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Diagnosis and Management of Gestational Diabetes Mellitus: An Overview of National and International Guidelines

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Importance: Gestational diabetes mellitus (GDM) represents one of the most frequent complications of pregnancy and is associated with increased maternal and neonatal morbidity. Its incidence is rising, mostly due to an increase in maternal age and maternal obesity rate.

Objective: The aim of this study was to review and compare the recommendations of the most recently published guidelines on the diagnosis and management of this condition.

Evidence Acquisition: A descriptive review of guidelines from the National Institute for Health and Care Excellence (NICE), the International Federation of Gynecology and Obstetrics, the Australasian Diabetes in Pregnancy Society (ADIPS), the Society of Obstetricians and Gynecologists of Canada (SOGC), the American College of Obstetricians and Gynecologists (ACOG), the American Diabetes Association, and the Endocrine Society on gestational diabetes mellitus was carried out.

Results: The NICE guideline recommends targeted screening only for women with risk factors, whereas the International Federation of Gynecology and Obstetrics, ADIPS, SOGC, and the ACOG recommend screening for all pregnant women at 24 to 28 weeks of gestation in order to diagnose and effectively manage GDM; they also state that women with additional risk factors should be screened earlier (ie, in the first trimester) and retested at 24 to 28 weeks, if the initial test is negative. These guidelines describe similar risk factors for GDM and suggest the same thresholds for the diagnosis of GDM when using a 75-g 2-hour oral glucose tolerance test. Of note, the NICE only assesses the fasting and the 2-hour postprandial glucose levels for the diagnosis of GDM. Moreover, the SOGC and the ACOG do not recommend this test as the optimal screening method. The Endocrine Society alone, on the other hand, recommends the universal testing of all pregnant women for diabetes before 13 weeks of gestation or as soon as they attend the antenatal service and retesting at 24 to 28 weeks if the initial results are normal. In addition, there is a general consensus on the appropriate ultrasound surveillance of pregnancies complicated with GDM, and all the medical societies, except the ADIPS, recommend self-monitoring of capillary glucose to assess the glycemic control and set the same targets for fasting and postprandial glucose levels. There is also agreement that lifestyle modifications should be the first-line treatment; however, the reviewed guidelines disagree on the medical management of GDM. In addition, there are controversies regarding the timing of delivery, the utility of hemoglobin A_{1c} measurement, and the postpartum and lifelong screening for persistent hyperglycemia and type 2 diabetes. However, all the guidelines state that all women in pregnancies complicated by GDM should

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undergo a glycemic test at around 6 to 12 weeks after delivery. Finally, there is a universal consensus on the importance of breastfeeding and preconception screening before future pregnancies.

Conclusions: As GDM is an increasingly common complication of pregnancy, it is of paramount importance that inconsistencies between national and international guidelines should encourage research to resolve the issues of controversy and allow uniform international protocols for the diagnosis and management of GDM, in order to safely guide clinical practice and subsequently improve perinatal and maternal outcomes.

Target Audience: Obstetricians and gynecologists, family physicians

Learning Objectives: After participating in this activity, the learner should be better able to identify all available screening methods for gestational diabetes mellitus; describe diagnostic procedures for gestational diabetes mellitus; and explain appropriate management issues during the antenatal, intrapartum, and postpartum period in pregnancies complicated by gestational diabetes mellitus.

Gestational diabetes mellitus (GDM) is defined as hyperglycemia or carbohydrate intolerance that is first detected during pregnancy and does not meet the criteria of preexisting diabetes.[1,2] Furthermore, GDM is classified as A1GDM when glycemic control is achieved with diet and exercise and as A2GDM when it requires medication.[3] Diabetes affects approximately 7% of pregnancies worldwide, and it is estimated that 84% of these cases involve GDM.[4] The incidence of GDM has doubled over the last 14 years, mainly due to the parallel increase of obesity and age of pregnant women.[5]

Gestational diabetes mellitus is associated with significant maternal morbidity, including cesarean delivery, preeclampsia, and high-risk of developing type 2 diabetes or cardiovascular disease later in life.[6–9] Moreover, numerous studies have shown that the in utero exposure to maternal hyperglycemia leads to several fetal and perinatal complications, such as congenital malformations, macrosomia, stillbirth, shoulder dystocia, birth trauma, neonatal hypoglycemia, polycythemia, and hyperbilirubinemia. Moreover, it increases the offspring's long-term cardiometabolic risk.[10–13]

Although congenital malformation rates associated with maternal hyperglycemia appear to decline over the recent years, perinatal mortality rates remain stable, and the risk of both these conditions is still significantly elevated compared with nondiabetic women.[5] Thus, the development of consistent international evidence-based algorithms for the prevention, diagnosis, and management of this disease will hopefully lower its incidence and optimize the pregnancy outcomes. Hence, the aim of this descriptive review was to synthesize and compare recommendations from influential guidelines on the diagnosis and management of GDM.

EVIDENCE ACQUISITION

The most recently published guidelines on GDM were retrieved, and a descriptive review was conducted. In particular, 7 guidelines were identified from the National Institute for Health and Care Excellence (NICE 2015),[14] the International Federation of Gynecology and Obstetrics (FIGO 2015),[1] the Australasian Diabetes in Pregnancy Society (ADIPS 2013),[15] the Society of Obstetricians and Gynecologists of Canada (SOGC 2019),[16] the American College of Obstetricians and Gynecologists (ACOG 2018),[3] the American Diabetes Association (ADA 2020),[17] and the Endocrine Society (ES 2013).[18] Of note, the ADIPS makes no recommendation on the management of GDM. An overview of the recommendations is presented in Table 1 (screening and diagnosis for GDM) and Table 2 (management of GDM during pregnancy, labor, and postpartum period).

RISK FACTORS FOR GDM

Five of the reviewed guidelines (NICE, FIGO, ADIPS, SOGC, and ACOG) mention risk factors for the occurrence of GDM, including ethnicity (African, Asian, Hispanic, Native American, Aboriginal), maternal age (>35 years), obesity (body mass index [BMI] >25–30-kg/m^2), family history of diabetes (first-degree relative with diabetes or sister with GDM), and previous GDM or delivery of a macrosomic neonate.[19] Other risk factors reported are preeclampsia or hypertension, excessive weight gain during pregnancy, low height, high parity, multiple gestation, acanthosis nigricans, physical inactivity, hemoglobin A_{1c} (HbA_{1c}) of 5.7% or greater, high-density lipoprotein cholesterol less than 35 mg/dL, triglyceride level greater than 250 mg/dL, and history of cardiovascular disease.[19,20] The ADIPS points out that women with either a BMI between 25 and 35 kg/m^2 or ethnicity as their only risk factor should be considered as "moderate risk," whereas those with both these factors or one of the others mentioned previosuly should be considered as "high risk." The NICE guideline also mentions that the detection of glycosuria at any time during antenatal care should raise suspicion of GDM.

Moreover, a recent umbrella review of meta-analyses on risk factors for GDM concluded that BMI greater

TABLE 1
Summary of Recommendations on Screening and Diagnosis of GDM

	NICE	FIGO	ADIPS	SOGC	ACOG	ADA	ES
Country	United Kingdom	International	Australia	Canada	United States	United States	International
Issued	February 2015	October 2015	May 2013	December 2019	February 2018	January 2020	November 2013
Title	Diabetes in Pregnancy: Management From Preconception to the Postnatal Period	The International Federation of Gynecology and Obstetrics (FIGO) Initiative on Gestational Diabetes Mellitus: A Pragmatic Guide for Diagnosis, Management, and Care	ADIPS Consensus Guidelines for the Testing and Diagnosis of Gestational Diabetes Mellitus in Australia	Guideline No. 393-Diabetes in Pregnancy	Gestational Diabetes Mellitus Practice Bulletin No. 190	14. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes—2020	Diabetes and Pregnancy: An Endocrine Society Clinical Practice Guideline
Pages	55	39	8	13	16	10	23
References	0	292	16	86	109	113	234
Risk factors for GDM	Ethnicity, previous GDM, FH of diabetes, BMI >30 kg/m^2, previous macrosomic neonate (≥4.5 kg). Glycosuria (2 + 1 time or 1 + 2 times or more)	Ethnicity, older maternal age, high parity, increased BMI, FH diabetes, excessive weight gain in pregnancy, low height, PCOS, previous poor pregnancy outcome, previous macrosomic baby, previous GDM, preeclampsia, multifetal pregnancy	Moderate: Ethnicity, BMI 25–35 kg/m^2 High: previous GDM, previous hyperglycemia, age ≥40 y, FH of diabetes, BMI >35 kg/m^2, previous macrosomia, PCOS, medication, corticosteroids' use.	Maternal age >35 y, BMI >30 kg/m^2, ethnicity, FH of DM, previous GDM, previous macrosomic neonate, PCOS, acanthosis nigricans, corticosteroids' use.	Ethnicity, older maternal age, obesity (BMI >25 kg/m^2), previous GDM, physical inactivity, FH of diabetes, previous macrosomic baby, hypertension, HbA_{1c} ≥5.7%, PCOS, high-density lipoprotein <35 mg/dL, triglyceride >250 mg/dL, acanthosis nigricans, history of CVD	Not discussed	Not discussed
Screening for GDM	At 24–28 weeks for women with risk factors. If previous GDM, test earlier. If negative, repeat testing at 24–28 wk	At 24–28 wk for all women. If high risk, test earlier. If negative, repeat testing at 24–28 wk	At 24–28 wk for all women. If high risk, test earlier. If negative, repeat testing at 24–28 wk	At 24–28 wk for all women. If high risk, test earlier. If negative, repeat testing at 24–28 wk	At 24–28 wk for all women. If obese with additional risk factor, test earlier. If negative, repeat testing at 24–28 wk	Not discussed	Before 13 wk or as soon as possible for all pregnant women. At 24–28 wk if previous results are negative

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TABLE 1. *(Continued)*

	NICE	FIGO	ADIPS	SOGC	ACOG	ADA	ES
Early screening	Only for women with previous GDM: self-monitoring of blood glucose or 75-g 2-h OGTT	75 g 2 h OGTT for high-risk women (FPG or HbA_{1c} to all women in high-resource countries and in medium- to low-resource ones with high-risk populations)	1 Moderate risk factor: random or FPG +/– OGTT. 1 High- or 2 moderate-risk factors: 75-g 2-h OGTT	Not discussed	Overweight women with additional risk factors. FPG, 75 g 2 h OGTT, HbA_{1c} or 2-step process starting with 50 g OGTT	Not discussed	FPG (92–125 mg/dL for GDM, ≥126 mg/dL for overt diabetes), random PG (≥200 mg/dL for overt diabetes) or HbA_{1c} (≥6.5% for overt diabetes). A second abnormal test on another day is required for overt diabetes' diagnosis
Screening for GDM at 24–28 wk	2-h pregnancy OGTT with 75-g oral glucose	2-h pregnancy OGTT with 75-g oral glucose	2-h pregnancy OGTT with 75-g oral glucose	50-g glucose 1-h screening test. If glucose <7.8 mmol/L, no further testing. If glucose = 7.8–11 mmol/L, perform a 75 g 2 h OGTT*. If glucose ≥11.1 mmol/L, GDM diagnosed. Alternatively, 2-h 75 g OGTT	50-g glucose 1-h screening test. If glucose >130–140 mg/dL, perform a 100-g 3-h OGTT†. Two or more thresholds are required for the diagnosis	Not discussed	2-h pregnancy OGTT with 75-g oral glucose
Criteria for GDM diagnosis with 2-h OGTT (at least 1 value should be met)	FPG ≥5.6 mmol/L 2-h glucose ≥7.8 mmol/L	FPG ≥5.1–6.9 mmol/L 1-h glucose ≥10 mmol/L 2-h glucose ≥8.5–11 mmol/L	FPG ≥5.1 mmol/L 1-h glucose ≥10 mmol/L 2-h glucose ≥8.5 mmol/L	FPG ≥5.1 mmol/L 1-h glucose ≥10 mmol/L 2-h glucose ≥8.5 mmol/L	FPG ≥5.1 mmol/L 1-h glucose ≥10 mmol/L 2-h glucose ≥8.5 mmol/L	Not discussed	FPG ≥5.1 mmol/L 1-h glucose ≥10 mmol/L 2-h glucose ≥8.5 mmol/L

*FPG ≥5.3 mmol/L, 1-hour glucose ≥10.6 mmol/L, and 2-hour glucose ≥9 mmol/L for the diagnosis of GDM.

†Two different sets of cutoff values are proposed. FPG >5.3 mmol/L, 1-hour PG >10 mmol/L, 2-hour PG >8.6 mmol/L, and 3-hour PG >7.8 mmol/L OR FPG >5.8mmo/L, 1-hour PG >10.6 mmol/L, 2-hour PG >9.2 mmol/L, and 3-hour PG >8 mmol/L.

FH, family history; PCOS, polycystic ovary syndrome; CVD, cardiovascular disease.

TABLE 2
Summary of Recommendations on the Management of GDM During Pregnancy, Labor, and the Postpartum Period

	NICE	FIGO	ADIPS	SOGC	ACOG	ADA	ES
Self-monitoring	Recommended. Fasting and 1-h postprandial glucose to all GDM women. Preprandial and bedtime when using multiple daily insulin injections	Recommended. Fasting and 1- or 2-h postprandial glucose (2–3/d) to all GDM women	Not discussed	Recommended. Fasting and 1- or 2-h postprandial glucose to all GDM women	Recommended. Fasting and 1- or 2-h postprandial glucose to all GDM women. (4/d)	Recommended. Fasting and postprandial glucose. Preprandial only when using insulin pumps or basal-bolus therapy	Recommended. Pre- and 1- or 2-h postprandial. Bedtime and during the night when indicated
Glucose targets	FPG <5.3 mmol/L 1-h postprandial <7.8 mmol/L 2-h postprandial <6.4 mmol/L Glucose >4 mmol/L	FPG <95 mg/L (5.3 mmol/L) 1-h postprandial <140 mg/dL (7.8 mmol/L) 2-h postprandial <120 mg/dL (6.7 mmol/L)	Not discussed	FPG <5.3 mmol/L 1-h postprandial <7.8 mmol/L 2-h postprandial <6.7 mmol/L	FPG <95 mg/L 1-h postprandial <140 mg/dL 2-h postprandial <120 mg/dL	FPG <95 mg/L (5.3 mmol/L) 1-h postprandial <140 mg/dL (7.8 mmol/L) 2-h postprandial <120 mg/dL (6.7 mmol/L)	FPG <95 mg/L (5.3 mmol/L) 1-h postprandial <140 mg/dL (7.8 mmol/L) 2-h postprandial <120 mg/dL (6.7 mmol/L)
HbA_1C targets	Not recommended. Measure HbA_{1c} only at the time of GDM diagnosis to identify preexisting DM	Only to verify the self-monitored glucose reports	Not discussed	Not discussed	Not discussed	<6% (achieved without hypoglycemia) <7% (to prevent hypoglycemia)	≤6.5–7% for pregnant women with preexisting diabetes
CGM	Only when severe hypoglycemia and unstable glucose levels. Or to get informed about glucose variability	No clear benefits	Not discussed	Not discussed	Not discussed	Only in addition to self-monitoring	Only when self-monitoring cannot assess the glycemic control
Antenatal fetal surveillance	Ultrasound at 28, 32, and 36 wk (AF and fetal growth) 38 and 39 wk: assessment of fetal well-being	Ultrasound every 2–4 wk from diagnosis to term (fetal growth) Assessment of fetal well-being is recommended	Not discussed	Ultrasound at 28, 32, and 36 wk (AF and fetal growth) Weekly from 36 wk: assessment of fetal well-being	From 32 wk: fetal testing and AF (mainly for women with poorly controlled GDM and A2GDM)	Not discussed	Not discussed
Initial management of GDM	Lifestyle interventions when FPG <7 mmol/L at diagnosis Insulin when FPG ≥7 mmol/L or 6–6.9 mmol/L + complications	Lifestyle interventions as first-line treatment Medical therapy when glucose targets are not achieved	Not discussed	Lifestyle interventions as first-line treatment Medical therapy when glucose targets are not achieved after 1–2 wk	Lifestyle interventions as first-line treatment Medical therapy when glucose targets are not achieved	Lifestyle interventions as first-line treatment Insulin when glucose targets are not achieved	Lifestyle interventions as first-line treatment Medical therapy when glucose targets are not achieved

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TABLE 2. *(Continued)*

	NICE	FIGO	ADIPS	SOGC	ACOG	ADA	ES
Nutritional interventions	Diet with low glycemic index	A minimum of 175 g of carbohydrate (35%–45% of total calories); 3 meals and 2–3 snacks, food with low glycemic index and high fiber content	Not discussed	Not discussed	Carbohydrate (ideally complex) intake: 33%–40% of calories, protein 20% and fat 40% of calories. Low glycemic index food; 3 meals and 2–3 snacks	A minimum of 175 g of carbohydrate (ideally complex), 71 g of protein and 28 g of fiber. Low saturated fat intake	Carbohydrate intake 35%–45% of total calories. 3 meals and 2–4 snacks
Insulin treatment	Rapid-acting analogs over soluble human insulin Insulin pumps if no control achieved with multiple daily injections	Combination of long or intermediate with rapid-acting insulin	Not discussed	Not discussed	Combination of long or intermediate with rapid-acting insulin Focused treatment if only isolated at specific time of the day abnormal values.	Not discussed	Rapid-acting analogs over soluble human insulin Insulin pumps if no control achieved with multiple daily injections
OAD agents	Metformin if glucose targets are not achieved with diet and exercise Insulin if metformin fails to achieve glucose targets or is contraindicated/ unaccepted Glyburide as an alternative to metformin or insulin	Metformin, insulin, or glyburide. Consider insulin as first-line treatment only if high risk of failure of oral medication	Not discussed	Insulin or oral hypoglycemic agents	Insulin (first-line medical treatment) Metformin if insulin is not accepted tolerated or afforded. Glyburide (not recommended as first-line)	Insulin (first-line medical treatment). Metformin and glyburide (not recommended as first-line)	Insulin (first-line medical treatment). Glyburide as an alternative, except when high risk of failure of oral medication. Metformin not as first-line
Timing of delivery	$<40^{+6}$ wk for uncomplicated GDM Induction of labor or elective cesarean delivery if no spontaneous birth until this time or earlier if complications exist	Induction at 38–39 wk if EFW = 3800–4000 g or LGA or poor glycemic control, previous stillbirth, vascular disease If not, continue to 40–41 wk If EFW >4000 g offer cesarean delivery	Not discussed	Induction between 38 and 40 wk depending on the glycemic control and the comorbid factors. (39 wk for insulin-treated GDM and 40 wk for diet-controlled GDM)	A1GDM 39–40^{+6} wk A2GDM 39–39^{+6} wk Earlier delivery if complications exist GDM not controlled even in hospital: 34–36^{+6} wk Cesarean delivery considered if EFW ≥4500 g	Not discussed	Not discussed
Blood glucose control during labor	Recommended. Monitoring of capillary PG every hour. Glucose target is 4–7 mmol/L	Recommended. Glucose target is 4–7 mmol/L	Not discussed	Not discussed	Not discussed	Not discussed	Recommended. Glucose target is 4–7 mmol/L

Postpartum screening	Discontinue any therapy and test for persistent hyperglycemia Measure FPG at 6–13 wk postpartum If >13 wk, FPG or HbA_{1c} (no routine OGTT)	75-g 2-h OGTT at 6–12 wk postpartum to all women with GDM (nonpregnancy diagnostic criteria)	75-g 2-h OGTT at 6–12 wk postpartum to all women with GDM (nonpregnancy diagnostic criteria)	75-g 2-h OGTT between 6 wk and 6 mo postpartum	75-g OGTT at 4–12 wk postpartum to all women with GDM	75-g 2-h OGTT at 4–12 wk postpartum to all women with GDM (nonpregnancy diagnostic criteria)	Discontinue any therapy. FPG or fasting self-monitoring for 24–72 h after delivery; 75-g 2-h OGTT at 6–12 wk postpartum to all women with GDM
Breastfeeding	Recommended	Recommended	Not discussed	Recommended	Not discussed	Recommended	Recommended
Lifelong screening for type 2 diabetes and prediabetes	To all women with history of GDM and negative postnatal test, HbA_{1c} every year	Recommended	To all women with history of GDM, FPG every 1–2 y	Not discussed	To all women with history of GDM, any glycemic test every 1–3 y	To all women with history of GDM, any glycemic test at least every 3 y	To all women with history of GDM and negative postnatal test, any glycemic test periodically
Preconception screening for diabetes	To all women with history of GDM, offer testing for diabetes (HbA_{1c}) if they plan another pregnancy	To all women with history of GDM in order to treat hyperglycemia and prevent congenital malformations	OGTT annually if they contemplate another pregnancy	Not discussed	Women with history of GDM should be screened more frequently if they want to conceive again	To all women with history of GDM in order to treat hyperglycemia and prevent congenital malformations	To all women with history of GDM

AF, amniotic fluid.

than 30 kg/m^2 and hypothyroidism were the 2 risk factors with the most convincing evidence of association with GDM. Prepregnancy BMI (as a continuous variable), overweight (BMI 25–30 kg/m^2), snoring, sleep-disordered breathing, polycystic ovary syndrome, and family history of diabetes demostrated to be highly suggestive evidence for GDM.[21]

SCREENING FOR GDM

All the reviewed guidelines, except from the one by the NICE, the ADA (makes no relevant recommendation), and the ES, recommend screening for all pregnant women at 24 to 28 weeks of gestation, in order to detect and early manage GDM. Moreover, the NICE recommends targeted screening only for women with risk factors for GDM (24–28 weeks). A multicenter randomized trial reported on the beneficial role of the appropriate treating of GDM for the reduction of some fetal and maternal complications.[22] Additionally, evidence from a systematic review on the benefits and harms of screening for GDM before and after 24 gestational weeks found a substantial benefit of screening after 24 weeks, but not earlier in pregnancy.[23] On the contrary, the ES recommends a universal first-trimester (ideally before 13 gestational weeks) testing for diabetes using fasting/random plasma glucose (PG) levels or HbA_{1c} in terms of preventing potential fetal complications of GDM in pregnancy, aknowledging that this strategy increases the false-positive results. This recommendation is based on a meta-analysis, which found that there is a statistically significant association between positive screening tests and pregnancies at high risk of adverse perinatal outcomes (macrosomia and gestational hypertension).[24] As reported by the ES, testing should be repeated at 24 to 28 gestational weeks with a 75-g 2-hour oral glucose tolerance test (OGTT), if overt or GDM is not diagnosed by the initial test.

Earlier screening (before universal screening at 24–28 weeks) is recommended by some of the other societies only for women who present with risk factors for developing GDM; if the results are normal, the screening should be repeated at 24 to 28 weeks.[25] According to the NICE, women with a previous history of GDM are considered as high risk and should be screened earlier because the recurrence rate of GDM in a subsequent pregnancy is reported to be as high as 45%.[26] Moreover, the FIGO recommends early screening in high-resource countries and low- to medium-resource ones with high-risk populations. The ADIPS and the ACOG, on the other hand, consider early screening for women with additional risk factors. Hence, according to all guidelines, pregnant women with risk factors for GDM should be considered as candidates for an early screening.

However, a controversy exists among the guidelines regarding the appropriate screening method, when early testing is indicated, that is, in high-risk patients. The NICE, FIGO, and the ADIPS recommend the performance of a 75-g 2-hour OGTT. The ACOG, based on an observational retrospective cohort study from 2016, mentions that HbA_{1c} may also be of value because its first-trimester levels are predictive of GDM, but has low accuracy (for a cutoff level of 5.25%, the sensitivity and the specificity were 74% and 51%, respectively).[27] The NICE also suggests self-monitoring of blood glucose levels for women with previous GDM as an alternative to OGTT. The FIGO points out that when early screening is indicated, it is prudent to measure fasting plasma glucose (FPG) or HbA_{1c} in all pregnant women during their first antenatal appointment. Of note, the SOGC and the ADA do not make any relevant recommendation. The different recommendations on the appropriate method of early screening probably reflect the different financial status of each related country.

DIAGNOSIS OF GDM

The FIGO, ADIPS, and the ES endorse the World Health Organization (2013) and International Association of the Diabetes and Pregnancy Study Groups (2010) criteria for the diagnosis of GDM at 24 to 28 weeks' gestation, which are based on the Hyperglycemia and Adverse Pregnancy Outcomes study of 2008.[25,28,29] The Hyperglycemia and Adverse Pregnancy Outcomes study included more than 20,000 pregnant women who underwent 2-hour OGTT at 24 to 32 gestational weeks and found that abnormal OGTT increases the risk of large-for-gestational-age (LGA) neonates, cesarean delivery, and neonatal hypoglycemia.[28] Hence, according to the aforementioned guidelines, the adequate screening method is the performance of a single-step 75-g 2-hour OGTT. If the FPG is equal to or more than 5.1 mmol/L (92 mg/dL), the 1-hour postload glucose is equal to or more than 10 mmol/L (180 mg/dL), or the 2-hour postload glucose is equal to or more than 8.5 mmol/L (153/dL), then a definitive diagnosis of GDM is established. Moreover, the NICE guideline states that the diagnosis of GDM is established if the FPG is equal to or more than 5.6 mmol/L or a 2-hour PG of 7.8 mmol/L or greater. Of note, an FPG of 7 mmol/L (126 mg/dL) or greater or a 2-hour value of 11.1 mmol/L (200 mg/dL) or greater is compatible with overt diabetes rather than GDM.[18]

On the other hand, the SOGC and the ACOG do not recommend the single-step approach as the optimal screening method; however, they consider it as a reasonable option. The SOGC recommends a 2-step approach starting with a 50-g glucose challenge screening test with measurement of PG level 1 hour postload. If the PG level is between 7.8 and 11 mmol/L, a 75-g 2-hour OGTT should be performed with the following thresholds: FPG of 5.3 mmol/L or greater, 1-hour PG of 10.6 mmol/L or greater, or 2-hour PG of 9 mmol/L or greater, for the diagnosis of GDM. If the PG 1 hour after the 50 g load is less than 7.8 mmol/L, there is no need for further testing, whereas if it exceeds the value of 11.1 mmol/L, GDM is diagnosed without requiring an OGTT. The ACOG also recommends a 2-step approach, with a 50-g glucose challenge test being the initial step, followed by a 100-g 3-hour OGTT if PG is greater than 130 or 140 mg/dL 1 hour later. As for the latter test, 2 or more abnormal values are required in order to diagnose GDM, and the ACOG proposes the use of 2 different sets of diagnostic criteria, either from the National Diabetes Data Group (105, 190, 165, and 145 mg/dL, respectively) or from Carpenter and Coustan (95, 180, 155, and 140 mg/dL, respectively) based mainly on the different prevalence of GDM in some communitites and the available resources.[30,31]

This variation among the reviewed guidelines is probably related to different studies. In particular, according to data from a recent meta-analysis of more than 2500 participants, the 1-step approach resulted in a lower risk of LGA neonates (relative risk [RR], 0.46; 95% confidence interval [CI], 0.25–0.83), admission to neonatal intensive care unit (RR, 0.49; 95% CI, 0.29–0.84), neonatal hypoglycemia (RR, 0.52; 95% CI, 0.28–0.95), and lower mean birth weight (mean difference [MD], −112.91 grams; 95% CI, −190.48 to −35.33).[32] However, evidence from a large retrospective cohort study of more than 23,000 women has shown that the 1-step approach was associated with a higher rate of cesarean deliveries and more neonatal intensive care unit admissions compared with the 2-step approach.[33] Table 3 summarizes the accuracy of each diagnostic method.[23]

MANAGEMENT OF GDM

Antenatal Care

Self-monitoring of PG Levels

Self-monitoring of capillary glucose is recommended by 6 of 7 reviewed guidelines (the ADIPS makes no recommendation) because it has been proven that it helps achieving a tight glycemic control and lowers the risk of fetal and maternal complications.[34] Following the diagnosis of GDM, women should measure daily the morning FPG and the 1- or 2-hour postprandial PG levels approximately 3 times a day. A prospective study including 112 women failed to find significant differences

TABLE 3
Estimated Accuracy for Different Diagnostic Tests for GDM

	Sensitivity	Specificity
Carpenter and Coustan (cutoff 140 mg/dL)	85%	86%
Carpenter and Coustan (cutoff 130 mg/dL)	99%	77%
FPG (cutoff 92 mg/dL)	76%	92%
HbA_{1c} (cutoff 7.2%)	64%	64%
HbA_{1c} (cutoff 5.5%)	82%	21%

between the 1- and 2-hour postprandial glucose measurements on the neonatal and obstetrical outcomes.[35] In addition, daily monitoring is preferred over weekly testing because it is associated with reduced rates of macrosomia (21.9% vs 29.5%; $P = 0.013$) and LGA neonates (23.1% vs 34.4%; $P \leq 0.001$), as reported by a retrospective cohort study.[36] The ES also recommends the preprandial PG monitoring, whereas the NICE and the ADA mention that preprandial and bedtime measuments should be restricted only in special cases of insulin therapy as they have been proven to be inferior to postprandial ones in controlling the fetal development.[37]

In general, there is consensus on the recommended glucose targets, which should be less than 5.3 mmol/L (95 mg/L) for the FPG and less than 7.8 mmol/L (140 mg/dL) and 6.7 mmol/L (120 mg/dL) for the 1- and the 2-hour postprandial PG, respectively. The ES sets a FPG cutoff point of 5 mmol/L (90 mg/dL), if it can be achieved without hypoglycemia, based on a recent meta-analysis, which proved that this value is associated with lower risk of macrosomia (odds ratio [OR], 0.53; 95% CI, 0.31–0.90; $P = 0.02$).[38] However, the SOGC mentions that these targets can be more "relaxed" in cases of low fetal abdominal circumference, since several randomized trials have shown that the outcomes are similar to those with strict criteria, in order to avoid the occurrence of small-for-gestational-age fetuses due to GDM overtreatment.[39,40] In addition, the NICE guideline highlights the importance of maintaining blood glucose levels greater than 4 mmol/L during medical treatment of GDM.

HbA_{1c} Targets

The NICE and the FIGO recommend the measurement of HbA_{1c} levels only to identify preexisting diabetes at the time of diagnosis or to confirm the reliability of self-monitored reports because they are not associated with any adverse pregnancy outcomes, except congenital malformations. In particular, a prospective study highlighted that the clinical role of HbA_{1c} is limited because of its poor predictability.[41] Moreover, the ES recommends the use of HbA_{1c} for pregnant women with preexisting diabetes.

On the other hand, the ADA recommends the measurement of HbA_{1c} during pregnancy at least once in each trimester and mentions that HbA_{1c} should be less than 6% in order to reduce fetal complications. This recommendation is based on evidence from a single-center prospective study that enrolled 1989 pregnant women and found that higher midpregnancy HbA_{1c} levels were significantly associated with increased risks of gestational hypertension or preeclampsia, preterm delivery, admission to the neonatal intensive care unit, low birth weight, and macrosomia (OR ranges, 1.20–9.98, 1.31–5.16, 0.88–3.15, 0.89–4.10, and 2.22–27.86, respectively).[42] Moreover, the ADA states that, if this target (6%) cannot be achieved without hypoglycemic events, a threshold of 7% is acceptable. However, HbA_{1c} should be an additional tool, not a substitute of self-monitoring, for the achievement of glycemic control.

Continuous Glucose Monitoring

According to the NICE guideline, continuous glucose monitoring (CGM) should be considered only for insulin-treated patients who experience severe hypoglycemic events or have variable PG levels or when information about the glucose variability is needed. Additionaly, the ES suggests the use of CGM if better glycemic control is required, because of its proven ability to accurately detect postprandial hyperglycemia and nocturnal hypoglycemic events that may not be recognized by intermittent blood glucose monitoring.[43] The ADA points out that self-monitoring combined with CGM is more likely to achieve HbA_{1c} targets. On the contrary, the FIGO states that there is no clear improvement in glycemic control and pregnancy outcome with the use of CGM. Hence, the reviewed guidelines agree that CGM should be used for specific cases where a stricter monitoring of glycemic control is needed.

Fetal Surveillance

There is an overall consensus among the NICE, FIGO, SOGC, and the ACOG guidelines regarding the appropriate ultrasound surveillance of pregnancies complicated with GDM. In particular, an ultrasound evaluation of the amniotic fluid volume and fetal growth every 4 weeks at minimum, starting from the time of diagnosis (usually at 28 weeks) until term, is strongly recommended. Moreover, clinicians should assess the fetal well-being (fetal kick count, nonstress test, or biophysical profile) weekly from 36 weeks (SOGC) or at 38 and 39 weeks (NICE) because stillbirth and perinatal mortality are significantly increased in pregnancies complicated by GDM.[44] In addition, the beneficial role of biophysical profile as the principal technique of antepartum fetal surveillance has

been studied in 238 well-controlled diabetic pregnancies.[45] In the presence of comorbid factors, a more intensive ultrasound evaluation of the fetus is justified according to the SOGC and the ACOG.

Lifestyle Management of GDM

All the reviewed medical societies (except from the ADIPS) state that the combination of nutritional interventions and physical activity constitutes the cornerstone in the management of GDM. The goal is to meet maternal and fetal nutritional needs, achieve and maintain optimal glycemic control, and avoid ketosis.[46] If glucose targets are not achieved with lifestyle interventions after 1 to 2 weeks, medical therapy is recommended, either with insulin or oral antidiabetic (OAD) drugs.[16] Regarding physical activity, regular aerobic exercise for 30 minutes 5 times a week or 150 minutes per week should be suggested[47]; 2 studies showed that this activity significantly reduces the FPG and postprandial PG levels and, subsequently, the daily insulin needs.[48,49] However, the optimal type, timing, and duration of physical activity are not well established yet. A recent meta-analysis (2015) showed that exercise interventions in pregnancy can also provide a slight protective effect against the development of GDM (RR, 0.72; 95% CI, 0.09–0.42; $P = 0.005$).[50] Of note, the NICE guideline points out that lifestyle interventions are not sufficient as first-line treatment when the FPG exceeds 7 mmol/L at diagnosis or if fetal complications exist; in such cases, immediate treatment of insulin is required.

Nutrition counseling and diet modification should be ideally individualized by a dietitian; the FIGO, ACOG, ADA and the ES recommend a diet composed of 35% to 45% complex carbohydrates, 20% protein, and 40% low saturated fat, although the actual dietary composition that improves pregnancy outcomes remains to be determined.[51] A pilot study in 2015 showed that a higher-complex-carbohydrate/lower-fat diet lowers maternal insulin resistance and infant adiposity.[52] Carbohydrate intake should be distributed in 3 meals and 2 to 4 snacks per day.[1] Pregnant women should also be advised to consume food with low glycemic index and high fiber content because this achieves a better glycemic target; according to a meta-analysis, glycated proteins were reduced 7.4% more in women following the low-glycemic compared with the high-glycemic index diet.[53]

Medical Management of GDM

There is a controversy among the reviewed guidelines on the first- and the second-line pharmacological treatment of GDM. Hence, whereas the ACOG, ADA, and the ES recommend the use of insulin when glycemic targets are not achieved with diet and exercise, the NICE and the FIGO suggest the addition of metformin when lifestyle changes alone fail to maintain euglycemia. Regarding the alternatives to insulin medication, the ES supports glyburide, whereas the ACOG and the ADA recommend the use of metformin. The latter has been proved to freely cross the placental barrier, and the fetus can be exposed in high concentrations.[54] In the largest randomized controlled trial, metformin was associated with a lower rate of neonatal hypoglycemia (3.3% vs 8.1%; $P < 0.008$), but a higher rate of preterm delivery (12.1% vs 7.6%; $P = 0.04$) than insulin.[55] Of note, no differences in congenital anomalies or serious perinatal outcomes were identified in the 2 groups.

Regarding insulin, the NICE states that it should be offered immediately, with or without metformin, when FPG is greater than 7 mmol/L at diagnosis or fetal complications exist. The FIGO and the ES state that insulin should be considered as a first-line treatment modality when OAD agents are likely to fail. Risk factors for OAD agents' failure include the diagnosis of GDM before 20 gestational weeks, the need of medical therapy after 30 weeks, weight gain during pregnancy more than 12 kg, and FPG greater than 110 mg/dL or 1-hour postprandial glucose greater than 140 mg/dL.[56,57] The FIGO and the ACOG state that the ideal insulin regimen consists of a combination of long- or intermediate-acting (detemir and glargine) with rapid-acting (aspart and lispro) insulin; the recommended dose is 0.7 to 1 U/kg per day and usually requires adjustment during pregnancy. The ACOG suggests a more focused treatment when abnormal values are observed only at a specific time of the day. The NICE and the ES recommend rapid-acting analogs over soluble human insulin and the use of insulin pumps when GDM cannot be controlled with multiple daily injections. Evidence from a prospective observational study that included 107 pregnant women found that lispro (a rapid-acting analog) provides better glycemic control (HbA_{1c} 5.9 vs 6.7; $P = 0.009$) and lower total insulin requirements during pregnancy compared with regular insulin, without increasing the risk of congenital malformations.[58]

The NICE and the FIGO recommend the use of metformin for the initial medical treatment of GDM, as 2 meta-analyses of 2015 proved that it performs slightly better than insulin and reduces several adverse maternal and neonatal outcomes.[59,60] They also point out that metformin should be added when glycemic targets are not met in 1 to 2 weeks of diet and exercise, whereas insulin should be considered in case of failure or contraindication to metformin. Furthermore, 3 recent meta-analyses proved that metformin yields equivalent outcomes to

insulin regarding the reduction of maternal and perinatal complications.[61–63] However, the ACOG, ADA, and the ES state that this OAD agent should be considered as a reasonable choice only for women who cannot accept, afford, or safely administer insulin therapy, in view of its lack of superiority and the fact that it is transferred through the placenta and there is no long-term safety data for the exposed offspring.[55,64,65] A 2019 systematic review and meta-analysis showed that metformin-exposed infants have lower average birth weight (MD, −107.7 g; 95% CI, −182.3 to −32.7; $P = 0.005$), but higher BMI during middle childhood (MD, 0.78 kg/m^2; 95% CI, 0.23–1.33; $P = 0.005$), compared with children whose mothers were treated with insulin[66]; this growth pattern has been associated with adverse long-term cardiometabolic outcomes.[66] Additionally, according to ADA, the use of metformin is contraindicated in the presence of hypertension, preeclampsia, and high-risk of fetal growth restriction because of its potential association with those pregnancy complications.[67]

Regarding glyburide, the NICE states that it should be considered for cases that glucose targets are not achieved with metformin, or the latter is intolerable, or women decline insulin therapy. Moreover, the ACOG and the ADA do not recommend this drug as first-line treatment, stating that it is inferior to both insulin and metformin in maintaining glycemic control and improving perinatal outcomes. According to a network meta-analysis (2015), glyburide, when compared with insulin, is associated with increased risk of neonatal hypoglycemia (OR, 2.64; 95% CI, 1.59–4.38), high neonatal birth weight (weight MD, 130.68 g; 95% CI, 55.98–205.38), and macrosomia (OR, 3.09; 95% CI, 1.59–6.04).[68] To date, long-term health data for the exposed to glyburide offspring are not available. In contrast, the ES suggests the administration of glyburide as an alternative to insulin, based on an earlier meta-analysis (2010) that proved the safety and effectiveness of this hypoglycemic agent.[69] Hence, the different recommendations on glyburide may be related to the different publication dates of the relevant data.

INTRAPARTUM CARE

Four of the reviewed guidelines (NICE, FIGO, SOGC, and ACOG) state that the timing of delivery for GDM pregnancies should be based on the glycemic control and the presence of complications or comorbid factors. According to the NICE, FIGO, and ACOG, uncomplicated and well-controlled cases of GDM should be managed expectantly until 40^{+6} weeks of gestation, and induction of labor should be offered if spontaneous delivery does not occur until that point.[70] In support of this approach, a randomized controlled trial found that in the absence of other fetal or maternal conditions, expectant management in diabetic pregnancies is a safe practice.[71] Moreover, the SOGC sets an upper limit of 40 weeks of gestation for these pregnancies. For insulin-treated GDM, delivery should be considered between 39 (SOGC) and 39^{+6} (ACOG) weeks. This recommendation is based on evidence from a retrospective cohort study, which found that in women with GDM, at 39 weeks the risk of expectant management exceeds that of delivery regarding fetal and neonatal mortality rates (RR, 1.8; 95% CI, 1.2–2.6).[72] Moreover, a randomized trial including 200 GDM cases showed that expectant management after 38 weeks increased the rate of shoulder dystocia and LGA neonates, without reducing the cesarean delivery rate.[73] Additionally, a decision analysis found that delivery of women with GMD at 38 or 39 weeks of gestation would reduce the perinatal mortality without affecting the cesarean delivery rates.[74] In the presence of fetal or maternal complications, induction of labor or elective cesarean delivery (if indicated) should be offered earlier.

Because of the increased risk of neonatal hypoglycemia in case of maternal hyperglycemia during labor,[75] the NICE, FIGO, and the ES recommend monitoring of blood glucose levels, which should be maintained between 4 and 7 mmol/L, whereas the other guidelines make no relevant recommendation.

Regarding the mode of delivery, elective cesarean section should be considered when the estimated fetal weight (EFW) is greater than 4000 g (at 38–39 weeks, according to FIGO) or 4500 g (timing of delivery is related to the type of treatment [ACOG]). This recommendation is based on a retrospective cohort study of 36,241 singleton pregnancies stratified by the diagnosis of GDM, which showed that neonates with birth weight of 4000 g or greater had higher probabilities of shoulder dystocia (10.5% vs 1.6%; $P < 0.001$), Erb's palsy (2.6% vs 0.2%; $P < 0.001$), respiratory distress syndrome (4.0% vs 1.5%; $P = 0.03$), and hypoglycemia (5.3% vs 2.6%; $P = 0.04$), when compared with those of birth weight less than 4000 g.[76] Thus, the policy of elective cesarean delivery, apart from being more cost-effective, may also reduce these adverse perinatal outcomes.[77] Of note, GDM is not a contraindication to vaginal birth after cesarean delivery.[78] A large retrospective study (2019) showed that the performance of ultrasound at 35^{+0}–36^{+6} weeks in predicting LGA neonates was modest (65% and 46% for neonates with birth weight >97th and >90th percentiles, respectively, at a screen-positive rate of 10%). Therefore, the authors concluded that routine fetal biometry at about 36 weeks is a screening rather than a diagnostic test for fetal macrosomia and proposed a 2-stage strategy for maximizing the prenatal

prediction of an LGA neonate: an EFW >70th percentile at 36 weeks should be used to identify pregnancies in need of another scan at 38 weeks, at which those with an EFW >85th percentile should be considered for iatrogenic delivery during the 38th week.[79]

Notably, in cases of anticipated preterm delivery, the presence of GDM should not be regarded as a contraindication to the administration of corticosteroids, but appropriate adjustments of insulin dosage are usually required (NICE, SOGC).[80] In addition, betamimetic agents should not be used for tocolysis in diabetic women (NICE).

POSTNATAL CARE

Postpartum Screening

After giving birth, women should discontinue any treatment for GDM because glucose intolerance frequently resolves immediately.[3] The NICE and the ES recommend blood glucose testing at 24 to 72 hours after delivery to exclude persistent hyperglycemia. Even if glucose returns to normal, the history of GDM increases the risk of developing type 2 diabetes later in life more than 7 times (RR, 7.43; 95% CI, 4.79–11.51), as shown by a meta-analysis (2009).[8] Thus, all the reviewed guidelines encourage the reevaluation of the glycemic status postpartum.

Moreover, it has been proven that 1 of 3 affected women will have persistent diabetes or impaired glucose tolerance during the postnatal period, according to a retrospective cohort study of 344 women with GDM.[81] Hence, the NICE recommends the measurement of FPG levels 6 to 13 weeks after delivery or the evaluation of HbA_{1c} if the woman presents later. All the other guidelines support the performance of a 75-g 2-hour OGTT using the nonpregnancy diagnostic criteria as the most sensitive screening method.[82] The appropriate time for this test varies between the guidelines: at 6 to 12 weeks (FIGO, ADIPS, ES), 4 to 12 weeks (ACOG, ADA), or 6 weeks to 6 months postpartum (SOGC). If the FPG is greater than 7 mmol/L or HbA_{1c} exceeds 6.5%, clinicians should offer their patients a diagnostic test to confirm type 2 diabetes. Women with FPG of less than 6 mmol/L or HbA_{1c} of less than 5.7% should be considered as low risk and advised to repeat testing.[31]

Thus, there is a consensus on postpartum screening in cases of GDM up to 12 weeks after delivery.

Breastfeeding

Breastfeeding contributes to long-term metabolic benefits for both the mother and the offspring and should be strongly advised to all women with GDM, according to the NICE, FIGO, SOGC, ADA, and the ES (the other guidelines make no relevant recommendation). Particularly, a 2012 cohort study of 522 participants with GDM showed that a higher intensity of lactation may improve maternal insulin resistance and glucose intolerance at 6 to 9 weeks postpartum, thus lowering the risk of diabetes later in life.[83] Moreover, a study that enrolled 15,253 infants identified an inverse association of breastfeeding with childhood obesity (OR, 0.66; 95% CI, 0.53–0.82).[84]

Lifelong Screening for Diabetes

All the reviewed guidelines (apart from the SOGC that makes no recommendation) recommend that women with history of GDM and normal postnatal screening test results should undertake lifelong screening for the development of prediabetes or type 2 diabetes. However, there is no established consensus on the appropriate screening method and interval. Hence, the NICE suggests the annual evaluation of HbA_{1c}, and the ADIPS supports the measurement of FPG every 1 to 2 years after delivery, whereas the ACOG and the ADA state that glycemic control should be conducted every 1 to 3 years using any of the available tests. This variation probably reflects national policies, which are related to cost-effective analyses.

Preconception Screening for Future Pregnancies

There is an overall agreement that women who experienced GDM in a previous pregnancy and plan another pregnancy should undergo glycemic control evaluation frequently, either with HbA_{1c} measurement (NICE) or OGTT (ADIPS). This strategy will alow early detection and treatment of hyperglycemia before fertilization and thus reduce the risk of congenital malformations and spontaneous abortions.[82]

CONCLUSIONS

This comparative review of 7 guidelines identified an overall consensus regarding the importance of screening and effectively managing GDM. Four of 7 guidelines (the FIGO, ADIPS, SOGC, and the ACOG) recommend universal screening at 24 to 28 weeks for GDM and testing those with additional risk factors earlier. Notably, the NICE recommends targeted screening at this period (24–28 weeks) only to women with risk factors. The ES proposes a different strategy of offering first-trimester screening to all pregnant women and retesting at 24 to 28 weeks if the initial results are negative, and the FIGO recommends the latter approach only for high-resource countries or medium- and low-resource countries with high-risk populations. In addition, all the medical societies point out that self-monitoring of capillary glucose levels

and a combined adoption of regular physical activity and adequate diet should be the first-line measures for achieving glycemic control. Moreover, there is agreement on the recommended fasting and postprandial blood glucose targets, the fetal surveillance protocols in GDM pregnancies, the beneficial role of breastfeeding, the importance of postpartum screening for persistent hyperglycemia, and the management of subsequent pregnancies.

On the other hand, the main issues of controversy are the preferred screening protocol for GDM diagnosis (either a 1-step or a 2-step strategy), the optimal first-line medical treatment (insulin or oral agents), the use of glyburide, the timing of delivery, and the postpartum and lifelong screening for diabetes.

Poorly controlled GDM may lead to adverse short- and long-term health impacts on both the mother and the fetus. In order to minimize the potential complications and thus optimize the pregnancy outcomes, it is crucial to find common pathways in all areas of controversy and adopt a consistent evidence-based strategy for the effective screening, diagnosis, and management of GDM. Further well-designed large-scale randomized controlled trials are required to investigate areas of controversy, including but not limited to the best timing and method of screening, the optimal treatment strategy, the optimal fetal monitoring, the timing and method of delivery, and postparum follow-up. These studies will subsequently allow universally recommended strategies that will obviously have to adapt to the specific resources and risk profiles of different populations, based on local cost-effectiveness studies.

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