

## Chapter 2

# Diagnosis of Gestational Diabetes

Donald R. Coustan

### Key Points

- International agreement with regard to the diagnosis of gestational diabetes is currently lacking.
- The two-step screening approach, with diagnostic criteria based on the use of a 100 g, 3-h OGTT, which is currently in wide use in the US and many other countries, is based upon the prediction of future diabetes in the mother rather than upon pregnancy outcomes.
- The former WHO criteria, using a 75 g, 2-h OGTT, were simply the same as the criteria for diabetes and prediabetes in nonpregnant individuals, and were not specially derived for pregnancy.
- The 75 g, 2-h OGTT is universally utilized for the diagnosis of diabetes and prediabetes in nonpregnant individuals.
- The HAPO study described the relationships between each of the 3 values on the 75 g, 20-h OGTT and various components of diabetic fetopathy.
- The IADPSG recommendations for diagnosing gestational diabetes are primarily based on data from the HAPO study, and are the only set of criteria based on pregnancy outcomes.
- International adoption of the IADPSG recommendations remains controversial, but once accomplished will allow direct comparisons among populations of the prevalence of GDM as well as treatment efficacy, using common criteria based upon pregnancy outcomes.

**Keywords** Gestational diabetes • Diagnostic criteria • International Association of Diabetes in Pregnancy Study Groups (IADPSG) • World Health Organization (WHO) • American College of Obstetricians and Gynecologists (ACOG) • American Diabetes Association (ADA) • The National Institute for Health and Care Excellence (NICE) • Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study • National Diabetes Data Group (NDDG) • International Federation of Gynecology and Obstetrics (FIGO)

### Abbreviations

OGTT Oral glucose tolerance test

GDM Gestational diabetes mellitus

---

D.R. Coustan (✉)

Warren Alpert Medical School of Brown University, Providence, USA

e-mail: [dcoustan@wihri.org](mailto:dcoustan@wihri.org)

D.R. Coustan

Attending Maternal-Fetal Medicine Specialist, Women & Infants Hospital of Rhode Island,  
101 Dudley Street, Providence, RI 02905-2401, USA

© Springer International Publishing AG 2018

R. Rajendram et al. (eds.), *Nutrition and Diet in Maternal Diabetes*,  
Nutrition and Health, [https://doi.org/10.1007/978-3-319-56440-1\\_2](https://doi.org/10.1007/978-3-319-56440-1_2)

## Introduction

Global estimates of the prevalence of diabetes in pregnancy [1], with the vast majority being gestational diabetes, average 16.9%, with the highest rate in Southeast Asia (25%) and the lowest rates in North America (10.4%). These estimates are handicapped by disparities in screening rates and in diagnostic criteria. There have been multiple schemes recommended for diagnosing gestational diabetes throughout the world, with glucose challenge doses of 50, 75, 100 g, and weight-based formulas and with varying diagnostic criteria. Table 2.1 lists some of the more commonly used approaches. The panoply of tests and criteria makes comparison of prevalence of gestational diabetes across populations virtually impossible. We shall describe some of the more commonly used criteria and put each into perspective.

## Development of the O’Sullivan and Mahan Criteria and Various Conversions

Gestational diabetes was described in 1882, although not named, by J. Matthews Duncan, who stated, “Diabetes may come on during pregnancy...diabetes may occur only during pregnancy...diabetes may cease with the termination of pregnancy...” [2]. Elsie Reed Carrington was the first to use the term “gestational diabetes” in 1957 [3]. Until the mid-1960s, the criteria most commonly used in the United States for diagnosing diabetes in pregnancy were those of the US Public Health Service, which required, in a 100 g, 3-h oral glucose tolerance test (OGTT) that both the fasting and 3-h values meet or exceed 7.2 mmol/L (130 mg/dL), or else one of the above two values exceed threshold and both the 1-h value meet or exceed 10.8 mmol/L (195 mg/dL) and the 2-h value exceed 7.8 mmol/L (140 mg/dL). These were the same criteria used in the nonpregnant state. In 1964, O’Sullivan and Mahan [4] observed that pregnancy changes carbohydrate metabolism such that glucose tolerance may be altered. Pointing out that nonpregnant norms may not be valid, they reported the results of

**Table 2.1** Various diagnostic criteria for gestational diabetes mellitus (GDM)

	NDDG <sup>a</sup>	C & C <sup>b</sup>	WHO <sup>c</sup>	ADIPS <sup>d</sup>	CDA <sup>e</sup>	IADPSG <sup>f</sup>
# elevated values	2	2	1 + nl fasting	1	1	1
Glucose challenge	100 g	100 g	75 g	75 g	75 g	75 g
Fasting threshold mmol/L (mg/dL)	5.8 (105)	5.3 (95)	NI < 7.0 (<126)	5.5 (99)	5.3 (95)	5.1 (92)
1-hr mmol/L (mg/dL)	10.8 (190)	10.0 (180)	NA	NA	10.6 (191)	10.0 (180)
2-hrs mmol/L (mg/dL)	9.2 (165)	8.6 (155)	7.8–11.1 (140–200)	8.0 (144)	9.0 (162)	8.5 (153)
3-hrs mmol/L (mg/dL)	8.0 (145)	7.8 (140)	NA	NA	NA	NA

<sup>a</sup>National Diabetes Data Group [5] conversion of O’Sullivan and Mahan criteria [4]; two or more elevated values needed to diagnose gestational diabetes

<sup>b</sup>Carpenter and Coustan [6] conversion of O’Sullivan and Mahan criteria [4]; two or more elevated values needed to diagnose gestational diabetes

<sup>c</sup>World Health Organization criteria [8]. Fasting plasma glucose must be normal and 2-h value elevated. If fasting is >7.0 or 2-hr > 11.1 diabetes mellitus is diagnosed. WHO adopted IADPSG criteria in 2013 [36]

<sup>d</sup>Australasian Diabetes in Pregnancy Society (ADIPS) criteria [44]; GDM is diagnosed if either the fasting and/or 2-h value is elevated. ADIPS adopted the IADPSG criteria in 2013–2014 [45]

<sup>e</sup>Canadian Diabetes Association criteria [46]. One or more elevated value diagnoses gestational diabetes. The IADPSG approach is considered an alternative, though not preferred

<sup>f</sup>International Association of Diabetes in Pregnancy Study Groups criteria [13]; one or more elevated values diagnoses gestational diabetes

100 g, 3-h OGTTs on 752 unselected pregnant women tested primarily in the late second and early third trimesters. Glucose was measured in venous whole blood samples, using the Somogyi–Nelson method of analysis. The investigators derived potential thresholds at 1, 2, and 3 standard deviations above the means for each of the four samples. The potential thresholds were then applied retrospectively to a second data set of OGTTs during pregnancy among 1333 women who had subsequently undergone periodic OGTTs in the nonpregnant state. Cutoffs of two standard deviations above the mean yielded a prevalence of GDM of 1.9%. It was determined that 22% of women whose pregnancy OGTTs met these thresholds developed diabetes within 8 years after pregnancy. The investigators explained that using cutoffs of one standard deviation would have labeled 16% of pregnant women with GDM, compared to a prevalence of diabetes in the nonpregnant community of 2%. They required that at least two of the four thresholds be met or exceeded, stating, “It was considered expedient...to require two or more values to be met or exceeded. In this way misclassification due to a laboratory error, or occasional single high peaks resulting from unusually rapid absorption of glucose, could be avoided.” The four cutoffs were then rounded off to the nearest 5 mg/dL for ease of remembering. These diagnostic criteria are depicted in Table 2.2.

While glucose was typically measured in whole blood when O’Sullivan and Mahan performed their study, plasma and serum samples subsequently became routine. When whole blood glucose is analyzed the red cells continue to metabolize glucose until measurement is carried out, leading to potential spuriously low values. By separating the red cells from plasma by centrifugation, or allowing the blood to clot and then decanting the serum, this problem can be potentially avoided (depending upon the time elapsing between blood draw and separation). However, when whole blood glucose is measured, the red cells make up some of the volume (denominator of the fraction) but do not contribute to the glucose measurement (numerator). Thus, whole blood glucose is lower than plasma or serum glucose measured simultaneously. In 1979, the National Diabetes Data Group [5] published a conversion of the O’Sullivan cutoffs by adding 15% to each of the already rounded thresholds, then rounding again to the nearest 5 mg/dL (see Table 2.3).

The NDDG conversion of the O’Sullivan and Mahan criteria was widely accepted in the United States. However, in 1982 [6] Carpenter and Coustan noted that the methodology for glucose measurement had been updated from the Somogyi–Nelson method, which measured about 5 mg/dL of reducing substances other than glucose, to enzymatic methods such as glucose oxidase or hexokinase, which measured only glucose. They converted the O’Sullivan and Mahan criteria to enzymatic methods by subtracting 5 mg/dL from each of the original unrounded cutoffs, then adding 14% to the resulting value which is a more accurate conversion from whole blood to plasma than the 15% used by the NDDG. These converted criteria for plasma or serum, using enzymatic methodologies, are shown in Table 2.4. The two conversions from the original O’Sullivan and Mahan criteria were compared by recreating the original methodology (whole blood, Somogyi–Nelson) and analyzing the same samples using plasma and enzymatic methodology [7]. The NDDG criteria were found to be within 95% confidence limits of

**Table 2.2** O’Sullivan and Mahan OGTT criteria to diagnose GDM, both unrounded and rounded to the nearest 5 mg/dL (0.27 mmol/L) [4]

	Unrounded	Rounded
Fasting	90 mg/dL (5 mmol/L)	90 mg/dL (5 mmol/L)
1 h	165 mg/dL (9.2 mmol/L)	165 mg/dL (9.2 mmol/L)
2 h	143 mg/dL (7.9 mmol/L)	145 mg/dL (8.0 mmol/L)
3 h	127 mg/dL (7.1 mmol/L)	125 mg/dL (6.9 mmol/L)

Venous whole blood, Somogyi–Nelson method of analysis  
Two or more elevated values required for the diagnosis of GDM

**Table 2.3** NDDG [5] conversions of the original O’Sullivan and Mahan [4] cutoffs

	Venous whole blood	Venous plasma
Fasting	90 mg/dL (5 mmol/L)	105 mg/dL (5.8 mmol/L)
1 h	165 mg/dL (9.2 mmol/L)	190 mg/dL (10.6 mmol/L)
2 h	145 mg/dL (8.0 mmol/L)	165 mg/dL (9.2 mmol/L)
3 h	125 mg/dL (6.9 mmol/L)	145 mg/dL (7.9 mmol/L)

Two or more elevated values required for the diagnosis of GDM

**Table 2.4** Carpenter and Coustan [6] conversions of original O’Sullivan and Mahan [4] criteria

	Venous whole blood <sup>a</sup>	Venous plasma <sup>b</sup>
Fasting	90 mg/dL (5 mmol/L)	95 mg/dL (5.3 mmol/L)
1 h	165 mg/dL (9.2 mmol/L)	180 mg/dL (10.0 mmol/L)
2 h	143 mg/dL (7.9 mmol/L)	155 mg/dL (8.6 mmol/L)
3 h	127 mg/dL (7.1 mmol/L)	140 mg/dL (7.8 mmol/L)

<sup>a</sup>Somogyi–Nelson methodology

<sup>b</sup>Glucose oxidase or hexokinase methodology

Two or more elevated values required for the diagnosis of gestational diabetes

the original O’Sullivan and Mahan methodology only for the fasting value; the other three were above the upper limits. The Carpenter and Coustan conversion were within 95% confidence limits for all samples. Both conversions are utilized in various settings in the United States.

## The World Health Organization (WHO) Criteria

Since 1998 [8], the WHO recommended the use of criteria for GDM which were the same as those used for impaired glucose tolerance and diabetes in nonpregnant individuals (Table 2.1). These were not derived specifically for particularly for pregnancy. In 2013 the WHO adopted the IADPSG criteria (see below).

## Development of the IADPSG Criteria

As early as 1991, the Third International Workshop Conference on Gestational Diabetes Mellitus (Metzger et al. 1991) concluded that the use of a variety of glucose challenges, and a variety of diagnostic criteria, made it impossible to compare prevalences of GDM across populations. Results of intervention studies were difficult to generalize. None of the available criteria were based on pregnancy outcomes. Furthermore, it was pointed out that the 75 g OGTT was universally accepted for nonpregnant individuals, and it was assumed that the same challenge would eventually become the standard for pregnancy. A 1992 NICHD sponsored International Workshop on Adverse Perinatal Outcomes of Gestational Diabetes [9] concluded, “...questions about...efforts to diagnose and treat GDM to prevent adverse perinatal effects cannot be resolved without additional carefully designed studies. [HAPO]...will enable the investigators to correlate various degrees of glucose intolerance with perinatal morbidity...”.

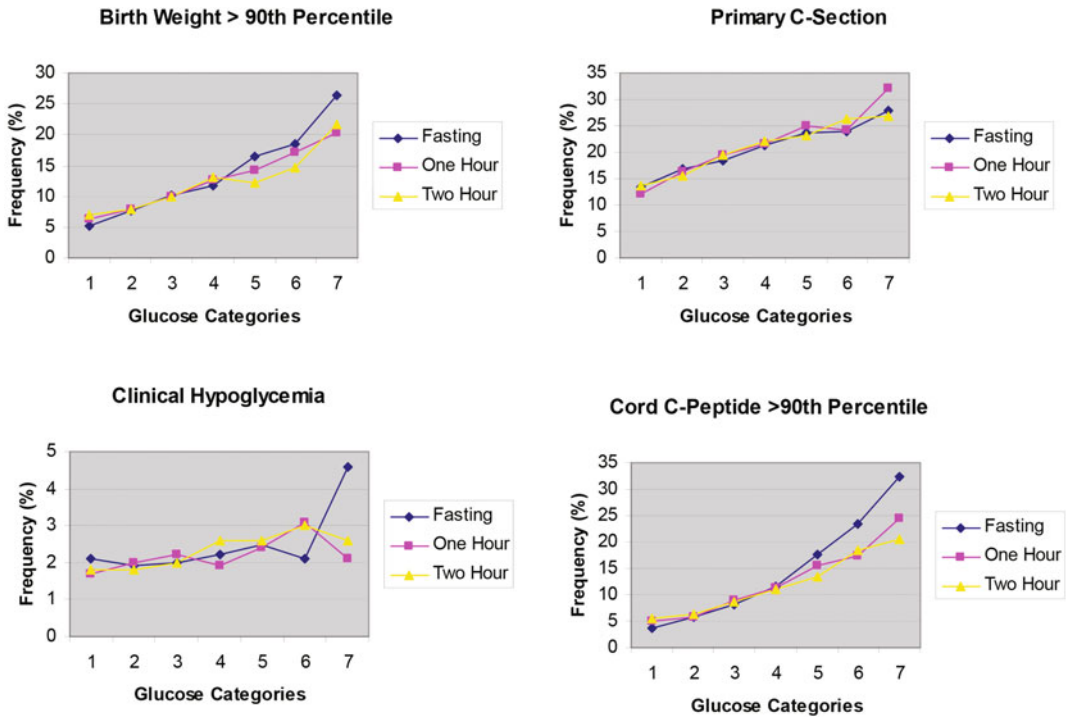
The above events led to the initiation of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, which was designed to determine what level of glucose intolerance during pregnancy,

short of diabetes, is associated with an increased risk of adverse outcomes [10]. HAPO was a purely observational, noninterventional study with participation from 15 field centers in nine different countries around the globe. Over 23,000 pregnant women completed the study, in which a 75 g, 2-h OGTT was administered at 24–32 weeks gestation (mean  $27.8 \pm 1.8$  weeks). The results were masked from subjects and their providers unless the 2-h value met or exceeded 11.1 mmol/L (200 mg/L) or the fasting value exceeded 5.8 mmol/L (105 mg/dL). Maternal and neonatal outcomes were recorded. Recruitment encompassed 6 years, from 2000 to 2006. Each of the four primary outcomes (birthweight >90th centile, primary cesarean section, neonatal hypoglycemia and cord C-peptide >90th centile [a proxy for fetal insulin]) was correlated to each of the three plasma glucose levels in a continuous fashion, without any inflection point (Fig. 2.1). These relationships held even when adjusted for such potential confounders as field center (a proxy for ethnicity and geographical location), maternal age, maternal BMI, and gestational age at the time of the OGTT, among others. A number of prespecified secondary outcomes (preeclampsia, shoulder dystocia/birth injury, premature delivery, and neonatal adiposity [11]) were similarly associated with GTT values in a linear and statistically significant fashion. These relationships were highly supportive of the “Pedersen Hypothesis,” namely that maternal hyperglycemia leads to fetal hyperglycemia, which leads to fetal hyperinsulinemia which is the primary cause of diabetic fetopathy [12], in that cord blood C-peptide was directly related to both OGTT glucose values and to neonatal macrosomia and adiposity.

Because there were no obvious inflection points in the HAPO data, the HAPO investigators understood that any recommendations for diagnosing gestational diabetes would be relatively arbitrary, and they decided not to recommend specific cutoffs lest the criteria become known as “HAPO criteria” and attaining international agreement would be more difficult. Since the only way to determine appropriate diagnostic criteria would be to consult a group of experts the International Association of Diabetes in Pregnancy Study Groups (IADPSG) convened 225 conferees from 40 different countries around the world in 2008. They considered the HAPO data as well as data from other available published studies. An IADPSG consensus panel was convened, and spent over a year considering the data and potential recommendations. It was decided to use large babies, primary cesarean sections and cord blood C-peptide above the 90th centile as the outcomes to be utilized for developing cutoffs for GDM, with the knowledge that any of the other adverse outcome variables could have as well be used because of the similarity of the relationships between OGTT glucose values and each of the primary and secondary outcomes. It was decided to use mean OGTT glucose values for comparison, and odds ratios for the above three outcomes were calculated for various levels of OGTT glucose above mean levels. The consensus was to use odds ratios of 1.75, and to diagnose GDM based on one or more glucose values above threshold, since the three OGTT values each independently identified individuals with elevated risk. These cutoffs would identify 16.1% of the HAPO population as having GDM, along with an additional 1.7% of subjects who were unblinded because their GTT values or random glucose values were a priori considered to require identification and treatment, bringing the grand total of GDM to 17.8% of the HAPO population. The recommended thresholds are shown in Table 2.5, and were published in 2010 [13].

Various critics have suggested that the IADPSG consensus group should have chosen an odds ratio of 2.0 rather than 1.75, on the assumption that a 1.75 odds ratio identified women with an approximately 75% increase in the likelihood of adverse outcomes, and a doubling would have been more reasonable [14, 15]. In fact, while the 1.75 odds ratio compares individuals with GDM to those whose plasma glucose levels all are at the population mean, a more appropriate comparison would be between those with GDM and all those in the population without GDM. Such a comparison is depicted in Table 2.6, which demonstrates that those with GDM have at least twice the likelihood of large babies, fat babies, hyperinsulinemic babies and preeclampsia, and a one-third greater likelihood of preterm birth, primary cesarean section, and shoulder dystocia.

The major drawback to adopting the IADPSG recommendations for diagnosing gestational diabetes seems to have been the fact that such a high proportion of pregnant women would be considered



**Fig. 2.1** Associations between each of the three GTT plasma glucose levels and each of the four primary outcomes in the HAPO study. Relationship of each of the three 75 g, 2-h OGTT values to each of the four primary outcomes in the HAPO study. (Reprinted with permission from New England Journal of Medicine. HAPO Study Cooperative Research Group [10]. Reprinted with permission). Copyright © 2008 Massachusetts Medical Society. *Legend* Glucose categories are defined as follows: fasting plasma glucose level—category 1, less than 75 mg per deciliter (4.2 mmol/L); category 2, 75–79 mg/dL (4.2–4.4 mmol/L); category 3, 80–84 mg/dL (4.5–4.7 mmol/L); category 4, 85–89 mg/dL (4.8–4.9 mmol/L); category 5, 90–94 mg/dL (5.0–5.2 mmol/L); category 6, 95–99 mg/dL (5.3–5.5 mmol/L); category 7, 100 mg/dL (5.6 mmol/L) or more. 1-h plasma glucose level—category 1, 105 mg/dL (5.8 mmol/L) or less; category 2, 106–132 mg/dL (5.9–7.3 mmol/L); category 3, 133–155 mg/dL (7.4–8.6 mmol/L); category 4, 156–171 mg/dL (8.7–9.5 mmol/L); category 5, 172–193 mg/dL (9.6–10.7 mmol/L); category 6, 194–211 mg/dL (10.8–11.7 mmol/L); category 7, 212 mg/dL (11.8 mmol/L) or more. 2-hr plasma glucose level—category 1, 90 mg/dL (5.0 mmol/L) or less; category 2, 91–108 mg/dL (5.1–6.0 mmol/L); category 3, 109–125 mg/dL (6.1–6.9 mmol/L); category 4, 126–139 mg/dL (7.0–7.7 mmol/L); category 5, 140–157 mg/dL (7.8–8.7 mmol/L); category 6, 158–177 mg/dL (8.8–9.8 mmol/L); category 7, 178 mg/dL (9.9 mmol/L) or more

**Table 2.5** IADPSG recommended thresholds for diagnosing gestational diabetes mellitus (IADPSG, 2008)

Fasting plasma glucose	1-h plasma glucose	2-h plasma glucose
5.1 mol/L (92 mg/dL)	10 mmol/L (180 mg/dL)	8.5 mmol/L (153 mg/dL)

Gestational diabetes is diagnosed if one or more of the above values is met or exceeded

to have GDM, and diagnosing 16–18% with this condition would place an undue burden on patients and the healthcare system [16]. It should be noted, however, that recent data from the National Health and Nutrition Examination Survey (NHANES) [17] show that, depending upon the diagnostic tests utilized, 12.2–14.3% of Americans aged 20 years or more had diabetes in 2011–2012; worldwide estimates are that this disease affects 9% of individuals aged 18 or more years [18]. The prevalence of prediabetes in the United States, among individuals aged 20 years or more, was 36.5–38% in 2011–2012 [17], meaning that at least 52% of American adults now have prediabetes or diabetes! The prevalence of diabetes in those aged 20–44 years, roughly the childbearing years, was 4.5–5.0% and

**Table 2.6** Outcomes of untreated subjects with gestational diabetes, using new IADPSG criteria (data from online appendix, Table B, IADPSG [13])

Outcome	All values < threshold (No. GDM) (%)	Any $\geq$ 92/180/153 gestational diabetes
Birthweight >90th percentile	8.3	16.2%@
Cord C-peptide >90th percentile	6.7	17.5%@
% Body fat >90th percentile	8.5	16.6%@
Preeclampsia	4.5	9.1%@
Preterm birth (<37 weeks)	6.4	9.4%@
Shoulder dystocia/birth injury	1.3	1.8%*
Primary cesarean section	16.8	24.4%@

\* $p < 0.01$ ; @ $p < 0.001$

of prediabetes 25.1–28.2%, meaning that 29–33% of Americans in the childbearing age range had disordered glucose metabolism. The IADPSG criteria for GDM resemble the criteria for prediabetes [impaired fasting glucose is 5.6–6.9 mmol/L (100–124 mg/dL) and impaired glucose tolerance is 7.8–11 mmol/L (140–199 mg/dL) at 2-h of the 75 g OGTT in nonpregnant individuals]. It should not be surprising that 18% of pregnant women have gestational diabetes. The criteria for diabetes and prediabetes in nonpregnant adults are similar if not the same throughout the world. The response to the epidemic of diabetes and prediabetes has not been to redefine these disorders in order to relieve the burden on healthcare systems. Instead, innovative approaches to providing cost-effective, evidence-based health care are being developed globally. This is the challenge for dealing with the increasing number of women with GDM. Potential targets for cost savings without adverse consequences include the use of group prenatal/diabetes visits [19], and the exploration of the practicality and safety of decreasing the frequency of blood glucose testing and fetal testing in women with milder forms of gestational diabetes [20].

Another concern that has been raised is whether it would be cost-effective to diagnose and treat GDM in so many pregnant women [16]. Mission et al. [21] performed a decision analysis comparing the two-step process ACOG [22] with the IADPSG one-step process and determined that the one-step process was more expensive, but more effective and more cost-effective. In another comparison, Werner et al. [23] reported that the IADPSG approach is more cost-effective as long as the women with GDM receive postdelivery counseling and care aimed at preventing type 2 diabetes. In the above analysis, the authors assumed that the rate of GDM would be 3.8% with the 2-step approach and 16.2% with the IADPSG approach. In fact, statewide reported rates of GDM in the United States ranged from 3.5 to 7% in 2008 [24], prior to publication of the IADPSG recommendations in 2010, so the 3.8% estimate of the GDM rate with the two-step approach is an underestimate; assuming a higher baseline rate of GDM would presumably make the adoption of the IADPSG recommendations even more cost-effective. This discussion raises the question of whether interventions after delivery can prevent type 2 diabetes in women with previous GDM. In a subgroup analysis of subjects with previous GDM and prediabetes who were enrolled in the Diabetes Prevention Program, Ratner et al. [25] demonstrated that the annual rate of conversion to type 2 diabetes was reduced by 50% in the group receiving metformin and the group receiving intensive lifestyle intervention compared to those randomized to placebo. The number needed to treat to prevent one conversion to type 2 diabetes over three years was 5 with lifestyle intervention and 6 with metformin.

Another question that has been raised is whether identification and treatment of milder forms of GDM, using the IADPSG recommendations, would be beneficial. While no randomized controlled trials (RCTs) of identification and treatment of GDM using the IADPSG recommendations have been published, there have been two RCTs of identification and treatment of mild forms of GDM using



other criteria. The NICHD Maternal-Fetal Medicine Units (MFMU) Network [26] randomized patients whose 3-h, 100 g OGTTs met the Carpenter and Coustan conversion of the O'Sullivan criteria, but had normal fasting plasma glucose levels ( $<5.3$  mmol/L or 95 mg/dL) to identification and treatment ( $N = 485$ ) or routine care ( $N = 473$ ). Caregivers and subjects randomized to routine care were masked to the OGTT values. Identification and treatment of mild GDM decreased fetal macrosomia, preeclampsia and shoulder dystocia by more than 50%. The ACHOIS study [27] similarly randomized patients whose GDM (plasma glucose 2 h after a 75 g glucose challenge of 7.8–11.0 mmol/L or 140–199 mg/dL; mean fasting value 4.8 mmol/L or 86 mg/dL) was even milder than those who would be identified by the IADPSG recommendations [2 h value of 8.5 mmol/L or greater (153 mg/dL or greater)]. Those whose mild GDM was identified and treated were 2/3 less likely to experience a composite of perinatal death, shoulder dystocia, bone fracture, or nerve palsy than those randomized to routine treatment (and blinded to the OGTT results). Furthermore, macrosomia was half as likely and preeclampsia was 33% less likely. Since the subjects in this RCT had milder OGTT results than those recommended by IADPSG, it is reasonable to extrapolate that identification and treatment of GDM using the IADPSG recommendations will lower rates of adverse outcomes.

Because the 75 g, 2-h OGTT is known to be an unstable test, critics of the IADPSG one-step approach have argued that there is an increased risk of false positive results when only a single test is used and a single elevated value diagnoses GDM [16]. The one-step, 75 g 2-h OGTT is universally accepted worldwide for diagnosing diabetes in nonpregnant individuals, and there is no reason to believe that pregnancy renders the test more unstable or less reliable. It has also been argued that patient acceptance will be lower with the requirement to fast and wait 2 h for the test to be completed than with the two-step process in which fasting is not required and a 1-h wait is needed for the first step. When Sacks et al. [28] offered the choice of the one-step 75 g, 2-h OGTT versus the traditional two-step test to 4078 gravidas, 3505 (86%) chose the one-step approach. These findings suggest that patient acceptance is unlikely to be a major problem.

The biggest difference between the modified O'Sullivan criteria and the IADPSG criteria is the requirement for only one, rather than two elevated values to diagnose GDM. The rationale for requiring two elevated values was as follows [4]: "It was considered expedient...to require two or more values to be met or exceeded. In this way misclassification due to a laboratory error, or occasional single high peaks resulting from unusually rapid absorption of glucose, could be avoided." Laboratory errors, while still possible, are much less likely in the present era of bar codes and universal precautions. Because the HAPO data [10] showed that each of the three OGTT values was independently predictive of adverse outcomes, and the IADPSG cutoffs for the three values were each based on a similar predictive value, one or more elevations now diagnose GDM.

## Early Pregnancy Testing for Preexisting Diabetes

One of the major issues confronting the IADPSG consensus panel was the identification of preexisting diabetes first diagnosed during pregnancy. As the prevalence of type 2 diabetes has reached epidemic proportions globally, there is an increasing likelihood that women will enter pregnancy with previously undiagnosed diabetes. Older definitions of gestational diabetes included any diabetes first diagnosed during pregnancy that subsequently disappeared postpartum, but of course one could not know the postpartum course until after completion of pregnancy. In the extreme, even a patient presenting in diabetic ketoacidosis in the first trimester would, strictly speaking, be labeled as having "gestational diabetes" until her type 1 diabetes could be found to remain after delivery. Thus, there was a need to develop criteria for the diagnosis of preexisting diabetes in early pregnancy. IADPSG [13] recommendations are that any of the standard definitions of diabetes outside of pregnancy, including fasting plasma glucose  $\geq 7$  mmol/L (126 mg/dL), A1c  $\geq 6.5\%$  or random plasma



glucose  $\geq 11.1$  mmol/L (200 mg/dL) when confirmed would diagnose preexisting diabetes in early pregnancy. One of the problems with the IADPSG guidelines is that if the fasting plasma glucose in early pregnancy is  $<7$  mmol/L (126 mg/dL) but  $\geq 5.1$  mmol/L (92 mg/dL) the recommendation was to diagnose GDM. The IADPSG GDM criteria were based on OGTT data from 24 to 32 weeks, and there is no evidence for or against their validity in early pregnancy. Another problem is that there is no certainty as to when in pregnancy the usual criteria for diagnosing diabetes in the nonpregnant state are no longer valid. A1c levels fall during pregnancy [29, 30] and may under diagnose pre-existing diabetes, while the hyperglycemia associated with GDM may raise A1c. Similarly, as pregnancy progresses it may be difficult to distinguish preexisting diabetes from GDM based on a random plasma glucose above 11.1 mmol/L.

## The National Institute for Health and Care Excellence (NICE) Guidelines

In 2015, the National Institute for Health and Care Excellence (NICE) in the United Kingdom published evidence-based recommendations for diagnosing GDM [31]. Risk factor screening is advised at the first prenatal visit. Gravidas with BMI  $>30$ , previous baby weighing 4.5 kg or more, previous GDM, diabetes in a first-degree relative, a minority ethnic family origin with a high prevalence of diabetes, or glycosuria of 1+ on 2 or more occasions or 2+ on one occasion are offered a 75 g, 2-h OGTT at 24–28 weeks. Those with previous GDM are offered earlier testing or self-glucose monitoring. GDM is diagnosed if the fasting plasma glucose is 5.6 mmol/L (101 mg/dL) or above or the 2-h value is 7.8 mmol/L (140 mg/dL) or above. The fasting plasma glucose cutoff is higher than the IADPSG recommendation of 5.1 mmol/L (92 mg/dL) and the 2-h cutoff is lower than the 8.5 mmol/L (153 mg/dL) recommended by IADPSG.

In a retrospective review of over 25,000 pregnancies in which 75 g, 2-h OGTTs were performed in 3848 women (based on risk factors), 387 had GDM by IADPSG cutoffs but not by NICE cutoffs [32], whereas 1055 had GDM by NICE criteria (794 of whom also met IADPSG criteria). The vast majority of patients with GDM by NICE criteria were offered treatment while none of those meeting only the IADPSG criteria were treated. The untreated women meeting only IADPSG cutoffs delivered more babies with birthweight  $>90$ th percentile than those without GDM (30 vs. 17%), and more than treated GDMs meeting only the NICE cutoffs (11.5%). Untreated women with fasting plasma glucose between the IADPSG cutoff (5.1 mmol/L or 92 mg/dL) and the NICE cutoff (5.5 mmol/L or 101 mg/dL) had the highest proportion of LGA infants (38%). The prevalence of GDM in this primarily Caucasian population was 4.1% with the NICE criteria and 4.6% with the IADPSG criteria, although GTTs were only performed in women whose 50 g, 1-hr screening test was  $>7.7$  mmol/L (43 mg/dL) so GDM may have been under-identified.

The NICE guidelines lower the 2-h cutoff by 0.7 mmol/L (13 mg/dL), raise the fasting cutoff by 0.5 mol/L (9 mg/dL) and reject the 1-h value of the IADPSG criteria. Each of the three IADPSG cutoffs are similarly associated with adverse outcomes, and are independent enough that omitting the 1-h test would have missed 26 and 30% of the GDMs diagnosed in the subjects at the two UK HAPO centers [33]. It is unfortunate that these diagnostic threshold recommendations, which are not so different from IADPSG, could not coincide. Another important difference is that the NICE recommendations are, in essence, a two-step process with the first step being screening by history. There is plentiful evidence that screening by risk factors is quite insensitive [34]. For example, a history of a large baby or previous GDM means that women having their first pregnancy cannot possibly demonstrate those factors. It is as if we are willing to allow the adverse outcome to occur in the first pregnancy, and then try to prevent it in future pregnancies.

## Current Recommendations Around the World

The IADPSG recommendations [13] were developed with the intention to produce guidelines and criteria for diagnosing gestational diabetes, which were based on evidence regarding pregnancy outcomes and were agreed upon by a consensus of experts from around the world, and would be adopted globally. Such worldwide agreement would remove confusion about definitions of GDM, allow comparisons among diverse populations with regard to prevalence and also with regard to treatment efficacy. As might be anticipated from examples such as UN deliberations on war and peace, and evolving attitudes toward climate change, reaching such agreement is arduous and time-consuming. However, a good deal of progress has been made since the recommendations were published, and this section of the chapter will describe the state of affairs as of the spring of 2016.

In the United States a consensus conference held in 2013 [16] recommended continuing the use of the two-step approach with either set of conversions of diagnostic criteria based on the O'Sullivan and Mahan 100 g, 3-h OGTT. The one-step IADPSG approach could be considered once further evidence of benefit has accumulated. The American College of Obstetricians and Gynecologists [22] makes similar recommendations. The American Diabetes Association [35] recommends either the ACOG two-step approach or the IADPSG one-step approach, and emphasizes the stronger evidence behind the IADPSG approach.

In 2013, the World Health Organization [36] adopted the IADPSG recommendations for diagnosing gestational diabetes, and for diagnosing preexisting diabetes during pregnancy, adding the opportunity for flexibility depending upon the availability of healthcare resources. In 2015, the International Federation of Gynecology and Obstetrics (FIGO) also adopted the IADPSG recommendations [37] with room for flexibility depending upon the availability of healthcare resources.

## Conclusions

Currently, the IADPSG recommendations are being implemented in a somewhat piecemeal fashion, in various parts of the world. Retrospective data have demonstrated that patients with unidentified, untreated GDM by IADPSG criteria are more likely to deliver macrosomic and LGA babies, and to experience cesarean delivery, than those with normal glucose tolerance [38]. While data from the US and Canada comparing hospital-wide pregnancy outcomes before and after the switch from Carpenter and Coustan criteria to IADPSG criteria failed to demonstrate an improvement in overall outcomes [39, 40] despite increases in the rate of identified and treated GDM, publications from Spain [41] Taiwan [42] and China [43] reported hospital-wide improvements in perinatal outcomes (cesarean sections in all three reports, large babies in China and Spain, hypertensive disorders of pregnancy in Spain, and a composite outcome of large babies, neonatal jaundice, NICU admissions and birth trauma in Taiwan) and overall cost savings in Spain. It remains to be seen when, if ever, we reach the goal of one glucose challenge dose and one set of diagnostic criteria in use throughout the world.

## References

1. Guariguata L, Linnenkamp U, Baegley J, Whiting DR, Cho NH. Global estimates of the prevalence of hyperglycaemia in pregnancy for 2013 for the IDF diabetes atlas. *Diab Res Clin Pract.* 2014;103:137–49.
2. Duncan JM. On puerperal diabetes. *Trans Obstet Soc Lond.* 1882;24:256–85.
3. Carrington ER, Shuman CR, Reardon HS. Evaluation of the prediabetic state during pregnancy. *Obstet Gynecol.* 1957;9:664–9.
4. O'Sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. *Diabetes.* 1964;13:278–85.

5. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes*. 1979;28:1039–57.
6. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol*. 1982;144:768–73.
7. Sacks DA, Abu-Fadil S, Greenspoon JS, Fotheringham N. Do the current standards for glucose tolerance testing in pregnancy represent a valid conversion of O'Sullivan's original criteria? *Am J Obstet Gynecol*. 1989;161:638–41.
8. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diab Med*. 1998;15:539–53.
9. Blank A, Grave GD, Metzger BE. Effects of gestational diabetes on perinatal morbidity reassessed: report of the international workshop on adverse perinatal outcomes of GDM. *Diab Care*. 1995;18:127–30.
10. HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008;358:1991–2002.
11. HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcome (HAPO) study: associations with neonatal anthropometrics. *Diabetes*. 2009;58:453–9.
12. Pedersen J. Diabetes and pregnancy: blood sugar of newborn infants. Ph.D Thesis. Copenhagen: Danish Science Press; 1952.
13. International Association of Diabetes and Pregnancy Study Groups (IADPSG) Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diab Care* 2010;33:676–682.
14. Ryan EA. Diagnosing gestational diabetes. *Diabetologia*. 2011;54:480–6.
15. Long H, Cundy T. Establishing consensus in the diagnosis of gestational diabetes following HAPO: where do we stand? *Curr Diab Rep*. 2013;13:43–50.
16. National Institutes of Health Consensus Development Conference Statement. Diagnosing gestational diabetes mellitus. *Obstet Gynecol*. 2013;122:358–69.
17. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988–2012. *JAMA*. 2015;314:1021–9.
18. World Health Organization. Diabetes fact sheet number 312 January 2015. <http://www.who.int/mediacentre/factsheets/fs312/en/>. Accessed 29 Feb 16.
19. Mazzoni SE, Hill PK, Webster KW, Heinrichs GA, Hoffman MC. Group prenatal care for women with gestational diabetes. *J Matern Fetal Neonatal Med*. 2015;23:1–5.
20. Mendez-Figueroa H, Daley J, Lopes VV, Coustan DR. Comparing daily versus less frequent blood glucose monitoring in patients with mild gestational diabetes. *J Matern Fetal Neonatal Med*. 2013;26:1268–72.
21. Mission JF, Ohno MS, Cheng YW, Caughey AB. Gestational diabetes screening with the new IDPSG guidelines: a cost-effectiveness analysis. *Am J Obstet Gynecol*. 2012;207:326e1–9.
22. American College of Obstetricians and Gynecologists (ACOG). Gestational diabetes mellitus. Practice bulletin no. 137. *Obstet Gynecol*. 2013;122:406–16.
23. Werner EF, Pettker CM, Zuckerwise L, Reel M, Funai E, Henderson J, Thung S. Screening for gestational diabetes mellitus: are the criteria proposed by the International Association of the Diabetes and Pregnancy Study Groups cost-effective? *Diab Care*. 2012;35:529–35.
24. Bardenheier BH, Elixhauser A, Imperatore G, Devlin HM, Kuklina EV, Geiss LS, Correa A. Variation in prevalence of gestational diabetes mellitus among hospital discharges for obstetric delivery across 23 states in the United States. *Diab Care*. 2013;35:1209–14.
25. Ratner RE, Christophi CA, Metzger BE, Dabelea D, Bennett PH, Pi-Sunyer X, Fowler S, Kahn SE, The Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *JCEM*. 2008;93:4774–9.
26. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *NEJM*. 2009;361:1339–48.
27. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, and Robinson JS for the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *NEJM*. 2005;352:2477–86.
28. Sacks DA, Greenspoon JS, Abu-Fadil S, Henry HM, Wolde-Tsadik G, Yao JFF. Toward universal criteria for gestational diabetes. *Am J Obstet Gynecol*. 1995;172:607–14.
29. Nielsen LR, Ekblom P, Damm P, Glümer C, Frandsen MM, Jensen DM, Mathiesen ER. HbA1c levels are significantly lower in early and late pregnancy. *Diab Care*. 2004;27:1200–1.
30. Mosca A, Paleari R, Dalfra MG, DiCianni G, Cucurru A, Pellegrini G, Malloggi L, Bonomo M, Granata S, Cariotti F, Castiglioni MT, Songini M, Tocco G, Masin M, Plebani M, Lapolla A. Reference intervals for hemoglobin A1c in pregnant women: data from an Italian multicenter study. *Clin Chem*. 2006;52:1138043.

31. National Institute for Health and Care Excellence. Nice guidance: diabetes in pregnancy: management from preconception to the postnatal period. February 2016. <http://www.nice.org.uk/guidance/ng3/chapter/1-Recommendations#gestational-diabetes-2>. Accessed 6 Mar 2016.
32. Meek CL, Lewis HB, Patient C, Murphy HR, Simmons D. Diagnosis of gestational diabetes mellitus: falling through the net. *Diabetologia*. 2015;58:2003–12.
33. Sacks DA, Hadden DR, Maresh M, Deerochanawong C, Dyer AR, Metzger BE, Lowe LP, Coustan DR, Hod M, Oats JJN, Persson B, Trimble ER, for the HAPO Study Cooperative Research Group. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel–recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study. *Diab Care*. 2012;35:526–8.
34. Östlund A, Hanson U. Occurrence of gestational diabetes mellitus and the value of different screening indicators for the oral glucose tolerance test. *Acta Obstet Gynecol Scand*. 2003;82:103–8.
35. American Diabetes Association. Standards of care. *Diab Care*. 2016;39(Suppl 1):S18–20.
36. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. Published in 2013. [http://www.who.int/diabetes/publications/Hyperglycaemia\\_In\\_Pregnancy/en/](http://www.who.int/diabetes/publications/Hyperglycaemia_In_Pregnancy/en/). Accessed 14 Feb 16.
37. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, Cabero Roura L, McIntyre HD, Morris JL, Divakar H. The International Federation of Gynecology and Obstetrics (FIGO) initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management, and care. *Int J Gynecol Obstet*. 2015;131:S173–211.
38. Ethridge JK Jr, Catalano PM, Waters TP. Perinatal outcomes associated with the diagnosis of gestational diabetes made by the International Association of the Diabetes and Pregnancy Study Groups Criteria. *Obstet Gynecol*. 2014;124:571–8.
39. Feldman RK, Tieu RS, Yasumara L. Gestational diabetes screening: the IADPSG compared with the C&C screening. *Obstet Gynecol*. 2016;127:10–7.
40. Kong JM, Lim K, Thompson DM. Evaluation of the International Association of the Diabetes in Pregnancy Study Group new criteria: gestational diabetes project. *Can J Diab*. 2015;39:128–32.
41. Duran A, Sáenz S, Torrejón MJ, Bordiú E, del Vzlle L, Galindo M, Perez N, Herraiz MA, Izquierdo N, Rubio MA, Runkle I, Pérez-Ferre N, CusiHuallpa MD, Montañez, Familiar C, Calle-Pascual AL. Introduction of IADPSG criteria for the screening and diagnosis of gestational diabetes mellitus results in improved pregnancy outcomes at a lower cost in a large cohort of pregnant women: the St. Carlos Gestational Diabetes Study. *Diab Care* 2014;37:2442–50.
42. Wu E-T, Nien F-J, Kuo C-H, Chen S-C, Chen K-Y, Chuang L-M, Li H-Y, Lee C-N. Diagnosis of more gestational diabetes lead to better pregnancy outcomes: comparing the International Association of the Diabetes and Pregnancy Study Group criteria, and the Carpenter and Coustan criteria. *J Diab Inv*. 2016;7:121–6.
43. Yumei W, Huixia Y, Weiwei Z, Hongyun Y, Haixia L, Jie Y, Cuilin Z. International Association of Diabetes and Pregnancy Study Group criteria is suitable for gestational diabetes mellitus diagnosis: further evidence from China. *Chin Med J*. 2014;127(20):3553–6.
44. Hoffman L, Nolan C, Wilson JD, Oats JJN, Simmons D. The Australasian diabetes in pregnancy society gestational diabetes mellitus management guidelines. *Med J Aust*. 1998;93–97:1998.
45. Nankervis A, McIntyre HD, Moses R, Ross GP, Callaway L, Porter C, Jeffries W, Boorman C, De Vries B, McElduff A for the Australasian Diabetes in Pregnancy Society. ADIPS consensus guidelines for the testing and diagnosis of gestational diabetes mellitus in Australia (as modified November 2014). [http://adips.org/downloads/2014ADIPSGDMGuidelinesV18.11.2014\\_000.pdf](http://adips.org/downloads/2014ADIPSGDMGuidelinesV18.11.2014_000.pdf). Accessed 14 Feb 16.
46. Thompson D, Berger H, Feig D, Gagnon R, Kader T, Keely E, Kozak S, Ryan E, Sermer M and MD, Vinokuroff C. Diabetes and Pregnancy. Canadian Diabetes Association Clinical Practice Guidelines. *Can J Diab*. 2013;37(Suppl 1):S168–83.

Nutrition and Diet in Maternal Diabetes

An Evidence-Based Approach

Rajendram, R.; Preedy, V.R.; Patel, V.B. (Eds.)

2018, XXXVI, 514 p. 66 illus., 44 illus. in color.,

Hardcover

ISBN: 978-3-319-56438-8

A product of Humana Press