 2-h glucose after a 75 g OGTT at time of GDM diagnosis. A fasting glucose level ≥5.5 mmol/l at GDM diagnosis was the strongest predictor of the need for insulin therapy [10]. Furthermore, the study showed that diet-treated primiparous women with GDM and women with higher weight gain during pregnancy had more pregnancy complications [10].

9 Conclusions

It may be difficult for observers outside the medical community to understand why and how the same data from the international medical literature can lead to considerable differences between guidelines across the world. This implies that in addition to hard data, local situations and circumstances, including patient casemix, including the prevalence of obesity and socioeconomic factors, organization of care, availability of health insurance plans, and patient preferences, as well as expert or non-expert opinion, financial resources or restraints, organization of care, fear of somatization and medicalization of pregnancy, and even budgetary considerations by health insurance companies will influence the specific content of a guideline. For this reason, some guidelines are specifically called "consensus documents." Several studies have shown that about 20–30% (depending on the applied diagnostic criteria) of the women screened for GDM had/have abnormal OGTT results, necessitating referral, active counseling, and treatment. By adopting the new IADPSG/WHO diagnostic criteria in several guidelines, the prevalence of GDM has increased, which has a major impact on the costs and the capacity of healthcare systems.

Recent data have suggested that women with fasting glucose below 5.1 mmol/l but a 2-h post-OGTT glucose level ≥7.8 and ≤8.4 mmol/l cannot be left untreated. In our clinical practice, 20% of these women needed insulin therapy, and estimates of the consequences of not treating these women indicate a higher incidence of newborns with LGA and probably also perinatal complications and the need for a cesarean section. Additional studies have shown that there are even arguments for lowering the diagnostic 2-h glucose thresholds to ≥7.5 mmol/l for Caucasian women and ≥7.2 mmol/l for women from South Asian background. There are not many studies that have evaluated whether the fasting threshold of 5.1 mmol/l, brought forward by the HAPO study results, can be safely increased to, for instance, 5.3 mmol/l, an internationally recognized goal for GDM treatment.

Finally, there is no international consensus on whether universal or risk factor–based screening is preferred, and most studies comparing these strategies have mainly reported data on GDM classification, not on GDM treatment or, even better, pregnancy outcomes. Some countries, therefore, follow a hybrid approach of partly risk factor–based and partly universal screening. The same holds for one-step versus two-step screening. The recently published systematic economic evaluation supports universal screening and the one-step approach as a more likely cost-effective strategy [61].

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